FDA Briefing Document

Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee

September 14, 2016

Serious Neuropsychiatric Adverse Events with Drugs for Smoking Cessation
DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the FDA-required postmarketing trial which evaluated neuropsychiatric adverse effects in patients randomized to Chantix (varenicline), Zyban (bupropion), nicotine replacement therapy or placebo, along with relevant published observational studies, to this Advisory Committee in order to gain the Committee’s insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
Food and Drug Administration
Center for Drug Evaluation and Research

Joint Meeting of the Psychopharmacologic Drugs Advisory Committee
and Drug Safety and Risk Management Advisory Committee

Serious Neuropsychiatric Adverse Events with Drugs for Smoking Cessation

September 14, 2016

Briefing Materials
Table of Contents

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Overview of the Points to Consider

DAAAP Integrated Summary Memorandum

Attachments:

1- Epidemiology Review

2- Statistical Evaluation of Observational Studies

3- Pharmacovigilance Review: Neuropsychiatric Adverse Events Update 2011-2015

4- Drug Utilization Review

5- Postmarketing Required Randomized Controlled Trial: Protocol

6- Chantix Proposed Labeling and Medication Guide – Submitted February 18, 2016 (Pfizer)

7- Chantix Approved Labeling and Medication Guide – October 15, 2014 (Pfizer)

8- Zyban Approved Labeling and Medication Guide

9- Nicotine Patch Drug Facts Labeling

10- FDA Background Package from 2014 Advisory Committee Meeting

11- Summary Minutes from the 2014 Advisory Committee Meeting

12- Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning

Section of Labeling for Human Prescription Drug and Biological Products-Content and Format
MEMORANDUM

Date:       August 9, 2016

From:       Judith A. Racoosin, MD, MPH
            Deputy Director for Safety
            Division of Anesthesia, Analgesia, and Addiction Products
            Office of Drug Evaluation II, CDER, FDA

            Rigoberto Roca, MD
            Deputy Division Director
            Division of Anesthesia, Analgesia, and Addiction Products
            Office of Drug Evaluation II, CDER, FDA

To:         Chair, Members, and Invited Guests

Re:         Overview of the September 14, 2016 Joint Meeting of the Psychopharmacologic
            Drugs Advisory Committee and Drug Safety and Risk Management Advisory
            Committee Meeting

Varenicline, marketed by Pfizer as Chantix in the US and Champix globally, is a partial α4β2
acetylcholine nicotinic receptor agonist approved in May 2006 as an aid to smoking cessation.
The treatment regimen is 1 mg twice daily for 12 weeks (with an initial one-week titration). A
second 12-week course may be taken to increase the chance of maintenance of abstinence.

Bupropion HCl is an aminoketone antidepressant originally approved under the proprietary name
Wellbutrin. As an antidepressant, Wellbutrin is thought to act primarily via noradrenergic
mechanisms, but also has some dopaminergic activity. Its mechanism of action as an aid to
smoking cessation is not known. The new drug application (NDA) for Bupropion HCl Sustained
Release Tablets (marketed by GSK under the proprietary name Zyban for this indication) was
approved in May 1997. The treatment regimen is 150 mg twice daily for 7-12 weeks (with an
initial three-day titration).
Based on postmarketing adverse event reports, both Chantix and Zyban labeling carry boxed warnings regarding the risk of serious neuropsychiatric events. In 2008, using the postmarketing safety authorities included in the FDA Amendments Act of 2007, FDA imposed a post marketing requirement (PMR), which required Pfizer and GSK to conduct a placebo-controlled postmarketing safety trial to further characterize the risk of neuropsychiatric adverse events and to evaluate whether a prior history of psychiatric illness was a risk modifier. Because patients with a history of psychiatric illness did not participate in the initial clinical efficacy trials that supported approval of the NDA, it was also important to ascertain whether the medications were effective in these patients, in order to understand the balance of risks and benefits. An active comparator of transdermal nicotine was included in the clinical trial design to determine whether nicotine replacement, another pharmacologic option for treating tobacco dependence, offers any advantage or disadvantage with respect to neuropsychiatric effects.

This PMR trial has now been completed. The background document that accompanies the background package describes in detail FDA’s review of the study design and results, as well as sensitivity analyses conducted by FDA review staff. As is conveyed in the background document, and will be discussed at the advisory committee meeting, FDA has identified concerns with the ascertainment of the primary neuropsychiatric adverse event outcome that impacts interpretation of the trial results. In brief, the interview tools that were developed to optimally capture the neuropsychiatric adverse events of concern were not utilized to the extent intended to get a nuanced understanding of such adverse events. In some cases, lack of information about the circumstances of events limited FDA’s ability to determine whether they were primary outcome events. Additionally, there was substantial variability among investigators in how the adverse event severity was coded and how the adverse event terms were applied, leading to variability in the number of neuropsychiatric adverse events included in the primary outcome. Finally, there was inconsistency in how suicidality cases were handled, with the Columbia Suicide Severity Rating Scale (C-SSRS) results not being reconciled with the adverse event reporting. All of these factors likely served to lower the overall number of primary outcome events, which may result in biasing towards a null finding. FDA conducted some sensitivity analyses to try and address some of the concerns raised by these ascertainment issues.

The background document and package also include relevant information on observational studies of neuropsychiatric adverse events with smoking cessation products, pharmacovigilance information on the smoking cessation products, and drug utilization information.

The Division and Agency are grateful for your participation in this important meeting and for providing your expertise and insight. We thank you in advance for your advice which will assist us in determining how the new evidence affects the understanding of the risk of serious neuropsychiatric adverse events with smoking cessation products, and how that may be communicated in labeling.
Draft topics for Discussion

1. Discuss the strengths and weaknesses of the completed randomized controlled trial (RCT) with regard to the study design including the novel primary endpoint.

2. Discuss the potential impact of the variability in data collection, adverse event coding, and application of the case definition on ascertainment of the primary endpoint. Because of this variability, discuss which analysis and results most appropriately describe the effect of the smoking cessation therapies on neuropsychiatric events.

3. Discuss how you weigh the evidence contributed by the observational studies when evaluating the risk of serious neuropsychiatric adverse events in patients taking smoking cessation products.

4. Based on the results of the clinical trial and observational studies, discuss the impact of psychiatric history on the occurrence of neuropsychiatric adverse events during smoking cessation therapy.

5. Based on the data presented on the risk of serious neuropsychiatric adverse events with smoking cessation products, what would you recommend?
   a. Remove the boxed warning statements regarding risk of serious neuropsychiatric adverse events
   b. Modify the language in the boxed warning
   c. Keep the current boxed warning

6. Explain the rationale for your answer to #5, and discuss any additional labeling actions you think the Agency should take regarding the risk of serious neuropsychiatric adverse events with smoking cessation products.
Serious Neuropsychiatric Adverse Events with Drugs for Smoking Cessation

September 14, 2016

Integrated Summary Memorandum

1 Introduction and Background ....................................................................................... 5
1.1 Initial Postmarketing Safety Reviews ................................................................. 6
1.2 Risk Evaluation and Mitigation Strategy (REMS)/ Postmarketing Requirement (PMR) Clinical Trial ................................................................. 8
1.3 October 2014 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee ................. 10
2 Clinical Pharmacology ............................................................................................... 12
2.1 Varenicline ......................................................................................................... 12
2.2 Bupropion ........................................................................................................... 13
2.3 Nicotine Transdermal System ............................................................................ 14
3 Post-Marketing Requirement Randomized Controlled Trial ................................. 14
3.1 Overview and Objective ..................................................................................... 15
3.2 Study Design and Endpoints .............................................................................. 15
3.3 Inclusion/Exclusion Criteria ............................................................................... 16
3.4 Procedures .......................................................................................................... 20
3.4.1 Study Treatments .......................................................................................... 21
3.4.2 Behavioral Treatment .................................................................................... 23
3.4.3 Schedule of Study Procedures ...................................................................... 23
3.4.4 Study Endpoints ............................................................................................ 28
3.4.5 Statistical Analysis Plan (SAP) ..................................................................... 29
3.5 Population and Subject Disposition ................................................................... 30
3.6 Study Conduct .................................................................................................... 36
3.6.1 General Issues on Data Quality and Reviewability ...................................... 36
3.6.2 Data Reliability Issues .................................................................................. 38
3.6.3 Issues Related to Capture of NPS Events ..................................................... 40
3.7 Analysis of NPS Primary Endpoint .................................................................... 43
3.7.1 Analysis of the Primary Neuropsychiatric Event .......................................... 44
3.7.2 Composite Neuropsychiatric Event Including Only Severe Adverse Events 47
3.7.3 Composite NPS+ Event ............................................................................... 47
3.7.4 NPS Event by Study Sites ............................................................................. 48
3.7.5 Statistical Models to Account for Extra Binomial Variation between Sites. 50
3.7.6 Analysis of Deaths ....................................................................................... 51
3.7.7 Analysis of the C-SSRS Instrument ............................................................... 52
3.7.8 Effect of Smoking vs Abstinence .................................................................. 53
3.7.9 Impact of Financial Involvement .................................................................. 57
3.8 Analysis of Efficacy ........................................................................................... 60
3.9 Analysis of General Safety Data ........................................................................... 64
LIST OF TABLES

Table 1 Dosing Schedule (Protocol) ................................................................. 21
Table 2 Schedule of Activities - Study Treatment Period ................................. 24
Table 3 Schedule of Activities - Post Treatment Period ................................. 25
Table 4 Summary of Baseline Characteristics (Non-PHx Cohort) – Safety Population 32
Table 5 Summary of Baseline Characteristics (PHx Cohort) – Safety Population 33
Table 6 Summary of Baseline Psychiatric Characteristics (PHx Cohort) - FAS Population ................................................................. 34
Table 7 Disposition in the Non-PHx Cohort ................................................. 35
Table 8 Disposition in the PHx Cohort ......................................................... 35
Table 9 Severe Treatment Emergent Neuropsychiatric Events by Cohort ............ 47
Table 10 Treatment Emergent NPS + Events by Treatment and Cohort .......... 48
Table 11 Deaths by Cohort and Treatment .................................................. 52
Table 12 Results of the C-SSRS in the Non-PHx Cohort – Treatment Emergent Events 53
Table 13 Results of the C-SSRS in the PHx Cohort – Treatment Emergent Events .... 53
Table 14. NPS Events in Primary Analysis and in Subset Excluding 32 Sites with Financial Involvement ................................................................. 58
Table 15. NPS Events by Country and Financial Involvement, Pooled Across All Treatments ................................................................. 58
Table 16. Risk Difference of NPS Events in Primary Analysis and in Subset ......... 59
Table 17. NPS+ Events in All Sites and in Subset Excluding 32 Sites with Financial Involvement ................................................................. 59
Table 18. Risk Difference of NPS+ Events in Primary Analysis and in Subset ...... 60
Table 19 Comparison of Continuous Abstinence Rates for Weeks 9-12 and Weeks 9-24 - FAS Population ................................................................. 61
Table 20 Number of Subjects in FAS and mFAS Datasets ............................. 62
Table 21 Comparison of Continuous Abstinence Rates for Weeks 9-12 and Weeks 9-24 - mFAS Population† ................................................................. 62
Table 22. Exposure to Treatment, Non-PHx - Safety Population ..................... 64
Table 23 Exposure to Treatment, PHx - Safety Population .............................. 65
Table 24 Fatal Adverse Events ....................................................................... 67
Table 25 Treatment-Emergent SAE incidence by treatment and history of psychiatric disease ................................................................. 67
Table 26 Description of 30 NPS SAEs .............................................................. 69
Table 27 Patients with Treatment-Emergent Adverse Events Leading to Dose Reductions or Discontinuations .......................................................... 75
Table 28 Adverse Events Leading to Study Drug Reduction or Discontinuation in \( \geq 1\% \) in Any Arm; Non-Phx Cohort ................................................................. 76
Table 29 Adverse Events Leading to Study Drug Reduction or Discontinuation in \( \geq 1\% \) in Any Arm; PHx Cohort ................................................................. 76
Table 30. Potential channeling bias in the Thomas et al. study a illustrated by their findings of the all-cause mortality risk among varenicline users and bupropion users .... 90
LIST OF FIGURES

Figure 1. Study Diagram .................................................................................................. 16
Figure 2. NPS Events in the Non-PHx ........................................................................ 44
Figure 3. NPS Events in the PHx Cohort ...................................................................... 45
Figure 4. Primary Analysis: Risk Difference of NPS Events by Cohort ....................... 46
Figure 5. Site Size and NPS Events in the Non-PHx Cohort ....................................... 49
Figure 6. Site Size and NPS Events in the PHx Cohort ............................................... 50
Figure 7. Rate Ratio for NPS Events from a Negative Binomial Model ..................... 51
Figure 8. Primary NPS AE Endpoint – Smoking Status by Week and Onset of AE - Non-Psychiatric History Cohort, Safety Population ............................................. 55
Figure 9. Primary NPS AE Endpoint – Smoking Status by Week and Onset of AE - Psychiatric History Cohort, Safety Population ......................................................... 55
Figure 10. Reviewer-generated forest plot of varenicline-associated neuropsychiatric (NPS) risk observed in all reviewed studies (reference group: nicotine replacement therapy, \textsuperscript{a,b,d,f} bupropion, \textsuperscript{c} or person-time that was unexposed to varenicline\textsuperscript{e}) .......... 88
Figure 11. Reviewer-generated forest plot of neuropsychiatric (NPS) risk observed in all reviewed studies that examined both varenicline- and bupropion- associated risk\textsuperscript{a,b} ...... 89
Figure 12. .................................................................................................................... 92
Figure 13. Nationally Estimated Number of Unique Patients Who Received Dispensed Prescriptions for Smoking Cessation Products* from U.S. Outpatient Retail Pharmacies, 2006-2015 .................................................................................................................. 93
1 Introduction and Background

Chantix (varenicline) is a partial α4β2 acetylcholine nicotinic receptor agonist approved in May 2006 as an aid to smoking cessation. The treatment regimen is 1 mg twice daily for 12 weeks (with an initial one-week titration). A second 12-week course may be taken to increase the chance of maintenance of abstinence.

Bupropion HCl is an aminoketone antidepressant originally approved under the proprietary name Wellbutrin. As an antidepressant, Wellbutrin is thought to act primarily via noradrenergic mechanisms, but also has some dopaminergic activity. Its mechanism of action as an aid to smoking cessation is not known. The NDA for Bupropion HCl Sustained Release Tablets (marketed under the proprietary name Zyban for this indication) was approved in May 1997. The treatment regimen is 150 mg twice daily for 7-12 weeks (with an initial three-day titration).

In May 2007, the European Medicines Agency (EMA- previously, EMEA) informed FDA that they were investigating a signal of suicidality-related adverse events with Chantix (marketed in the EU as Champix). Later that same summer, a fatal case involving bizarre and aggressive behavior by a Chantix-treated patient became highly-publicized. FDA subsequently undertook evaluations of the postmarketing data regarding cases of suicide and cases of bizarre and aggressive behavior and concluded that there were cases that could be attributed to Chantix treatment. In a number of cases, the reporters provided rich and detailed narratives about the events, describing experiences involving symptoms in a variety of neuropsychiatric domains, including cognition, perception, mood, and general functioning. A series of incremental changes to labeling were made to address the emerging understanding of the nature of the risk. A subsequent review of post-marketing data on Zyban and various nicotine replacement therapies identified similar cases associated with Zyban. A chronology of the subsequent regulatory actions and public communications that followed is shown below.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 1997</td>
<td>NDA approval of bupropion(^1) for smoking cessation (tradename “Zyban”)</td>
</tr>
<tr>
<td>May 2006</td>
<td>NDA approval of varenicline in the U.S. (tradename “Chantix”)</td>
</tr>
<tr>
<td>September 2006</td>
<td>Approval of varenicline in the European Union (tradename “Champix”)</td>
</tr>
<tr>
<td>May 2007</td>
<td>European Medicines Agency informed FDA that they were investigating a signal of suicidal-related events with varenicline and had asked Pfizer to submit a postmarketing suicidal-event analysis.</td>
</tr>
<tr>
<td>Nov 2007</td>
<td>Information added to ADVERSE REACTIONS section of varenicline labeling; Early communication of an ongoing safety review</td>
</tr>
<tr>
<td>Jan/Feb 2008</td>
<td>Serious neuropsychiatric adverse events information upgraded to the WARNINGS AND PRECAUTIONS section of the varenicline labeling; Public health advisory issued</td>
</tr>
<tr>
<td>April 2008</td>
<td>Center Director briefing to discuss varenicline and serious neuropsychiatric adverse events, the benefits of varenicline to help patients achieve smoking cessation vs. the risk of serious neuropsychiatric adverse events</td>
</tr>
</tbody>
</table>

\(^1\) NDA approval for bupropion first occurred in December 1985 for major depressive disorder (tradename “Wellbutrin”).
May 2008 | Division required Risk Evaluation and Mitigation Strategy (REMS) for varenicline; issued a postmarketing requirement (PMR) to assess the serious risk of neuropsychiatric symptoms with varenicline; Public health advisory updated. FAA bans use of varenicline by pilots and air traffic controllers

Feb 2009 | Division required Risk Evaluation and Mitigation Strategy (REMS) for bupropion and issued a postmarketing requirement (PMR) to assess the serious risk of neuropsychiatric symptoms with bupropion

July 2009 | Added BOXED WARNING section to varenicline and bupropion labeling; Public health advisory issued regarding addition of boxed warning to both varenicline and bupropion

March 2010 | Formalized PMR description and milestone dates for varenicline and bupropion to require a placebo- and active- controlled randomized controlled trial (RCT) to assess the serious risk of neuropsychiatric symptoms with treatments for smoking cessation

Oct 2011 | Drug Safety Communication reported the results of two FDA-sponsored epidemiology studies that evaluated the risk of serious neuropsychiatric adverse events associated with varenicline

Oct 2014 | Joint meeting of Psychiatric Drugs Advisory Committee/Drug Safety and Risk Management Committee to consider Pfizer’s request to remove the boxed warning from the Chantix label based on meta-analyses of randomized controlled trials and observational studies. Committee voted to wait until the PMR RCT results were available.

### 1.1 Initial Postmarketing Safety Reviews

Prior to the addition of the boxed warning for serious neuropsychiatric adverse events, the Division of Adverse Event Analysis II completed two reviews of AERS cases- one focused on suicidality events (finalized July 2008) and the other focused on neuropsychiatric adverse events not related to suicidality (finalized Dec 2008).

Briefly, the review of suicidality events showed that from initial marketing through November 2007, AERS had 262 cases of suicidal-related events for the smoking cessation drugs as shown in the table below. Despite the shortest time on the market, varenicline had the highest number of cases. Median time to event was 14 days or less for all three drugs.

<table>
<thead>
<tr>
<th></th>
<th>varenicline</th>
<th>bupropion</th>
<th>NRT</th>
</tr>
</thead>
<tbody>
<tr>
<td># cases</td>
<td>153</td>
<td>75</td>
<td>34</td>
</tr>
<tr>
<td>Suicidal ideation (%)</td>
<td>76</td>
<td>61</td>
<td>47</td>
</tr>
<tr>
<td>Attempted/completed</td>
<td>24</td>
<td>39</td>
<td>53</td>
</tr>
</tbody>
</table>

2 The Division of Adverse Event Analysis II is now called the “Division of Pharmacovigilance II”.
3 The FDA Adverse Events Reporting System (FAERS) was called “Adverse Event Reporting System (AERS)” at the time these reviews were done.
4 Bupropion was approved for the treatment of depression as Wellbutrin about a decade before it was approved as Zyban for smoking cessation. In order to limit the review to those exposed to bupropion for the treatment of smoking cessation, included cases had to either reference bupropion by the trade name Zyban, or mention the indication of smoking cessation in the report.
Varenicline had the largest proportion of reports (24%) in which it was explicitly stated that the suicidal event(s) were a first-time significant behavior change from the past, followed by bupropion (15%) and nicotine (none). Varenicline cases had the most reports that described pre-existing psychiatric disease worsening (17%) compared to nicotine (12%) and bupropion (8%); depression was the most common pre-existing psychiatric condition that worsened for all three drugs. The overall conclusion was that AERS data suggested a possible association between suicidal events and the use of varenicline and bupropion, given that there were postmarketing cases of positive dechallenge and a few positive rechallenges, a close temporal relationship between the event and drug use, and the occurrence of suicidal events in patients without any psychiatric history.

Based on the AERS review of suicidality events, a recommendation was made to add a boxed warning section to highlight the risk of serious neuropsychiatric adverse events and to request a PMR to determine the incidence of serious neuropsychiatric adverse events with varenicline, especially in patients with preexisting psychiatric disorders. For Zyban (bupropion), which was included as a comparator in this review, there was a similar recommendation to add language to the already existing boxed warning section about the risk of suicidality in those using bupropion for smoking cessation.

A review of AERS cases describing neuropsychiatric adverse events other than suicidality was completed in December 2008. Because of the increased awareness that there was “stimulated” reporting5 starting in September 2007, this review was conducted from market approval through August 2007. Additionally, because there were few evaluable cases reported with nicotine replacement therapies (NRT), the review focused on only case reports for varenicline and bupropion.

For both varenicline and bupropion, anxiety and depression were the two most commonly reported events. For both drugs, ~20% of the cases reported psychosis/mania or aggression-related events. For varenicline, the most common event for the psychosis/mania and aggression groups was hallucination and aggression respectively; for bupropion it was paranoia and hostility respectively. There was a temporal association between the two drugs and all groups of events with a median onset time between three and seven days. Positive dechallenge was reported in 33% and 63% of the varenicline and bupropion cases, respectively.

For all event groups, patients with no reported psychiatric history ranged from 17 to 33% for varenicline and 13 to 30% for bupropion. For all event groups, patients with no reported concomitant psychiatric medications ranged from 4 % to 13% for varenicline and 0 to 25% for bupropion. There were more cases with varenicline (29-33%) that reported a behavioral change from the patient’s past (i.e., either new experience or disease worsening) than with bupropion (0-9%).

5Stimulated reporting is an increase in adverse event reporting that often occurs following any risk communication or media attention to a particular safety issue due to enhanced awareness.
More varenicline patients (27%-53%) had a history of psychiatric disease than bupropion (0%-20%); however, there was a portion of the bupropion population for which unknown medical history was very high (78%). The most commonly reported psychiatric history across the case series was depression and bipolar disorder. Psychiatric medication use ranged from 13% to 73% for varenicline and 21% to 70% for bupropion, depending on event group.

The recommendations included enhancements to the proposed boxed warning and other parts of labeling to warn of the risk of these other neuropsychiatric adverse events.

The need for a boxed warning was discussed extensively at the highest levels of Center management and it was determined that the events met criteria for placement in a boxed warning. Specifically, because the events were of a serious nature and had adverse consequences that could be prevented by close monitoring.

1.2 Risk Evaluation and Mitigation Strategy (REMS)/Postmarketing Requirement (PMR) Clinical Trial

As the understanding of the serious neuropsychiatric adverse events with varenicline evolved, it was determined that a REMS was necessary to ensure that the benefits of varenicline outweighed the risks. In May 2008, FDA issued a letter to Pfizer that required a REMS and also included issuance of a postmarketing requirement (PMR) for a clinical trial to assess the known serious risk of neuropsychiatric adverse events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions related to the use of varenicline products. A similar REMS and PMR for Zyban was required of Glaxo SmithKline.

The design of the study presented a number of challenges. The fundamental problem was that the types of cases reported in the postmarket setting were of a heterogeneous nature and subsumed a variety of disturbing symptoms. Focus on a single endpoint, such as suicide or psychiatric hospitalization, was considered but it was felt that this would miss the full range of neuropsychiatric symptoms that were reported, and additionally, that the sample size for such a study might need to be so large as to be impracticable. Instead, a composite endpoint would be needed that could capture the types of events reported in the AERS cases—events often involving a cluster of emotional, cognitive, perceptual, and behavioral symptoms that were identified by the patient or the patient’s family as unusual, out of character, and extremely disturbing.

After internal deliberation and discussion with Pfizer and GlaxoSmithKline (sponsor of bupropion), further guidance on the PMR was issued in a letter dated June 2, 2009. As seen in the description below, FDA determined that a randomized controlled clinical trial would be required to meet the PMR goals:

A large randomized, double-blind, active- and placebo-controlled trial to compare the risk of clinically significant neuropsychiatric adverse events, including but not limited to suicidality, in individuals using varenicline, bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation over 12 weeks of treatment, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for
development of clinically significant neuropsychiatric adverse events compared to individuals without prior history of psychiatric disorders while using varenicline as an aid to smoking cessation. The study should be sufficiently powered to adequately assess clinically significant neuropsychiatric adverse events with each treatment and in both of the two subgroups (i.e., with and without psychiatric disorders).

Pfizer and GSK were encouraged to collaborate on this trial. Pfizer took the lead on designing and conducting the PMR trial, with financial support and study drug supplied by GSK (who also markets nicotine transdermal products). After a series of discussions internally and with the sponsors, the PMR protocol was found acceptable around July 2010 (see Attachment 1 for the protocol). In recognition of the variable and ill-defined nature of the neuropsychiatric adverse events reported, and the difficulty of capturing such events in traditional MedDRA coding\(^6\), a composite endpoint was developed specifically for the PMR trial and instruments to solicit relevant events were included in the trial procedures. The 16 “components” of the primary endpoint were agreed-upon in the protocol—however, selection of the specific MedDRA preferred terms that mapped to each of the components were left to the sponsors to determine and included in the statistical analysis plan (SAP). Following FDA review, we suggested some additional terms that should be included, and these were incorporated into the primary endpoint before the final analysis.

The intent for this endpoint was to avoid “noise” by excluding mild events, because some emotional and cognitive symptoms such as irritability and impaired concentration are well-recognized symptoms of nicotine withdrawal encountered during smoking cessation. Such symptoms may be expected in patients quitting smoking without pharmacotherapy. The Neuropsychiatric Adverse Event Inventory (NAEI) was intended to be used as a semi-structured interview, wherein any positive responses would be followed up in order to get a full picture of the context of the symptom, co-occurring symptoms, and a rich narrative of the event. The NAEI was developed for the purposes of the PMR trial and was intended to be administered by trained interviewers. Follow-up questions were to be used for “clarification, frequency/duration, severity, and degree of functional impairment related to the symptom.” Sample follow-up questions were provided in the training materials. The interviewer was instructed to “probe as needed to assess the subject’s experiences and to make an appropriate assessment.” Narratives were to be constructed for neuropsychiatric (NPS) cases that pulled together all relevant information from reporters who could include the patient, significant others, health care providers, or other sources.

\(^6\) MedDRA (Medical Dictionary for Regulatory Activities) is an international standardized lexicon of medical terms used to code adverse events. MedDRA was developed by the ICH (International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and released in 1999 with regular updates released since then. MedDRA contains about 21,000 different preferred terms (PTs, e.g., nausea, hypotension) for various adverse events. These PTs are vertically grouped into 3 levels. The highest level for a PT is the System Organ Class, of which there are 26 (e.g., Cardiac disorders, Infections and infestations).

http://www.meddra.org/sites/default/files/guidance/file/intguide_17_1_english.pdf
1.3 October 2014 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

In April 2014, Pfizer submitted a labeling supplement for varenicline (Chantix, NDA 21-928) proposing changes to the varenicline labeling relating to the risk of serious neuropsychiatric adverse events. In the cover letter of this supplement, Pfizer asserted that, “…since 2009, more reliable data on the NPS [neuropsychiatric] safety of Chantix have become available, including meta-analyses of placebo-controlled clinical trials and data from observational studies comparing varenicline to other smoking cessation pharmacotherapies. As presented in this submission, these data do not support an association between treatment with Chantix and serious NPS [neuropsychiatric] events.”

Based on Pfizer-conducted meta-analyses of randomized controlled trials of varenicline and a Pfizer-conducted review of five publications of observational studies of patients treated with varenicline compared to patients treated with nicotine replacement therapy (NRT) or bupropion, Pfizer proposed the following major changes to the varenicline labeling:

- **Highlights of Prescribing Information:**
  - Remove Boxed Warning on Serious Neuropsychiatric Events
  - Under Warnings and Precautions, add a Warning on Serious Neuropsychiatric Events in bolded font

- **BOXED WARNING section of the Full Prescribing Information (FPI):**
  - Remove the box (i.e., remove the single black line) around the Warning on Serious Neuropsychiatric Events and add summaries of information from neuropsychiatric meta-analyses of clinical trial data and observational studies

- **WARNINGS AND PRECAUTIONS section of the FPI**
  - In section 5.1 WARNINGS AND PRECAUTIONS / Neuropsychiatric Symptoms and Suicidality, add information from neuropsychiatric meta-analyses of clinical trial data and observational studies

The original signal for serious neuropsychiatric adverse events came from cases reported to the FDA and described in the medical literature. In this supplement, Pfizer argued that the information garnered from the meta-analyses they conducted and the published observational studies they reviewed is reassuring and trumped the information culled from the case reports that originally led to the Boxed Warning and Warnings and Precautions statements in varenicline labeling, and that the sum of this new evidence did not support the presence of a boxed warning for serious neuropsychiatric adverse events.

The FDA review team, including clinicians, biostatisticians, and epidemiologists, had concerns about the validity of the findings from Pfizer’s meta-analyses and the published observational studies. The limitations of the findings described in each of their reviews raised questions as to how to best interpret the findings of the meta-analyses and observational studies.

Furthermore, when FDA issued the postmarketing requirement for the randomized controlled trial to evaluate the neuropsychiatric adverse events with varenicline in 2008, FDA stated that observational studies would not be adequate to address this safety question. This decision was
made because there was a lack of confidence that the kinds of coded data used in observational studies could capture the neuropsychiatric adverse events of interest, and concern about differential selection of patients for treatment with varenicline and the associated bias that could be introduced into comparisons. The required clinical trial included randomization to treatment, and the neuropsychiatric outcome of interest was custom designed as a composite outcome of a series of neuropsychiatric adverse events of a certain severity with the aim to capture the kinds of events described in the spontaneous reports.

Based on FDA’s review of the meta-analyses and observational studies submitted by Pfizer, FDA determined that some information about these data could be included in the varenicline labeling so that prescribers have a full picture of what analyses and studies have been conducted to enhance the understanding of varenicline-associated serious neuropsychiatric adverse events.

However, the determination of whether to remove a boxed warning is a decision for which there is limited precedent. At the time of the October 2014 advisory committee meeting, FDA believed that the PMR trial prospectively designed to evaluate the risk of serious neuropsychiatric adverse events with smoking cessation agents, whose final study report of that trial was expected in a year, should be reviewed and considered as part of such a regulatory action. However, because Pfizer believed the collection of observational and meta-analytic data were alone sufficient to support removal of the boxed warning, the Agency brought this issue to the advisory committees for discussion.

The committees were asked to discuss how they would weigh the evidence contributed by the randomized controlled trial (RCT) meta-analyses, observational studies, and spontaneous case reports when they were evaluating the risk of serious neuropsychiatric adverse events in patients taking varenicline. In general, many of the committee members expressed concerns with the quality of the data presented. The concerns included, but were not limited to, statistical limitations of the trials, misclassification of adverse events, outcome ascertainment in observational studies, and arbitrary cut off points for the outcomes which questioned whether the outcomes were being categorized correctly.

The committee members were also asked based on the data presented on the risk of serious neuropsychiatric adverse events with varenicline, which of the following options would they recommend. The number of committee members voting for each option follows each option.

A. Removal of the boxed warning statements regarding risk of serious neuropsychiatric adverse events (1)
B. Modification of the language in the boxed warning (6)
C. Retain the current boxed warning statements and reassess once the ongoing postmarketing randomized controlled trial designed to capture serious neuropsychiatric adverse events is completed (11)

The majority of the committee agreed that more data were needed and recommended to retain the current boxed warning statements and reassess once the ongoing post-marketing randomized controlled trial designed to capture serious neuropsychiatric adverse events was completed. Some of the panel members voted to modify labeling by strengthening the language in the boxed warning to include a description of the risk for sleep disturbances.

In addition, some of the committee members expressed concerns that a portion of the Boxed Warning describing the benefits of smoking cessation was promotional, and recommended
removal of this content. The member who voted to remove the Boxed Warning stated that the data did not show a definitive safety signal, and that varenicline is no riskier than other drugs with a similar range of neuropsychiatric adverse effects that do not have Boxed Warnings.

Based on the FDA’s assessment of the data submitted, and the recommendations of the advisory committees, Pfizer’s proposal to remove the boxed warning for neuropsychiatric adverse events was not approved.

2 Clinical Pharmacology

The following is excerpted from approved labeling for Chantix and for Zyban. Information on the transdermal nicotine replacement product used in the study is taken from labeling from the era when it was a prescription product.

2.1 Varenicline

Varenicline binds with high affinity and selectivity at \( \alpha 4 \beta 2 \) neuronal nicotinic acetylcholine receptors. The efficacy of Chantix in smoking cessation is believed to be the result of varenicline's activity at \( \alpha 4 \beta 2 \) sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to these receptors.

Absorption/Distribution: Maximum plasma concentrations of varenicline occur typically within 3–4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was ~90%. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing. Plasma protein binding of varenicline is low (≤20%) and independent of both age and renal function.

Metabolism/Elimination: The elimination half-life of varenicline is approximately 24 hours. Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

The recommended dose of Chantix is 1 mg twice daily following a 1-week titration as follows:

- Days 1 – 3: 0.5 mg once daily
- Days 4 – 7: 0.5 mg twice daily
- Day 8 – end of treatment: 1 mg twice daily

The usual duration of treatment is 12 weeks. Treatment is initiated a week or more prior to quit day.

\(^7\) These products are now available over-the-counter.
2.2 Bupropion

The exact mechanism by which ZYBAN enhances the ability of patients to abstain from smoking is not known but is presumed to be related to noradrenergic and/or dopaminergic mechanisms. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine, and does not inhibit the reuptake of serotonin. Bupropion does not inhibit monoamine oxidase.

The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

Absorption

The absolute bioavailability of ZYBAN in humans has not been determined because an intravenous formulation for human use is not available. However, it appears likely that only a small proportion of any orally administered dose reaches the systemic circulation intact. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

In humans, following oral administration of ZYBAN, peak plasma concentration (Cmax) of bupropion is usually achieved within 3 hours.

Distribution

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg per mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion; whereas, the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism

Bupropion is extensively metabolized in humans. Three metabolites are active: hydroxybupropion, which is formed via hydroxylation of the tert-butyl group of bupropion, and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 enzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one-half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance, because the plasma concentrations of the metabolites are as high as or higher than those of bupropion.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg per day.

Elimination
Following oral administration of 200 mg of 14C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. Only 0.5% of the oral dose was excreted as unchanged bupropion.

The recommended dosing for ZYBAN is:
• Begin dosing with one 150-mg tablet per day for 3 days.
• Increase dose to 300 mg per day given as one 150-mg tablet twice each day with an interval of at least 8 hours between each dose.
• Do not exceed 300 mg per day.

The usual duration of treatment is 7-12 weeks. Treatment is initiated 1-2 weeks prior to quit day.

### 2.3 Nicotine Transdermal System

The Nicotine Replacement Therapy product used in the trial was a nicotine transdermal system delivering 21 mg over 24 hours, with taper doses of 14 mg/24 hours and 7 mg/24 hours for the last four weeks of treatment.

Nicotine in the adhesive layer is absorbed into and then through the skin, causing the initial rapid rise in plasma concentrations. The nicotine from the reservoir is released slowly through the membrane with a release rate constant approximately 30 times smaller than the skin absorption rate constant… therefore the slow decline of plasma nicotine concentrations during 4 to 24 hours is determined primarily by the release of nicotine from the system. Following the second daily system application, steady-state plasma nicotine concentrations are achieved and are on average 30% higher compared with single-dose applications. Following removal of the system, plasma nicotine concentrations decline in an exponential fashion with an apparent mean half-life of 3-4 hours due to continued absorption from the skin depot. Most non-smoking patients will have non-detectable nicotine concentrations in 10-12 hours.

The usual dosing regimen is shown below, and is to begin on the patient’s planned quit day.

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>STEP 2</th>
<th>STEP 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use one 21 mg patch/day</td>
<td>Use one 14 mg patch/day</td>
<td>Use one 7 mg patch/day</td>
</tr>
<tr>
<td>Weeks 1-6</td>
<td>Weeks 7-8</td>
<td>Weeks 9-10</td>
</tr>
</tbody>
</table>

### 3 Post-Marketing Requirement Randomized Controlled Trial

*Phase 4, Randomized, Double Blind, Active- and Placebo-Controlled Multi-Center Study Evaluating the Neuropsychiatric Safety and Efficacy of Varenicline and Bupropion for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorders*\(^8\)

Protocol # A3051123
Conducted November 30 2011-January 13 2015

\(^8\) The sponsor refers to this trial as the “EAGLES” trial.
3.1 Overview and Objective

The purpose of the study was to assess varenicline and bupropion as aids to smoking cessation treatment in subjects with and without an established diagnosis of major psychiatric disorder and to characterize the NPS safety profile in both of these cohorts. This study was required by the FDA as a a Postmarketing Requirement (PMR) for varenicline and bupropion and also qualified as a Post-Authorization Safety Study (PASS) in the European Union (EU) for varenicline and bupropion. The population was to be characterized by the presence or absence of an established and stable diagnosis of a major psychiatric disorder, current or past, as defined by the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR).

Primary Safety Objectives:

- To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo in the incidence of the primary neuropsychiatric AE endpoint for subjects with and without a diagnosis of psychiatric disorder

- To characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).

Primary Efficacy Objective:

- To compare smoking abstinence rates of varenicline and bupropion relative to placebo for the last 4 weeks of treatment and continuously through Week 24, as measured by CO-confirmed continuous abstinence rate (CAR) CAR 9-12 and CAR 9-24, respectively, separately for subjects with and without a diagnosis of psychiatric disorder.

Secondary Efficacy Objective:

- To assess if there is a difference between cohorts in the placebo adjusted relative abstinence rates (CAR 9-12 and CAR 9-24) of varenicline and bupropion, separately.

Another secondary objective of the study was to perform the following comparisons with respect to the primary safety and efficacy endpoints:

1. NRT vs. Placebo;
2. Varenicline vs. Bupropion;
3. Varenicline vs. NRT;
4. Bupropion vs NRT.

3.2 Study Design and Endpoints

The study was a 24-week, double-blind, active- and placebo-controlled, multi-center, parallel group study designed to assess the safety and efficacy of varenicline 1 mg BID and bupropion hydrochloride 150 mg BID for smoking cessation. The primary comparisons were to be varenicline vs. placebo and bupropion vs. placebo. NRT was included as an active control and study medications were to be given via a triple-dummy design. The duration of active treatment
was 12 weeks followed by a non-treatment follow-up phase for an additional 12 weeks (Figure 1). Approximately 2000 subjects in each of four treatment arms were to be randomized, for a total of 8000 subjects at approximately 200 sites.

Subjects were to be classified into one of the two cohorts—those with an established and stable diagnosis of psychiatric disorder, confirmed by the Structured Clinical Interview for DSM-IV Axis 1 and 2 Disorders (SCID I and II) conducted at screening; and those without a diagnosis of a psychiatric disorder. An equal number of subjects with or without a diagnosis of a psychiatric disorder were to be enrolled and randomized among the four treatment arms (varenicline, bupropion, NRT, and placebo) in 1:1:1:1 ratio. All clinic visits were in an outpatient clinic setting.

Figure 1. Study Diagram

3.3 Inclusion/Exclusion Criteria

Subjects both with and without a diagnosis of a major psychiatric disorder were eligible for this study. To be included in the non-psychiatric (Non-PHx) stratum, the subject must not have had any previous diagnosis of a psychiatric disorder confirmed by SCID I and II.

To be eligible for enrollment into the study, subjects were required to meet the following criteria:

- Male or female cigarette smokers, 18-75 years, motivated to stop smoking and considered suitable for a smoking cessation attempt.
- Smoked an average of at least 10 cigarettes per day during past year and during the month prior to the screening visit, and exhaled carbon monoxide (CO) >10 ppm at screening.
- Females who are of childbearing potential could be included provided that they were not pregnant or nursing, and agreed to use medically acceptable contraception.

Subjects were to be included in the psychiatric cohort, if they were considered clinically stable and met criteria, either current or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and had met diagnostic criteria before the initiation of study treatment.

Psychotic Disorders limited to:
- Schizophrenia
- Schizoaffective Disorder

Affective Disorders limited to:
- Major Depression
- Bipolar-I, Bipolar-II

Anxiety Disorders limited to:
- Panic Disorder with or without Agoraphobia
- Post-Traumatic Stress Disorder
- Obsessive-Compulsive Disorder
- Social Phobia
- Generalized Anxiety Disorder

Personality Disorders limited to past history of:
- Borderline Personality Disorder

Axis I and II diagnosis (current and/or past) were based on DSM IV TR criteria on clinical assessment and confirmed by SCID:

- A “current” diagnosis was defined as the subject meeting the established criteria in the prior month
- A “past” diagnosis (“lifetime” diagnosis where applicable) could have occurred anytime in the past medical history

All subjects with an Axis I or II diagnosis were to be judged to be clinically stable including the following:
- No acute exacerbation of their condition in the preceding six months
- If on treatment for their condition, must have been on stable treatment for a minimum of three months (e.g., stable drug and dose three months)
- No change in treatment was anticipated for the duration of the study

---

9 Oral contraceptive, IUD, implantable or injectable contraceptive for at least a month before entering the study and through 30 days after the last dose; or a double barrier method during the study and 30 days after the last dose.
10 Administered by a clinician or a qualified person trained in clinical mental health, i.e., a PhD level clinical psychologist, or an individual with master level training in related areas (masters level psychologist, social worker who has been trained to use the SCID).
• In the opinion of the Investigator, the patient was not at high risk of self-injury or suicidal behavior
• In the event the Investigator was not a mental health professional (MHP), the subject was to be evaluated by a MHP to confirm the SCID I or II diagnosis and determine if the subject was stable. A MHP must be a psychiatrist or licensed PhD level clinical psychologist. A subject who required new treatment or was judged not to be clinically stable was not randomized.

Subjects who did not meet study inclusion criteria could be re-screened if deemed clinically stable at a later date.

Subjects who presented with a past or present diagnosis of any of the following disorders were to be excluded from the study:

• Schizophreniform Disorder
• Delusional Disorder
• Psychotic Disorder NOS
• All Delirium, Dementia, and Amnestic and Other Cognitive Disorders
• All Substance-Induced Disorders (Other than nicotine)
• All Factitious Disorders
• All Dissociative Disorders
• All Impulse Control Disorders
• Evidence of substance abuse/misuse or dependence severe enough to compromise the subject’s ability to comply with the study requirements
• Subjects with antisocial, schizotypal, or any other personality disorder severe enough to compromise the subject’s ability to comply with the study requirements
• Subjects with a past history of a comorbid condition listed in the above exclusion criteria were considered for inclusion in the study and placed in the “psychiatric stratum” if the subject was:
  ▪ Concurrently diagnosed with an inclusionary diagnosis
  ▪ Considered to be in sustained full remission for substance abuse or misuse (no criteria for abuse or dependency being met in the last 12 months), and the patient was not taking opioid agonists or partial agonists (i.e., methadone, buprenorphine).

If the subjects described above (i.e., those with an exclusionary co-morbid psychiatric condition) did not meet a primary diagnosis listed in inclusion criteria of the psychiatric arm, they were not to be eligible for the study. Subjects who met a primary diagnosis listed in the inclusion criteria of the psychiatric arm, and who had a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) were considered to be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent condition was stable and did not prevent the subject from safely complying with study procedures.

Subjects were also excluded for:
• Pregnancy or nursing
• Having an Axis I diagnosis according to DSM IV TR criteria, a rating of 5 or higher on the Clinical Global Impression- Severity (CGI-S)
• Being at risk for suicide at screening, baseline, or after assessment by a qualified MHP if a risk assessment interview was required after screening or baseline using the Columbia Suicide Severity Rating Scale (C-SSRS)
• Suicidal ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS
• Previous history of suicide behaviors in the past year
• Displaying self-injuring behaviors, in the opinion of the investigator
• A positive urine drug screen at screening or baseline for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition
• Taking an investigational drug within 30 days before the Baseline visit and at any time during the study period
• Taking varenicline, bupropion, or NRT within 30 days prior to Baseline visit
• Seizure disorder
• Abrupt discontinuation of alcohol or sedatives (including benzodiazepines)
• Current or prior diagnosis of anorexia or bulimia nervosa
• Taking a monoamine oxidase (MAO) inhibitor within the past fourteen days (prior to the Baseline visit)
• Taking the following narrow therapeutic range medications which are metabolized by CYP2D6; desipramine, nortriptyline, Type 1C antiarrhythmics (e.g., propafenone, flecainide), thioridazine.
• Intending to donate blood or blood components while receiving study drug or within one month of the completion of the treatment phase of the study
• Severe chronic obstructive pulmonary disease (COPD) ¹¹
• A recent (<5 years) history of cancer. Subjects with a remote (>5 years) history of cancer were to be considered pending discussion with the study clinician. Subjects with cured basal cell or squamous cell carcinoma of the skin were allowed.
• Evidence or history of clinically significant allergic reactions to drugs (e.g., severe cutaneous and/or systemic allergic reactions).
• Baseline SGOT (AST) or SGPT (ALT) greater than three times the upper limit of normal (ULN) or total bilirubin greater than two times the ULN.
• Clinically significant cardiovascular disease in the past two months ¹²
• Clinically significant cerebrovascular disease (CVA, TIA) in the past two months.
• Not agreeing to abstain from using non-cigarette tobacco products (including, e.g., pipe tobacco, cigars, snuff, chewing tobacco, hookah, etc.) or marijuana during study participation.

¹¹ Defined as any subject who fulfills any of the following criteria: History of repeated exacerbations of COPD (greater than or equal to 3 in 3 years); Requires systemic corticosteroid maintenance (e.g., oral prednisolone) for management of chronic symptoms; Is maintained on oxygen therapy for management of chronic symptoms.
¹² Myocardial infarction; Coronary artery bypass graft (CABG); Percutaneous transluminal coronary angioplasty (PTCA); Severe or unstable angina; A serious arrhythmia; Clinically significant ECG conduction abnormalities; Hospitalizations for heart failure.
• Not agreeing to abstain from using nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during study participation (both the treatment phase and the post-treatment follow-up).
• Previously experiencing an adverse drug reaction that the investigator considered potentially due to treatment with any of the active drugs in this study.
• Other severe acute or chronic medical or psychiatric condition or laboratory abnormalities that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
• Taking a concomitant medication that was prohibited by this protocol (see below)
• Skin conditions resulting in red, broken, or irritated skin that may hinder the use of the nicotine replacement therapy (NRT) patch

Disallowed concomitant medications included:

• Drugs containing bupropion
• Varenicline (Chantix®/Champix®)
• Nicotine replacement therapy and other aids to smoking cessation
• Naltrexone
• Insulin
• Theophylline
• Warfarin
• Monoamine oxidase (MAO) inhibitors
• Over the counter and prescribed stimulants and anorectic agents
• Narrow therapeutic range medications which are metabolized by CYP2D6; desipramine, nortriptyline, Type 1C antiarrhythmics (e.g., propafenone, flecainide), thioridazine
• Milnacipran (Savella)

3.4 Procedures

The study began with a screening period of 3-14 days. Results of screening laboratory evaluations and the electrocardiogram were reviewed during this period to assure subject eligibility. Determination of diagnosis of a psychiatric disorder for each subject was to be confirmed at screening using DSM IV TR based on clinical assessment and confirmed by SCID I and II.

Subjects who met all inclusion criteria at the screening visit then progressed to the baseline visit. At the baseline visit only those subjects who continued to meet all other criteria were to be randomized. A computer-generated randomization schedule was to be used to assign subjects to treatment, with two-level stratification by the presence or absence of a diagnosis of psychiatric disorder. An equal number were enrolled in each of the two cohorts. When the planned enrollment was achieved in one of the cohorts, enrollment was to continue only into the other cohort until recruitment goals were reached.
Within the cohort with a diagnosis of a psychiatric disorder, treatment assignment was stratified with respect to the four major diagnosis groups (Psychotic, Affective, Anxiety, and Personality Disorders).

The 12-week placebo-controlled treatment period had periodic clinic visits for safety and efficacy assessments and smoking cessation counseling. There were weekly clinic visits up to and including Week 6, and then biweekly clinic visits between Week 6 and Week 12. On weeks with no scheduled clinic visits, telephone contact visits occurred to collect smoking status.

During the active treatment phase, varenicline and bupropion dosing began on the Baseline day with a one-week titration followed by 11 weeks of 1 mg BID and 150 mg BID, respectively. NRT dosing began at the Week 1 visit with a 21 mg patch per day for 7 weeks, followed by a 14 mg patch per day for 2 weeks, and then a 7 mg patch for 2 weeks. All subjects were to set a target quit date (TQD) to coincide with the Week 1 visit. The Week 1 visit occurred at the end of the first week of the treatment phase (Day 8).

### 3.4.1 Study Treatments

The study utilized a triple-dummy design as shown in Table 1 (below). Subjects randomized to one of the three active dosing groups were to take that active medication and the other two medications in matching placebo form. Subjects randomized to placebo were to receive matching placebo for varenicline, bupropion, and NRT, and follow the same titration and dosing schedules as those randomized to each of the active medication groups. Because both varenicline and bupropion are initiated before quit day while NRT is initiated on quit day, during the first week of treatment no patches were applied. All subjects began their transdermal medication (active or placebo) in Week 2.

### Table 1 Dosing Schedule (Protocol)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Day 1-3</th>
<th>Day 4-7</th>
<th>Week 1*-8</th>
<th>Week 8-10</th>
<th>Week 10-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline (V)</td>
<td>0.5 mg V QD 1 placebo B QD</td>
<td>0.5 mg V BID 1 placebo B BID</td>
<td>1 mg V BID 1 placebo B BID 1 placebo NRT QD</td>
<td>1 mg V BID 1 placebo B BID 1 placebo NRT QD</td>
<td>1 mg V BID 1 placebo B BID 1 placebo NRT QD</td>
</tr>
<tr>
<td>Bupropion (B)</td>
<td>150 mg B QD 1 placebo V QD</td>
<td>150 mg B BID 1 placebo V BID</td>
<td>150 mg B BID 1 placebo V BID 1 placebo NRT QD</td>
<td>150 mg B BID 1 placebo V BID 1 placebo NRT QD</td>
<td>150 mg B BID 1 placebo V BID 1 placebo NRT QD</td>
</tr>
<tr>
<td>NRT patch</td>
<td>1 placebo V QD 1 placebo B QD</td>
<td>1 placebo V BID 1 placebo B BID</td>
<td>21 mg NRT QD 1 placebo V BID 1 placebo B BID</td>
<td>14 mg NRT QD 1 placebo V BID 1 placebo B BID</td>
<td>7 mg NRT QD 1 placebo V BID 1 placebo B BID</td>
</tr>
<tr>
<td>Placebo</td>
<td>1 placebo V QD 1 placebo B QD</td>
<td>1 placebo V BID 1 placebo B BID</td>
<td>1 placebo V BID 1 placebo B BID 1 placebo NRT QD</td>
<td>1 placebo V BID 1 placebo B BID 1 placebo NRT QD</td>
<td>1 placebo V BID 1 placebo B BID 1 placebo NRT QD</td>
</tr>
</tbody>
</table>
*On day of Week 1 visit, the varenicline dose was 2-0.5 mg tablets (or 2 placebo varenicline tablets) in the AM and 1 mg tablet (or 1 placebo varenicline tablet) in the PM.

**Dosing Regimens**

- Subjects randomized to varenicline were titrated to the full dose during the first week in the following manner: 0.5 mg QD x 3 days, 0.5 mg BID x 4 days, then 1 mg BID for 11 weeks.
- Subjects randomized to bupropion received 150 mg QD x 3 days and then took 150 mg BID for the remainder of the treatment period (11 weeks and 4 days).
- Subjects randomized to NRT started active dosing the morning of the Week 1 visit and received a 21 mg transdermal patch per day x 7 weeks, followed by a 14 mg transdermal patch per day x 2 weeks, and then a 7 mg transdermal patch x 2 weeks for a total of 11 weeks of treatment.

Dosing was to occur with 240 ml of water, and it was recommended that subjects eat prior to dosing. It was recommended that there be at least 8 hours between the morning and evening dosing.

Dosing continued until the Week 12 visit. All subjects were then to be followed for an additional 12 weeks in the non-treatment phase of the protocol. At the discretion of the Investigator, dosing with blinded tablet medications (varenicline, bupropion, matching placebos) may have been reduced, temporarily discontinued, or stopped for subjects who had intolerable adverse events (e.g., nausea); or for subjects who in the opinion of the Investigator required a dose reduction due to use of concurrent medications.

If a subject endorsed suicidality on items 4, 5 (active suicidal ideation with or without intent/plan) or to any behavioral question on the CSSRS, the subject was to have a risk assessment by a qualified mental health professional to determine whether it was safe to continue active dosing in the trial. In the event the risk assessment could not be immediately performed, it would be at the discretion of the Investigator to determine if study drug was to be discontinued (temporarily or permanently) until the risk assessment was completed.

Study drug was to be discontinued immediately for any female subject who became pregnant during the treatment period of the study.

A dose reduction for tablet medication was performed by decreasing both blinded tablet medications to once per day dosing. If a dose reduction was required, both blinded tablet medications were to be reduced at the same time. Dosing with blinded NRT (NRT or matching placebo) may have been temporarily discontinued or stopped for subjects who had intolerable adverse events. It was not possible to reduce the dose of blinded NRT. If any of the study drugs needed to be permanently discontinued then all three blinded study medications (varenicline/placebo, bupropion/placebo, and NRT/placebo) were to be permanently discontinued.

Subjects who discontinued treatment were to be encouraged to continue participation in the study and all planned assessments/evaluations. Such subjects were referred to as “OTIS” (off-treatment, in study). If a subject withdrew from the study, but did not withdraw consent, he/she was to be contacted at the end of the trial to assess vital status/cardiovascular events. If the
subject withdrew from the study, and also withdrew consent for disclosure of future information, no further evaluations were to be performed, and no additional data was to be collected. All reasonable efforts were to be made to contact subjects who were lost to follow up to ascertain their reason(s) for not continuing in the study. A determination was to be made if they were truly lost to follow up, and not withdrawing for another reason (e.g., adverse event or lack of efficacy).

3.4.2 Behavioral Treatment

Smoking cessation counseling up to 10 min duration was to be provided at each clinic visit consistent with the Agency for Healthcare Research and Quality (AHRQ) guidelines beginning at Baseline, then during the treatment and non-treatment periods. The counseling was 1:1, and individually tailored to each subject’s needs. Whenever possible, counseling was conducted by the same counselor throughout, so that the relationship was built and brought additional value to the sessions.

Participants were expected to abstain from the use of tobacco products such as pipe tobacco, cigars, snuff, chewing tobacco, hookah, and the use of marijuana. Subjects were expected to refrain from using any form of nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during both the treatment and non-treatment follow-up phases.

3.4.3 Schedule of Study Procedures
The following time-and-events tables illustrate the planned schedule of assessments.
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screen</th>
<th>BL</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consentb</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History, Cardiovascular Medical History, Demography, Smoking history/ height</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs (PR, BP)</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td>X X</td>
<td></td>
</tr>
<tr>
<td>SCID I and II</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Volunteered reporting</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S</td>
<td>X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression Questionnaire</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview (NAEI)</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBQ-R</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagerström Test</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled CO</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense Study Drugs</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td>X</td>
<td>X X</td>
<td></td>
</tr>
<tr>
<td>CBC, Blood Chemistry</td>
<td>X</td>
<td>X X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Tests (urine or serum)</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Drug Screend (dipstick at site)</td>
<td>X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Contact Information Card</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric Evaluation</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect cardiovascular events of interest</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3 Schedule of Activities - Post Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Wk 13</th>
<th>Wk 14*</th>
<th>Wk 15*</th>
<th>Wk 16</th>
<th>Wk 17*</th>
<th>Wk 18*</th>
<th>Wk 19*</th>
<th>Wk 20</th>
<th>Wk 21*</th>
<th>Wk 22*</th>
<th>Wk 23*</th>
<th>Wk 24</th>
<th>ET*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital Signs (PR, BP)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Volunteered reporting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CGI-I</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HADS</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NUI</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exhaled CO</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Psychiatric Evaluation*</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Collect cardiovascular events of interest</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy Test* (urine or serum)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

* Designates telephone visit
a If ET is before the Week 12 visit.
b Must be signed prior to any protocol procedures being performed.
c All females unless surgically sterilized or at least 2 years postmenopausal.
d May be performed at other visits at investigator’s discretion.
e If deemed needed per protocol section 7.1.10.

The following assessments were used to collect information about patient experiences:

- Hospital Anxiety and Depression Scale (HADS) at baseline, Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20, and 24
  - 14 individual item responses, ranging in increasing severity from 0 to 3.
  - Anxiety subscale score (sum of the 7 odd-numbered item response scores; ranges: 0-7 = normal, 8-10 = suggestive, 11-21 = probable).
  - Depression subscale score (sum of the 7 even-numbered item response scores; ranges: 0-7 = normal, 8-10 = suggestive, 11-21 = probable).
- C-SSRS at baseline, Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20, and 24.
- Clinical Global Impression of Improvement (CGI-I) at Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20, and 24
  - A single item response (a 7-point rating, with 4 being no change and 1 to 3 being levels of improvement and 5 to 7 being levels of worsening).
<table>
<thead>
<tr>
<th>Neuropsychiatric Adverse Event Inventory (NAEI)</th>
<th>Neuropsychiatric Adverse Events Interview Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Have you felt depressed (sad, blue, down, empty, as if you didn’t care)?</td>
<td>· Do you find that you have lost interest in things or get less pleasure from things that you used to enjoy?</td>
</tr>
<tr>
<td>· Have you cried or felt like crying?</td>
<td></td>
</tr>
<tr>
<td>· Have you been worried or scared?</td>
<td>· Have you been nervous or anxious?</td>
</tr>
<tr>
<td>· Have you felt panicky at all?</td>
<td>· Some people have panic attacks when they suddenly feel very frightened and have physical symptoms like heart palpitations (your heart is pounding and/or beating rapidly), shortness of breath and chest pains. Have you had this?</td>
</tr>
<tr>
<td>· Have you had times when you felt extremely agitated?</td>
<td>· Have you had times when you felt like you had to be always moving or even pacing?</td>
</tr>
<tr>
<td>· Have you felt unusually cheerful, or happy, not just your normal self, so that other people noticed?</td>
<td>· Have you had much more energy than usual to do things?</td>
</tr>
<tr>
<td>· Have you needed less sleep than usual to feel rested?</td>
<td></td>
</tr>
<tr>
<td>· Have you felt hostile towards others?</td>
<td>· Have you been involved in any serious arguments or fights?</td>
</tr>
<tr>
<td>· Have you been involved in any serious arguments or fights?</td>
<td>· Have you had the urge to injure or harm someone?</td>
</tr>
<tr>
<td>· Have you felt that people have been talking about you?</td>
<td></td>
</tr>
<tr>
<td>· Have you felt that someone may be after you, or trying to harm you in some way?</td>
<td></td>
</tr>
<tr>
<td>· Has there been anything unusual about the way things look or sound or smell?</td>
<td>· Have you heard things that other people couldn’t hear, like noises or voices of people talking when there was no one around?</td>
</tr>
<tr>
<td>· Have you seen things that other people couldn’t see?</td>
<td></td>
</tr>
<tr>
<td>· Has your mind been playing tricks on you in any way?</td>
<td>· Have you had any ideas that other people might not understand or might find strange?</td>
</tr>
<tr>
<td>· Have things seemed unreal to you?</td>
<td>· Have you felt that you are detached from or have trouble connecting with other people?</td>
</tr>
<tr>
<td>· Have you felt strange or unnatural in any other way?</td>
<td></td>
</tr>
</tbody>
</table>
When reporting an AE, verbatim text was also to be recorded on a supplemental AE reporting page. Reported events by a household member of the subject, personal physician, or other, that were judged to be AEs by the investigator were to be captured as AEs, and the reporters’ verbatim texts of these events were also to be captured.

At each visit, assessments were to be done in the following order:
1. Volunteered AE report – opening question on how the subject has been feeling in general
2. Follow up on previously reported AEs that are still ongoing
3. Clinical rating scales as specified in the protocol
4. NAEI
5. Columbia Suicide Severity Rating Scale.

All assessment instruments used in the A3051123 study were translated into the local language and were administered in that language, and the results were recorded on worksheets that were replicas of the case report forms translated into the local language. Conversations between the site staff and the study subjects regarding their volunteered adverse events and conversations intended to gain more details about the subjects’ positive responses on the NAEI were conducted in the local language. The results of those assessments and conversations were then to be translated by the site staff and were entered into the electronic case report form in English.

Investigators, raters, and study coordinators were to be trained at the investigators’ meetings on the assessment instruments used in the study and on the subjective concepts that they were intended to assess. Familiarity with these subjective concepts was refreshed in web-based training that was required every 6 to 24 months depending on the assessment. In addition, various aspects of the assessments were highlighted in periodic study newsletters provided to all sites by the study team. The training instructed site staff to “ask follow up questions, if needed, to assess if the symptom is clinically significant and determine the severity, based on frequency, duration, and impact on subject’s function.”
3.4.4 Study Endpoints

Safety:

As described above, the primary pre-specified safety endpoint was a 16 component composite of the following elements:

- at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility and/or
- the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide.

This composite endpoint includes 241 MedDRA preferred terms mapped to the 16 components. This endpoint is referred to as the NPS endpoint.

Treatment-emergent events were defined as events that occurred after the first dose of randomized study treatment and before the last dose of study treatment plus 30 days. Note that this means that the primary NPS endpoint was based on events observed only during the 12 week treatment phase of the trial plus 30 days.

Adverse events were classified as Mild, Moderate or Severe according to the following definitions:

- Mild – does not interfere with subject’s usual function.
- Moderate – interferes to some extent with subject’s usual function.
- Severe – interferes significantly with subject’s usual function.

According to the study protocol, NPS events were collected through any of the following means:

- Volunteered adverse event.
- Actively collected adverse event. NPS events were collected through a neuropsychiatric adverse event interview at each clinic visit.
- Report by a family member and judged to be an adverse event by the investigator.
- Suicide related AEs solicited through the C-SSRS questionnaire at each clinic visit.

Secondary safety endpoints included the components of the NPS endpoint as well as the scores of three questionnaires: Hospital Anxiety and Depression Scale (HADS), Columbia Suicide Severity Rating Scale (C-SSRS), and the Clinical Global Impression of Improvement (CGI-I). Deaths were also analyzed as a secondary safety endpoint of interest.

Efficacy:

The primary measures of efficacy were carbon monoxide (CO)-confirmed continuous abstinence (CA) from Week 9 through Week 12 (CA 9-12) and CO-confirmed CA from Week 9 through Week 24 (CA 9-24). Smoking status was assessed by use of the Nicotine Use Inventory (NUI) questionnaire, which was administered at each study visit (in-clinic visits and telephone contacts) and confirmed by CO levels measured at in-clinic visits. Subjects were considered responders
(abstainers) if they answered ‘no’ to questions 1 and 2 on the NUI at each week included in the assessment period and had CO levels ≤ 10 ppm. The questions asked whether the subject had smoked any cigarettes (‘even a puff’) since the last visit/contact and whether they had used any other nicotine-containing products including other tobacco products and NRT products (other than the study medication) for Weeks 9 through 12, and any tobacco products for Weeks 13 through 24.

3.4.5 Statistical Analysis Plan (SAP)

3.4.5.1 Safety
The trial was not designed to rule out a pre-specified margin of risk for NPS events (i.e. there was no pre-defined hypothesis to be tested). Rather, the trial was sized based on the desired precision of the estimated risk difference (RD) for the NPS event comparing varenicline to placebo.

In the cohort with no-prior history of psychiatric disease (Non-PHx cohort), the Sponsor assumed a true incidence rate (IR) of 3.5 events per 100 subjects in the placebo arm and an IR of 6.13% in the varenicline arm, equivalent to an incidence rate ratio of 1.75. Under these assumptions, and with a sample size of 1,000 subjects per treatment arm in the Non-PHx cohort, the expected RD and corresponding 95% confidence interval for the NPS event comparing varenicline to placebo would be 2.63% (0.75%, 4.50%).

In the cohort with prior history of psychiatric disease (PHx cohort), the Sponsor assumed a true IR of 7.0% in the placebo arm and 12.25% in the varenicline arm, also equivalent to an incidence rate ratio of 1.75. Under these assumptions, and with a sample size of 1,000 subjects per treatment arm in the PHx cohort, the expected RD and corresponding 95% confidence interval for the NPS event comparing varenicline to placebo would be 5.25% (2.68%, 7.82%).

The SAP detailed a process to evaluate the unblinded primary event rate during the conduct of the trial and re-estimate the trial’s sample size if needed.

The primary safety analysis estimated the risk difference of NPS events for all six pairwise treatment comparisons (varenicline - placebo, bupropion - placebo, etc…) by cohort of previous diagnosis of a psychiatric disorder. The risk difference of NPS events was estimated through a generalized linear model for binary data with an identity link function. The model included covariates for treatment (4 levels), cohort (2 levels: Non-PHx vs. PHx), treatment by cohort interaction, and region of randomization (2 levels: USA vs. non-USA).

The SAP did not pre-specify any statistical hypotheses to be tested. All confidence intervals for the risk difference of NPS events were calculated at a nominal 95% confidence level and no corrections were made for multiple comparisons.

3.4.5.2 Efficacy
The efficacy analysis population was the Full Analysis Set (FAS) consisting of all randomized subjects.

The primary efficacy analysis (CAR 9-12) was evaluated using a logistic regression model with terms for treatment (varenicline, bupropion, NRT, and placebo), cohort (psychiatric and non-
psychiatric), region (US and non-US), plus the 2-way and 3-way interactions. Interactions terms would be removed if non-significant, p-value ≥ 0.1. The secondary efficacy analysis (CAR 9-24) utilized the same logistic regression model. The odds ratio (OR) and its 95% confidence interval (CI) were estimated for all pairwise comparisons. This estimation was done both overall and by cohort. The comparisons of varenicline to placebo and bupropion to placebo were considered primary and all other pairwise comparisons were considered secondary. There was no adjustment for multiplicity.

Subjects who discontinued the study or were lost to follow-up were assumed to be non-responders (smokers) for the remainder of the study. The protocol stipulated that missing CO measurements were imputed as negative. Missing NUI data were imputed using the next non-missing NUI response. If no response was available the subject was considered a non-responder.

### 3.5 Population and Subject Disposition

A total of 11,186 subjects were screened for participation in the study, of which 8144 subjects at 140 investigative centers (in 16 countries) were randomized in an approximate 1:1:1:1 ratio; 8058 ultimately received treatment distributed as varenicline (n=2016), bupropion (n=2006), NRT (n=2022), and placebo (n=2014).

Approximately half the subjects (4260) were randomized at 65 sites in the US. Participating sites were located in the following countries.

<table>
<thead>
<tr>
<th>Country</th>
<th>Sites Enrolling Subjects</th>
<th>Number of Subjects Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>2</td>
<td>333</td>
</tr>
<tr>
<td>Australia</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>Brazil</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>10</td>
<td>490</td>
</tr>
<tr>
<td>Canada</td>
<td>6</td>
<td>279</td>
</tr>
<tr>
<td>Chile</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Denmark</td>
<td>2</td>
<td>113</td>
</tr>
<tr>
<td>Finland</td>
<td>6</td>
<td>505</td>
</tr>
<tr>
<td>Germany</td>
<td>7</td>
<td>892</td>
</tr>
<tr>
<td>Mexico</td>
<td>4</td>
<td>188</td>
</tr>
<tr>
<td>New Zealand</td>
<td>1</td>
<td>125</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>9</td>
<td>126</td>
</tr>
<tr>
<td>Slovakia</td>
<td>5</td>
<td>202</td>
</tr>
<tr>
<td>South Africa</td>
<td>9</td>
<td>296</td>
</tr>
<tr>
<td>Spain</td>
<td>6</td>
<td>240</td>
</tr>
<tr>
<td>United States</td>
<td>65</td>
<td>4260</td>
</tr>
</tbody>
</table>

---

13 This is not the customary approach; a sensitivity analysis imputing missing values as positive was performed and is discussed below.

14 Ten additional centers did not enroll any subjects; one center enrolled only a single subject who did not take any study medication, and therefore did not contribute to the Safety population.
Sites included contract research organizations (CROs), general medical centers, and specialty psychiatric centers. Sites enrolled as few as 1 and as many as 287 subjects. Some sites had 15 or more sub-investigators while at other sites, only one or two people were involved in administering the protocol. At one US site, 41 individuals were listed as sub-investigators.

Selected demographic and baseline characteristics of the subjects are shown in the tables below.
## Table 4 Summary of Baseline Characteristics (Non-PHx Cohort) – Safety Population

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Varenicline (N = 990)</th>
<th>Bupropion (N = 989)</th>
<th>NRT (N = 1006)</th>
<th>Placebo (N = 999)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>45.8 (13.0)</td>
<td>46.0 (13.0)</td>
<td>46.1 (12.8)</td>
<td>45.9 (12.8)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>18, 73</td>
<td>18, 75</td>
<td>18, 75</td>
<td>18, 74</td>
</tr>
<tr>
<td><strong>Gender</strong>, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>510 (51.5)</td>
<td>503 (50.9)</td>
<td>497 (49.4)</td>
<td>489 (48.9)</td>
</tr>
<tr>
<td>Female</td>
<td>480 (48.5)</td>
<td>486 (49.1)</td>
<td>509 (50.6)</td>
<td>510 (51.1)</td>
</tr>
<tr>
<td><strong>Race</strong>, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>819 (82.7)</td>
<td>820 (82.9)</td>
<td>837 (83.2)</td>
<td>817 (81.8)</td>
</tr>
<tr>
<td>Black</td>
<td>135 (13.6)</td>
<td>116 (11.7)</td>
<td>127 (12.6)</td>
<td>126 (12.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>14 (1.4)</td>
<td>16 (1.6)</td>
<td>13 (1.3)</td>
<td>19 (1.9)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (2.2)</td>
<td>37 (3.7)</td>
<td>29 (2.9)</td>
<td>37 (3.7)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>980</td>
<td>984</td>
<td>1000</td>
<td>992</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>80.0 (19.5)</td>
<td>80.4 (20.1)</td>
<td>81.6 (19.6)</td>
<td>80.6 (19.3)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>39.8, 176.8</td>
<td>40.5, 171.5</td>
<td>38.4, 201.8</td>
<td>42.0, 169.2</td>
</tr>
<tr>
<td><strong>Prior psychiatric medications, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychoanaleptics</td>
<td>27 (2.7)</td>
<td>27 (2.7)</td>
<td>33 (3.3)</td>
<td>36 (3.6)</td>
</tr>
<tr>
<td>Psycholeptics</td>
<td>61 (6.2)</td>
<td>58 (5.9)</td>
<td>68 (6.8)</td>
<td>73 (7.3)</td>
</tr>
<tr>
<td><strong>Total number of years subject smoked</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27.8 (12.8)</td>
<td>28.2 (13.0)</td>
<td>28.2 (12.8)</td>
<td>28.2 (12.6)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>2, 64</td>
<td>2, 60</td>
<td>1, 63</td>
<td>2, 62</td>
</tr>
<tr>
<td><strong>Total number of lifetime serious quit attempts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None, n (%)</td>
<td>181 (18.3)</td>
<td>181 (18.3)</td>
<td>174 (17.3)</td>
<td>204 (20.4)</td>
</tr>
<tr>
<td>≥1 previous serious quit attempt, n (%)</td>
<td>809 (81.7)</td>
<td>808 (81.7)</td>
<td>832 (82.7)</td>
<td>795 (79.6)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.3 (13.8)</td>
<td>3.4 (10.3)</td>
<td>3.1 (4.2)</td>
<td>3.2 (7.4)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0, 400</td>
<td>0, 300</td>
<td>0, 31</td>
<td>0, 108</td>
</tr>
<tr>
<td><strong>Previous use of medication for quit attempt (most recent attempt), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varenicline</td>
<td>132 (13.3)</td>
<td>144 (14.6)</td>
<td>152 (15.1)</td>
<td>136 (13.6)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>92 (9.3)</td>
<td>91 (9.2)</td>
<td>93 (9.2)</td>
<td>90 (9.0)</td>
</tr>
<tr>
<td>NRT</td>
<td>272 (27.5)</td>
<td>307 (31.0)</td>
<td>325 (32.3)</td>
<td>305 (30.5)</td>
</tr>
<tr>
<td>Average number of cigarettes per day over the last month prior to study entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>990</td>
<td>989</td>
<td>1005</td>
<td>999</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>20.8 (8.3)</td>
<td>20.6 (7.8)</td>
<td>20.8 (8.2)</td>
<td>20.5 (7.9)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>10, 80</td>
<td>6, 60</td>
<td>10, 60</td>
<td>10, 60</td>
</tr>
<tr>
<td>FTND (Total Score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>989</td>
<td>987</td>
<td>1006</td>
<td>998</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.49 (1.98)</td>
<td>5.50 (2.02)</td>
<td>5.56 (1.95)</td>
<td>5.51 (2.01)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0, 10</td>
<td>0, 10</td>
<td>0, 10</td>
<td>0, 10</td>
</tr>
<tr>
<td>C-SSRS Lifetime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>49 (4.9)</td>
<td>44 (4.4)</td>
<td>52 (5.2)</td>
<td>49 (4.9)</td>
</tr>
<tr>
<td>HADS (Total Score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.35 (4.44)</td>
<td>4.08 (4.09)</td>
<td>4.20 (4.11)</td>
<td>4.50 (4.33)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.28</td>
<td>0.24</td>
<td>0.25</td>
<td>0.22</td>
</tr>
</tbody>
</table>

**Abbreviations:** C-SSRS = Columbia-Suicide Severity Rating Scale; FTND = Fagerström Test for Nicotine Dependence; HADS = Hospital Anxiety and Depression Scale.

a. The gender for 4 subjects randomized to treatment was inaccurately recorded (see ERRATA). b. Serious quit attempt = more than 24 hours.

c. Positive C-SSRS response for suicidal behavior or/and ideation.

Source: Pfizer’s Section 14, Tables 14.1.2.1, 14.1.2.4, 14.1.2.6.1, 14.1.2.6.2, 14.1.2.6.3, 14.1.2.9.1, 14.4.3, 14.5.1.1, and 14.5.2.
### Table 5 Summary of Baseline Characteristics (PHx Cohort) – Safety Population

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Varenicline (N = 1026)</th>
<th>Bupropion (N = 1017)</th>
<th>NRT (N = 1016)</th>
<th>Placebo (N = 1015)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>47.2 (11.8)</td>
<td>46.7 (12.2)</td>
<td>47.6 (11.5)</td>
<td>46.9 (11.5)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>18, 74</td>
<td>18, 75</td>
<td>18, 75</td>
<td>18, 75</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>392 (38.2)</td>
<td>387 (38.1)</td>
<td>384 (37.8)</td>
<td>387 (38.1)</td>
</tr>
<tr>
<td>Female</td>
<td>634 (61.8)</td>
<td>630 (61.9)</td>
<td>632 (62.2)</td>
<td>628 (61.9)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>849 (82.7)</td>
<td>816 (80.2)</td>
<td>804 (79.1)</td>
<td>822 (81.0)</td>
</tr>
<tr>
<td>Black</td>
<td>145 (14.1)</td>
<td>165 (16.2)</td>
<td>176 (17.3)</td>
<td>155 (15.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (0.5)</td>
<td>10 (1.0)</td>
<td>11 (1.1)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>27 (2.6)</td>
<td>26 (2.6)</td>
<td>25 (2.5)</td>
<td>30 (3.0)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1024</td>
<td>1014</td>
<td>1015</td>
<td>1012</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>83.0 (21.5)</td>
<td>82.5 (21.3)</td>
<td>80.8 (20.1)</td>
<td>82.7 (21.3)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>43.0, 230.0</td>
<td>43.2, 174.3</td>
<td>39.6, 191.5</td>
<td>44.6, 189.1</td>
</tr>
<tr>
<td><strong>Prior psychiatric medications, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychoanalectics</td>
<td>423 (41.2)</td>
<td>354 (34.8)</td>
<td>369 (36.3)</td>
<td>380 (37.4)</td>
</tr>
<tr>
<td>Psycholeptics</td>
<td>309 (30.1)</td>
<td>298 (29.3)</td>
<td>326 (32.1)</td>
<td>295 (29.1)</td>
</tr>
<tr>
<td><strong>Total number of years subject smoked</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>28.9 (11.8)</td>
<td>28.2 (12.4)</td>
<td>28.9 (11.9)</td>
<td>28.3 (11.6)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>2, 60</td>
<td>2, 56</td>
<td>2, 58</td>
<td>2, 56</td>
</tr>
<tr>
<td><strong>Total number of lifetime serious quit attempts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None, n (%)</td>
<td>171 (16.7)</td>
<td>174 (17.1)</td>
<td>165 (16.2)</td>
<td>161 (15.9)</td>
</tr>
<tr>
<td>≥1 previous serious quit attempt, n (%)</td>
<td>855 (83.3)</td>
<td>843 (82.9)</td>
<td>851 (83.8)</td>
<td>854 (84.1)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.4 (7.7)</td>
<td>3.5 (6.9)</td>
<td>3.3 (5.3)</td>
<td>3.6 (10.9)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0, 200</td>
<td>0, 100</td>
<td>0, 77</td>
<td>0, 300</td>
</tr>
<tr>
<td><strong>Previous use of medication for quit attempt (most recent attempt), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varenicline</td>
<td>149 (14.5)</td>
<td>194 (19.1)</td>
<td>168 (16.5)</td>
<td>161 (15.9)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>102 (9.9)</td>
<td>114 (11.2)</td>
<td>101 (9.9)</td>
<td>101 (10.0)</td>
</tr>
<tr>
<td>NRT</td>
<td>372 (36.3)</td>
<td>326 (32.1)</td>
<td>356 (35.0)</td>
<td>338 (33.3)</td>
</tr>
<tr>
<td><strong>Average number of cigarettes per day over the last month prior to study entry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>20.6 (8.0)</td>
<td>20.5 (8.2)</td>
<td>20.8 (9.1)</td>
<td>20.7 (8.2)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>5, 70</td>
<td>10, 60</td>
<td>10, 120</td>
<td>10, 70</td>
</tr>
<tr>
<td><strong>FTND (Total Score)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1025</td>
<td>1017</td>
<td>1016</td>
<td>1015</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.04 (1.93)</td>
<td>6.06 (1.91)</td>
<td>5.96 (1.95)</td>
<td>5.91 (2.02)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0, 10</td>
<td>0, 10</td>
<td>0, 10</td>
<td>0, 10</td>
</tr>
<tr>
<td><strong>HADS (Total Score)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1026</td>
<td>1017</td>
<td>1015</td>
<td>1015</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.26 (6.45)</td>
<td>8.74 (6.92)</td>
<td>8.37 (6.58)</td>
<td>8.21 (6.22)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0, 30</td>
<td>0, 36</td>
<td>0, 31</td>
<td>0, 36</td>
</tr>
<tr>
<td><strong>C-SSRS Lifetime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>353 (34.4)</td>
<td>363 (35.7)</td>
<td>339 (33.4)</td>
<td>358 (35.3)</td>
</tr>
</tbody>
</table>

Abbreviations: C-SSRS = Columbia Suicide Severity Rating Scale; FTND = Fagerström Test for Nicotine Dependence; HADS = Hospital Anxiety and Depression Scale.

a. The gender for 2 subjects randomized to treatment was inaccurately recorded (see ERRATA). b. C-SSRS (positive response for suicidal behavior or/and ideation).

Source: Pfizer’s Section 14, Tables 14.1.2.1, 14.1.2.4, 14.1.2.6.1, 14.1.2.6.2, 14.1.2.6.3, 14.1.2.9.1, 14.4.3, 14.5.1.1, and 14.5.2.
The treatment groups were similar at baseline with respect to demographic characteristics and smoking history. About 20% in each arm of the non-PHx cohort and about 16-17% in each arm of the PHx cohort had never made a 24 hour attempt to quit smoking. The group mean scores on the Fagerstrom Test of Nicotine Dependence (FTND) were approximately 5.5 in the non-PHx cohort and 6 in the PHx, denoting a fairly low level of dependence, and some people in each cohort scored 0 on the FTND. The motivation of these patients who had never attempted to quit smoking for enrolling in a clinical trial is not clear.

Of those who had made at least one prior attempt in the NPHx cohort, ~17% had used varenicline on their most recent quit attempt, 11% had used bupropion, and nearly 40% had used NRT. In the PHx cohort, 17-20% of those with a prior quit attempt had used varenicline, about 12% had used bupropion, and 40% had used NRT. The willingness of these experienced patients to enroll in the study suggests that they tolerated the medication previously and may have been at lower risk for serious events.

The proportion of subjects who were followed until the completion of the trial at 24 weeks was approximately 78% in both cohorts. The proportion of subjects who completed the 12 week treatment phase of the trial was approximately 79% among subjects in the non-PHx cohort and 74% in the PHx cohort. The two most common reasons given for study discontinuations were being “no longer willing to participate in the study” (11.0%) and being “lost to follow-up” (6.6%). Subjects in the Non-PHx cohort randomized to placebo were more likely to discontinue treatment due to being “no longer willing” (8.9%) and less likely to discontinue treatment due to adverse events (2.6%) than subjects randomized to varenicline, bupropion, or NRT. Subjects in the PHx cohort randomized to placebo were more likely to discontinue treatment due to being “no longer willing” (8.2%) than those randomized to any of the three active treatments (6.5%).
### Table 7 Disposition in the Non-PHx Cohort

<table>
<thead>
<tr>
<th></th>
<th>Pooled</th>
<th>Varenicline</th>
<th>Bupropion</th>
<th>NRT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>3984</td>
<td>990</td>
<td>989</td>
<td>1006</td>
<td>999</td>
</tr>
<tr>
<td>Completed Study (24 wks)</td>
<td>3124 (78.4%)</td>
<td>787 (79.5%)</td>
<td>783 (79.2%)</td>
<td>767 (76.2%)</td>
<td>787 (78.8%)</td>
</tr>
<tr>
<td>Discontinued Study:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No longer willing</td>
<td>439 (11.0%)</td>
<td>94 (9.5%)</td>
<td>103 (10.4%)</td>
<td>118 (11.7%)</td>
<td>124 (12.4%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>266 (6.7%)</td>
<td>68 (6.9%)</td>
<td>67 (6.8%)</td>
<td>72 (7.2%)</td>
<td>59 (5.9%)</td>
</tr>
<tr>
<td>Completed Treatment (12 wks)</td>
<td>3145 (78.9%)</td>
<td>793 (80.1%)</td>
<td>772 (78.1%)</td>
<td>777 (77.2%)</td>
<td>803 (80.4%)</td>
</tr>
<tr>
<td>Discontinued Treatment:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No longer willing</td>
<td>292 (7.3%)</td>
<td>61 (6.2%)</td>
<td>63 (6.4%)</td>
<td>79 (7.9%)</td>
<td>89 (8.9%)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>230 (5.8%)</td>
<td>57 (5.8%)</td>
<td>74 (7.5%)</td>
<td>73 (7.3%)</td>
<td>26 (2.6%)</td>
</tr>
</tbody>
</table>

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt and Subevg.xpt

*The set of subjects who discontinued treatment is not a subset of those who discontinued study. Because the treatment phase lasted 12 weeks and the full study lasted 24 weeks, it is possible for a subject to have completed treatment but have discontinued study, and vice versa.

### Table 8 Disposition in the PHx Cohort

<table>
<thead>
<tr>
<th></th>
<th>Pooled</th>
<th>Varenicline</th>
<th>Bupropion</th>
<th>NRT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>4074</td>
<td>1026</td>
<td>1017</td>
<td>1016</td>
<td>1015</td>
</tr>
<tr>
<td>Completed Study (24 wks)</td>
<td>3169 (77.8%)</td>
<td>811 (79.0%)</td>
<td>803 (79.0%)</td>
<td>790 (77.8%)</td>
<td>765 (75.4%)</td>
</tr>
<tr>
<td>Discontinued Study:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No longer willing</td>
<td>446 (10.9%)</td>
<td>101 (9.8%)</td>
<td>115 (11.3%)</td>
<td>106 (10.4%)</td>
<td>124 (12.2%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>266 (6.5%)</td>
<td>67 (6.5%)</td>
<td>59 (5.8%)</td>
<td>72 (7.1%)</td>
<td>68 (6.7%)</td>
</tr>
<tr>
<td>Completed Treatment (12 wks)</td>
<td>3023 (74.2%)</td>
<td>772 (75.2%)</td>
<td>765 (75.2%)</td>
<td>761 (74.9%)</td>
<td>725 (71.4%)</td>
</tr>
<tr>
<td>Discontinued Treatment:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No longer willing</td>
<td>281 (6.9%)</td>
<td>62 (6.0%)</td>
<td>70 (6.9%)</td>
<td>66 (6.5%)</td>
<td>83 (8.2%)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>388 (9.5%)</td>
<td>108 (10.5%)</td>
<td>101 (9.9%)</td>
<td>85 (8.4%)</td>
<td>94 (9.3%)</td>
</tr>
</tbody>
</table>

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt and Subevg.xpt

*The set of subjects who discontinued treatment is not a subset of those who discontinued study. Because the treatment phase lasted 12 weeks and the full study lasted 24 weeks, it is possible for a subject to have completed treatment but have discontinued study, and vice versa.
3.6 Study Conduct

3.6.1 General Issues on Data Quality and Reviewability

The approach to review of the results began with examination of the case narratives. Following, FDA review of a subset of the original narratives submitted in the clinical study report, the division required Pfizer to resubmit narratives for subjects who experienced events coded to the primary NPS endpoint to provide adequate information needed to assess the cases.

An example of one of the original narratives is shown below, demonstrating the inadequacy of the original narratives in providing information needed to assess events of potential interest. In this case, an event coded to the term “skull fracture” is reported in the narrative without providing any context for how the patient came to sustain the skull fracture. (Subsequent information requests revealed the injury was inflicted by her boyfriend, also a trial participant, a potentially relevant piece of information.)

The subject was randomized to varenicline 1 mg twice a day (BID) treatment, and received the first dose of double blind study drug on [ ]. The final dose of study drug was received on [ ] after 40 days of actual treatment. The subject was withdrawn from the study drug on [ ] due to an adverse event of skull fracture and completed the study on [ ].

On [ ], the subject experienced skull fracture which was considered severe in intensity and serious (due to hospitalization or prolonged hospitalization) by the investigator. Study drug was permanently stopped on [ ] due to the event though it resolved on [ ]. Concurrent with the event, the subject also experienced moderate ear injury, moderate ear pain, moderate dizziness, mild depression and mild insomnia. The subject underwent suture insertion on [ ] for laceration left ear. The subject received treatment with ondansetron hydrochloride for the nausea on [ ]; hydromorphone hydrochloride for the headache/left ear pain from [ ] to [ ]; meclizine [sic] for the dizziness from [ ] to [ ]; cefazolin for the skull fracture from [ ] to [ ]; fluoxetine for the situational depression and a dose change for trazodone for insomnia, both since [ ] (and ongoing). The events of ear injury, ear pain and skull fracture resolved on [ ]; the dizziness on [ ]; and the depression, the headache and the insomnia were still present at the end of the study. The investigator considered the events of ear injury, ear pain, skull fracture, dizziness, depression and headache to be not related to the study drug but due to trauma and the insomnia to be related to head injury.

Pfizer had also created narratives for other events they deemed potentially of interest, including traumatic injuries (which could have occurred in the context of violence-related symptoms or cognitive impairment) and some cases coded to terms such as irritability or terms in the endpoint that did not meet the severity threshold for inclusion in the primary NPS endpoint; the FDA clinical team reviewed this list and identified cases that needed new narratives to be constructed. New more informative narratives were submitted for all NPS cases and a subset of events of potential interest numbering over 500 cases.

Review of a sample of approximately 100 case narratives was undertaken, and it was determined that it was neither feasible nor possible to attempt to independently adjudicate the cases based on
the provided information. However, the review team identified a number of issues related to the coding of events and the assessment of severity which are assumed to apply across the database. These are discussed below.

Prior to submitting the Supplement proposing labeling changes, Pfizer initially submitted a Clinical Study Report without full datasets and sought the Division’s feedback on the presentation of the results. The full dataset of treatment-emergent adverse events (over 23,500 events) was not available to be reviewed in detail to select cases for narratives prior to the final submission of the study report and accompanying data. Therefore, the review team’s selection of cases for revised narratives was based on a subset already identified by Pfizer as being of potential interest.

Following submission of the Supplement, the full dataset was probed to determine whether additional cases that should have had narratives prepared based on the reporter’s verbatim or the adverse event coding had been omitted from the group of events of potential interest; it was apparent that many events of potential interest were not flagged, and no narratives were constructed. As discussed further below, once it became apparent that not all cases of potential NPS events had been identified by the investigators or Sponsors, rather than request multiple additional narratives, certain sensitivity analyses were conducted to estimate the impact of potential NPS events having been omitted.

The instructions provided to the investigators for assessment of relatedness do not appear to have resulted in a full capture of potentially related events. Examples include emotional symptoms frequently attributed to “stress” or to specific social situations, worsening symptoms of a pre-existing psychiatric illness almost always coded as “not related to study drug,” and assessments such as “The investigator considered the SAE of foot fracture to be not related to the study drug but due to fractured right heel” were provided. For this reason, investigator assessment of relatedness has been altogether disregarded in this review.

In many cases, no verbatim term for the adverse event was recorded at all so it is not possible to determine how coding was assigned or how severity was assessed. Pfizer stated that the “requirement to record subject verbatim terms as part of AE collection was an important and novel aspect of this protocol. Moreover, many site investigators and staff did not have prior experience recording subject verbatim in this manner. Training on how to promptly and accurately record subject verbatim was given at the Investigator Meetings and Site Initiation visits. The importance of the collection of subject verbatim was reinforced and emphasized via newsletters and monitor interactions with the sites. This continued site education improved the collection rate of subject verbatim as the study progressed.”

Review of the financial disclosures identified that seven investigators at six sites (including Site 1077 described below) disclosed financial arrangements or payments from Pfizer exceeding the $25,000 threshold for reporting to FDA. In particular, at two sites, the investigators reported multiple (as many as 60) separate honoraria for speaking engagements and consulting fees. On further inquiry, it was also determined that a number of investigators received ongoing payments from Pfizer for involvement in speaking engagements or other activities not necessarily related to Chantix that did not meet the $25,000 threshold. This included 39 investigators at 27 sites outside the US and four investigators at four US sites. No investigators had any financial
relationships with GSK that met the threshold for reporting. Evaluation of the impact of these issues is discussed below.

3.6.2 Data Reliability Issues

Pfizer’s quality management system included on-site monitoring, compliance oversight visits to the study sites, and investigator site audits. A total of 4451 on-site monitoring visits were conducted during the course of the study across all 142 sites that screened subjects. A total of 404 compliance oversight visits to assess study site adherence to the protocol and to ensure monitoring practices were completed at 140 sites during the conduct of the study.

Investigator site audits were conducted to assess compliance with GCP, International Conference on Harmonisation (ICH) Guidelines, the study protocol, Pfizer Corporate Policies and Procedures, and Pfizer Standard Operating Procedures (SOPs). Site audits were carried out at the investigator sites and included interviews with the investigator and site staff, facility tours where study activities were conducted, and reviews of source documentation and study subject data. A total of 26 investigator site audits were conducted over the study period (22 routine; 4 directed/for-cause), representing approximately 18% of sites that enrolled subjects. This represents approximately 70% of the top 10% of enrolling sites.

Pfizer’s own audits of their clinical sites identified two sites with such significant violations that they concluded the data were not reliable. At these sites, 1002 and 1077, 7 NPS primary events in 105 subjects were reported at site 1002 and 0 events in 31 subjects at site 1077. Sensitivity analyses to explore the impact of inclusion of these sites are discussed below.

At Site 1002, the audit findings included:

- The Principal Investigator did not provide sufficient or effective support and guidance to his staff to fully oversee this clinical trial. For example, adverse events (AEs) and Neuropsychiatric Adverse Event Interviews (NAEIs) were not properly assessed for causality and severity by the Principal Investigator (PI) in a timely manner.

- The site changed data without appropriate substantiation. This occurred for AEs, source documentation, and investigational product (IP) compliance. It was also noted that entries were made more than a year later by site staff after subjects had completed the study, were lost to follow up (LTFU), or withdrawn from the study.

- Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID) data changes were made by the only MHP approved for the study up to 28 months after the original SCID was completed. The approved MHP reviewed the SCIDs for all subjects in the study. Concerns were raised by Pfizer regarding SCID assessments that had been performed at screening by a MHP not approved to work in the study. These reviews with changes involved 26 of 63 subjects randomized to the psychiatric cohort and resulted in two subjects no longer meeting study eligibility criteria.

Additionally, other violations observed included inconsistencies between electronic case report forms and source data, missing documents, missing safety assessments and failure to record adverse events, and personnel performing diagnostic interviews and mental health evaluations who did not meet the mental health professional qualification requirements.
At Site 1077, a for-cause audit was performed after the study monitor identified problems such as potentially fabricated weights, unreported AEs, late entry of data into the CRF, incomplete or missing SCID interviews, large gaps between event dates and the date of the PI’s signature, signature dates that did not align with the signer’s schedule at the site, assessments performed by staff member not approved for these tasks. The for-cause audit identified the following issues:

- Principal Investigator (PI) oversight of study conduct was inadequate in regard to ensuring accurate and complete study data, management of adverse events (AEs), and clinical assessments.

- Source data and documentation was inadequate for consistently confirming data integrity for 11 of 18 subjects reviewed.

- The clinical study was not conducted in accordance with the approved protocol and adherence to the approved protocol could not be confirmed with source data/documentation present at the time of the audit for 4 of 18 subjects reviewed.

- Adverse event (AE) assessment, reporting, and follow-up was inadequate for 5 of 18 subjects reviewed.

- Source data, documentation, and data reported on case report forms (CRFs) were inadequate for 9 of 18 subjects reviewed forms.

- Two (2) of 8 site study staff performed study related procedures and assessments although the procedures/assessments were not in accordance with site staff education, professional training, or scope of practice.

- The training and experience of the site’s Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID I and II) (“SCID”) Administrator was not in accordance with the approved protocol.

Pfizer reported that six sites had individuals performing the role of MHP (reviewing the SCID for subjects enrolled in the psychiatric cohort to confirm the diagnosis and the stability of the subject and evaluating the subject when needed, such as in the case of positive response on the C-SSRS or depression scores >11 on the HADS) who were not approved for the study because they did not meet study requirements, either based on professional training and experience or on failure to complete study-required training and certification. Pfizer also noted that the results of the SCID were reviewed by staff of Worldwide Clinical Trials before subjects could be randomized. Based on these reviews of completed SCIDs, 22 sites had individuals who required retraining on performing the SCID.

Office of Scientific Investigation inspections of several of these sites have been requested, as well as inspections other sites in which similar issues were listed among the protocol violations. The results of these inspections are pending at this time.
3.6.3 Issues Related to Capture of NPS Events

The trial was designed in a well-intentioned attempt to capture somewhat ill-defined and complex neuropsychiatric phenomena. However, many problems in the implementation were apparent upon review of the collected data. These are enumerated below.

1. Ineffective Use of NAEI

The NAEI was intended to be used as a starting point to identify symptoms of potential concern, and then the full description of the patient’s experience was to be sought and recorded. The investigator was to determine whether the solicited symptom did or did not qualify as an adverse event. It appears that, at many sites, the NAEI was, instead, used as a checklist. No additional information was recorded beyond the patient endorsing one of the symptoms mentioned. It appears that some sites or investigators may have entered any endorsed symptom into the database as an adverse event. The dataset includes some events where no verbatim term whatsoever is recorded (this was the case at some sites throughout the trial) or where the verbatim is simply the NAEI term (e.g., “moderate agitation”) without any context or description. Many narratives are therefore unhelpful in providing insight into the nature of the adverse event or the impact on the patient.

2. Inconsistent Investigator Assessment of Severity

The investigator assessment of severity was intended to distinguish adverse events that reached a certain threshold of interference of a patient’s usual functioning. However, some narratives suggest a level of interference in the patient’s usual functioning not reflected in the investigator’s rating of severity. Some of these cases are included in the NPS primary endpoint because they were assigned codes and severity ratings included in the composite, whereas other cases in which the narratives describe very similar symptoms and impacts are not, either because the term selected is not in the composite (e.g., irritability) or because the investigator rating of severity did not meet criteria for inclusion in the NPS primary endpoint.

In a number of cases, subjects reported events that were coded to terms such as depression and mood disturbance which had a documented interference in their functioning but were only rarely assessed as “severe.” Some are assessed as “mild” despite the patient report of missing days of work or other significant impact. A patient (10941008) reporting “Severe change in my mood. Low patience for others, no hope for my future. I was more argumentative. I've noticed less pleasure from spending time with my family and my work. I have thought about crying,” on treatment Day 31 was not included in the depression component. The patient had a HADS depression score of 14 (from 0 at baseline) and endorsed a wish to be dead on the C-SSRS, but this was rated as “moderate” and not considered treatment-related. This patient, as well as some other similar cases, was flagged as having an NPS events by virtue of a co-occurring symptom (in this case, disturbance in attention) but others who probably should have been flagged as having an NPS event were not.

In reviewing the dataset for events in the domains of interest that were not coded to the NPS endpoint, several cases of events coded to a new psychiatric diagnosis (major depression) in
subjects who were in the non-psychiatric cohort were noted. These cases did not meet the “severity” criterion and were not flagged as NPS cases, and no narratives were prepared.\textsuperscript{15}

These types of cases further underscored the concern that the severity criterion for inclusion in the NPS endpoint may have been inappropriate to capture events of concern. There may have been a disconnect between what subjects with no previous psychiatric issues consider severe (even missing a day of work) and what a health care provider accustomed to caring for seriously mentally ill patients would regard as “severe” (possibly only an event requiring hospitalization). However, even hospitalization may not have been assessed as “severe” by some investigators; an additional case was identified among the SAE narratives, where a subject appears to have been hospitalized for depression after about 3 weeks of treatment with bupropion, but the event was assessed as “mild” by the investigator. (“On \textsuperscript{(b)}, the subject experienced depression which was considered mild in intensity and serious due to hospitalization or prolonged hospitalization by the investigator.”)

A sensitivity analysis that includes events of depressed mood assessed as “moderate” was undertaken to capture more of these cases (although the SAE mentioned above would not have been captured).

3. Inconsistent Mapping of Events to Sub-Components of the Composite

The endpoint was a composite of various emotional, cognitive, and perceptual experiences that subjects might experience because the post-marketing adverse events typically described patients experiencing multiple symptoms simultaneously. However, the coding of events did not facilitate identification of subjects who might have been experiencing a cluster of symptoms. Pfizer’s analysis included tabulation of events separated out into categories such as agitation, depression, psychosis, and panic.

Review of the narratives, where sufficient information about the patient report is provided to assess the coding, reveals a number of issues. Overall, the mapping of events to the sub-components was not consistent. There are subjects whose events included a constellation of cognitive and emotional and behavioral experiences but the investigator may not have coded all of the events such that the NPS threshold was reached for all of them. Additionally, there are errors in the assignment of terms to components (for some reason, “dysphoria” is included in the aggression component), and, unfortunately, there is no cognitive component at all. Cognitive symptoms are included in the “agitation” component.

Therefore, it does not appear helpful or informative to analyze the cases by component of the NPS endpoint.

4. Inconsistent Application of Coding

\textsuperscript{15} An example of a case located in review of the verbatim terms in the dataset and \textit{not} coded to the NPS endpoint or selected for construction of a narrative is a case in which the subject reported the following: “I think I am having a major depression. I am worried, I cry easily, I have apathy, I have no desire to do things, insomnia, increased apetite [sic], guilt, I have death thoughts (without suicidal ideation)”
Some terms, notably “agitation,” appear to have been applied inconsistently to a variety of symptoms. In a number of cases, there is sufficient information to determine that the term was interpreted to refer to motor agitation (akathisia); in others it refers to emotional upset and distress (which was the intended meaning in the protocol stage). In some cases another term in another component of the NPS endpoint (e.g., “anger”) was stated by the patient but the term “agitation” was chosen for coding. In still other cases, the patient reported insomnia, leading to selection of the term “restlessness” (i.e., the patient was not getting “rest”), which then coded to “agitation”—clearly not what was intended.

For many subjects whose only event is “moderate agitation,” there is virtually no additional information on the event to allow us to understand how that was manifested and in what way it was disruptive to the patient’s functioning (which is what makes it “moderate”). The only information recorded appears to be that the patient endorsed this symptom on the “checklist.” In some cases, subject verbatim terms containing concepts in NPS endpoint (e.g. “anger”) were coded to terms not in the NPS endpoint (irritability). There are also many subjects with verbatim terms coded to the term “irritability” where the description of the event is identical to other subjects coded to “agitation,” but they are not considered NPS cases. However, it isn’t possible to re-adjudicate all cases coded to “irritability” because many lack further information. Although irritability was intentionally excluded from the endpoint because of its well-known association with nicotine withdrawal, it seemed sensible to perform a sensitivity analysis on the NPS primary endpoint that included subjects with moderate to severe events coded to “irritability.”

5. Inconsistent Handling of Apparent Cases Involving Suicidality

The suicide component of the endpoint is problematic because, although the C-SSRS was administered, no attempt was made to reconcile the C-SSRS results with the adverse event reporting. Some subjects had AEs reported based on C-SSRS results while others did not. The subject described above who endorsed suicidal ideation during the protocol-specified mental health evaluation prompted by his NPS-endpoint qualifying event was not coded as having suicidal ideation. Two patients who took deliberate overdoses of medication were not coded as making suicide attempts. These cases were not even selected for preparation of narratives as being of “potential” interest.

6. Lack of Information About Circumstances of Events

Several narratives had insufficient information to understand the context of the event and whether it occurred in the setting of the type of neuropsychiatric problems that are of interest in the trial. A patient who was killed in a motor vehicle accident is described as having an event of “head-on collision” and information about whether or not the patient was the driver is missing from the narrative.

A subject sustained a fractured skull when her boyfriend (also a trial participant, although per protocol this should not have occurred) hit her in the head with a gun. The narrative for the event (reported for both subjects) does not capture whether this occurred in the context of an altercation, was associated with treatment-emergent symptoms of anger/hostility/aggression, etc., or was otherwise an event of relevance to the NPS primary endpoint.
In one case (10991338), a subject with a prior psychiatric diagnosis of a single, remote, past episode of major depression and a past diagnosis of obsessive-compulsive disorder who was not symptomatic or ill at baseline, made a suicide attempt one day after completing study treatment (with bupropion) and received a diagnosis of schizoaffective disorder. This was reported as an NPS event. However, no explanation of this diagnosis, which requires the presence of psychotic symptoms over a period of time without affective symptoms, appears to have been sought, and no description of any such symptoms is provided.

7. Miscellaneous Coding Errors

As with any large dataset, other coding errors were identified, such as a case included in the “psychosis” component in which the subject did not experience psychosis. The subject was appropriately included in the NPS endpoint because of suicidal ideation, but the narrative shows that the subject reported being "down and lonely," investigator term was "depressed affect" and this was coded to "flat affect," which is a symptom of psychosis. Similarly, a subject who reported withdrawing from social activity was coded to the term “detachment” which was interpreted as “flat affect” and therefore psychosis. As noted above, insomnia was sometimes translated to “restlessness” and then to “agitation.” The study was conducted globally in a variety of languages not all site personnel were trained mental health care professionals. This may have complicated the coding of the collected AE data relevant to the NPS endpoint.

Case examples are provided in the Appendix.

3.7 Analysis of NPS Primary Endpoint

The primary safety analysis conducted by the FDA review team estimated the risk difference of NPS events for all six pairwise treatment comparisons (varenicline - placebo, bupropion - placebo, etc…) by cohort of previous diagnosis of a psychiatric disorder. The risk difference of NPS events was estimated through a generalized linear model for binary data with an identity link function. The model included covariates for treatment (4 levels), cohort (2 levels: Non-PHx vs. PHx), treatment by cohort interaction, and region of randomization (2 levels: USA vs. non-USA).

The SAP did not pre-specify any statistical hypotheses to be tested, and therefore no p-values are discussed in this document. All confidence intervals for the risk difference of NPS events were calculated at a nominal 95% confidence level and no corrections were made for multiple comparisons.

The following secondary analyses of the NPS primary endpoint were conducted by the FDA statistics review team:

- Analysis of NPS events by study site and cohort to evaluate potential site heterogeneity.
- Analysis of NPS events through alternative statistical models to account for extra binomial variation between study sites.

Additionally, the FDA reviewers conducted a descriptive analysis of two alternative treatment emergent composite neuropsychiatric events in order to assess the robustness of the primary NPS safety results to changes in the endpoint definition:
A composite event that includes only severe NPS events.

An ‘NPS+’ composite endpoint that includes all NPS events plus moderate or severe adverse events with an associated MedDRA Preferred Term (PT) of ‘Irritability’ or High Level Group Term (HGLT) of ‘Depressed mood disorders’.

A descriptive analysis of deaths observed in the trial and an analysis of the C-SSRS instrument was also conducted.

3.7.1 Analysis of the Primary Neuropsychiatric Event

Figure 2 and Figure 3 show the number and proportion of subjects who experienced a treatment-emergent NPS event in the trial, as well as the timing of these events, by treatment arm and cohort of psychiatric history diagnosis at baseline (PHx and Non-PHx). The observed rate of NPS events among subjects in the Non-PHx cohort was lowest among subjects randomized to varenicline (1.3%) and was similar for subjects randomized to bupropion, NRT, or placebo (2.2% to 2.5%). The observed rate of NPS events in the PHx cohort was highest among subjects randomized to varenicline and bupropion (6.5% and 6.7% respectively) and was lowest among subjects randomized to placebo (4.9%). Subjects randomized to bupropion or varenicline in the PHx cohort (Figure 3) experienced more NPS events within the first seven days after randomization (21 subjects on bupropion, 12 on varenicline) than subjects randomized to NRT (4) or placebo (4).

Figure 2. NPS Events in the Non-PHx

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt
Figure 3. NPS Events in the PHx Cohort

![Graph showing NPS events over time in the PHx Cohort](image)

Table 1: NPS Events by Treatment and Cohort

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Non-PHx</th>
<th>PHx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
<td>67 / 1026 (6.5%)</td>
<td>50 / 1015 (4.9%)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>68 / 1017 (6.7%)</td>
<td>53 / 1016 (5.2%)</td>
</tr>
<tr>
<td>NRT</td>
<td>53 / 1016 (5.2%)</td>
<td>50 / 1015 (4.9%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>67 / 1026 (6.5%)</td>
<td>53 / 1016 (5.2%)</td>
</tr>
</tbody>
</table>

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

Figure 4 shows the estimated risk differences and corresponding nominal 95% confidence intervals for the risk difference of NPS events for each of the six pairwise treatment comparisons in each of the two cohorts based on the pre-specified primary analysis. The figure shows in the Non-PHx cohort a nominally protective effect associated with varenicline relative to placebo: RD = -1.28 NPS events per 100 subjects, 95% CI (-2.40,-0.15), and in the PHx cohort a numerically increased risk associated with varenicline: RD = 1.59 NPS events per 100 subjects, 95% CI (-0.42, 3.59). In the Non-PHx cohort varenicline showed a nominally protective effect relative to bupropion: RD = -1.19 NPS events per 100 subjects, 95% CI (-2.30, -0.09), and in the PHx cohort no meaningful difference in risk: RD = -0.20, 95% CI (-2.34, 1.95).
Figure 4. Primary Analysis: Risk Difference of NPS Events by Cohort

V = Varenicline, B = Bupropion, N = Nicotine Replacement Therapy, P = Placebo

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt
3.7.2 Composite Neuropsychiatric Event Including Only Severe Adverse Events

The primary composite NPS event included treatment emergent adverse events that met a minimum severity threshold as described in Section 2.2. The FDA review team conducted a sensitivity analysis of treatment emergent neuropsychiatric adverse events that included only severe adverse events. Table 9 shows a summary of subjects with at least one severe treatment emergent neuropsychiatric event by treatment arm and cohort.

Table 9 Severe Treatment Emergent Neuropsychiatric Events by Cohort

<table>
<thead>
<tr>
<th></th>
<th>Varenicline events / N (%)</th>
<th>Bupropion events / N (%)</th>
<th>NRT events / N (%)</th>
<th>Placebo events / N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PHx Cohort</td>
<td>1 / 990 (0.1%)</td>
<td>4 / 989 (0.4%)</td>
<td>3 / 1006 (0.3%)</td>
<td>5 / 999 (0.5%)</td>
</tr>
<tr>
<td>PHx Cohort</td>
<td>14 / 1026(1.4%)</td>
<td>14 / 1017 (1.4%)</td>
<td>14 / 1016 (1.4%)</td>
<td>13 / 1015 (1.3%)</td>
</tr>
</tbody>
</table>

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.7.3 Composite NPS+ Event

The FDA reviewers conducted a sensitivity analysis of an alternative NPS+ event that includes all NPS events plus adverse events rated as moderate or severe coded to the MedDRA Preferred Term (PT) of ‘Irritability’ or High Level Group Term (HGLT) of ‘Depressed mood disorders’. Table 10 shows a summary of these events by cohort and randomized treatment arm. Analyses of this alternative NPS+ endpoint were consistent with analyses of the primary NPS endpoint.
Table 10 Treatment Emergent NPS + Events by Treatment and Cohort

<table>
<thead>
<tr>
<th></th>
<th>Varenicline events / N (%)</th>
<th>Bupropion events / N (%)</th>
<th>NRT events / N (%)</th>
<th>Placebo events / N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PHx Cohort</td>
<td>32 / 990 (3.2%)</td>
<td>35 / 989 (3.5%)</td>
<td>38 / 1006 (3.8%)</td>
<td>44 / 999 (4.4%)</td>
</tr>
<tr>
<td>PHx Cohort</td>
<td>118 / 1026 (11.5%)</td>
<td>109 / 1017 (10.7%)</td>
<td>89 / 1016 (8.8%)</td>
<td>100 / 1015 (9.9%)</td>
</tr>
</tbody>
</table>

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt, Pidcha.xpt, Subhev.xpt and Advers.xpt

3.7.4 NPS Event by Study Sites

Subjects were randomized and treated in 139\(^{16}\) sites in 16 countries (117 sites with subjects in the Non-PHx cohort, 127 sites with subjects in the PHx cohort). Prior to the submission of the trial results, the Sponsor informed the Agency of problems regarding the conduct of the trial at two sites (site 1002 with 112 subjects, and site 1077 with 31 subjects) as described in Section 4.6.2. The FDA review team conducted sensitivity analyses that excluded these two sites and found the results to be consistent with those of the primary analysis discussed above. However, due to the potential for additional unidentified sites with problems in the conduct of the trial, the review team at the FDA conducted analyses of various endpoints by site, including the primary NPS endpoint.

The figures below show findings by site where the number of subjects who were treated in each study site is shown on the horizontal axis, and the number of subjects who experienced at least one treatment-emergent NPS event is shown on the vertical axis. The blue (red + blue) shaded area in these figures shows a 95% (99%) prediction band for the expected number of subjects with an NPS event under the assumption that the number of subjects who experience an event in any given site follows a binomial distribution with a common rate of events for all sites in the same cohort. The sites identified by a red solid circle fall outside of the 99% prediction band, i.e. they had either fewer or more subjects with an event than would be expected for a site with the same number of subjects 99% of the time. Figure 5 shows that the Non-PHx cohort observed less heterogeneity between sites than the PHx cohort. Figure 6 shows that sites in the PHx cohort exhibited high heterogeneity in the rate of NPS events. One example of the high

\(^{16}\) 140 sites randomized patients, but at one site only one patient was randomized and did not take any doses of study drug. Therefore, the FAS for efficacy analysis includes 140 sites and the safety population includes 139.
heterogeneity observed in the PHx cohort is that the largest site, site 1088, recorded an NPS event in 28 out of 186 subjects (15.1%), but the second largest site, site 1059, recorded 0 events in 147 subjects.

The PHx cohort also observed more sites with 0 NPS events than would be expected under the assumption of a binomial distribution for the number of events within sites (45 expected sites with no NPS events vs. 60 sites observed with no NPS events). This level of site heterogeneity is highly improbable to have occurred by chance alone under the assumption of a common rate of NPS events. One potential concern is that the subjective nature of the NPS endpoint may have led to different interpretations of what constitutes an event across sites. Section 4.7.5 discusses sensitivity analyses that account for extra-binomial variation of NPS events across sites.

Figure 5. Site Size and NPS Events in the Non-PHx Cohort

1Red circles represent sites that fall outside of the 99% prediction band
2Black circles represent sites that fell outside of the 99% prediction band in the PHx cohort (Figure 6)
3The pooled rate of subjects with an NPS event across all sites in the Non-PHx cohort was 2.1%

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt
Figure 6. Site Size and NPS Events in the PHx Cohort

1Red circles represent sites that fall outside of the 99% prediction band

2The pooled rate of subjects with an NPS event across all sites in the PHx cohort was 5.8%

Source: Created by Dr. Andraca-Carrera using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

3.7.5 Statistical Models to Account for Extra Binomial Variation between Sites

The FDA review team fit alternative statistical models to account for the extra-binomial variation in the rate of NPS events observed across sites in the trial. Four models were explored:

- the primary pre-specified binomial model,
- a Poisson model for the number of subjects with an NPS event in each site,
- a negative binomial (NB), and
- a zero-inflated negative binomial (ZINB) model.

The Akaike information criterion (AIC) was used to compare these models; the AIC is a measure of the goodness of fit of a statistical model to a given set of data. The NB model was found to have the smallest AIC and therefore to fit the data significantly better than the other three models. This suggests that the primary binomial model may underestimate the heterogeneity of NPS rates across study sites.
Figure 7 shows estimated rate ratios (RR) and corresponding 95% confidence intervals for the risk of NPS events for each pair-wise treatment comparison by cohort based on a NB model for correlated data with observations clustered by site and with covariates for cohort, country of randomization (USA vs. others), and randomized treatment. Parameter estimates from this model were obtained through generalized estimating equations using SAS 9.4 PROC GENMOD. The results of this analysis show that even though the rate of NPS events in the PHx cohort was more heterogeneous than originally anticipated in the primary binomial model, the interpretations of the NB model and the primary binomial model are consistent.

**Figure 7. Rate Ratio for NPS Events from a Negative Binomial Model**

V = Varenicline, B = Bupropion, N = Nicotine Replacement Therapy, P = Placebo

Source: Created by Dr. Andracac-Carrera using datasets Demog.xpt, Pidcha.xpt, Subevg.xpt and Advers.xpt

### 3.7.6 Analysis of Deaths

Table 11 lists all deaths observed in the Full Analysis Set, defined as the full study follow-up from randomization to the last recorded study visit. Additionally one subject not shown in Table
11 died before randomization and one subject randomized to placebo delivered a premature baby which died following birth. The small number of observed deaths in the trial precludes a precise analysis of the risk of death associated with any of these treatments.

Table 11 Deaths by Cohort and Treatment

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Varenicline deaths / N</th>
<th>Bupropion deaths / N</th>
<th>NRT deaths / N</th>
<th>Placebo deaths / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PHx Cohort</td>
<td>0 / 990 (0%)</td>
<td>1 / 989 (0.1%)</td>
<td>1 / 1006 (0.1%)</td>
<td>3 / 999 (0.3%)</td>
</tr>
<tr>
<td>PHx Cohort</td>
<td>0 / 1026 (0%)</td>
<td>2 / 1017 (0.2%)</td>
<td>1 / 1016 (0.1%)</td>
<td>1 / 1015 (0.1%)</td>
</tr>
</tbody>
</table>

Source: Created by Dr. Andraca-Carrera using dataset Death.xpt

3.7.7 Analysis of the C-SSRS Instrument

Suicidal behavior, suicidal ideation, and completed suicide are three components of the primary NPS endpoint. Adverse events that are part of these components were captured through several mechanisms, including routine collection of adverse events, investigator reports, and responses to the C-SSRS questionnaire. The C-SSRS questionnaire was routinely collected at every clinic visit during the 12 week treatment phase. Table 12 and Table 13 show the number of subjects with treatment emergent suicidal behavior, suicidal ideation, and self-injurious behavior based on the results of the C-SSRS questionnaire. Note that some of the events listed in Table 12 and Table 13 were categorized as “mild” and therefore did not qualify as NPS events. Similarly, some moderate and severe events related to suicidal ideation and behavior that were part of the NPS endpoint were not captured through the C-SSRS instrument and are not included in these tables. The results of the C-SSRS show no conclusive evidence of a treatment effect on the risk of any of suicidal behavior, suicidal ideation, or self-injurious behavior.
Table 12 Results of the C-SSRS in the Non-PHx Cohort – Treatment Emergent Events

<table>
<thead>
<tr>
<th></th>
<th>Varenicline</th>
<th>Buproproion</th>
<th>NRT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 990</td>
<td>N = 989</td>
<td>N = 1006</td>
<td>N = 999</td>
</tr>
<tr>
<td>Suicidal Behavior</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>7 (0.7%)</td>
<td>4 (0.4%)</td>
<td>3 (0.3%)</td>
<td>6 (0.6%)</td>
</tr>
<tr>
<td>Self-Injurious Behavior</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Source: Created by Dr. Andraca-Carrera using datasets Css1.xpt and Css2.xpt

Table 13 Results of the C-SSRS in the PHx Cohort – Treatment Emergent Events

<table>
<thead>
<tr>
<th></th>
<th>Varenicline</th>
<th>Buproproion</th>
<th>NRT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1026</td>
<td>N = 1017</td>
<td>N = 1016</td>
<td>N = 1015</td>
</tr>
<tr>
<td>Suicidal Behavior</td>
<td>0 (0%)</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>27 (2.6%)</td>
<td>15 (1.5%)</td>
<td>20 (2.0%)</td>
<td>25 (2.5%)</td>
</tr>
<tr>
<td>Self-Injurious Behavior</td>
<td>2 (0.2%)</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

Source: Created by Dr. Andraca-Carrera using datasets Css1.xpt and Css2.xpt

3.7.8 Effect of Smoking vs Abstinence

When the safety signal for neuropsychiatric adverse events with Chantix originally came to light, Pfizer (and others, including smoking cessation researchers) theorized that the events were related not to the drug itself, but due to smoking cessation. Mood changes such as depression and irritability have been observed in association with nicotine withdrawal, and the possibility existed that the events could be explained by this phenomenon. However, case review revealed that many people reporting neuropsychiatric events had not stopped smoking; some had reduced their smoking but others were smoking at their baseline level. In most cases, however, the
smoking status at the time of the event was not recorded. In this study, it was emphasized that the smoking status at the time of the event should be captured and described. This was not always the case, moreover, case narratives did not place the smoking status into the chronological narrative in a way that allowed the temporal relationship between smoking, study drug, and adverse events to be understood.

At best, it is possible to view the relationship between smoking and Sponsor-designated NPS events, where smoking status is known, in the graphic displays shown below (constructed by Pfizer). These analyses used information from the NUI, which was administered weekly during the study, to determine smoking status and AE data to determine the onset of the NPS AE endpoint event.

The figures below illustrate the relationship between smoking status by week and the onset of NPS events. Smoking status is classified as completely abstinent for the week, abstinent during part of the week (≥2 days), smoked during the entire week (abstinent <1 day) – with the occurrence of the NPS AE superimposed on the week it started (Figures 8 and 9) for each subject who reported an NPS AE endpoint event. Data are shown through Week 16 to cover the treatment-emergent period of 12 weeks plus 30 days.
Figure 8. Primary NPS AE Endpoint – Smoking Status by Week and Onset of AE - Non-Psychiatric History Cohort, Safety Population

Varenicline (13 subjects)
Bupropion (22 subjects)

NRT (25 subjects)
Placebo (24 subjects)

Black=smoker, dark grey=partial abstainer, light grey=abstainer, white=no further Nicotine Use Inventory data available.
Red diamonds show onset of NPS AE.
NPS AE=neuropsychiatric adverse event; NRT=nicotine replacement therapy.
Source: A3051123 CSR Appendix 16, Figures 16.2.7.4a, 16.2.7.4b, 16.2.7.4c, and 16.2.7.4d.

Figure 9. Primary NPS AE Endpoint – Smoking Status by Week and Onset of AE - Psychiatric History Cohort, Safety Population
Varenicline (67 subjects)  
Bupropion (68 subjects)
Although some subjects in each treatment group had NPS AEs that occurred during or following a week of partial or complete abstinence, these graphs showed no consistent association between the occurrence of an NPS AE in the composite endpoint and abstinence in any of the treatment groups. The analysis is also affected by lack of specificity of actual days in the week a subject was abstinent, missing data imputation methods which did not account for partial abstinence, and the lack of consideration for reduction in the number of cigarettes smoked.

### 3.7.9 Impact of Financial Involvement

Investigators in 32 sites received payments from Pfizer between November 2011 and October 2015 in excess of the $25,000 threshold for reporting to FDA as part of speaking services related to CHANTIX (12 of 32 sites) and/or other products marketed by Pfizer (21 of 32 sites). We conducted sensitivity analysis of the primary NPS event excluding these 32 sites.
Table 14 shows the number of subjects with at least one NPS event by cohort and by randomized treatment in the primary safety analysis set including all 139 sites and in the subset excluding the 32 sites with at least one investigator who received payment from Pfizer. The exclusion of these 32 sites resulted in the loss of 9 subjects with NPS events from the Non-PHx cohort (4 bupropion, 1 NRT, 4 placebo), and 9 subjects with NPS events from the PHx cohort (2 varenicline, 4 bupropion, 2 NRT, 1 placebo).

Table 14. NPS Events in Primary Analysis and in Subset Excluding 32 Sites with Financial Involvement

<table>
<thead>
<tr>
<th></th>
<th>Varenicline events / N</th>
<th>Bupropion events / N</th>
<th>NRT events / N</th>
<th>Placebo events / N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-PHx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sites</td>
<td>13 / 990</td>
<td>22 / 989</td>
<td>25 / 1006</td>
<td>24 / 999</td>
</tr>
<tr>
<td>Excluding 32 sites</td>
<td>13 / 804</td>
<td>18 / 841</td>
<td>24 / 864</td>
<td>20 / 862</td>
</tr>
<tr>
<td><strong>PHx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sites</td>
<td>67 / 1026</td>
<td>68 / 1017</td>
<td>53 / 1016</td>
<td>50 / 1015</td>
</tr>
<tr>
<td>Excluding 32 sites</td>
<td>65 / 887</td>
<td>64 / 896</td>
<td>51 / 900</td>
<td>49 / 899</td>
</tr>
</tbody>
</table>

Table 15 shows the pooled number and percentage of NPS events observed by country and cohort comparing sites without financial involvement (107 total sites) and sites with financial involvement (32 total sites). Overall, sites without financial involvement observed a higher percentage of NPS events than sites with financial involvement in both cohorts (2.2% vs. 1.5% in the Non-PHx cohort, 6.4% vs. 1.8% in the PHx cohort). However, the observed difference in NPS event rates between sites with and without financial involvement may be attributable to chance due to the small sample size among sites with financial involvement and the high heterogeneity in event rates across sites.

Table 15. NPS Events by Country and Financial Involvement, Pooled Across All Treatments

<table>
<thead>
<tr>
<th>Country</th>
<th>Non-PHx Cohort</th>
<th>PHx Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Financial Involvement</td>
<td>Financial Involvement</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Argentina</td>
<td>2/169 (1.2%)</td>
<td>0/49 (0%)</td>
</tr>
<tr>
<td>Brazil</td>
<td>0/2 (0%)</td>
<td>0/7 (0%)</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>0/184 (0%)</td>
<td>0/76 (0%)</td>
</tr>
<tr>
<td>Canada</td>
<td>0/28 (0%)</td>
<td>3/108 (2.8%)</td>
</tr>
<tr>
<td>Germany</td>
<td>13/359 (3.6%)</td>
<td>2/41 (4.9%)</td>
</tr>
<tr>
<td>Mexico</td>
<td>3/81 (3.7%)</td>
<td>0/52 (0%)</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>0/17 (0%)</td>
<td>0/51 (0%)</td>
</tr>
<tr>
<td>South Africa</td>
<td>2/195 (1%)</td>
<td>2/29 (6.9%)</td>
</tr>
<tr>
<td>Spain</td>
<td>0/15 (0%)</td>
<td>2/132 (1.5%)</td>
</tr>
<tr>
<td>USA</td>
<td>50/1807 (2.8%)</td>
<td>0/68 (0%)</td>
</tr>
<tr>
<td>All countries in trial</td>
<td>75 / 3371 (2.2%)</td>
<td>9 / 613 (1.5%)</td>
</tr>
</tbody>
</table>
Table 16 shows that the estimated risk differences of NPS events between treatments and their corresponding nominal 95% confidence intervals were generally consistent in the primary analysis including all 139 sites and the sensitivity analysis excluding the 32 sites with financial involvement. In the Non-PHx cohort the risk differences comparing varenicline to placebo, and varenicline to bupropion were nominally significant in the analysis including all sites, but were no longer nominally significant after excluding the 32 sites.

Table 16. Risk Difference of NPS Events in Primary Analysis and in Subset Excluding 32 Sites with Financial Involvement

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Cohort</th>
<th>Risk Difference of NPS Events (95% CI)</th>
<th>All sites</th>
<th>Excluding 32 sites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All sites</td>
<td>Excluding 32 sites</td>
</tr>
<tr>
<td>V-P</td>
<td>Non-PHx</td>
<td>-1.28 (-2.40, -0.15)</td>
<td>-0.83 (-2.12, 0.47)</td>
<td></td>
</tr>
<tr>
<td>B-P</td>
<td>Non-PHx</td>
<td>-0.08 (-1.38, 1.21)</td>
<td>-0.09 (-1.47, 1.29)</td>
<td></td>
</tr>
<tr>
<td>N-P</td>
<td>Non-PHx</td>
<td>-0.21 (-1.54, 1.12)</td>
<td>0.26 (-1.22, 1.74)</td>
<td></td>
</tr>
<tr>
<td>V-N</td>
<td>Non-PHx</td>
<td>-1.07 (-2.21, 0.08)</td>
<td>-1.09 (-2.46, 0.29)</td>
<td></td>
</tr>
<tr>
<td>B-N</td>
<td>Non-PHx</td>
<td>0.13 (-1.19, 1.45)</td>
<td>-0.35 (-1.82, 1.13)</td>
<td></td>
</tr>
<tr>
<td>V-B</td>
<td>Non-PHx</td>
<td>-1.19 (-2.30, -0.09)</td>
<td>-0.74 (-2.02, 0.54)</td>
<td></td>
</tr>
<tr>
<td>V-P</td>
<td>PHx</td>
<td>1.59 (-0.42, 3.59)</td>
<td>1.86 (-0.40, 4.12)</td>
<td></td>
</tr>
<tr>
<td>B-P</td>
<td>PHx</td>
<td>1.78 (-0.24, 3.81)</td>
<td>1.69 (-0.55, 3.93)</td>
<td></td>
</tr>
<tr>
<td>N-P</td>
<td>PHx</td>
<td>0.37 (-1.53, 2.27)</td>
<td>0.27 (-1.84, 2.38)</td>
<td></td>
</tr>
<tr>
<td>V-N</td>
<td>PHx</td>
<td>1.22 (-0.81, 3.25)</td>
<td>1.59 (-0.69, 3.87)</td>
<td></td>
</tr>
<tr>
<td>B-N</td>
<td>PHx</td>
<td>1.42 (-0.63, 3.46)</td>
<td>1.42 (-0.84, 3.68)</td>
<td></td>
</tr>
<tr>
<td>V-B</td>
<td>PHx</td>
<td>-0.20 (-2.34, 1.95)</td>
<td>0.17 (-2.23, 2.57)</td>
<td></td>
</tr>
</tbody>
</table>

Table 17 shows that the removal of these 32 sites from analyses resulted in 24 fewer subjects with an NPS+ event in the Non-PHx cohort (4 varenicline, 10 bupropion, 2 NRT, 8 placebo) and 38 fewer subjects with an NPS+ event in the PHx cohort (9 varenicline, 11 bupropion, 5 NRT, 13 placebo).

Table 17. NPS+ Events in All Sites and in Subset Excluding 32 Sites with Financial Involvement

<table>
<thead>
<tr>
<th></th>
<th>Varenicline events / N</th>
<th>Bupropion events / N</th>
<th>NRT events / N</th>
<th>Placebo events / N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All sites</td>
<td>Excluding 32 sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PHx</td>
<td>32 / 990</td>
<td>28 / 804</td>
<td>38 / 1006</td>
<td>44 / 999</td>
</tr>
<tr>
<td>PHx</td>
<td>118 / 1026</td>
<td>109 / 887</td>
<td>89 / 1016</td>
<td>100 / 1015</td>
</tr>
</tbody>
</table>
Table 18 shows that the estimated risk differences of NPS+ events between treatments and their corresponding nominal 95% confidence intervals were generally consistent between the analysis including all 139 sites and the sensitivity analysis excluding the 32 sites with financial involvement. The differences between the two analyses were reasonably explained by chance.

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Cohort</th>
<th>Risk Difference of NPS+ Events (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excluding 32 sites</td>
</tr>
<tr>
<td>V-P</td>
<td>Non-PHx</td>
<td>-1.25 (-2.93, 0.43)</td>
</tr>
<tr>
<td>B-P</td>
<td>Non-PHx</td>
<td>-0.74 (-2.46, 0.97)</td>
</tr>
<tr>
<td>N-P</td>
<td>Non-PHx</td>
<td>-0.75 (-2.49, 0.99)</td>
</tr>
<tr>
<td>V-N</td>
<td>Non-PHx</td>
<td>-0.50 (-2.11, 1.11)</td>
</tr>
<tr>
<td>B-N</td>
<td>Non-PHx</td>
<td>0.01 (-1.67, 1.69)</td>
</tr>
<tr>
<td>V-B</td>
<td>Non-PHx</td>
<td>-0.51 (-2.12, 1.10)</td>
</tr>
<tr>
<td>V-P</td>
<td>PHx</td>
<td>1.65 (-1.03, 4.33)</td>
</tr>
<tr>
<td>B-P</td>
<td>PHx</td>
<td>0.85 (-1.79, 3.49)</td>
</tr>
<tr>
<td>N-P</td>
<td>PHx</td>
<td>-1.10 (-3.63, 1.42)</td>
</tr>
<tr>
<td>V-N</td>
<td>PHx</td>
<td>2.75 (0.14, 5.37)</td>
</tr>
<tr>
<td>B-N</td>
<td>PHx</td>
<td>1.96 (-0.62, 4.53)</td>
</tr>
<tr>
<td>V-B</td>
<td>PHx</td>
<td>0.80 (-1.92, 3.52)</td>
</tr>
</tbody>
</table>

**3.8 Analysis of Efficacy**

The results of the analyses for CAR 9-12 and CAR 9-24 are presented in Table 14 by psychiatric cohort using the FAS population. The primary comparisons of varenicline versus placebo and bupropion versus placebo and the secondary comparison of NRT versus placebo for CAR 9-12 and CAR 9-24 were statistically significant (p < 0.001). All other pairwise comparisons were also considered statistically significant except for bupropion versus NRT (results not shown).
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Varenicline (%)</th>
<th>Bupropion (%)</th>
<th>NRT (%)</th>
<th>Placebo (%)</th>
<th>Odds ratio</th>
<th>V/P</th>
<th>B/P</th>
<th>N/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR 9-12</td>
<td>33.5</td>
<td>22.6</td>
<td>23.4</td>
<td>12.5</td>
<td>3.60*</td>
<td>2.06*</td>
<td>2.14*</td>
<td></td>
</tr>
<tr>
<td>CAR 9-24</td>
<td>21.9</td>
<td>16.2</td>
<td>15.7</td>
<td>9.4</td>
<td>2.73*</td>
<td>1.88*</td>
<td>1.80*</td>
<td></td>
</tr>
<tr>
<td>Non-PHx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR 9-12</td>
<td>38.0</td>
<td>26.1</td>
<td>26.4</td>
<td>13.7</td>
<td>4.00*</td>
<td>2.26*</td>
<td>2.30*</td>
<td></td>
</tr>
<tr>
<td>CAR 9-24</td>
<td>25.5</td>
<td>18.8</td>
<td>18.5</td>
<td>10.5</td>
<td>2.99*</td>
<td>2.00*</td>
<td>1.96*</td>
<td></td>
</tr>
<tr>
<td>PHx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR 9-12</td>
<td>29.2</td>
<td>19.3</td>
<td>20.4</td>
<td>11.4</td>
<td>3.25*</td>
<td>1.87*</td>
<td>2.00*</td>
<td></td>
</tr>
<tr>
<td>CAR 9-24</td>
<td>18.3</td>
<td>13.8</td>
<td>13.0</td>
<td>8.3</td>
<td>2.50*</td>
<td>1.77*</td>
<td>1.65*</td>
<td></td>
</tr>
</tbody>
</table>

V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo
* p-value <0.001, using a logistic regression with terms treatment, cohort, region, and treatment by cohort interaction, and region by cohort interaction. Region used 2-level classification (US, non-US).
Source: Statistical reviewer Yi Ren

These results were consistent with Pfizer’s conclusion that varenicline was superior to bupropion, NRT, and placebo with respect to smoking cessation. Bupropion was also considered superior to placebo. Although the observed rates for CAR 9-12 and CAR 9-24 were numerically lower in the PHx cohort than in the non-PHx cohort, there was no statistically significant interaction between treatment and cohort.

Pfizer’s analysis considered missing CO values as negative, i.e. a subject could be considered a non-smoker according only to self-report. Although this is not the customary approach to analysis of smoking cessation studies, the conclusion did not change when these subjects were considered non-responders (results not shown).

The review team undertook an additional exploratory analysis to address the possibility that some subjects had tried the various study drugs before the trial. If by chance these subjects were randomized to a drug they were previously unable to tolerate, they would likely drop out and be considered non-responders. In a study primarily designed to assess comparative efficacy, patients already known to be intolerant to one of the study drugs would have been screened out. To explore the impact of this possibility, these subjects were excluded and the data was reanalyzed. This modified population is referred as the modified Full Analysis Set (mFAS). The table below provides a summary of the number of patients in the FAS and mFAS datasets.
### Table 20 Number of Subjects in FAS and mFAS Datasets

<table>
<thead>
<tr>
<th>Treatment/Cohort</th>
<th>Varenicline</th>
<th>Bupropion</th>
<th>NRT</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS Population</td>
<td>2037</td>
<td>2034</td>
<td>2038</td>
<td>2035</td>
<td>8144</td>
</tr>
<tr>
<td>mFAS Population</td>
<td>1333</td>
<td>1262</td>
<td>1296</td>
<td>1322</td>
<td>5213</td>
</tr>
<tr>
<td><strong>Non-PHx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS Population</td>
<td>1005</td>
<td>1001</td>
<td>1013</td>
<td>1009</td>
<td>4028</td>
</tr>
<tr>
<td>mFAS Population</td>
<td>690</td>
<td>641</td>
<td>656</td>
<td>670</td>
<td>2657</td>
</tr>
<tr>
<td><strong>PHx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS Population</td>
<td>1032</td>
<td>1033</td>
<td>1025</td>
<td>1026</td>
<td>4116</td>
</tr>
<tr>
<td>mFAS Population</td>
<td>643</td>
<td>621</td>
<td>640</td>
<td>652</td>
<td>2556</td>
</tr>
</tbody>
</table>

Source: Statistical reviewer Yi Ren

The primary comparisons of varenicline versus placebo and bupropion versus placebo and the secondary comparison of NRT versus placebo for CAR 9-12 and CAR 9-24 using the mFAS are summarized by psychiatric cohort in Table 16.

### Table 21 Comparison of Continuous Abstinence Rates for Weeks 9-12 and Weeks 9-24 - mFAS Population†

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Varenicline (%)</th>
<th>Bupropion (%)</th>
<th>NRT (%)</th>
<th>Placebo (%)</th>
<th>V/P</th>
<th>B/P</th>
<th>N/P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR 9-12</td>
<td>31.9</td>
<td>22.8</td>
<td>22.1</td>
<td>12.5</td>
<td>3.39*</td>
<td>2.09*</td>
<td>1.98*</td>
</tr>
<tr>
<td>CAR 9-24</td>
<td>21.5</td>
<td>15.5</td>
<td>15.4</td>
<td>9.8</td>
<td>2.60*</td>
<td>1.70*</td>
<td>1.68*</td>
</tr>
<tr>
<td><strong>Non-PHx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR 9-12</td>
<td>34.9</td>
<td>26.2</td>
<td>26.5</td>
<td>14.3</td>
<td>3.33*</td>
<td>2.14*</td>
<td>2.16*</td>
</tr>
<tr>
<td>CAR 9-24</td>
<td>23.8</td>
<td>18.3</td>
<td>18.3</td>
<td>11.6</td>
<td>2.42*</td>
<td>1.70*</td>
<td>1.68**</td>
</tr>
<tr>
<td><strong>PHx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR 9-12</td>
<td>28.6</td>
<td>19.3</td>
<td>17.5</td>
<td>10.6</td>
<td>3.45*</td>
<td>2.04*</td>
<td>1.82*</td>
</tr>
<tr>
<td>CAR 9-24</td>
<td>19.0</td>
<td>12.6</td>
<td>12.3</td>
<td>7.8</td>
<td>2.78*</td>
<td>1.70**</td>
<td>1.68**</td>
</tr>
</tbody>
</table>

V = varenicline, B = bupropion, N = nicotine replacement therapy, P = placebo

* p-value < 0.001, using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction.

** p-value < 0.05, using the same model above.

† FAS population excluding those subjects who used concomitant medications and/or had failed lifetime serious quit attempts on the study medications.

Source: Statistical reviewer Yi Ren

The results indicated that varenicline, bupropion, and NRT were all superior to placebo with respect to smoking cessation, p-value < 0.05.

Even though the observed rates of CAR 9-12 and CAR 9-24 were lower in the PHx cohort than in the non-PHx cohort, there was no statistically significant interaction between treatment and cohort. The observed rates and estimated odds ratios for CAR 9-24 were lower than those reported for CAR 9-12.
As mentioned in Section 4.6.2, Pfizer conducted investigator site audits at 26 sites and showed concerns with two US sites (1002 and 1077) in terms of reliability and overall data quality. To examine the impact of this finding, a sensitivity analysis was performed excluding the data from these two sites using the mFAS population. The treatment effect was not dependent on the presence of data from these two sites.

Excluding sites which reported financial involvement with Pfizer also did not change the conclusions.

The treatment effect for varenicline, bupropion, and NRT was also examined for differences due to age (18-44 years, 45-64 years, and > 64 years), sex (male and female), race (White, Black, and Other), and region (US and non-US) based on the FAS population. The treatment effects on CAR 9-12 were consistent across these subgroups.
3.9 Analysis of General Safety Data

Exposure by duration is shown in Pfizer’s tables below.

Table 22 Exposure to Treatment, Non-PHx - Safety Population

<table>
<thead>
<tr>
<th>Exposure in Days*</th>
<th>Varenicline N = 990</th>
<th>Bupropion N = 989</th>
<th>NRT N = 1006</th>
<th>Placebo N = 999</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 7</td>
<td>17 (1.7)</td>
<td>18 (1.8)</td>
<td>15 (1.5)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>8 - 14</td>
<td>16 (1.6)</td>
<td>25 (2.5)</td>
<td>32 (3.2)</td>
<td>28 (2.8)</td>
</tr>
<tr>
<td>15 - 21</td>
<td>22 (2.2)</td>
<td>30 (3.0)</td>
<td>25 (2.5)</td>
<td>21 (2.1)</td>
</tr>
<tr>
<td>22 - 28</td>
<td>25 (2.5)</td>
<td>22 (2.2)</td>
<td>27 (2.7)</td>
<td>27 (2.7)</td>
</tr>
<tr>
<td>29 - 35</td>
<td>17 (1.7)</td>
<td>20 (2.0)</td>
<td>14 (1.4)</td>
<td>16 (1.6)</td>
</tr>
<tr>
<td>36 - 42</td>
<td>19 (1.9)</td>
<td>16 (1.6)</td>
<td>12 (1.2)</td>
<td>13 (1.3)</td>
</tr>
<tr>
<td>43 - 49</td>
<td>14 (1.4)</td>
<td>13 (1.3)</td>
<td>16 (1.6)</td>
<td>20 (2.0)</td>
</tr>
<tr>
<td>50 - 56</td>
<td>15 (1.5)</td>
<td>12 (1.2)</td>
<td>13 (1.3)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>57 - 63</td>
<td>15 (1.5)</td>
<td>17 (1.7)</td>
<td>30 (3.0)</td>
<td>19 (1.9)</td>
</tr>
<tr>
<td>64 - 70</td>
<td>11 (1.1)</td>
<td>17 (1.7)</td>
<td>18 (1.8)</td>
<td>14 (1.4)</td>
</tr>
<tr>
<td>71 - 77</td>
<td>28 (2.8)</td>
<td>31 (3.1)</td>
<td>34 (3.4)</td>
<td>24 (2.4)</td>
</tr>
<tr>
<td>78+</td>
<td>791 (79.9)</td>
<td>768 (77.7)</td>
<td>770 (76.5)</td>
<td>799 (80.0)</td>
</tr>
</tbody>
</table>

**Statistics (Days)**

<table>
<thead>
<tr>
<th></th>
<th>Varenicline N = 990</th>
<th>Bupropion N = 989</th>
<th>NRT N = 1006</th>
<th>Placebo N = 999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>75.92</td>
<td>74.61</td>
<td>74.53</td>
<td>76.13</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>83 - 86</td>
<td>81 - 86</td>
<td>80 - 86</td>
<td>82 - 86</td>
</tr>
<tr>
<td>Median</td>
<td>85</td>
<td>85</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>21.59</td>
<td>22.87</td>
<td>22.82</td>
<td>21.44</td>
</tr>
<tr>
<td>Range</td>
<td>2 - 103</td>
<td>1 - 96</td>
<td>1 - 100</td>
<td>1 - 110</td>
</tr>
</tbody>
</table>

Abbreviations: N = number of subjects randomized to study treatment who received at least 1 partial dose of study medication; NRT = nicotine replacement therapy.

*Note: May not sum to total due to rounding.

Q1 and Q3 are the first quartile and third quartile statistics, respectively.

Lost-to-follow-up subjects were imputed as having used all study drug dispensed at last contact visit in a per protocol manner.

Source: Pfizer’s Section 14, Table 14.4.1.2.
3.10 Deaths

There were ten deaths in the study; one occurred possibly prior to initiation of study treatment and two were recorded post-study (~6 months after last dose of study treatment).

In one case, it is not known whether or not the patient had taken study drug, and it is reported as occurring prior to initiation of study drug. This case illustrates the review team’s concerns about lack of rigor regarding the Sponsor’s data collection, reporting, and coding. The narrative indicates that the 57-year-old black female subject with current major depressive disorder and no recorded history of drug use was randomized to NRT on . She experienced an event of “septic shock” two days later, and ultimately died 10 days afterwards. The narrative provides the information that “A heroin overdose was suspected as the emergency medical technicians (EMTs) found her in the front yard of a suspected drug house. Multisystem organ failure ensued with ultimate full septic shock. The subject received treatment for the event with norepinephrine bitartrate and bicarbonate infusion.” There is no information explaining why this event was coded as “septic” shock or “sepsis”, and it does not appear that the patient was treated for an infectious process.

Another example of incomplete documentation by the sponsor is a patient who was in the placebo arm who completed study treatment and several months of follow-up, and on Study Day 258 was killed in a car accident. The narrative provides the following information: “On the subject was in a "head on car collision" that resulted in death at the scene of the
accident. The subject died on __________. An autopsy was performed and determined the cause of death was multiple blunt force trauma to the chest and abdomen and hemorrhage. The toxicology evaluation was negative for drugs or other substances. No relevant tests were reported. The action taken in response to the event for study drug was “post-therapy”. Outcome of the SAE "head on car collision" was fatal. The investigator considered there was not a reasonable possibility that the event "head on car collision" was related to the study drug, concomitant medications or a study procedure.” Notably, no information is provided about the circumstances of the accident, even whether or not the patient was the driver of the vehicle. Because this is an event happening well after treatment ended, it is reasonable to dismiss this case as unlikely to be related to study drug or to quitting smoking, but the failure of the investigator, the study monitor, or the individuals preparing the report to determine how this event occurred is an illustration of the lack of rigor that was taken to documentation of safety data in general.

Finally, another death narrative provides only this information: “On __________, the subject experienced a fatal event of cardiovascular disorder which was considered severe in intensity and serious (due to death) by the investigator. No action was taken with the study drug due to the event. The subject received no treatment for the event. The outcome of the event was death on the same day __________. At the time of the event, average daily cigarette use was 12 __________. The investigator considered the cardiovascular disorder to be not related to the study drug but due to other illness related to background of cardiovascular risk.”
Table 24 Fatal Adverse Events

<table>
<thead>
<tr>
<th>Cohort/Subject ID</th>
<th>Treatment Group</th>
<th>Sex/Age at Death/Race</th>
<th>Day of Last Dose</th>
<th>Day of Death</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10011089</td>
<td>Placebo</td>
<td>M/32/White</td>
<td>85</td>
<td>258</td>
<td>Road Traffic Accident</td>
</tr>
<tr>
<td>10341029</td>
<td>Bupropion</td>
<td>M/32/White</td>
<td>19</td>
<td>19</td>
<td>Heroin Overdose</td>
</tr>
<tr>
<td>11771014</td>
<td>NRT</td>
<td>M/62/White</td>
<td>77</td>
<td>208</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td>11321005</td>
<td>Placebo</td>
<td>M/64/Asian</td>
<td>86</td>
<td>128</td>
<td>Myocardial Infarction Suicide</td>
</tr>
<tr>
<td>11441029</td>
<td>Placebo</td>
<td>F/30/White</td>
<td>29</td>
<td>32</td>
<td>Suicide</td>
</tr>
<tr>
<td>11121093</td>
<td>Placebo</td>
<td>F/42/Black</td>
<td>60</td>
<td>60</td>
<td>Pulmonary Embolism</td>
</tr>
<tr>
<td>11081201</td>
<td>Bupropion</td>
<td>M/52/White</td>
<td>77</td>
<td>77</td>
<td>“Cardiovascular Disorder” (No additional information provided)</td>
</tr>
<tr>
<td>10881021</td>
<td>NRT</td>
<td>M/62/White</td>
<td>64</td>
<td>238</td>
<td>Esophageal cancer</td>
</tr>
<tr>
<td>10591239</td>
<td>NRT</td>
<td>F/57/Black</td>
<td>N/A</td>
<td>N/A</td>
<td>Possible overdose (coded as sepsis but no information supporting this diagnosis)</td>
</tr>
</tbody>
</table>

Randomized but not treated:

Table 25 Treatment-Emergent SAE incidence by treatment and history of psychiatric disease

<table>
<thead>
<tr>
<th></th>
<th>Varenicline (n/N; %)</th>
<th>Bupropion (n/N; %)</th>
<th>NRT (n/N; %)</th>
<th>Placebo (n/N; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PHx</td>
<td>16/990</td>
<td>19/989</td>
<td>21/1006</td>
<td>16/999</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>PHx</td>
<td>23/1026</td>
<td>29/1017</td>
<td>24/1016</td>
<td>25/1015</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

3.11 Serious Adverse Events

There were 72 patients with treatment-emergent SAEs in the non-PHx cohort and 101 in the PHx cohort.
All 173 patients were reviewed with an eye towards identifying NPS cases of interest. A number of serious adverse events in other domains (e.g., cardiovascular) were also reported but this review focuses on the NPS events. After reviewing the SAE narratives for potential NPS cases, the review team identified 30 cases for which a relationship to study drug could not be ruled out. Notably, one of these cases was not included in the NPS endpoint because the investigator rated the event of depression as “mild” although it resulted in hospitalization. Cases of both treatment-emergent and discontinuation-emergent symptoms were noted. NPS events in bupropion-treated patients in the PHx cohort included cases that appear to be precipitation of mania in patients with bipolar disorder, a known and labeled risk of bupropion and other antidepressants.
The following table includes a description of 30 NPS SAEs

### Table 26  Description of 30 NPS SAEs

<table>
<thead>
<tr>
<th>Patient #, demographics, primary diagnosis</th>
<th>Description of event</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHx Cohort</td>
<td></td>
</tr>
<tr>
<td>Varenicline</td>
<td></td>
</tr>
<tr>
<td>10091085 WM 34 bipolar disorder</td>
<td>Treatment Day 58, subject reported increased anxiety, auditory hallucinations, and &quot;checked himself into&quot; a psychiatric hospital. Study drug discontinued. Investigator believed complaints were factitious. Subject also reported command hallucinations and suicide attempt by jumping in front of a bus.</td>
</tr>
<tr>
<td>10341001 WM 19 major depressive disorder</td>
<td>Subject completed 87 days of study drug treatment. Approximately two weeks after discontinuing study drug, subject &quot;did not sleep for three nights&quot; and experienced symptoms described as &quot;panicky, nervous, anxious,&quot; and cut his wrists &quot;as an act of self-mutilation and not as a suicide attempt.&quot; He was psychiatrically hospitalized for three days. He was smoking 3 cigarettes/day (Baseline [BL]: 15) at the time of the events.</td>
</tr>
<tr>
<td>10341034 WM 33 schizoaffective/bipolar</td>
<td>After four weeks of study drug, subject presented to an emergency room after a fight with his parents, seeking admission, stating he was depressed; he reported suicidal thoughts but it was believed this claim was factitious. However, he reported that while on study drug &quot;his depression had gotten worse.&quot; Study medications were discontinued; patient did not return for further visits.</td>
</tr>
<tr>
<td>10401030 WM 47 bipolar disorder, PTSD, panic</td>
<td>Subject took study medication for ~16 days. A few days after discontinuing medication, he relapsed to alcohol use reportedly &quot;due to the death of his father&quot; and was lost to follow-up to the study site. Approximately two weeks after resuming drinking he was found unconscious and hospitalized for alcohol poisoning and management of withdrawal.</td>
</tr>
<tr>
<td>10571099 WM 36 bipolar disorder</td>
<td>After 20 days of study drug, subject &quot;was upset and had brief thought of death (&quot;I had a suicide thought about taking my sleeping medication&quot;), called a crisis line, and went into an outpatient stabilization unit.&quot; He had missed two doses of his mood stabilizer (valproate) and antidepressant (citalopram). Smoking decreased from 20 to 5 cigarettes/day at time of event. Study medication was continued. Event resolved.</td>
</tr>
<tr>
<td>Subject ID</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------</td>
</tr>
<tr>
<td>12471067</td>
<td>bipolar disorder</td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
</tr>
<tr>
<td>10451027</td>
<td>bipolar disorder, panic</td>
</tr>
<tr>
<td>10571028</td>
<td>bipolar disorder</td>
</tr>
<tr>
<td>10881338</td>
<td>major depressive disorder</td>
</tr>
<tr>
<td>Subject ID</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>10941125 WF 59</td>
<td>bipolar disorder</td>
</tr>
<tr>
<td>11871003 WF 25</td>
<td>bipolar disorder</td>
</tr>
<tr>
<td>12341066 WM 37</td>
<td>schizophrenia</td>
</tr>
<tr>
<td>NRT</td>
<td></td>
</tr>
<tr>
<td>10741015 WM 28</td>
<td>schizophrenia</td>
</tr>
<tr>
<td>10741026 WM 53</td>
<td>major depressive disorder</td>
</tr>
<tr>
<td>11261120 WF 38</td>
<td>major depressive disorder</td>
</tr>
<tr>
<td>Disorder</td>
<td>Detailed Description</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>Depression worsened (subject had omitted antidepressant for ~4 days) and subject required hospitalization for depression. Smoking was unchanged from baseline.</td>
</tr>
<tr>
<td>Placebo</td>
<td>On Treatment Day 6, subject reported feeling &quot;irritable over small things,&quot; 18 days later she reported feeling depressed and having suicidal thoughts. She reportedly was admitted to a psychiatric hospital and was hospitalized for a month. Study drug was discontinued. Smoking at time of hospitalization is not known.</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>Subject failed to return after the Week 4 visit; however, the site learned through subject's girlfriend (also a subject in the study) that he had hit her in the head with a gun and fractured her skull. She noted that he had been violent before. He had been drinking at the time of the event.</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>On Study Day 42, the subject began treatment with disulfiram &quot;to control alcohol intake.&quot; (Alcohol abuse is noted as a &quot;past&quot; diagnosis; the implication is that the subject relapsed to serious alcohol use requiring treatment.) The subject discontinued using study drug at that time. A psychiatric evaluation was done &quot;due to an increase of depressive and anxious symptoms&quot; but no adverse event was reported. Approximately a month later, the subject took an impulsive overdose of clorazepate stating &quot;I felt nervous and distressed...I felt very sad and anxious and decided to take some pills and not wake up.&quot; There were minimal sequelae of the overdose. Smoking was reduced from BL 25 to 12 cigarettes/day.</td>
</tr>
<tr>
<td>Major depressive disorder, borderline PD</td>
<td>After 9 days of study drug treatment, subject attempted suicide by ingesting 56 aripiprazole and 30 diazepam tablets along with her week's supply of blinded study medications together with alcohol. The subject was hospitalized very briefly. Study medications were discontinued. Her cigarette use was reduced from BL 24 cigarettes/day at baseline to 20 cigarettes/day. Approximately 10 days later, the subject was rehospitalized for &quot;recurrent symptoms of borderline personality disorder,&quot; and a few days later had again been &quot;monitored in the hospital psychiatric department.&quot; Smoking was increased to 30 cigarettes/day.</td>
</tr>
<tr>
<td>Major depression</td>
<td>Within two days of initiating study drug treatment, subject reported feeling more depressed since starting the study medication, and experiencing increasing anxiety after a couple of days of study drug treatment, and endorsed feeling that &quot;it would be easier to be dead&quot; on C-SSRS. He also reported insomnia. Study drug was discontinued. ~1 week later, the subject</td>
</tr>
</tbody>
</table>
was hospitalized for a medical illness (shortness of breath diagnosed as pulmonary embolus and cardiac failure); while hospitalized, he left the hospital, went home, and took 20 tablets of paracetamol 500 mg/codeine 30 mg. He returned to the hospital and reported the overdose but denied intent to kill himself. The patient required treatment with n-acetylcysteine for elevated acetaminophen level. The investigator did not consider this serious and did not consider it a suicide attempt.

### Non-PHx

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Gender</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>10101013 WM 53</td>
<td>M</td>
<td>53</td>
</tr>
<tr>
<td>10251031 WF 74</td>
<td>F</td>
<td>74</td>
</tr>
<tr>
<td>10341029 WM 32</td>
<td>M</td>
<td>32</td>
</tr>
<tr>
<td>11311005 BM 40</td>
<td>M</td>
<td>40</td>
</tr>
<tr>
<td>11101153 WM 23</td>
<td>M</td>
<td>23</td>
</tr>
</tbody>
</table>

#### Bupropion

- **Treatment Day 13**, subject was hospitalized for ~2 days for evaluation after mentioning that he "felt like blowing his brains out." This was later dismissed by the subject as a "misunderstanding." He was started on an antidepressant and declined further participation in the study.

- **After ~1 month on study drug**, subject first noticed "intermittent left hemiparesthesia and subjective confusion." Symptoms resolved and then recurred, with four instances in a month of "a foggy feeling in my head" and "stabbing cold pains." Symptoms became persistent after ~2 months on study drug; she was admitted to the hospital to be evaluated for stroke. Workup negative; study drug discontinued.

- **On Treatment Day 19**, subject was found dead (reported by his sister). Toxicology report showed opiates. Patient had history of occasional use of heroin.

- **After 24 days of study drug treatment**, "the subject experienced depression which was considered mild in intensity and serious due to hospitalization or prolonged hospitalization by the investigator." Study drug was discontinued, patient was treated with psychotropic medication. Patient had reduced smoking from 28 to cigarettes/day 5 at the time of event. No other information is provided.

- **Subject was randomized into non-PHx cohort**; after events occurred MHP in retrospect felt subject had "underlying mood disorder (probably bipolar) and PTSD." After five days of study drug, patient reported that he had experienced three days of worsening symptoms, including sweating and pacing, "I felt like I took drugs." "Mild anxiety" and "moderate hostility" were also recorded with no detail. Study drug was decreased and then discontinued. He had reduced

---

$q$ In the Non-PHx, there were no neuropsychiatric SAEs reported in the varenicline treatment arm without obvious alternative explanations.
smoking from BL 15 to 9-10 cigarettes/day. About a month after discontinuing study drug, the subject revealed that he had been hitting himself in the head with his fists and had repeatedly placed a loaded gun into his mouth with intent to commit suicide. He had been taken to see a psychiatrist outside the study and was taking quetiapine. He completed the study off treatment.

### NRT

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Gender</th>
<th>Age</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10161040</td>
<td>WF</td>
<td>47</td>
<td>After three weeks of treatment with NRT, in the context of drinking alcohol, subject &quot;decided on the spur of the moment to pack and leave her apartment. In the process of packing, she saw a knife and impulsively started to cut herself. She said her husband saw her cutting, stopped her, and took her to the ER. She shared that she did feel that the combination of the alcohol and the drug trial she was on may have caused her to be more emotional than usual during the time when she cut herself.&quot; Study drug was discontinued; subject had a second episode of suicidal ideation with plan a month later. Smoking was decreased from BL 20 to 6-9 cigarettes/day at the time of the events.</td>
</tr>
</tbody>
</table>

### Placebo

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Gender</th>
<th>Age</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10981060</td>
<td>WM</td>
<td>34</td>
<td>(Subject was randomized to placebo but event occurred during initial week of placebo pill dosing before patch began) After a week of study drug (placebo pills) treatment, patient &quot;reported a panic attack that led to binge drinking&quot;, and that he was hospitalized for five days for treatment. Smoking had not changed.</td>
</tr>
<tr>
<td>11441029</td>
<td>WF</td>
<td>30</td>
<td>Subject began taking study drug and stopped smoking between the Week 1 and Week 2 visits. She had no complaints other than insomnia reported during the first week of treatment. She did not appear for the Week 5 visit, and the site subsequently learned she had committed suicide by jumping from a high monument three days after her Week 4 visit, leaving a note saying &quot;everything was too much.&quot; The subject had no prior psychiatric history and no lifetime suicidal attempts or ideation.</td>
</tr>
<tr>
<td>10981113</td>
<td>WM</td>
<td>47</td>
<td>After ~2 months of study medication and ~2 weeks after last dose, the subject was hospitalized for orthostatic hypotension and numbness in his hand. He required treatment with dopamine and adjustment of his antihypertensives, and was hospitalized for four days. After discharge from the hospital, he reported &quot;physical problems overwhelming, hanging up on me,&quot; and endorsed suicidal ideation about twice a week without plan. About 10 days later he endorsed suicidal thoughts of overdosing; he required crisis assessment at a local psychiatric facility. He had reduced smoking but not quit.</td>
</tr>
</tbody>
</table>
Subject completed 85 days of study drug. At the Week 13 (post-treatment visit) the site documented "since stopping the meds, subject reports depression," and that symptoms of a prior eating disorder had re-emerged "appetite down, fasting, binging, and purging," and that two days after completing the course of treatment, he experienced vague suicidal ideation with no intent or plan; on C-SSRS he endorsed "easier to be dead." No change in smoking level. He was referred to a psychiatrist but the nature of treatment is not documented; narrative states that the event resolved.

3.12 Adverse Events Leading to Dose Reduction or Discontinuation

Overall, adverse events leading to temporary or permanent discontinuation of study drug or to dose reduction were reported in 115 subjects. In the non-PHx group, all active treatment arms had a higher rate of dose reductions or discontinuations than the placebo arm; in the PHx cohort, rates were similar.

<table>
<thead>
<tr>
<th>Table 27 Patients with Treatment-Emergent Adverse Events Leading to Dose Reductions or Discontinuations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
</tr>
<tr>
<td>Non-PHx Cohort</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>PHx Cohort</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Only discontinuation was possible
Prepared by clinical reviewer from Sponsor’s dataset

The tables below, grouped by MedDRA Higher Level Group Term (HLGT), show types of events leading to reduction or discontinuation in at least 1% of subjects in any of the treatment arms.
Table 28 Adverse Events Leading to Study Drug Reduction or Discontinuation in ≥1% in Any Arm; Non-Phx Cohort

<table>
<thead>
<tr>
<th>SOC</th>
<th>HLGT</th>
<th>Varenicline N = 990</th>
<th>Bupropion N = 989</th>
<th>NRT N = 1006</th>
<th>Placebo N = 999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Inner ear and VIIIth cranial nerve disorders</td>
<td>1 0%</td>
<td>5 1%</td>
<td>1 0%</td>
<td>0 0%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>GI motility &amp; defaecation conditions</td>
<td>8 1%</td>
<td>1 0%</td>
<td>6 1%</td>
<td>3 0%</td>
</tr>
<tr>
<td></td>
<td>GI signs and symptoms</td>
<td>49 5%</td>
<td>16 2%</td>
<td>20 2%</td>
<td>13 1%</td>
</tr>
<tr>
<td>General disorders and</td>
<td>Administration site reactions</td>
<td>2 0%</td>
<td>6 1%</td>
<td>32 3%</td>
<td>3 0%</td>
</tr>
<tr>
<td>administration site conditions</td>
<td>General system disorders NEC</td>
<td>10 1%</td>
<td>14 1%</td>
<td>10 1%</td>
<td>5 1%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infections - pathogen unspec</td>
<td>7 1%</td>
<td>14 1%</td>
<td>6 1%</td>
<td>5 1%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headaches</td>
<td>12 1%</td>
<td>5 1%</td>
<td>15 1%</td>
<td>3 0%</td>
</tr>
<tr>
<td></td>
<td>Neurological disorders NEC</td>
<td>10 1%</td>
<td>13 1%</td>
<td>10 1%</td>
<td>7 1%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Anxiety disorders &amp; symptoms</td>
<td>10 1%</td>
<td>19 2%</td>
<td>12 1%</td>
<td>7 1%</td>
</tr>
<tr>
<td></td>
<td>Depressed mood disorders and disturbances</td>
<td>9 1%</td>
<td>4 0%</td>
<td>4 0%</td>
<td>6 1%</td>
</tr>
<tr>
<td></td>
<td>Mood disorders and disturbances NEC</td>
<td>7 1%</td>
<td>3 0%</td>
<td>3 0%</td>
<td>3 0%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Sleep disorders and disturbances</td>
<td>17 2%</td>
<td>26 3%</td>
<td>33 3%</td>
<td>14 1%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Angioedema and urticaria</td>
<td>0 0%</td>
<td>6 1%</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Epidermal and dermal conditions</td>
<td>6 1%</td>
<td>15 2%</td>
<td>15 1%</td>
<td>3 0%</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 29 Adverse Events Leading to Study Drug Reduction or Discontinuation in ≥1% in Any Arm; PHx Cohort

<table>
<thead>
<tr>
<th>SOC</th>
<th>HLGT</th>
<th>Varenicline N = 1026</th>
<th>Bupropion N = 1017</th>
<th>NRT N = 1016</th>
<th>Placebo N = 1015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac arrhythmias</td>
<td>3 0%</td>
<td>2 0%</td>
<td>0 0%</td>
<td>6 1%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>GI motility &amp; defaecation conditions</td>
<td>10 1%</td>
<td>0 0%</td>
<td>4 0%</td>
<td>6 1%</td>
</tr>
<tr>
<td></td>
<td>GI signs and symptoms</td>
<td>62 6%</td>
<td>19 2%</td>
<td>20 2%</td>
<td>13 1%</td>
</tr>
<tr>
<td>General disorders and</td>
<td>Administration site reactions</td>
<td>0 0%</td>
<td>4 0%</td>
<td>19 2%</td>
<td>2 0%</td>
</tr>
<tr>
<td>administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Within the non-psychiatric history cohort, the three most frequent treatment-emergent adverse events in each of the four treatment groups were:

- **Varenicline**: nausea (243 [24.5%]), headache (116 [11.7%]), and insomnia (95 [9.6%]);
- **Bupropion**: insomnia (126 [12.7%]), nausea (90 [9.1%]), and headache (87 [8.8%]);
- **NRT**: headache (129 [12.8%]), abnormal dreams (111 [11.0%]), and nausea (95 [9.4%]); and
- **Placebo**: headache (95 [9.5%]), insomnia (73 [7.3%]), and nasopharyngitis (73 [7.3%]).

Within the psychiatric history cohort, the most frequent treatment-emergent adverse events in the four treatment groups were:

- **Varenicline**: nausea (268 [26.1%]), headache (129 [12.6%]), and abnormal dreams (118 [11.5%]);
- **Bupropion**: insomnia (119 [11.7%]), nausea (111 [10.9%]), and anxiety (105 [10.3%]);
- **NRT**: abnormal dreams (140 [13.8%]), headache (104 [10.2%]), insomnia (104 [10.2%]), and nausea (104 [10.2%]); and
- **Placebo**: headache (104 [10.2%]), nausea (74 [7.3%]), and irritability (67 [6.6%]).

A table showing the occurrence of common adverse events by HLGT is found in the Appendix B.
4 Observational Studies

4.1 Review methods and materials

Division of Epidemiology II (DEPI II) conducted a search of the National Library of Medicine’s PubMed database on June 17, 2016. Studies were selected for review if they reported the relative risk of neuropsychiatric events between any of the three FDA approved prescription smoking cessation products—varenicline, bupropion, and nicotine replacement therapy (NRT), used an adequate design to differentiate temporal relationship between drug exposure and outcomes, and attempted to account for baseline group differences because of the observational design. DEPI II’s literature search identified a total of six observational studies for in-depth review. Please see the DEPI-II review of the labeling supplement regarding neuropsychiatric adverse events associated with varenicline for details on the literature search strategy and findings (Attachment 1, Section 2, Section 3, Appendix I).

4.2 Review results

The six reviewed studies—Meyer et al. 2013, Cunningham et al. 2016, Pasternak et al. 2013, Thomas et al. 2013, Kotz et al. 2015, and Molero et al. 2015— included five that assessed the risk of neuropsychiatric medical encounters associated with smoking cessation products (Meyer et al. 2013, Cunningham et al. 2016, Pasternak et al. 2013, Kotz et al. 2015, and Molero et al. 2015), and three that evaluated the association between smoking cessation products and risk of suicide or non-fatal self-harm (Thomas et al. 2013, Kotz et al. 2015, and Molero et al. 2015). Two of these six articles describe studies from collaborative research projects between the FDA and other federal agencies through Inter-Agency Agreements: the Meyer et al. publication described the study by the U.S. Army Office of the Surgeon General (OTSG) U.S. ARMY MEDICAL COMMAND (U.S. Army Medical Command MEDCOM)’s Pharmacovigilance Center (PVC) (referred to hereafter as the “DoD study”) and the Cunningham et al. publication described the study by the Department of Veterans Affairs (VA) Center for Medication Safety (VAMedSAFE) (referred to hereafter as the “VA study”).

All reviewed studies were retrospective, population-based studies. DEPI II consulted the Division of Biometrics VII (DB VII) to evaluate the advanced statistical methods used in two

---

7 Two members of the DEPI review team are listed as authors on the Meyer et al. study. Dr. Meyer was the primary investigator, and David Moeny was a co-author.
publications (Kotz et al. and Molero et al.). Please see the DEPI-II review for a summary of each reviewed study (Attachment 1) and the DB VII review (Attachment 2).

The findings of the six reviewed epidemiological studies showed inconsistent results (Figure 10 and Figure 11). Four of the studies (DoD study/ Meyer et al. 2013, VA study/Cunningham et al. 2016, Pasternak et al. 2013, Thomas et al. 2013) did not observe a statistically significant difference in the risk of neuropsychiatric adverse events between varenicline versus NRT, varenicline versus bupropion, or bupropion versus NRT; the point estimates did not suggest a consistent trend of association. One study (Kotz et al. 2015) found a significant reduction in neuropsychiatric risk among varenicline users (34% reduction in risk of outpatient depression visit and 44% reduction in the risk of outpatient visit for suicide or non-fatal self-harm) and a 25% reduction in risk of depression visit in bupropion users, comparing to NRT users. Yet, another study (Molero et al. 2015) observed that while varenicline use was not associated with significant risk of suicide-related behaviors, the risk of neuropsychiatric in- or out-patient visits significantly increased by 18% during varenicline-exposed time compared to unexposed time in varenicline users.

4.3 Assessment of the observational studies

Each of the reviewed studies had key study design limitations. We will address the specific limitations of the existing observational studies in section 4.3.1 to 4.3.3.

4.3.1 Concerns on validity of outcome measures

The outcomes examined in these studies—suicide, self-harm, and neuropsychiatric medical encounters—did not cover the full range of the neuropsychiatric adverse events that have been described in postmarketing spontaneous adverse event reports associated with smoking cessation products. Furthermore, all studies mainly relied on diagnostic codes recorded during medical encounters (ICD-9, ICD-10, or Read codes) to ascertain outcomes, but only one study (by Pasternak et al.) reported some measure of validity for some of the ICD-10 codes used to identify their outcomes. We are concerned that diagnostic codes cannot accurately capture and characterize all of the neuropsychiatric adverse events that have been associated with varenicline. The events described in the adverse event reports have involved abrupt behavioral and/or mood changes, which are difficult to accurately translate into a medical coding system. Adverse events may have also resulted in patient contact with legal, rather than medical,

---

Y We note that the study described in the Cunningham et al. publication included additional findings to the VA study final report submitted in response to the Interagency Agreement, because the final report was based on the findings of the analyses for their first objective, which examined the risk of inpatient neuropsychiatric events associated with varenicline. The Cunningham publication included additional findings on the second objective, which broadened the scope to examine the risk of outpatient neuropsychiatric events associated with varenicline. The published Cunningham study also made changes in the analytical plan from the submitted VA study protocol, including some additional post-hoc analyses. We summarized the VA study methods and findings based mostly on the pre-specified analytical plan described within the protocol and final report that were submitted to the FDA.

Z For example some adverse events that have been reported among patients who used varenicline include: changes in mood, agitation, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, changes in behavior, anxiety, panic, suicidal ideation, suicide attempt and completed suicide.

^Pasternak et al. had reported high positive predictive value (>90%) for the ICD-10 codes used to identify a schizophrenia-spectrum disorder and a single depressive episode. However, the two conditions are only some of several psychiatric adverse events that the study targeted.
systems. Without a detailed exploration of medical charts to identify all codes that might have been used to capture these outcomes, as well as patient and provider interviews to determine behavior and coding practices, it is not possible to estimate how many events are misclassified or not captured in these studies. Such problems are inherent to the study of behavioral and psychiatric outcomes, which present different challenges than studying other medical diagnoses.

In the studies that examined the association between smoking cessation products and neuropsychiatric hospitalizations or emergency room visits (Meyer et al. VA study and Pasternak et al.), clinically important psychiatric events that did not include hospitalization (such as a completed suicide without hospitalization) were not captured. Although both the Meyer and the VA studies also examined a secondary outcome that included outpatient visits with a neuropsychiatric diagnosis, this metric may be simply capturing pre-existing psychiatric comorbidities, rather than treatment emergent psychiatric events. Moreover, an acute worsening of a psychiatric condition without a health care professional encounter would be missed. In light of the stigma that can be attached to psychiatric diagnoses in medical records, particularly in the military, this possibility cannot be ruled out.

Undercounting of the outcome is also a concern with respect to the Thomas study that examined suicide-related outcomes due to the stigma that can be attached to such diagnoses, the difficulty in determining intentionality of injury, and the fact that such attempts are not always brought to medical attention. Although Thomas et al. used both the hospital admission data and the UK mortality records to capture suicide-related outcomes (fatal/non-fatal self-harm), this approach only enhanced the capture of a part of the outcome—fatal self-harm, but not the other part that still relied on diagnostic codes used in hospital records (i.e., attempted suicide). In fact, a high proportion (approximately 90%) of the observed suicide-related outcome in the Thomas et al. study were non-fatal self-harm. The author reported that a total of 92 cases of suicide and non-fatal self-harm were identified from the study population, with suicides accounting for six of those events in the NRT group, two in the varenicline group, and none in the bupropion group.

The Read codes used by the Kotz study have been shown to be unreliable for detecting suicide death and under-report non-fatal self-harm. The authors did not address the validity of Read codes to identify depression. In addition, the study was based on the general practitioner (GP) encounter data; suicide death, as well as severe cases of depression or suicide attempt that led to emergency room visits, hospitalizations, or required treatment by a psychiatrist were likely missed in the study. If varenicline or bupropion causes more severe neuropsychiatric adverse events than NRT, this under-ascertainment of outcome would be more pronounced in the varenicline or bupropion group than NRT groups. Furthermore, the study did not differentiate depression visits for new or existing conditions. The fact that varenicline and bupropion use significantly decreased the number of depression visits could be evidence of an adverse effect if planned follow-up visits for a pre-existing condition were missed (i.e., could be evidence of worsening depression).

Although Molero et al. used both hospital and outpatient data to identify neuropsychiatric events, and excluded diagnoses during planned visits such as follow-up or referral, only some of the inpatient diagnosis codes (for schizophrenia and personality disorder) used by Molero et al. were previously validated. The validity of the majority of the diagnostic codes, especially those occurring in the outpatient setting, is still unclear. Under-ascertainment of suicide attempt is still likely for the reasons that have been addressed previously, even though the study used hospital and mortality records to identify suicide-related outcomes.
4.3.2 Channeling bias and residual confounding

Another major concern of the existing observational data is residual confounding and channeling bias, especially, among the three studies by Thomas et al., Kotz et al., and Molero et al. that included data from the timeframe after the publicity of the neuropsychiatric safety concern associated with varenicline and bupropion. Adverse publicity may have resulted in patients with a history of neuropsychiatric illness being preferentially prescribed NRT, and healthier patients or patients at lower risk of neuropsychiatric events being preferentially prescribed the other two drugs (i.e., channeling bias). In fact, varenicline users and bupropion users in the Thomas study and the Kotz study were less likely to have a history of chronic disease or psychiatric illness or had a lower frequency of previous use of hypnotics, antipsychotics, and antidepressants; these patients were shown to be less likely to be at risk for neuropsychiatric event compared to NRT users. The study by Pasternak et al. also included data after the publicity of varenicline and bupropion’s neuropsychiatric risk. Because the publicity on varenicline’s neuropsychiatric safety concern was more widespread than that of bupropion, channeling bias could have existed in the Pasternak study and led to a healthier varenicline group with lower baseline neuropsychiatric risk than the bupropion group. However, the distribution of baseline psychiatric history and psychotropic drug use was generally similar between the two groups in the study. The preferential prescribing of bupropion over varenicline among patients with higher neuropsychiatric risk, if existed, may not have biased the findings of the Pasternak study significantly.

Three studies (Thomas et al., Kotz et al., Molero et al.) implemented advanced designs or advanced analytical approaches to handle the potential bias due to baseline patient selection, but we cannot be sure that their analyses adequately controlled for the baseline differences in patients due to channeling. We will comment on the methods of each study in the following section.

The Thomas study

Thomas et al. conducted three analyses: a conventional Cox regression analysis, and two advanced analyses—a propensity score (PS) matched analysis and an instrumental variable (IV) analysis—in order to attempt to account for the potential bias due to baseline selection into treatment cohorts. Despite using multiple analytical approaches, their findings are still likely to be biased due to residual confounding. The issue of residual confounding was illustrated by the findings of their secondary analysis that examined all-cause mortality risk associated with the study drugs as described in the following paragraphs.

As shown in Table 30, the all-cause mortality risk at 3 months from their Cox regression and PS matching analyses were significantly lower among both varenicline users and bupropion users, compared to NRT users. Given that three months is too short of a timeframe for realizing the survival benefits of smoking cessation, the reduced risk in all-cause mortality seen in the Cox regression and PS matching analyses most likely indicates that varenicline users and bupropion users are generally healthier than NRT users. Therefore, the effect estimates of the suicide-related outcome (Table 30) from those two analyses would likely carry the impact of the residual baseline differences.

Their third analysis using an IV approach appeared to reduce the impact of residual confounding when comparing varenicline users to NRT users, because the difference in 3-month mortality risk between varenicline and NRT users became smaller (from ~1.4 to -2 per 1,000 patient-years...
based on Cox regression or PS matching analyses, to -0.8 per 1,000 patient-years in the IV analysis, Table 30). However, the IV analyses might still carry bias in estimating varenicline’s effect on suicide-related outcome. In order for IV analysis to work well, the chosen IV needs to be strongly associated with the actual treatment and be independent of any factors that have impact on the targeted outcome (i.e. suicide or self-harm). Thomas et al. choose physicians’ prescribing preference as the IV, and they used physicians’ prescribing patterns as the proxy of “prescribing preference”. We noticed that physicians’ characteristics, something that can influence prescribing preferences, are not used to estimate physician’s preference. If the prescribing preferences are related to a physician’s familiarity with current literature and the ability to make use of the information, physicians who prefer varenicline over NRT because of its higher efficacy could be more vigilant of the risk of smoking cessation itself on depression or suicide and monitor their patients more frequently. In this scenario, patients who were seen by physicians who prefer varenicline or bupropion would have lower suicide risk that is unrelated to drug effect. The implication is that the effect estimates from IV analyses can still be biased by differences in the physician characteristics, and this study may have under-estimated the true suicide risk associated with varenicline.

With regard to the bupropion findings, the IV analyses did not seem to reduce the impact of residual confounding. Although we do not expect a reduction of all-cause mortality within three months of bupropion use because it is too short of a timeframe for realizing the survival benefits of smoking cessation, the IV findings indicated that bupropion is associated with an even larger reduction in 3-month mortality than the findings from the Cox regression and PS matching analyses (~1 to -3 per 1,000 patient-years based on Cox regression or PS matching analyses, to -4.2 per 1,000 patient-years in the IV analysis, Table 30). Nevertheless, the effect estimate of all-cause mortality risk in the IV analysis was not statistically significant. The reduced risk of suicide-related outcome associated with bupropion in the IV analyses might still be biased due to the healthier bupropion users than NRT users.

*The Kotz study*

Similar to the Thomas study, the baseline characteristics of the study population indicated potential differential prescribing, i.e., varenicline and bupropion seems to be given to patients who were younger, less socioeconomically deprived and less likely to have a history of psychiatric illness. Although the author stated that those measured baseline differences were balanced in the statistical models (i.e., multivariable Cox regression and propensity score matching) used for their analyses, some important confounders were unmeasured and could still have biased the study findings. One such unmeasured confounder is prior or concurrent use of psychotropic medications, which had been reported to be imbalanced among smoking cessation product users in the aforementioned Thomas study, which was based on a similar data source (i.e., UK general practices data) as the Kotz study and likely had similar prescribing and utilization patterns. Recognizing the potential of residual confounding from unmeasured confounders, the authors conducted a sensitivity analysis and concluded that the observed reduced risk associated with varenicline use is unlikely to be reversed by unmeasured confounder(s). This is because the distribution of the unmeasured confounder would need to be extremely imbalanced among comparison groups to reverse the findings. One caveat of this sensitivity analysis is that it only models the impact of a single unmeasured confounder that is not associated with any of the measured confounders in the study; therefore, it does not address the impact of the unmeasured psychotropic medication use, which is likely to be associated with
psychiatric comorbidities. In this case, the distribution of the unmeasured psychotropic medication use might not need to be as imbalanced between the comparison groups to reverse the effect estimates.

The Molero study

Molero et al. implemented a “within-person comparison” (i.e., self-controlled design using patients as their own controls) as the principle analysis instead of the “between-person” comparison that compared users of different smoking cessation products that was used in the other reviewed studies. The self-controlled design handled the concern of the confounding due to the potential differential prescribing of smoking cessation products based on a patient’s baseline mental comorbidities because varenicline users were compared to themselves. However, the self-controlled design introduced a different type of confounding. Specifically, this design is unable to account for confounding that can change over time. As the author acknowledged, one of the potential time-varying confounders was the impact of nicotine withdrawal syndrome. Because nicotine includes psychoactive compounds that mimic an antidepressant effect, smoking cessation could induce nicotine withdrawal symptoms that include depression and anxiety. It was unclear whether the increased neuropsychiatric risk that was observed in the Molero study was due to varenicline use or to the choice of the comparison periods. The comparison periods could have included periods of smoking cessation attempts without medications, with other medications, or periods during which the patient was not trying to quit smoking.

4.3.3 Other Design or Methodological issues

The study by Pasternak et al. compared risk of neuropsychiatric emergency department visits or hospitalizations between varenicline users and bupropion users; the study found a non-significant 15% lower risk associated with varenicline use compared with bupropion use (HR: 0.85. 95% CI: 0.55- 1.30; Table 3-1, Appendix II). However, given that bupropion also has been associated with psychiatric adverse events and carries a boxed warning alerting about this possibility, this finding does not provide reassurance of varenicline’s neuropsychiatric safety.

All of the reviewed studies included patients with pre-existing psychiatric disorders with the intention to improve the generalizability over the premarking trials, because these patients were typically excluded from the clinical trials conducted with varenicline before it was approved. However, not all of the studies examined the impact of psychiatric history on smoking cessation products’ neuropsychiatric risk. Additionally, the four studies that had investigated the impact of psychiatric history all had limitations. We are unable to evaluate the impact of psychiatric history on varenicline-associated neuropsychiatric risk because the subgroup findings carried bias. For Molero et al., the bias was due to the impact of nicotine withdrawal syndrome, because of the self-controlled design (as addressed in section 4.3.2). Findings of the Meyer study and VA study both suggest that varenicline users with psychiatric history might have a higher neuropsychiatric risk than those without because the majority of the neuropsychiatric events were observed among patients with psychiatric history. In both studies, HRs of the patients with psychiatric history were also numerically higher than that of the overall cohort. However, the small cohort of patients with psychiatric history and/or the few observed outcomes in the subgroup without psychiatric history prevented a definitive conclusion about the additional impact of psychiatric history on the association between smoking cessation products and neuropsychiatric events. The
Pasternak et al. study reported a similar trend that the observed HRs of psychiatric events associated with varenicline appeared lower in participants without a history of psychiatric disorder than in participants with a history, but the point estimates were imprecise and the confidence intervals both crossed one. As addressed earlier, the choice of bupropion as the reference group to examine varenicline’s neuropsychiatric risk also made it difficult to interpret the findings.

4.3.4 Summary of the assessment of observational studies

To briefly summarize our assessment of the six reviewed observational studies:

- Studies that examined varenicline’s neuropsychiatric risk
  - The DoD/Meyer et al. study and VA/Cunningham et al. study that examined risk of neuropsychiatric hospitalizations found “no increased risk” associated with varenicline relative to NRT, but those findings were not reassuring of varenicline’s neuropsychiatric safety. The use of diagnostic codes to capture neuropsychiatric events in these studies is likely to have under-ascertained true events. Under-ascertainment of events that did not differ by cohort would result in an imprecise relative effect estimate with wide confidence intervals, as observed in the two studies. Those imprecise effect estimates did not suggest a consistent trend of association between varenicline and neuropsychiatric risk.
  - The study by Pasternak et al. compared risk of neuropsychiatric emergency department visits or hospitalizations between varenicline users and bupropion users; the study found a non-significant 15% lower risk associated with varenicline use compared with bupropion use. Given that bupropion also has been associated with psychiatric adverse events and carries a boxed warning alerting about this possibility, this finding does not provide reassurance of varenicline’s neuropsychiatric safety.
  - In the study by Thomas et al., the two analyses (Cox regression and propensity score matching analysis) that indicated a negative association for suicide/non-fatal self-harm risk for varenicline use both carried a potential bias due to differences in baseline characteristics resulting from channeling. The third analysis (IV analysis) appeared to have reduced some of the bias in the comparison between varenicline to NRT, but not in the comparison between bupropion and NRT. The IV-based analyses suggested varenicline might have a higher risk of fatal or non-fatal self-harm than NRT. Although the risk increase was numerically small, it was likely an under-estimation of true risk because of the under-ascertainment of non-fatal self-harm. However, because the effect estimate of varenicline-associated neuropsychiatric risk was imprecise and the confidence interval crossed zero, the data are inconclusive.
  - The significant reduction of neuropsychiatric risk associated with varenicline observed in the Kotz study needs to be interpreted cautiously for multiple reasons. First, the study was solely based on general practitioner (GP) data which did not capture severe neuropsychiatric events that lead to hospitalization or death. In addition, the study did not differentiate whether depression visits were for a new
or existing condition. The fact that varenicline use significantly decreased the occurrence of a depression visit could be an adverse effect if those visits were meant for following up a pre-existing condition, rather than treatment emergent events. Despite the authors’ effort to address possible influence from unmeasured confounding, their sensitivity analyses did not examine the impact of multiple unmeasured confounders or those that are associated with the captured confounders, such as previous or concurrent use of psychotropic drugs. Comparing to NRT users, the varenicline users in the study were less likely to have a history of psychiatric illness which suggested that patients who were shown to be less likely to be at risk for neuropsychiatric event were prescribed varenicline instead of NRT. The potential differential patient selection at baseline still would explain the observation of a reduced risk of neuropsychiatric risk among varenicline users. Lastly, the study excluded patients who had received overlapping prescriptions for smoking cessation drugs during the follow-up period to focus the assessment on patients receiving a single smoking cessation treatment. Because this approach also excluded patients who switched from one smoking cessation drug to another, it would likely under-estimate the risk associated with varenicline, if the reason for switching was because of neuropsychiatric adverse events.

- The self-controlled designed used by Molero et al. inadvertently introduced confounding due to the impact from nicotine withdrawal syndrome due to the comparison of time periods during a smoking cessation attempt to periods when patients are not attempting to stop smoking. It is unclear whether the increased neuropsychiatric risk that was observed in the study was due to varenicline use, the choice of comparator periods, or both. In addition, it is unclear how exposed and unexposed periods were defined and how Cox proportional hazards regression was used for the self-control study.

- Studies that examined bupropion-associated neuropsychiatric risk

  - Although all three analyses in the Thomas et al. study consistently found a negative association between bupropion use and suicide/non-fatal self-harm risk, they also suggested that bupropion use was associated with a reduced 3-month all-cause mortality risk, which is unlikely. Bupropion users in the Thomas study were less likely to have a history of chronic disease or psychiatric illness or had a lower frequency of previous use of hypnotics, antipsychotics, and antidepressants, compared to NRT users. The reduced risk therefore is also likely due to the bias from the imbalance of baseline patient characteristics, rather than due to bupropion use alone.

  - The limitations of the Kotz et al. study in assessing varenicline-associated neuropsychiatric risk are all applicable the assessment of bupropion-associated risk. The study did not capture severe neuropsychiatric events that led to hospitalization or death, because the study was based on GP data. It also could not determine whether the identified GP depression visit was for new or existing condition. Furthermore, the bupropion users in the study were less likely to have a
history of psychiatric illness. This suggests that patients who were shown to be less likely to be at risk for neuropsychiatric events were prescribed bupropion, instead of NRT, which introduced residual confounding due to the differential patient selection at baseline. The exclusion of patients who switched from one smoking cessation drug to another would likely under-estimate the risk associated with bupropion, if the reason for switching was because of neuropsychiatric adverse events.

- In all reviewed studies
  - The impact of psychiatric history on the neuropsychiatric risk associated with varenicline or bupropion use was either not examined (Thomas et al. and Kotz et al.) or could not be appropriately assessed; either due to small sample size or small number of observed events in the subgroup (Meyer et al., VA study, and Pasternak et al.); or because of inappropriate study design that could not rule out confounding by nicotine withdrawal syndrome (Molero et al.).
  - The outcomes examined did not cover the full range of the neuropsychiatric adverse events that have been associated with varenicline in the spontaneous case reports.

Each of the reviewed studies had key study design limitations. The most important limitations were: 1) use of outcome measures with suboptimal sensitivity and specificity, 2) residual confounding, 3) use of bupropion (another smoking cessation drug with neuropsychiatric risk) as reference group to examine varenicline’s neuropsychiatric risk and 4) inability to assess the influence of pre-existing psychiatric illness on the association between smoking cessation treatments and neuropsychiatric outcomes.

All studies relied on diagnostic codes to capture neuropsychiatric adverse outcomes, which likely underestimated the absolute risk of events. It is difficult to estimate how many outcome events were missed in each study or to know whether or not the proportion of outcome under-ascertainment varied among study drugs, which resulted in decreased precision of estimates and unpredictable direction of bias.

In the studies that included data from the timeframe after the publicity of the neuropsychiatric safety concern associated with varenicline and, to a lesser degree, with bupropion, the potential for residual confounding was due to differential prescribing of smoking cessation therapies based on a physician or patient’s perceived underlying risk of neuropsychiatric outcomes (i.e., channeling bias); in the other studies, it was due to the impact of other unmeasured factors, such as nicotine withdrawal syndrome. “Channeling bias” makes varenicline or bupropion appear to reduce neuropsychiatric risk when compared to another prescription smoking cessation therapy. “Confounding by nicotine withdrawal syndrome” makes all smoking cessation drugs appears to elevate neuropsychiatric risk (relative to non-users), even if they were in fact risk-neutral.

When the potential biases are considered in combination, they restrict our ability to predict the direction of the relative risk associated with any smoking cessation product. One study’s use of bupropion as the reference group to examined varenicline’s neuropsychiatric risk was
problematic because finding no increased risk of NPS events comparing to bupropion does not reassure us of varenicline’s neuropsychiatric safety, given that both products are labeled for these adverse events. The inability to assess the risk among those with pre-existing psychiatric illness further restricts the generalizability of the findings. The evidence from the existing observational studies alone is of insufficient quality to either rule in or rule out an increased neuropsychiatric risk associated with either varenicline use or bupropion use. Observational data alone also are inadequate to inform whether or not neuropsychiatric risk associated with varenicline or bupropion could be different between smokers with and without psychiatric history. The neuropsychiatric safety of smoking cessation products should be assessed based on the totality of the evidence, including case reports, observational studies, and clinical trial data.
Figure 10. Reviewer-generated forest plot of varenicline-associated neuropsychiatric (NPS) risk observed in all reviewed studies (reference group: nicotine replacement therapy, bupropion, or person-time that was unexposed to varenicline)

NPS: Neuropsychiatric; HR: Hazard ratio; PTSD: Posttraumatic stress disorder


b Final report of the VA study: Varenicline and Mental Health Disorders, dated May 2011, revised June 2011


Figure 11. Reviewer-generated forest plot of neuropsychiatric (NPS) risk observed in all reviewed studies that examined both varenicline- and bupropion-associated risk\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient visit for depression—varenicline versus NRT\textsuperscript{b}</td>
<td>0.66 (0.63-0.69)</td>
</tr>
<tr>
<td>Inpatient visit for depression—bupropion versus NRT\textsuperscript{b}</td>
<td>0.75 (0.67-0.83)</td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from hospitalization or mortality data)—varenicline versus NRT\textsuperscript{b}</td>
<td>0.88 (0.52-1.49)</td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from hospitalization or mortality data)—bupropion versus NRT\textsuperscript{b}</td>
<td>0.83 (0.30-2.31)</td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from outpatient data)—varenicline versus NRT\textsuperscript{a}</td>
<td>0.56 (0.46-0.68)</td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from outpatient data)—bupropion versus NRT\textsuperscript{a}</td>
<td>0.74 (0.48-1.16)</td>
</tr>
</tbody>
</table>

NRT: nicotine replacement therapy


\textsuperscript{b} Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self-harm in the Clinical Practice Research Datalink: prospective cohort study. \textit{BMJ}. 2013;347:f57
Table 30  Potential channeling bias in the Thomas et al. study\textsuperscript{a} illustrated by their findings of the all-cause mortality risk among varenicline users and bupropion users

<table>
<thead>
<tr>
<th>Analytical approaches</th>
<th>Exposure</th>
<th>3-month suicide and non-fatal self-harm</th>
<th>3-month all-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Effect estimate (95% Confidence interval)</td>
<td>(Reference: NRT users)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hazard ratio</td>
<td>Risk difference per 1000 person-years</td>
</tr>
<tr>
<td>Cox regression analyses</td>
<td>Varenicline</td>
<td>0.88 (0.52 to 1.49)</td>
<td>-0.1\textsuperscript{c}</td>
</tr>
<tr>
<td>Propensity score matching analyses</td>
<td>Varenicline</td>
<td>0.87 (0.51 to 1.48)</td>
<td>-0.1\textsuperscript{c}</td>
</tr>
<tr>
<td>Instrumental variable analyses</td>
<td>Varenicline</td>
<td>-</td>
<td>0.4 (-0.8 to 1.5)</td>
</tr>
<tr>
<td>Cox regression analyses</td>
<td>Bupropion</td>
<td>0.83 (0.30 to 2.31)</td>
<td>-0.1 to -0.2\textsuperscript{c}</td>
</tr>
<tr>
<td>Propensity score matching analyses</td>
<td>Bupropion</td>
<td>0.87 (0.31 to 2.4)</td>
<td>0.1\textsuperscript{c}</td>
</tr>
<tr>
<td>Instrumental variable analyses</td>
<td>Bupropion</td>
<td>-</td>
<td>-3.9\textsuperscript{b} (-7.0 to -0.9)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. BMJ. 2013;347:f57

\textsuperscript{b} p value < 0.05.

\textsuperscript{c} see the calculation from HRs to risk differences in Attachment 1 Appendix III
5 Pharmacovigilance Review

The Division of Pharmacovigilance II (DPV II) analyzed adverse events reported with use of smoking cessation drugs to FDA’s Adverse Event Reporting System (FAERS) to provide an update to their previous reviews. The complete review is located in the background package (Attachment 3).

DPV II retrieved 5,542 serious, domestic FAERS reports for smoking cessation drugs (varenicline, n=2,864; bupropion, n=1,864; NRT, n=893) with an event year between 2011 and 2015. Of the 1,864 bupropion reports, 99 reported use for smoking cessation. The reviewers characterized the adverse event profile for all three smoking cessations products, with a focus on NPS events.

About 70% of varenicline and bupropion (all indications or smoking cessation) reports included at least one event from the Psychiatric disorders or Nervous system disorders SOCs. The top four NPS events for both varenicline and bupropion for smoking cessation were depression, anxiety, feeling abnormal, and suicidal ideation; reports of suicide attempt, completed suicide, and homicidal ideation were also identified for both products. For NRT, a smaller proportion of the reports included one or more events from the Psychiatric disorders and Nervous system disorders SOCs, and there was not a preponderance of NPS events in the top reported events.

Although there was an overall decrease in the number of FAERS reports for varenicline over the five year period (2011-2015), the SOCs Psychiatric disorders and Nervous system disorders consistently accounted for most reported adverse events. Similar to varenicline, the Psychiatric disorders and Nervous system disorders SOCs were also the most common for bupropion for smoking cessation throughout the time period of 2011 to 2015.

Serious NPS events continue to be reported in spontaneous postmarket data for both varenicline and bupropion. These data are consistent with current product labeling for varenicline and bupropion.

6 Drug Utilization of Smoking Cessation Products

Division of Epidemiology II (DEPI II) also conducted an analysis on the utilization of smoking cessation products. Please see the DEPI-II review for the full analysis and data sources used (Attachment 4).

The overall sales of prescription (Rx) and over-the-counter (OTC) smoking cessation products from manufacturers to various settings of care increased by 11% from approximately 6.9 million bottles/packages sold in 2011 to 7.7 million bottles/packages sold in 2015. In 2015, Rx products accounted for approximately 39% and OTC products

28 Bupropion is also approved for major depressive disorder and prevention of seasonal affective disorder.
accounted for approximately 61% of the total sales of smoking cessation products. Prescription products include Chantix, Zyban, and two nicotine replacement products that are still available only by prescription, Nicotrol Inhaler and Nicotrol Nasal spray. Other nicotine products (gums, patches, and lozenges) are sold OTC. Of note, the market share and trends in OTC sales across time should be interpreted with caution due to the limitations of data resources available. The OTC sales data shown for the smoking cessation products are likely an underestimation of total OTC sales in the U.S. Projections of all OTC products in this data source are estimated to be approximately 50% of the total U.S. OTC market.

**Figure 12.**

Sales of smoking cessation products* in packages/bottles sold by prescription status (OTC vs Rx) to all U.S. channels of distribution, 2011-2015

![Graph showing sales of smoking cessation products](image)

*These data only include products labelled for smoking cessation and do not include products that may be used off label, as other bupropion products such as Wellbutrin brand and generic equivalents.


Figure 13 (below) shows the nationally estimated number of unique patients who received dispensed prescriptions for smoking cessation products from 2006-2015 in the context of various regulatory actions taken by FDA. Note that there is likely higher use of bupropion for smoking cessation than shown in this analysis because other bupropion products not labeled for smoking cessation were not included.
Discussion and Points for Consideration

It is not a simple matter to design and conduct a trial to capture a complex and subjective endpoint. Unlike cardiovascular outcome trials, there is not a well-established case definition for the primary outcomes nor an established approach to outcome adjudication. Furthermore, the identification of cases in the postmarketing trial was complicated by the subjective nature of the experiences and of the method of assessing severity or impact on the patient.

Postmarketing reports clearly articulating an impact of Chantix and Zyban on patients’ lives in domains of mood, cognition, behavior, and overall functioning continue to be received. Events are variable, and often ill-defined, resulting in the application of non-specific MedDRA codes such as “feeling abnormal.” This is one of the most common terms in postmarketing reports (verbatim reports coded to the MedDRA term “Feeling
abnormal” most commonly involved the patient describing feeling “bad”, “weird”, “strange”, or that the patient did not feel “good” or like him/herself.) Notably, only 12 subjects in the 8000 patient trial had events coded to the term “feeling abnormal.” Another eight experienced events coded to “thinking abnormal.”

Despite efforts to actively solicit information about the range of complex and ill-defined experiences that patients have reported in postmarketing cases, this trial did not seem to have identified many of the types of cases that had been previously identified to be of concern. It is apparent that the practice of capturing the subject’s full report was unfamiliar to the study staff, and that the concept of using the NAEI as a tool to prompt an interview that would lead to a full description of the subject’s experience was poorly understood or implemented. It is also clear that not all NPS adverse events were captured using the case definition defined in the protocol. Inconsistent investigator assessment of severity was a clear problem in this regard—the example of a subject who required hospitalization for depression that was rated “mild” by the investigator illustrates the problem. There are also a number of examples in which the person completing the Clinician Global Assessment viewed the subject as unchanged from baseline and not at all ill, in the face of subject reports of significant symptoms (and sometimes in the face of hospitalization). It seems reasonable to conclude that the exact incidence of neuropsychiatric adverse events of significance and perhaps scope of neuropsychiatric adverse events of significance was not accurately captured by the study.

However, a variety of approaches to analysis still support similar conclusions about the relative rates of events. In patients without prior psychiatric history, events do not seem to be more frequent in Chantix-treated, Zyban-treated, or NRT-treated patients than in placebo-treated patients. Events are more common in patients with psychiatric history than without, regardless of treatment arm; however, the increased risk of NPS primary outcome events in patients with the psychiatric history randomized to Chantix or Zyban compared to placebo trended toward statistical significance. This trend was not observed in NRT-treated patients.

Regarding efficacy, this trial provides clear confirmation that all three medications are more effective than placebo in patients with and without histories of psychiatric diagnoses. Because patients with psychiatric conditions were not included in the clinical trials supporting approval, it is valuable to have confirmation that such patients can benefit from treatment with Chantix, Zyban, or transdermal NRT. In keeping with established findings, patients with psychiatric diagnoses were less successful in quitting smoking than patients without psychiatric diagnoses, but all three medications were efficacious in both groups.

The five observational studies reviewed by DEPI II were subject to various biases that impacted the interpretation of the study findings. When the potential biases were considered in combination, they restricted our ability to predict the direction of the relative risk associated with any smoking cessation product. The inability to assess the risk among those with pre-existing psychiatric illness further restricts the generalizability of the findings. The evidence from the existing observational studies alone is of
insufficient quality to either rule in or rule out an increased neuropsychiatric risk associated with either varenicline use or bupropion use. Observational data alone also are inadequate to inform whether or not neuropsychiatric risk associated with varenicline or bupropion could be different between smokers with and without psychiatric history.

A review of FAERS reports found that most reports for varenicline and bupropion included at least one event from the Psychiatric disorders or Nervous system disorders SOCs. The top four NPS events for both varenicline and bupropion for smoking cessation were depression, anxiety, feeling abnormal, and suicidal ideation; reports of suicide attempt, completed suicide, and homicidal ideation were also identified for both products. For NRT, a smaller proportion of the reports included one or more events from the Psychiatric disorders or Nervous system disorders SOCs, and there was not a preponderance of NPS events in the top reported events. Serious NPS events continue to be reported in spontaneous postmarket data for both varenicline and bupropion. These data are consistent with current product labeling for varenicline and bupropion, but differ from the results of the trial which found few cases of suicidality, homicidal ideation, or the very commonly-reported “feeling abnormal.”
8 APPENDIX A: Illustrative NPS Cases

The following cases illustrate some of the problems in coding and capture of adverse events:

1. Case included in NPS Endpoint: multiple psychiatric symptoms subsumed under single term “agitation.”

   Subject 10571036
   • 63-year-old WM enrolled in PHx (anxiety disorders) cohort.
   • History included depression and anxiety, current diagnoses included post-traumatic stress disorder.
   • Randomized to bupropion and took medication for 9 days. Continued in study off-treatment through completion.
   • On Study Day 4, the subject reported “Something isn’t right. I don’t feel like myself. I’ve been crying, and I have lots of rage, like I want to pick up my kitchen table and throw it. I’ve also been having nightmares and have a feeling of doom and gloom”
   • This was coded as “agitation,” and assessed as moderate in intensity and non-serious by the investigator.
   • A mental health evaluation was performed at the Week 1 visit (Study Day 9) and the subject was advised to discontinue study medication.
   • The mental health professional noted a history of generalized anxiety disorder and “exacerbation of grief then feeling of decreased impulse control and strong urge to destroy property.”
   • HADS scores were 17 for anxiety and 14 for depression (Baseline: 5 and 6)
   • Subject hadn’t quit smoking
   • This case was flagged as an NPS primary endpoint event because it was coded to “agitation” and assessed as moderate.

2. Case involving multiple significant psychiatric symptoms that was NOT included in NPS endpoint:

   Subject 10771034
   • 45-year-old WF enrolled in PHx (anxiety disorders) cohort
   • History included PTSD diagnosed >10 years earlier; treated w/Xanax for a few months, no previous psychiatric hospitalizations.
   • Randomized to varenicline, took medication for 30 days. Continued in study off-treatment through completion
   • On Study Day 23, the subject reported events coded to the terms “disinhibition,” (no verbatim recorded) auditory hallucination (“hearing voices in her house”) irritability, “mild cognitive disorder” (“trouble with thinking clearly”), “mild
nightmare” (reported as “having bad dreams”), “mild paranoia” (“subject felt like people were doing things to agitate her”),

• A mental health evaluation was performed at Week 4 visit (Study Day 30)
  o HADS 9 for anxiety and 14 for depression (Baseline: 10 and 3) CGI-I was much worse compared to Baseline.
  o Psych evaluation concluded “stop study drug. No additional intervention”

• Study drug was d/c’d and all of the AEs were resolved by Day 32
  o HADS scores declined to 5 and 2 CGI-I was very much improved.

• This case was NOT flagged as an NPS primary endpoint event because all events were assessed as mild in intensity.

3. Case of Deliberate Overdose NOT coded as suicide attempt and NOT coded to NPS

Subject: 12181086

• 49 yo WM subject enrolled in PHx (affective disorder) cohort
• History include current major depression, treated with escitalopram for ~4 years; olanzapine added 4 months before enrollment
• Randomized to placebo; took study drug x 8 days
• Subject reported symptoms beginning on Treatment Day 2
  o “After starting the study medication, I have felt more depressed,” “After a couple of days of starting the study medicine, my anxiety has been increasing,” “I have had troubles to fall asleep, and I wake up several times at night.”
  o An evaluation at the Week 1 visit concluded “Subject has recurrent depression and anxiety. His condition has been stable for over six months, but has got worse over the last week.”
  o HADS scores were 18 for anxiety and 15 for depression (BL 13 and 10), CGI-I “much worse” from Baseline. CSSRS: “Subject has been thinking it would be easier to be dead,”

• Study drug d/c’d. No change in baseline smoking level.
• Five days later, the subject was hospitalized for a pulmonary embolus attributed to a long airplane flight taken a few weeks prior.
  o While hospitalized, the subject left the hospital against medical advice, went home, took 20 tablets of his acetaminophen/codeine medication (for osteoarthritis), returned to the hospital and reported taking the medication.
  o He required treatment with acetylcysteine for elevated acetaminophen level. He denied intent to kill himself.

• Event was not considered an NPS event; “The investigator considered the overdose to be not related to the study drug but due to the subject’s existing depression, and did not consider it a suicide-related event.”
9 APPENDIX B: Common Adverse Events

Table S3: Most Frequent All Causality Treatment –Emergent Adverse Events (HLGT≥ 5% in Varenicline Group and More Commonly than Placebo Group, and PT ≥ 1% in Varenicline Group
<table>
<thead>
<tr>
<th>Varenicline 1.0 mg</th>
<th>Bupropion 150 mg BID</th>
<th>NRT 21/14/7 mg QD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Evaluable for adverse events</td>
<td>2016 (74.6)</td>
<td>2006 (72.1)</td>
<td>2022 (71.0)</td>
</tr>
<tr>
<td>With adverse events</td>
<td>1503 (74.6)</td>
<td>1446 (72.1)</td>
<td>1436 (71.0)</td>
</tr>
<tr>
<td>Discontinued due to adverse events</td>
<td>166 (8.2)</td>
<td>176 (8.8)</td>
<td>162 (8.0)</td>
</tr>
</tbody>
</table>

Number (%) of Subjects with Adverse Events by:
- System Organ Class
- and High Level Group Term
- and MedDRA (v18.0) Preferred Term

<table>
<thead>
<tr>
<th>GASTROINTESTINAL DISORDERS</th>
<th>BID</th>
<th>Bupropion 150 mg BID</th>
<th>NRT 21/14/7 mg QD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal motility and defaecation conditions</td>
<td>786 (39.0)</td>
<td>527 (26.3)</td>
<td>480 (33.7)</td>
<td>414 (20.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>178 (8.8)</td>
<td>140 (7.0)</td>
<td>140 (6.9)</td>
<td>107 (5.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>90 (4.5)</td>
<td>76 (3.8)</td>
<td>49 (2.4)</td>
<td>37 (1.8)</td>
</tr>
<tr>
<td>Gastrointestinal signs and symptoms</td>
<td>77 (3.7)</td>
<td>57 (2.8)</td>
<td>76 (3.8)</td>
<td>56 (2.8)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>436 (31.5)</td>
<td>312 (15.6)</td>
<td>306 (15.1)</td>
<td>251 (12.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>22 (1.1)</td>
<td>12 (0.6)</td>
<td>6 (0.3)</td>
<td>17 (0.8)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>31 (1.5)</td>
<td>18 (0.9)</td>
<td>10 (0.5)</td>
<td>21 (1.0)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>43 (2.1)</td>
<td>23 (1.1)</td>
<td>27 (1.3)</td>
<td>25 (1.2)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>46 (2.3)</td>
<td>34 (1.7)</td>
<td>46 (2.2)</td>
<td>31 (1.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (3.5)</td>
<td>18 (0.9)</td>
<td>23 (1.1)</td>
<td>18 (0.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>511 (25.3)</td>
<td>203 (10.0)</td>
<td>199 (9.8)</td>
<td>137 (6.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</th>
<th>BID</th>
<th>Bupropion 150 mg BID</th>
<th>NRT 21/14/7 mg QD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>General system disorders NRC</td>
<td>270 (13.4)</td>
<td>241 (12.0)</td>
<td>404 (26.0)</td>
<td>229 (11.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>223 (11.1)</td>
<td>196 (9.8)</td>
<td>198 (9.6)</td>
<td>177 (8.8)</td>
</tr>
<tr>
<td></td>
<td>124 (6.2)</td>
<td>57 (2.8)</td>
<td>75 (3.7)</td>
<td>83 (4.1)</td>
</tr>
<tr>
<td></td>
<td>533 (26.4)</td>
<td>475 (23.7)</td>
<td>494 (26.4)</td>
<td>596 (28.6)</td>
</tr>
</tbody>
</table>

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
ILGTs with incidences > 4.5% and < 5% appear through rounding as 5%, but do not meet the cut-off point of >= 5% to be included in this table.
MedDRA (v18.0) coding dictionary applied.
Pfizer Confidential Source Data: Table 16.2.7.2  Date of Reporting Dataset Creation: 28MAY2015  Date of Table Generation: 13JAN2016 (13:40)
<table>
<thead>
<tr>
<th>Number (%) of Subjects with Adverse Events by, System Organ Class</th>
<th>Varilicline 1.0 mg</th>
<th>Dupropion 150 mg</th>
<th>NXT 21/14/7 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>and High Level Group Term</td>
<td>BID</td>
<td>BID</td>
<td>OD</td>
<td></td>
</tr>
<tr>
<td>and MedDRA (v18.0) Preferred Term</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>27 (1.3)</td>
<td>29 (1.4)</td>
<td>38 (1.9)</td>
<td>39 (1.9)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>36 (1.8)</td>
<td>32 (1.6)</td>
<td>36 (1.9)</td>
<td>36 (1.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>174 (8.6)</td>
<td>156 (7.8)</td>
<td>126 (6.2)</td>
<td>135 (6.7)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>31 (1.5)</td>
<td>30 (1.5)</td>
<td>32 (1.6)</td>
<td>24 (1.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>109 (5.4)</td>
<td>104 (5.2)</td>
<td>97 (4.8)</td>
<td>115 (5.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>23 (1.1)</td>
<td>21 (1.0)</td>
<td>12 (0.6)</td>
<td>17 (0.8)</td>
</tr>
<tr>
<td>NERVOUS SYSTEM DISORDERS</td>
<td>440 (21.6)</td>
<td>440 (21.9)</td>
<td>445 (21.9)</td>
<td>374 (18.5)</td>
</tr>
<tr>
<td>Headaches</td>
<td>250 (12.6)</td>
<td>195 (9.7)</td>
<td>249 (12.3)</td>
<td>209 (10.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>245 (12.2)</td>
<td>106 (5.3)</td>
<td>232 (11.5)</td>
<td>199 (9.9)</td>
</tr>
<tr>
<td>Neurological disorders NEC</td>
<td>180 (8.9)</td>
<td>228 (11.4)</td>
<td>175 (8.9)</td>
<td>154 (7.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>180 (8.9)</td>
<td>98 (4.9)</td>
<td>86 (4.2)</td>
<td>66 (3.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>180 (8.9)</td>
<td>98 (4.9)</td>
<td>86 (4.2)</td>
<td>66 (3.3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>29 (1.4)</td>
<td>19 (0.9)</td>
<td>28 (1.4)</td>
<td>16 (0.8)</td>
</tr>
<tr>
<td>PSYCHIATRIC DISORDERS</td>
<td>720 (35.7)</td>
<td>767 (38.2)</td>
<td>721 (35.7)</td>
<td>613 (30.4)</td>
</tr>
<tr>
<td>Anxiety disorders and symptoms</td>
<td>236 (11.7)</td>
<td>294 (14.7)</td>
<td>239 (11.8)</td>
<td>222 (11.1)</td>
</tr>
<tr>
<td>Agitation</td>
<td>79 (3.9)</td>
<td>85 (4.2)</td>
<td>67 (3.3)</td>
<td>66 (3.3)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>132 (6.5)</td>
<td>169 (8.4)</td>
<td>138 (6.8)</td>
<td>120 (6.0)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>132 (6.5)</td>
<td>169 (8.4)</td>
<td>138 (6.8)</td>
<td>120 (6.0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>35 (1.7)</td>
<td>37 (1.8)</td>
<td>28 (1.4)</td>
<td>36 (1.8)</td>
</tr>
<tr>
<td>Depressed mood disorders and disturbances</td>
<td>175 (8.7)</td>
<td>143 (7.1)</td>
<td>151 (7.5)</td>
<td>161 (8.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>78 (3.8)</td>
<td>60 (3.0)</td>
<td>76 (3.9)</td>
<td>81 (4.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>78 (3.8)</td>
<td>60 (3.0)</td>
<td>76 (3.9)</td>
<td>81 (4.0)</td>
</tr>
<tr>
<td>Sleep disorders and disturbances</td>
<td>437 (21.5)</td>
<td>456 (22.7)</td>
<td>483 (23.9)</td>
<td>295 (14.6)</td>
</tr>
</tbody>
</table>

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
HIATTs with incidences > 4.5% and < 5% appear through rounding as 5%, but do not meet the cut-off point of > 5% to be included in this table.
MedDRA (v18.0) coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.2 Date of Reporting Dataset Creation: 28MAY2015 Date of Table Generation: 13JAN2016 (13:40)
<table>
<thead>
<tr>
<th></th>
<th>Varenicline 1.0 mg</th>
<th>Bupropion 150 mg BID</th>
<th>NRT 21/14/7 mg QD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>201 (10.0)</td>
<td>131 (6.5)</td>
<td>251 (12.4)</td>
<td>92 (4.6)</td>
</tr>
<tr>
<td>Initial insomnia</td>
<td>22 (1.1)</td>
<td>14 (0.7)</td>
<td>20 (1.0)</td>
<td>6 (0.3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>189 (9.4)</td>
<td>245 (12.2)</td>
<td>195 (9.6)</td>
<td>139 (6.9)</td>
</tr>
<tr>
<td>Nightmare</td>
<td>22 (1.1)</td>
<td>16 (0.8)</td>
<td>56 (2.8)</td>
<td>17 (0.8)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>65 (3.2)</td>
<td>73 (3.6)</td>
<td>45 (2.2)</td>
<td>42 (2.1)</td>
</tr>
<tr>
<td><strong>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory disorders NHC</td>
<td>146 (7.2)</td>
<td>127 (6.3)</td>
<td>149 (7.4)</td>
<td>141 (7.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>104 (5.2)</td>
<td>92 (4.6)</td>
<td>114 (5.6)</td>
<td>103 (5.1)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>35 (1.7)</td>
<td>35 (1.7)</td>
<td>38 (1.9)</td>
<td>40 (2.0)</td>
</tr>
<tr>
<td></td>
<td>20 (1.0)</td>
<td>21 (1.0)</td>
<td>29 (1.4)</td>
<td>27 (1.3)</td>
</tr>
</tbody>
</table>

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
HLGTs with incidences > 4.95% and < 5% appear through rounding as 5%, but do not meet the cut-off point of ≥ 5% to be included in this table.
MedDRA (v18.0) coding dictionary applied.
Pfizer CONFIDENTIAL Source Data: Table 16.2.7.2 Date of Reporting Dataset Creation: 28MAY2015 Date of Table Generation: 13JAN2016 (13:40)
Epidemiology: Review of epidemiological studies on neuropsychiatric events associated with smoking cessation products

Date:

Reviewer(s): Chih-Ying Chen, Ph.D.
Division of Epidemiology II

Team Leader: Tamra Meyer, Ph.D., M.P.H.
Division of Epidemiology II

Division Director: David Moeny, R.Ph. M.P.H.
Division of Epidemiology II

Drug Name(s): Varenicline (Chantix)

Subject: Review of epidemiological studies on neuropsychiatric events associated with smoking cessation products

Application Type/Number: NDA 21-928
Submission Number: 040
Applicant/sponsor: Pfizer
OSE RCM #: 2016-640
# TABLE OF CONTENTS

EXECUTIVE SUMMARY ............................................................................................................. 2

1. INTRODUCTION ................................................................................................................... 4

2. REVIEW METHODS and MATERIALS ............................................................................... 5

3. REVIEW RESULTS ............................................................................................................... 5
   3.1 Overview of studies evaluated ....................................................................................... 6
   3.2 Findings of individual studies ......................................................................................... 8

4. DISCUSSION ....................................................................................................................... 18
   4.1 Concerns on validity of outcome measures ................................................................. 18
   4.2 Channeling bias and residual confounding ................................................................... 19
   4.3 Other Design or Methodological issues ........................................................................ 22
   4.4 Summary assessment ..................................................................................................... 23

5. CONCLUSION ..................................................................................................................... 25

6. REFERENCES ...................................................................................................................... 41
EXECUTIVE SUMMARY

In February 2015, Pfizer submitted a labeling supplement with regard to varenicline’s neuropsychiatric safety, including data from a completed postmarketing requirement trial and published observational studies. The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Division of Epidemiology II (DEPI II) to review the observational studies submitted by Pfizer, as well as any additional published observational studies on neuropsychiatric risk associated with smoking cessation prescription medications. This document describes DEPI II’s literature search and assessment of all three FDA approved prescription smoking cessation products—varenicline, bupropion and nicotine replacement therapy (NRT).

DEPI II’s literature search identified a total of six observational studies for in-depth review. The findings of the reviewed epidemiological studies showed inconsistent results. Four of the studies did not observe a statistically significant difference in the risk of neuropsychiatric adverse events between varenicline and NRT, varenicline and bupropion, or between bupropion and NRT; the point estimates did not suggest a consistent trend of association. One study found a significant reduction in neuropsychiatric risk among varenicline users (34% reduction in risk of outpatient depression visit and 44% reduction in the risk of outpatient visit for suicide or non-fatal self-harm) and a 25% reduction in risk of depression visit in bupropion users, comparing to NRT users. Yet, another study observed that while varenicline use was not associated with significant risk of suicide-related behaviors, the risk of neuropsychiatric in- or out-patient visits significantly increased by 18% during varenicline-exposed time compared to unexposed time in varenicline users.

Each of the reviewed studies had key study design limitations. The most important limitations were: 1) use of outcome measures with suboptimal sensitivity and specificity, 2) residual confounding, 3) use of bupropion (another smoking cessation drug with neuropsychiatric risk labeled in a boxed warning) as a reference group to examine varenicline’s neuropsychiatric risk and 4) inability to assess the influence of pre-existing psychiatric illness on the association between smoking cessation treatments and neuropsychiatric outcomes. All studies relied on diagnostic codes to capture neuropsychiatric adverse outcomes, which likely underestimated the absolute risk of events. It is difficult to estimate how many outcome events were missed in each study, or to know whether or not the proportion of outcome under-ascertainment varied among study drugs resulting in decreased precision of estimates and unpredictable direction of bias. In the studies that included data from the timeframe after the publicity of the neuropsychiatric safety concern associated with varenicline and, to a lesser degree, with bupropion, the potential for residual confounding was due to differential prescribing of smoking cessation therapies based on a physician or patient’s perceived underlying risk of neuropsychiatric outcomes (i.e., channeling bias); in the other studies, it was due to the impact of other unmeasured factors, such as nicotine withdrawal syndrome. “Channeling bias” makes varenicline or bupropion appear to reduce neuropsychiatric risk when compared to another prescription smoking cessation therapy. “Confounding by nicotine withdrawal syndrome” makes all smoking cessation drugs appear to elevate neuropsychiatric risk (relative to non-users), even if they were in fact risk-neutral. When the potential biases are considered in combination, they restrict our ability to predict the direction of the relative risk associated with any smoking cessation product. One study’s use of bupropion as the reference group to examine varenicline’s neuropsychiatric risk was problematic because
finding no increased risk of NPS events comparing to bupropion does not reassure us of varenicline’s neuropsychiatric safety, given that both products are labeled for these adverse events. The inability to assess the risk among those with pre-existing psychiatric illness further restricts the generalizability of the findings. The evidence from the existing observational studies, alone, is of insufficient quality to either rule in or rule out an increased neuropsychiatric risk associated with either varenicline use or bupropion use. Observational data alone also are inadequate to inform whether or not neuropsychiatric risk associated with varenicline or bupropion could be different between smokers with and without psychiatric history. Neuropsychiatric safety of smoking cessation products should be assessed based on the totality of data streams, including case reports, observational and clinical trial data.
1. INTRODUCTION

Varenicline was approved in the US under the trade name of Chantix as an aid to smoking cessation treatment for adults in May 2006. In May 2007, the European Medicines Agency (EMA- previously, EMEA) informed FDA that they were investigating a signal of suicidality-related adverse events with varenicline (marketed in the EU as Champix). While FDA was assessing the potential association of neuropsychiatric adverse events with varenicline, the mainstream media in the US reported a highly publicized case of erratic behavior in a patient using varenicline for smoking cessation in September 2007. This case received considerable public attention. Two months later (November 2007), FDA issued an Early Communication about this ongoing safety review of varenicline. At the same time, the information regarding the neuropsychiatric adverse events was added to ADVERSE REACTIONS section of varenicline’s labeling. After FDA completed the evaluation of the postmarketing data, neuropsychiatric events were added to the Warnings and Precautions section of the labeling of varenicline in January 2008, a medication guide was approved in May 2008 and a boxed warning was added to the labeling in July 2009. A subsequent review of post-marketing data on the other smoking cessation products (i.e. bupropion and various nicotine replacement therapies) identified similar cases of neuropsychiatric adverse events associated with bupropion use, a boxed warning was also added to bupropion’s labeling in July 2009. Additionally, a postmarketing requirement (PMR) was issued in May 2008 to the sponsor, Pfizer, to conduct a large randomized, double-blind, active- and placebo-controlled study to compare the risk of clinically significant neuropsychiatric (NPS) events, including but not limited to, events related to suicide in smokers using varenicline, bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation. Another important aim was to determine whether individuals with a history of psychiatric disorders are at greater risk for development of clinically significant NPS events compared to smokers without a history of psychiatric disorders, while using these smoking cessation treatments.

In April 2014, Pfizer submitted a label supplement requesting updates to the varenicline label to reflect available neuropsychiatric data from both clinical trial meta-analyses and observational studies published since 2009. On the basis of these data, Pfizer requested that FDA remove the boxed warning regarding the risk of serious neuropsychiatric events and update the content of the warning in the latter part of the label by adding information from the newly-available controlled clinical trials and observational studies. While these studies did not show an increased risk of neuropsychiatric side effects with Chantix, they did not examine all types of neuropsychiatric side effects, and they had limitations that prevented FDA from drawing reliable conclusions. FDA updated the Warnings and Precautions section of the label to include information about these studies, including the limitations of their findings. FDA also held an Advisory Committee (AC) meeting in October 2014 to discuss the sponsor’s proposal to remove the boxed warning. The AC voted against the proposal and suggested revisiting the issue after the completion of the required postmarketing clinical trial.

In February 2015, the sponsor submitted another labeling supplement, including data from the completed PMR trial (Study A3051123, EAGLES trial) and additional observational studies published after their previous submission in 2014. They again proposed revisions to the Warnings and Precautions section of the label regarding the risk of neuropsychiatric adverse events with Chantix and removal of the boxed warning. The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Division of Epidemiology II (DEPI II) to
review the observational studies submitted by Pfizer and to conduct a literature review of any published observational studies on neuropsychiatric risk associated with any smoking cessation product. Smoking cessation products other than varenicline were considered since the PMR trial results included new safety information that pertained to bupropion (Zyban) and nicotine replacement therapy (NRT). This document reports the results of DEPI II’s literature search and assessment of current observational epidemiologic literature on neuropsychiatric risk associated with all three smoking cessation products—varenicline, bupropion and NRT.

2. REVIEW METHODS AND MATERIALS

DEPI II conducted a search of the National Library of Medicine’s PubMed database on June 17th 2016. The search strategy is described in detail in Appendix I. Briefly, we first used search strings of smoking cessation products names and the neuropsychiatric adverse events to identify English language observational epidemiologic studies that examined neuropsychiatric adverse outcomes associated with a smoking cessation product. Studies were selected for review if they reported the relative risk of neuropsychiatric events between smoking cessation product and used an adequate design and analytical approach to examine the association.

3. REVIEW RESULTS

Using search strings of smoking cessation products names and the neuropsychiatric adverse events, we identified 412 English language articles. We excluded:

- 48 Animal studies, cell studies, pharmacokinetic studies, or pharmacodynamics studies
- 271 Publications that did not report on a research study (e.g., commentaries and reviews), non-observational studies (e.g., randomized control trials), or non-comparative studies (e.g., case reports, case series)
- 67 Studies that did not examine drug-related neuropsychiatric risk (e.g., studies that examined predictors of smoking cessation drug use among smokers with a mental disorder, studies that examined how pre-existing mental disorders impact success of smoking cessation treatment)
- 17 Studies that did not report relative risk of neuropsychiatric events between smoking cessation products or studies that did not use adequate designs and analytical approaches to examine neuropsychiatric risk of smoking cessation products, for example:
  - Cross-sectional studies
  - Studies without comparator groups
  - Studies that did not account for confounding when comparing risk of neuropsychiatric events between smoking cessation products

Among a total of eight articles that were eligible for in-depth review, we further excluded two publications:

- The publication by Gibbons et al.\textsuperscript{5} used the same study dataset (i.e., the same data from the same patients during the same study timeframe) as a prior publication by Meyer et al.\textsuperscript{6} to examine the association between varenicline and several neuropsychiatric disorders. The analyses in the Gibbons et al.\textsuperscript{5} study were similar to analyses conducted in the Meyer
et al.\textsuperscript{6} study\textsuperscript{ab}. The only difference was that the Gibbons et al.\textsuperscript{5} analyses included fewer covariates than the Meyer et al.\textsuperscript{6} analyses. Because the Gibbons et al.\textsuperscript{5} study was a re-analysis of a study already included in the in-depth review, and because they did not control for as many potential confounding variables as in the Meyer et al.\textsuperscript{6} analysis, we excluded the Gibbons et al.\textsuperscript{5} study from our in-depth analysis.

- The publication by Gunnell et al.\textsuperscript{7} utilized the same data source and had overlapping data time frames as a later publication by Thomas et al.\textsuperscript{8} which was included in our in-depth review.

Two of the six articles included in the in-depth review describe studies that were collaborative research projects between the FDA and other federal agencies through Inter-Agency Agreements: the Meyer et al.\textsuperscript{6} publication described the study by the U.S. Army Office of the Surgeon General (OTSG) U.S. ARMY MEDICAL COMMAND (U.S. Army Medical Command MEDCOM)’s Pharmacovigilance Center (PVC) (referred to hereafter as the “DoD study”\textsuperscript{b}) and the Cunningham et al.\textsuperscript{9} publication described the study by the Department of Veterans Affairs (VA) Center for Medication Safety (VAMedSAFE) (referred to hereafter as the “VA study”). DEPI also reviewed information from the following documents relevant to the DoD and VA studies that were submitted to the FDA:

- Final report of the DoD study: Rate of Neuropsychiatric Events in Varenicline Users Compared to Nicotine Replacement Therapy Patch Users, Military Health System, August 1, 2006 to August 31, 2007, dated May 04, 2012
- Draft protocol of the VA study: Varenicline and Mental Health Disorders, dated March 2009
- Final report of the VA study: Varenicline and Mental Health Disorders, dated May 2011, revised June 2011

3.1 **Overview of Studies Evaluated**

The six reviewed studies included five which assessed the risk of neuropsychiatric medical encounters associated with smoking cessation products (VA study/Cunningham et al.\textsuperscript{9}, DoD study/Meyer et al.,\textsuperscript{6} Kotz et al.\textsuperscript{10}, Molero et al.\textsuperscript{11} and Pasternak et al.\textsuperscript{12}), and three which evaluated the association between smoking cessation products and risk of suicide or non-fatal self-harm (Thomas et al.,\textsuperscript{8} Kotz et al.,\textsuperscript{10} Molero et al.\textsuperscript{11}). All reviewed studies were retrospective, population-based, cohort studies. DEPI II consulted the Division of Biostatistics (DB7) to evaluate the advanced statistical methods used in the publications by Molero et al.\textsuperscript{11} and Kotz et al.\textsuperscript{10} The statistical review of these two studies will be submitted separately. Although some studies\textsuperscript{8,10,11} examined risk of non-neuropsychiatric events associated with smoking cessation drugs, we focused on the study methods and findings that were relevant to neuropsychiatric risk in this review. One of the studies (Thomas et al.\textsuperscript{8}) reported the association between smoking

\textsuperscript{a} Although Meyer et al. did not report certain analyses in their publication, the FDA received the full report of the findings from the Meyer study.

\textsuperscript{b} Two members of the DEPI review team are listed as authors on the Meyer et al. study. Dr. Meyer was the primary investigator, and David Moeny was a co-author.
cessation drug use and the likelihood of antidepressant initiation, as a proxy for incident depression. Prescribing of antidepressants is not a specific measure of incident depression, since antidepressants are also used to treat other disorders, including non-psychiatric indications like pain. Therefore, we did not discuss those findings in this review.

The design, data sources, methods, and main findings of the six included studies are summarized in Appendix II Table 1, Appendix II Table 2, Figure 3-1 and Figure 3-2. We summarized the VA study methods and findings based mostly on the pre-specified analytical plan described within the protocol and final report that were submitted to the FDA. This is because the VA study had two objectives. Objective one resulted in the final report submitted to FDA in 2011; this was based on the findings of the analyses for the first objective, which examined the risk of inpatient neuropsychiatric events associated with varenicline. The Cunningham publication\(^9\) included additional findings of the second objective, which expanded the scope to examine the risk of outpatient neuropsychiatric events associated with varenicline.

To briefly summarize the findings:

- **Four studies** (DoD study/Meyer et al.,\(^6\) VA study, Thomas et al.,\(^8\) and Kotz et al.\(^10\)) compared varenicline-associated neuropsychiatric risk to NRT. Their findings did not suggest a consistent trend of association—some effect estimates (Hazard ratios) were above, and some were below the null (1.0). Most of the effect estimates were imprecise, and their confidence intervals crossed the null. Only the study by Kotz et al.\(^10\) found a statistically significant difference between varenicline and NRT. They reported that varenicline use was associated with a 34% reduction in risk of an outpatient depression visit and 44% reduction in the risk of an outpatient visit for suicide or non-fatal self-harm within six months after treatment initiation.

- **One study** by Pasternak et al.\(^12\) used bupropion as the reference group to evaluate risk of emergency department visit or hospitalization for neuropsychiatric events. Varenicline use was shown to be associated with a 15% lowered neuropsychiatric risk compared with bupropion use, but the confidence interval of the point estimate was wide and crossed the null.

- **One study** by Molero et al.\(^11\) used a self-controlled design that compared varenicline exposed time to un-exposed time among varenicline users. They observed that while varenicline use was not associated with significant risk of suicide-related behaviors, the risk of a neuropsychiatric in- or out-patient visit significantly increased by 18% during varenicline-exposed time.

- **Two studies** also examined bupropion-associated neuropsychiatric risk relative to NRT:
  - Thomas et al.\(^8\) suggested an inverse association between bupropion use and neuropsychiatric adverse outcomes; however, the effect estimate was imprecise and did not reach statistical significance in most analyses.
  - Kotz et al.\(^10\) reported a 25% reduction in the risk of an outpatient visit for depression in bupropion users, which reached statistical significance.
Four studies (Meyer et al., VA study, Pasternak et al., and Molero et al.) examined the risk of neuropsychiatric adverse outcomes among users of smoking cessation treatment with and/or without prior mental illness history:

- The Meyer et al. study and the VA study both were unable to report the neuropsychiatric risk in all the subgroups stratified by psychiatric history because of small sample size or small observed numbers of outcome events in one of the subgroups.
- Pasternak et al. reported that the observed HRs of psychiatric events associated with varenicline, compared to bupropion, appeared lower in participants without a history of psychiatric disorder than in participants with a history, but the point estimates were imprecise and the confidence intervals both crossed one.
- In the Molero et al. study, the increased risk of psychiatric conditions were only among people with pre-existing psychiatric disorders. Most of the effect estimates of neuropsychiatric risk associated with varenicline exposed time (relative to varenicline unexposed time) were numerically higher among patients without history of psychiatric disorder, but the confidence intervals of the point estimates were wide and crossed the null.

We will describe each study in more detail in the following sections.

3.2 Findings of Individual Studies

3.2.1 Effect of smoking cessation treatment among overall study population

The Meyer study

The study by Meyer et al. compared the rates of hospitalizations for neuropsychiatric adverse events among new users of varenicline and the NRT patch (i.e., no varenicline or NRT patch use in the prior 6 months) that started therapy between August 1, 2006 and August 31, 2007 in the Military Health System. The study time frame was restricted to the period before the first FDA warning on varenicline-related neuropsychiatric risk to reduce the potential of channeling bias (further discussed in section 4.2). Varenicline users were matched using propensity scores (reflecting demographic characteristics, health insurance benefits, psychiatric history, chronic pain diagnosis history, past neuropsychiatric or pain medication use and past healthcare utilizations), to NRT users. After propensity score matching, there were 11,978 varenicline users and an equal number of NRT users in the study sample. The main outcome was a primary hospital discharge diagnosis for one of a number of neuropsychiatric conditions (Appendix II Table 1) within 30 days of drug initiation. In the study’s propensity score matched samples there were 16 psychiatric hospitalizations among varenicline users and 14 among NRT users. Comparing to NRT users, risk of neuropsychiatric hospitalization was numerically higher in varenicline users (HR=1.14; 95% CI=0.56 to 2.34), however, the effect estimate was unstable and the confidence interval crossed the null (i.e., 1.0). The finding was similar when patients were followed for 60 days after drug initiation instead of 30 days. Findings were similar when using any inpatient diagnosis as the outcome measure (HR=0.79; 95% CI=0.50-1.24). The HR estimate was within the range reported for the main outcome, but indicated a lowered risk of outpatient neuropsychiatric visits (HR=0.71, 95% CI=0.60-0.84) for varenicline users compared to NRT users.
The VA study

The VA study evaluated the incidence of neuropsychiatric hospitalizations among veterans using varenicline or NRT. Patients starting varenicline or NRT between May 1, 2006 and September 30, 2007, but with no varenicline or NRT use in the previous year, were selected and matched in a 1:1 ratio by use of propensity scores (reflecting demographic characteristics, comorbidities, psychiatric history and past psychotropic use). Similar to the Meyer et al. study,6 the study time frame was restricted to the period before the first FDA warning2 on varenicline-related neuropsychiatric risk to reduce the potential of channeling bias. The study’s pre-specified main outcome was 30-day risk of psychiatric hospitalization, defined as hospitalizations with a primary discharge diagnosis of a range of mental health disorders (Appendix II). The study population included 14,131 varenicline users and an equal number of NRT users. Among these patients, there were 16 psychiatric hospitalizations in varenicline-treated patients, and 21 in NRT patients. The HRs for the composite outcome (0.76; 95% CI=0.40 to 1.46) of any hospitalized mental health disorder and for each component of the composite were not increased for varenicline compared with NRT use, except for the risk of hospitalization due to depression (Appendix Table II), however, the confidence intervals of the point estimates were all wide and crossed the null (i.e., 1.0).

Findings on primary outcomes (i.e., inpatient neuropsychiatric visit) in the Cunningham et al.9 publication were similar to what was reported in the VA study final report. In contrast, a positive association was reported between varenicline use and outpatient neuropsychiatric visit in the Cunningham et al.9 study, although most of the effect estimates did not reach statistical significance. One estimate showed a significantly elevated risk of outpatient visits for schizophrenia (HR=1.27, 95% CI=1.07-51).9

The Pasternak study12

The study by Pasternak et al. compared the rates of emergency department visit or hospital admission for a psychiatric diagnosis (Appendix II) that had occurred within 30 days of treatment initiation among new users of varenicline or bupropion who started therapy between January 1st 2007 and December 31 2010 in Denmark. Patients who had fewer than two years of registered residence in Denmark prior to the cohort entry and those with use of varenicline or bupropion prior to 2007 were excluded. Overall, 59,790 new users of varenicline and 17,936 new users of bupropion were identified. In this unmatched cohort, the distribution of baseline characteristics was generally similar between the two groups. To further control for confounders, 17,935 varenicline users were matched 1:1 to bupropion users based on a propensity score. The propensity score was estimated based on a range of variables, including age, sex, place of birth, place of living, medical history, comorbidities, selected prescription medications use and indicators of health-care use. A total of 85 psychiatric events occurred (39 events in varenicline group versus 46 events in bupropion group). There were three cases of suicide attempt or completed suicide among varenicline users and one case among bupropion users. Varenicline use was shown to be associated with a 15% lower neuropsychiatric risk compared with bupropion use (HR: 0.85. 95% CI: 0.55- 1.30), but the confidence interval of the point estimate was wide and crossed the null.

The Thomas study8

Thomas et al.8 examined the 3-month risk of suicide-related outcomes and all-cause mortality among adults in 31,260 varenicline users, 6,741 bupropion users and 81,545 NRT users who
received their first prescription between September 01, 2006 and October 31, 2011 (no use of varenicline, bupropion, or NRT in past year). Ninety-two cases of suicide and non-fatal self-harm were identified from the linked UK CPRD, Office for National Statistics (ONS) mortality data and Health Episode Statistics (HES) data during 3 months of follow-up after the date of treatment initiation: 69 among NRT users, 4 among bupropion users and 19 among varenicline users. The multivariate-adjusted HR for fatal and non-fatal self-harm included the null when comparing varenicline users to NRT users (HR=0.88, 0.52 to 1.49), as well as when comparing bupropion users to NRT users (HR=0.83, 0.30 to 2.31). Similar findings were reported using propensity score-adjusted methods, but not in the instrumental variable analyses (Table 3-1, See section 4.2 for further discussions). The trend did not change in most of the sensitivity analyses that extended the follow-up to 6-, or 9-months, as well as when restricting to first-time users of smoking cessation drugs.

**The Kotz study**

The Kotz study is a retrospective cohort study that used UK QResearch database (National Health Service general practices) to compare neuropsychiatric and cardiovascular events among new users (ages 18-100 years) of varenicline (N=51,450), bupropion (N=6,557) and NRT (N=106,759) between Jan 1, 2007, and June 30, 2012. The study excluded patients if they had used one of the drugs during the 12 months before the start date of the study, had received overlapping prescriptions for these drugs during the follow-up period (indicating that they were on concomitant therapy), or were temporary residents. Patients were followed up for 6 months to estimate risk of neuropsychiatric events using Cox proportional hazards models (reference group: NRT), adjusted for potential confounders. Varenicline was associated with a significantly reduced risk of depression (HR=0·66; 95% CI=0·63 to 0·69), and self-harm (HR=0·56; 95% CI=0·46 to 0·68), while bupropion was associated with a significant reduction in depression risk (HR=0.75; 95% CI=0.67 to 0.83) and a reduction of risk of self-harm that did not reach statistical significance (HR=0.74; 95% CI=0.48 to 1.16), which could be due to lack of power, given the wide confidence interval. The trend was similar in the analyses using propensity score matching to account for confounding. All of the analyses yielded similar results when the investigators examined neuropsychiatric events during 3 months of follow-up. The authors also used an approach described by Lin and colleagues to model the effects of any potential unmeasured confounding. The modeling explores the range of the HRs and 95% CIs in varenicline versus NRT users for each of the events for a hypothetical, unmeasured, binary confounder, with an HR of 3 and various combinations of prevalence in the two exposure groups. According to the authors, the modelling of unmeasured confounding showed that missing a true increased risk of any of the neuropsychiatric events due to a single unmeasured confounder was very unlikely. For example, it would have required an unmeasured confounder to be very strongly associated with the outcome (hypothetical HR of 3) for the direction of the association with self-harm to be reversed from a reduced risk to an increased risk. The hypothetical unmeasured confounder would need to be distributed very differently among the two exposure groups (i.e., the prevalence of this confounder would need to be only 10% in varenicline users and be in at least 80% among NRT users) to achieve this reversing of the association.

**The Molero study**

The Molero study is a cohort study that used the Swedish population-based health care data to examine the association of varenicline use and several outcomes, including three psychiatric
conditions (psychoses, mood conditions, and anxiety conditions) and suicidal behavior. The study implemented within-person comparison (i.e., using patients as their own control to compare a varenicline-exposed period to an unexposed period) as their primary analysis in order to control for bias due to channeling and other unmeasured confounders that do not change over time. The study identified 69,757 people (ages 15 years and older) who had varenicline prescribed between November 22, 2006 (that is, the introduction of varenicline in Sweden) and December 31 2009 from the Swedish Prescribed Drug Register. Varenicline exposed periods were defined as starting at the date of the first collected prescription and ending 12 weeks later. No exclusions for prior varenicline use were made. Because varenicline is often divided into several prescriptions for the same 12-week treatment, all prescriptions within the 12 weeks after the first collected prescription were considered to be part of the same treatment period. Patients were allowed to contribute multiple exposed periods if they had a varenicline prescription(s) after a 12-week window from the first prescription. The unexposed period included the time before the first observed varenicline-exposed period, between varenicline-exposed periods and after the last observed varenicline-exposed period. The studied neuropsychiatric outcomes were medical encounters for new psychiatric conditions and suicidal behavior. Information on the incidence of new psychiatric conditions came from the Swedish Patient Register, which includes diagnoses from both hospital admissions and outpatient visits for specialized care. Diagnoses received during planned visits (that is, follow-ups and referrals) were excluded from the analyses. Psychiatric conditions included three diagnostic categories: psychoses (ICD-10 (international classification of diseases, 10th revision) codes: F20-F29), mood conditions (F30-F39), and anxiety conditions (F40-F45, F48). Suicidal behavior included suicide attempts and suicides, defined as emergency inpatient or outpatient hospital visits or death due to intentional self-harm (ICD-10: X60-X84). The information on suicide attempts was collected from the Patient Register and information on suicides was collected from the Cause of Death Register. Stratified cox proportional-hazards regression, adjusted for age as a time-varying covariate, was used to estimate the risk of an outcome comparing between varenicline-exposed time and unexposed time. The analyses were repeated in patients with and without pre-existing psychiatric diagnoses (ICD-9: 295-302, 307-316; ICD-10: F20-F48, F50-F69, F90-F98; diagnosed before 1 November 2006). The findings showed that being treated with varenicline was not associated with significantly increased risk of suicidal behavior, but varenicline was associated with an increased hazard of new psychiatric conditions (HR=1.18, 95% CI=1.05 to 1.31). When further examining the associations by analyzing each diagnostic category separately, the results showed that varenicline was associated with increased risk for anxiety (HR=1.27, 95% CI=1.06 to 1.51) and mood conditions (HR=1.28; 95% CI= 1.07 to 1.52), but did not appear to be associated with the psychoses risk (HR= 0.94; 95% CI= 0.73 to 1.20) (Table 3-2).

3.2.2 Effect of smoking cessation treatment among patients with and/or without psychiatric history

The Meyer study

Psychiatric history was defined as having one inpatient or two outpatient codes (the same ICD-9 codes as those used to identify the study outcome, Appendix Table I) on different days within the 365 days prior to the index prescription date. Most of the 55 primary outcome events (30-day neuropsychiatric hospitalization, 18 of the 23 with varenicline exposure, and 25 of the 32 with NRT exposure, Table 3-2) occurred in patients with psychiatric history, although such patients formed a minority of the cohorts (2,595 in the varenicline cohort and 1,762 in the NRT cohort).
The effect estimates among the population with a history of psychiatric disease could not be calculated in the propensity-matched cohort because of the small sample size. However, the effect estimates among the population without a history of psychiatric disease (HR = 0.80; 95% CI=0.21 to 2.98, Table 3-2) were numerically lower than that of the overall population in the propensity-matched cohort (HR=1.14; 95% CI=0.56 to 2.34, Table 3-2). Nevertheless, both estimates had wide confidence intervals that crossed the null. The researcher also calculated the HRs among the subgroups from a model that included the propensity score as a continuous variable (i.e., propensity score-adjusted analyses). The effect estimates were not significantly different between patients with (HR = 0.93, 95% CI: 0.48 to 1.82, Table 3-2) or without (HR = 0.77, 95% CI: 0.21 to 2.84, Table 3-2) psychiatric history, although the HRs were numerically lower among patients without prior psychiatric disease.

**The VA study**

In the VA study, patients with psychiatric history were defined as having been hospitalized with an inpatient diagnosis for mental health disorders (Appendix Table I) within the 24 months prior to the index date. Patients without psychiatric history were defined as having no mental health diagnoses, identified by ICD-9-CM codes in inpatient and outpatient records, and no prescriptions for medications used to treat mental health disorders within the 24 months prior to the index date. Among patients without psychiatric history, there was only one case of hospitalization for a mental health disorder (in the varenicline group); therefore, the HRs of inpatient mental disorder cannot be calculated among this subgroup. The effect estimates among the population with a history of psychiatric disease (HR = 1.07; 95% CI=0.46 to 2.46, Table 3-2) was numerically higher than that of the overall population in the propensity-matched cohort (HR=0.76; 95% CI=0.40 to 1.46, Table 3-2), but both were with wide confidence intervals that crossed the null.

The sample size and outcome event numbers were slightly different between the Cunningham et al. publication\(^9\) and the VA study report, because of the changes in the propensity score matching approach,\(^5\) however, the subgroup findings on the primary outcomes were similar. The point estimates of the HRs were generally higher among patients with psychiatric history than the overall population, although they were all imprecise and did not reach statistical significance.\(^9\) There was a significant difference in outpatient visits for schizophrenia between varenicline and NRT (HR=1.40, 95% CI=1.09-1.80) in the subgroup with psychiatric history.\(^9\) No patients in either the varenicline or NRT groups presented with outpatient visits for schizophrenia in the subgroup without psychiatric history.\(^9\)

**The Pasternak study\(^12\)**

Using the propensity score matched cohort, the study estimated HRs in participants with and without a history of psychiatric disorder. The history of psychiatric disorder was defined as any psychiatric diagnosis listed in Appendix II, or antidepressant or antipsychotic drug use within the one year before varenicline or bupropion initiation. The risk of psychiatric events associated with varenicline compared with bupropion appeared lower in participants without a history of psychiatric disorder (HR=0.33, 95% CI=0.09-1.22, Table 3-2) than in participants with a history

\(^{\dagger}\) The publication by Cunningham et al. reported results based on a 1:2 propensity score-matching instead of a 1:1 propensity score-matched cohort as specified in the VA study protocol.
(HR=1.01, 95% CI=0.64-1.59, Table 3-2) although this was based on few cases, and the difference in risk of psychiatric events associated with varenicline versus bupropion by history of psychiatric disorder was not statistically significant (P=0.12).

*The Molero study*¹¹

This study reported the risk of each psychiatric diagnostic category (mood condition, anxiety condition and psychosis) in patients with and without pre-existing psychiatric diagnoses (ICD-9: 295-302, 307-316; ICD-10: F20-F48, F50-F69, F90-F98; diagnosed before 1 November 2006). Similar to the findings in the overall population, varenicline use was associated with an increased risk for anxiety and mood conditions, although the effect estimates were not statistically significant among users without prior psychiatric illness (Table 3-2). The trend of psychosis risk was opposite when the analyses were stratified by prior psychiatric illness, but both effect estimates were wide and crossed null (HR=0.90, 95% CI=0.70-1.16 among users with prior psychiatric illness versus HR=3.52, 95% CI=0.81-15.27 among users without prior psychiatric illness, Table 3-2).
Figure 3-1 Reviewer-generated forest plot of varenicline-associated neuropsychiatric (NPS) risk observed in all reviewed studies (reference group: nicotine replacement therapy, a,b,d,f bupropion, e or person-time that was unexposed to varenicline e)

<table>
<thead>
<tr>
<th>Event (Primary Diagnosis)</th>
<th>HR= 0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPS hospitalization (primary diagnosis)</td>
<td>1.14 (0.56-2.34)</td>
<td>0.79 (0.50-1.24)</td>
<td>0.71 (0.60-0.84)</td>
<td>0.76 (0.40-1.46)</td>
<td>1.14 (0.41-3.15)</td>
</tr>
<tr>
<td>NPS hospitalization (all diagnoses) a</td>
<td>0.85 (0.55-1.30)</td>
<td>0.66 (0.63-0.69)</td>
<td>0.37 (0.10-1.41)</td>
<td>0.3</td>
<td>0.45</td>
</tr>
<tr>
<td>NPS outpatient visits a</td>
<td>0.94 (0.73-1.20)</td>
<td>0.88 (0.52-1.49)</td>
<td>0.56 (0.46-0.68)</td>
<td>1.00 (0.72-1.37)</td>
<td></td>
</tr>
<tr>
<td>NPS hospitalization (primary diagnosis) b</td>
<td>1.18 (1.05-1.31)</td>
<td>1.27 (1.06-1.51)</td>
<td>1.28 (1.07-1.52)</td>
<td>0.94 (0.73-1.20)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for depression b</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
</tr>
<tr>
<td>Hospitalization for bipolar b</td>
<td>0.50 (0.05-5.51)</td>
<td>0.79 (0.50-1.24)</td>
<td>0.71 (0.60-0.84)</td>
<td>0.76 (0.40-1.46)</td>
<td>1.14 (0.41-3.15)</td>
</tr>
<tr>
<td>Hospitalization for schizophrenia b</td>
<td>0.37 (0.10-1.41)</td>
<td>0.37 (0.10-1.41)</td>
<td>0.37 (0.10-1.41)</td>
<td>0.37 (0.10-1.41)</td>
<td>0.37 (0.10-1.41)</td>
</tr>
<tr>
<td>NPS Emergency department visit or hospitalization c</td>
<td>0.85 (0.55-1.30)</td>
<td>0.66 (0.63-0.69)</td>
<td>0.37 (0.10-1.41)</td>
<td>0.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Outpatient visit for depression d</td>
<td>0.94 (0.73-1.20)</td>
<td>0.88 (0.52-1.49)</td>
<td>0.56 (0.46-0.68)</td>
<td>1.00 (0.72-1.37)</td>
<td></td>
</tr>
<tr>
<td>NPS in- or outpatient visit e</td>
<td>1.18 (1.05-1.31)</td>
<td>1.27 (1.06-1.51)</td>
<td>1.28 (1.07-1.52)</td>
<td>0.94 (0.73-1.20)</td>
<td></td>
</tr>
<tr>
<td>In- or outpatient visit for anxiety condition e</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
</tr>
<tr>
<td>In- or outpatient visit for mood condition e</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
<td>1.14 (0.41-3.15)</td>
</tr>
<tr>
<td>In- or outpatient visit for psychosis e</td>
<td>0.37 (0.10-1.41)</td>
<td>0.37 (0.10-1.41)</td>
<td>0.37 (0.10-1.41)</td>
<td>0.37 (0.10-1.41)</td>
<td>0.37 (0.10-1.41)</td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from hospitalization or mortality data) f</td>
<td>0.94 (0.64-1.38)</td>
<td>0.94 (0.64-1.38)</td>
<td>0.94 (0.64-1.38)</td>
<td>0.94 (0.64-1.38)</td>
<td>0.94 (0.64-1.38)</td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from outpatient data) d</td>
<td>0.85 (0.55-1.30)</td>
<td>0.66 (0.63-0.69)</td>
<td>0.37 (0.10-1.41)</td>
<td>0.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from hospitalization or mortality data) e</td>
<td>0.94 (0.73-1.20)</td>
<td>0.88 (0.52-1.49)</td>
<td>0.56 (0.46-0.68)</td>
<td>1.00 (0.72-1.37)</td>
<td></td>
</tr>
</tbody>
</table>

NPS: Neuropsychiatric; HR: Hazard ratio; PTSD: Posttraumatic stress disorder
b Final report of the VA study: Varenicline and Mental Health Disorders, dated May 2011, revised June 2011
Figure 3-2 Reviewer-generated forest plot of neuropsychiatric (NPS) risk observed in all reviewed studies that examined both varenicline- and bupropion- associated risk\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>H.R. 0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient visit for depression-varenicline versus NRT\textsuperscript{a}</td>
<td>0.66 (0.63-0.69)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visit for depression-bupropion versus NRT\textsuperscript{a}</td>
<td>0.75 (0.67-0.83)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (From hospitalization or mortality data)-varenicline versus NRT\textsuperscript{b}</td>
<td>0.88 (0.52-1.49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (From hospitalization or mortality data)-bupropion versus NRT\textsuperscript{b}</td>
<td>0.83 (0.30-2.31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from outpatient data)-varenicline versus NRT\textsuperscript{a}</td>
<td>0.56 (0.46-0.68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide or non-fatal self-harm (from outpatient data)-bupropion versus NRT\textsuperscript{a}</td>
<td>0.74 (0.48-1.16)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRT: nicotine replacement therapy


\textsuperscript{b} Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self-harm in the Clinical Practice Research Datalink: prospective cohort study. BMJ. 2013;347:f57
Table 3-1 Reviewer-generated summary table of the risks of suicide and non-fatal self-harm among varenicline users and bupropion users observed in the Thomas et al. study

<table>
<thead>
<tr>
<th>Analytical approaches</th>
<th>Exposure</th>
<th>Effect estimate (95% Confidence interval)</th>
<th>Reference (NRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hazard ratio</td>
<td>Risk difference per 1000 person-year</td>
</tr>
<tr>
<td>3-month suicide and non-fatal self-harm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cox regression analyses</td>
<td>Varenicline</td>
<td>0.88 (0.52 to 1.49)</td>
<td>-0.1c</td>
</tr>
<tr>
<td>Propensity score matching analyses</td>
<td>Varenicline</td>
<td>0.87 (0.51 to 1.48)</td>
<td>-0.1c</td>
</tr>
<tr>
<td>Instrumental variable analyses</td>
<td>Varenicline</td>
<td>-</td>
<td>0.4 (-0.8 to 1.5)</td>
</tr>
<tr>
<td>Cox regression analyses</td>
<td>Bupropion</td>
<td>0.83 (0.30 to 2.31)</td>
<td>-0.1 to -0.2c</td>
</tr>
<tr>
<td>Propensity score matching analyses</td>
<td>Bupropion</td>
<td>0.87 (0.31 to 2.4)</td>
<td>0.1c</td>
</tr>
<tr>
<td>Instrumental variable analyses</td>
<td>Bupropion</td>
<td>-</td>
<td>-3.9b (-7.0 to -0.9)</td>
</tr>
</tbody>
</table>

p value < 0.05.
see the calculation from HRs to risk differences in Appendix III
Table 3-2 Reviewer-generated summary table of varenicline-associated neuropsychiatric risk stratified by psychiatric history

<table>
<thead>
<tr>
<th></th>
<th>Overall cohort</th>
<th>Cohort WITHOUT psychiatric history</th>
<th>Cohort WITH psychiatric history</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meyer et al.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>N=19,933</td>
<td>N=15,867</td>
<td>N=17,338</td>
</tr>
<tr>
<td></td>
<td>N=15,867</td>
<td>N=14,105</td>
<td>N=2,595</td>
</tr>
<tr>
<td>NPS hospitalization</td>
<td>23</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>HR 95% CI</td>
<td>1.14 (0.56-2.34)</td>
<td>0.80 (0.21-2.98)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>VA study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>N=14,131</td>
<td>N=14,131</td>
<td>N=13,811</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=13,811</td>
<td>N=2,034</td>
</tr>
<tr>
<td>NPS hospitalization</td>
<td>16</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>HR 95% CI</td>
<td>0.76 (0.40-1.46)</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td><strong>Pasternak et al.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>17,935</td>
<td>17,935</td>
<td>14,089</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13,962</td>
<td>3,846</td>
</tr>
<tr>
<td>NPS hospitalization</td>
<td>39</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>HR 95% CI</td>
<td>0.85 (0.55 to 1.30)</td>
<td></td>
<td>0.33 (0.09 to 1.22)</td>
</tr>
<tr>
<td><strong>Molero et al.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>N=69,757</td>
<td>N=60,366</td>
<td>N=9,391</td>
</tr>
<tr>
<td>Anxiety conditions</td>
<td>1.27 (1.06 to 1.51)</td>
<td></td>
<td>1.41 (0.99 to 2.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.23 (1.01 to 1.51)</td>
<td></td>
</tr>
<tr>
<td>Mood conditions</td>
<td>1.28 (1.07 to 1.52)</td>
<td></td>
<td>1.17 (0.86 to 1.60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.31 (1.06 to 1.63)</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>0.94 (0.73 to 1.20)</td>
<td></td>
<td>3.52 (0.81 to 15.27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.90 (0.70 to 1.16)</td>
<td></td>
</tr>
</tbody>
</table>


b Final report of the VA study: Varenicline and Mental Health Disorders, dated May 2011, revised June 2011


e Based on propensity score-matched cohort

fp value < 0.05.
4. DISCUSSION

The findings were conflicting across studies, and each of the reviewed studies had a number of study design limitations that complicate the interpretation of their results. We will address the specific limitations of the existing observational studies in sections 4.1 to 4.3.

4.1 CONCERNS ON VALIDITY OF OUTCOME MEASURES

The outcomes examined in these studies—suicide, self-harm and neuropsychiatric medical encounters—did not cover the full range of the neuropsychiatric adverse events that have been seen in post-marketing spontaneous adverse event reports associated with smoking cessation products. Furthermore, all studies relied primarily on diagnostic codes recorded during medical encounters (ICD-9, ICD-10, or Read codes) to ascertain outcomes; only one study reported some measure of validity for some of the ICD-10 codes used to identify their outcomes. We are concerned that diagnostic codes cannot accurately capture and characterize all of the neuropsychiatric adverse events that have been associated with varenicline. The events described in the adverse event reports have involved abrupt behavioral and/or mood changes, which are difficult to accurately translate into a medical coding system. Adverse events may have also resulted in patient contact with legal, rather than medical, systems. Without a detailed exploration of medical charts to identify all codes that might have been used to capture these outcomes, as well as patient and provider interviews to determine behavior and coding practices, it is not possible to estimate how many events are misclassified or not captured in these studies. Such problems are inherent to the study of behavioral and psychiatric outcomes, which present different challenges than studying other medical diagnoses.

In the studies that examined the association between smoking cessation products and neuropsychiatric hospitalizations or emergency room visits, clinically important psychiatric events that did not include emergency room visit or hospitalization (such as a successful suicide without hospitalization) were not captured. Although both the Meyer and the VA studies also examined a secondary outcome that included outpatient visits with a neuropsychiatric diagnosis, this metric may be simply capturing pre-existing psychiatric comorbidities, rather than treatment emergent psychiatric events. Moreover, an acute worsening of a psychiatric condition without a health care professional encounter would be missed. In light of the stigma that can be attached to psychiatric diagnoses in medical records, particularly in the military, this possibility cannot be ruled out.

Undercounting of the outcome is also a concern with respect to the Thomas study that examined suicide-related outcomes due to the stigma that can be attached to such diagnoses, the difficulty in determining intentionality of injury, and the fact that such attempts are not always brought to medical attention. Although Thomas et al. used both the hospital admission data and the UK

---

\[d\] For example, some adverse events that have been reported among patients who used varenicline include changes in mood, agitation, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, changes in behavior, anxiety, panic, suicidal ideation, suicide attempt and completed suicide.

\[e\] Pasternak et al. had reported high positive predictive value (>90%) for the ICD-10 codes used to identify a schizophrenia-spectrum disorder and a single depressive episode. However, the two conditions are only some of several psychiatric adverse events that the study targeted.
mortality records to capture suicide-related outcomes (fatal/non-fatal self-harm), this approach only enhanced the capture of a part of the outcome—fatal self-harm, but not the other part that still relied on diagnostic codes used in hospital records (i.e., attempted suicide). In fact, a high proportion (approximately 90\%) of the observed suicide-related outcome in the Thomas et al.\textsuperscript{8} study were non-fatal self-harm. The author reported that a total of 92 cases of suicide and non-fatal self-harm were identified from the study population, but only six suicides were recorded in the NRT group, two in the varenicline group and none in the bupropion group.\textsuperscript{8}

The Read codes used by the Kotz study\textsuperscript{10} have been shown to be unreliable for detecting suicide death and under-report non-fatal self-harm.\textsuperscript{14} The authors did not address the validity of Read codes to identify depression. In addition, the study was based on the general practitioner (GP) encounter data; suicide death, as well as severe cases of depression or suicide attempt that lead to emergency room visits, hospitalizations or requiring treatment by a psychiatrist were likely missed in the study. If varenicline or bupropion causes more severe neuropsychiatric adverse events than NRT, this under-ascertainment of outcome would be more pronounced in the varenicline or bupropion group than NRT groups. Furthermore, the study did not differentiate depression visits for new or existing conditions. The fact that varenicline and bupropion use significantly decreased the number of depression visits could be evidence of an adverse effect if planned follow-up visits for a pre-existing condition were missed (i.e., could be evidence of worsening depression).

Although Molero et al.\textsuperscript{11} used both hospital and outpatient data to identify neuropsychiatric events, and excluded diagnoses during planned visits such as follow-up or referral, only some of the inpatient diagnosis codes (for schizophrenia and personality disorder) used by Molero et al.\textsuperscript{11} were previously validated\textsuperscript{15}. The validity of the majority of the diagnostic codes, especially those occurring in the outpatient setting, is still unclear. Under-ascertainment of suicide attempt is still likely for the reasons that have been addressed previously, even though the study used hospital and mortality records to identify suicide-related outcomes.

4.2 CHANNELING BIAS AND RESIDUAL CONFOUNDING

Another major concern of the existing observational data is residual confounding and channeling bias, especially, among the three studies by Thomas et al., Kotz et al., and Molero et al.\textsuperscript{11} that included data from the timeframe after the publicity of the neuropsychiatric safety concern associated with varenicline and bupropion.\textsuperscript{16} Adverse publicity may have resulted in patients with a history of neuropsychiatric illness being preferentially prescribed NRT, and healthier patients or patients at lower risk of neuropsychiatric events being preferentially prescribed the other two drugs (i.e., channeling bias). In fact, varenicline users and bupropion users in the Thomas study and the Kotz study were less likely to have a history of chronic disease or psychiatric illness,\textsuperscript{8,10} or had a lower frequency of previous use of hypnotics, antipsychotics, and antidepressants;\textsuperscript{8} these patients were shown to be less likely to be at risk for neuropsychiatric event compared to NRT users. The study by Pasternak et al. also included data after the publicity of varenicline and bupropion’s neuropsychiatric risk. Because the publicity on varenicline’s neuropsychiatric safety concern was more widespread than that of bupropion, channeling bias could have existed in the Pasternak study,\textsuperscript{8,12} and led to a healthier varenicline group with lower baseline neuropsychiatric risk than the bupropion group. However, the distribution of baseline psychiatric history and psychotropic drug use was generally similar between the two groups in the study. The preferential prescribing of bupropion over varenicline among patients with higher
neuropsychiatric risk, if it existed, may not have biased the findings of the Pasternak study significantly.

The three studies by Thomas et al.,8 by Kotz et al.,10 and by Molero et al.11 implemented advanced designs or advanced analytical approaches to handle the potential bias due to baseline patient selection, but we cannot be sure that their analyses adequately controlled for the baseline differences in patients due to channeling. We will comment on the methods of each study in the following section.

*The Thomas study*

Thomas et al. conducted three analyses: a conventional Cox regression analysis, and two advanced analyses—a propensity score [PS] matched analysis and an instrumental variable [IV] analysis—in order to attempt to account for the potential bias due to baseline selection into treatment cohorts. Despite using multiple analytical approaches, their findings are still likely to be biased due to residual confounding. The issue of residual confounding was illustrated by the findings of their secondary analysis that examined all-cause mortality risk associated with the study drugs as described in the following paragraphs.

As shown in Table 4-1, the all-cause mortality risk at 3 months from their Cox regression and PS matching analyses were significantly lower among both varenicline users and bupropion users, compared to NRT users. Given that three months is too short of a timeframe for realizing the survival benefits of smoking cessation, the reduced risk in all-cause mortality seen in the Cox regression and PS matching analyses most likely indicates that varenicline users and bupropion users are generally healthier than NRT users. Therefore, the effect estimates of the suicide-related outcome (Table 3-1) from those two analyses would likely carry the impact of the residual baseline differences.

### Table 4-1 Potential channeling bias in the Thomas et al. study illustrated by their findings of the all-cause mortality risk among varenicline users and bupropion users

<table>
<thead>
<tr>
<th>Analytical approaches</th>
<th>Exposure</th>
<th>Effect estimate (95% Confidence interval)</th>
<th>3-month all-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(Reference: NRT users)</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>Cox regression analyses</td>
<td>Varenicline</td>
<td>0.44(^b) (0.30 to 0.63)</td>
<td>-1.4 to -2(^c)</td>
</tr>
<tr>
<td>Propensity score matching analyses</td>
<td>Varenicline</td>
<td>0.37(^b) (0.26 to 0.53)</td>
<td>~-2(^c)</td>
</tr>
<tr>
<td>Instrumental variable analyses</td>
<td>Varenicline</td>
<td>-</td>
<td>-0.8 (-2.8 to 1.1)</td>
</tr>
<tr>
<td>Cox regression analyses</td>
<td>Bupropion</td>
<td>0.39(^b) (0.16 to 0.95)</td>
<td>-1 to -2(^c)</td>
</tr>
<tr>
<td>Propensity score matching analyses</td>
<td>Bupropion</td>
<td>0.34(^b) (0.14 to 0.82)</td>
<td>-2 to -3(^c)</td>
</tr>
<tr>
<td>Instrumental variable analyses</td>
<td>Bupropion</td>
<td>-</td>
<td>-4.2 (-10.5 to 2.1)</td>
</tr>
</tbody>
</table>

\(^a\) Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. BMJ. 2013;347:f57

\(^b\) p value < 0.05.

\(^c\) see the calculation from HRs to risk differences in Appendix III
Their third analysis using an IV approach appeared to reduce the impact of residual confounding when comparing varenicline users to NRT users, because the difference in 3-month mortality risk between varenicline and NRT users became smaller (from \(-1.4\) to \(-2\) per 1,000 patient-years based on Cox regression or PS matching analyses, to \(-0.8\) per 1,000 patient-years in the IV analysis, Table 4-1). However, the IV analyses might still carry bias in estimating varenicline’s effect on suicide-related outcome. In order for IV analysis to work well, the chosen IV needs to be strongly associated with the actual treatment and be independent of any factors that have impact on the targeted outcome (i.e. suicide or self-harm). Thomas et al.\(^8\) choose physician’s prescribing preference as the IV and they used physicians’ prescribing patterns as the proxy of “prescribing preference”. We noticed that physicians’ characteristics, something that can influence prescribing preferences, are not used to estimate physician’s preference. If the prescribing preferences are related to a physician’s familiarity with current literature and the ability to make use of the information, physicians who prefer varenicline over NRT because of its higher efficacy\(^7\) could be more vigilant of the risk of smoking cessation itself on depression or suicide and monitor their patients more frequently. In this scenario, patients who were seen by physicians who prefer varenicline or bupropion would have lower suicide risk that is unrelated to drug effect. The implication is that the effect estimates from IV analyses can still be biased by differences in the physician characteristics, and this study may have under-estimated the true suicide risk associated with varenicline.

With regard to the bupropion findings, the IV analyses did not seem to reduce the impact of residual confounding. Although we do not expect a reduction of all-cause mortality within three months of bupropion use because it is too short of a timeframe for realizing the survival benefits of smoking cessation, the IV findings indicated that bupropion is associated with an even larger reduction in 3-month mortality than the findings from the Cox regression and PS matching analyses (\(-1\) to \(-3\) per 1,000 patient-years based on Cox regression or PS matching analyses, to \(-4.2\) per 1,000 patient-years in the IV analysis, Table 4-1). Nevertheless, the effect estimate of all-cause mortality risk in the IV analysis was not statistically significant. The reduced risk of suicide-related outcome associated with bupropion in the IV analyses might still be biased due to the healthier bupropion users than NRT users.

*The Kotz study*\(^10\)

Similar to the Thomas study,\(^8\) the baseline characteristics of the study population indicated potential differential prescribing, i.e., varenicline and bupropion seems to be given to patients who were younger, less socioeconomically deprived and less likely to have a history of psychiatric illness. Although the author stated that those measured baseline differences were balanced in the statistical models (i.e., multivariable Cox regression and propensity score matching) used for their analyses, some important confounders were unmeasured and could still have biased the study findings. One such unmeasured confounder is prior or concurrent use of psychotropic medications, which had been reported to be imbalanced among smoking cessation product users in the aforementioned Thomas study,\(^8\) which was based on a similar data source (i.e., UK general practices data) as the Kotz\(^10\) study and likely had similar prescribing and utilization patterns. Recognizing the potential of residual confounding from unmeasured confounders, the authors conducted a sensitivity analysis and concluded that the observed reduced risk associated with varenicline use is unlikely to be reversed by unmeasured confounder(s). This is because the distribution of the unmeasured confounder would need to be extremely imbalanced among comparison groups to reverse the findings.\(^10\) One caveat of this
sensitivity analysis is that it only models the impact of a single unmeasured confounder that is not associated with the any measured confounders in the study; therefore, it does not address the impact of the unmeasured psychotropic medication use, which is likely to be associated with psychiatric comorbidities. In this case, the distribution of the unmeasured psychotropic medication use might not need to be as imbalanced between the comparison groups to reverse the effect estimates.

The Molero study

Molero et al. implemented a “within-person comparison” (i.e., self-controlled design using patients as their own controls) as the principle analysis instead of the “between-person” comparison that compared users of different smoking cessation products) that was used in the other reviewed studies. The self-controlled design handled the concern of the confounding due to the potential differential prescribing of smoking cessation products based on a patient’s baseline mental comorbidities because varenicline users were compared to themselves. However, the self-controlled design introduced a different type of confounding. Specifically, this design is unable to account for confounding that can change over time. As the author acknowledged, one of the potential time-varying confounders was the impact of nicotine withdrawal syndrome. Because nicotine includes psychoactive compounds that mimic an antidepressant effect, smoking cessation could induce nicotine withdrawal symptoms that include depression and anxiety. It was unclear whether the increased neuropsychiatric risk that was observed in the Molero study was due to varenicline use or to the choice of the comparison periods. The comparison periods could have included periods of smoking cessation attempts without medications, with other medications, or periods during which the patient was not trying to quit smoking.

4.3 OTHER DESIGN OR METHODOLOGICAL ISSUES

The study by Pasternak et al. compared risk of neuropsychiatric emergency department visits or hospitalizations between varenicline users and bupropion users; the study found a non-significant 15% lower risk associated with varenicline use compared with bupropion use (HR: 0.85. 95% CI: 0.55- 1.30; Table 3-1, Appendix II). However, given that bupropion also has been associated with psychiatric adverse events and carries a boxed warning alerting about this possibility, this finding does not provide reassurance of varenicline’s neuropsychiatric safety.

All of the reviewed studies included patients with pre-existing psychiatric disorders with the intention to improve the generalizability over the premarketing trials, because these patients were typically excluded from the clinical trials conducted with varenicline before it was approved. However, not all of the studies examined the impact of psychiatric history on smoking cessation products’ neuropsychiatric risk. Additionally, the four studies that had investigated the impact of psychiatric history all had limitations. We are unable to evaluate the impact of psychiatric history on varenicline-associated neuropsychiatric risk because the subgroup findings carried bias. For Molero et al., the bias was due to the impact of nicotine withdrawal syndrome, because of the self-controlled design (as addressed in section 4.2). Findings of the Meyer study and VA study both suggest that varenicline users with psychiatric history might have a higher neuropsychiatric risk than those without because the majority of the neuropsychiatric events were observed among patients with psychiatric history. In both studies, HRs of the patients with psychiatric history were also numerically higher than that of the overall cohort. However, the small cohort of patients with psychiatric history and/or the few observed outcomes in the subgroup without
psychiatric history prevented a definitive conclusion about the additional impact of psychiatric history on the association between smoking cessation products and neuropsychiatric events. The Pasternak et al. study reported a similar trend that the observed HRs of psychiatric events associated with varenicline appeared lower in participants without a history of psychiatric disorder than in participants with a history, but the point estimates were imprecise and the confidence intervals both crossed one. As addressed earlier, the choice of bupropion as the reference group to examine varenicline’s neuropsychiatric risk also make it difficult to interpret the findings. All of the reviewed studies included patients with pre-existing psychiatric disorders with the intention to improve the generalizability over the premarketing trials, because these patients were typically excluded from the clinical trials conducted with varenicline before it was approved. However, not all of the studies examined the impact of psychiatric history on smoking cessation products’ neuropsychiatric risk. Additionally, the four studies that investigated the impact of psychiatric history all had limitations. We are unable to evaluate the impact of psychiatric history on varenicline-associated neuropsychiatric risk because the subgroup findings carried bias. For Molero et al., the bias was due to the impact of nicotine withdrawal syndrome, because of the self-controlled design (as addressed in section 4.2). Findings of the Meyer study and VA study both suggest that varenicline users with psychiatric history might have a higher neuropsychiatric risk than those without because the majority of the neuropsychiatric events were observed among patients with psychiatric history. In both studies, HRs of the patients with psychiatric history were also numerically higher than that of the overall cohort. However, the small cohort of patients with psychiatric history and/or the few observed outcomes in the subgroup without psychiatric history prevented a definitive conclusion about the additional impact of psychiatric history on the association between smoking cessation products and neuropsychiatric events. The Pasternak et al. study reported a similar trend that the observed HRs of psychiatric events associated with varenicline appeared lower in participants without a history of psychiatric disorder than in participants with a history, but the point estimates were imprecise and the confidence intervals both crossed one. As addressed earlier, the choice of bupropion as the reference group to examine varenicline’s neuropsychiatric risk also made it difficult to interpret the findings.

4.4 SUMMARY ASSESSMENT

To briefly summarize our assessment of the six reviewed observational studies:

- Studies that examined varenicline’s neuropsychiatric risk
  - The studies by Meyer et al. and VA study that examined risk of neuropsychiatric hospitalizations found “no increased risk” associated with varenicline relative to NRT, but those findings were not reassuring of varenicline’s neuropsychiatric safety. The use of diagnostic codes to capture neuropsychiatric events in these studies is likely to have under-ascertained true events. Under-ascertainment of events that did not differ by cohort would result in an imprecise relative effect estimate with wide confidence intervals, as observed in the two studies. Those imprecise effect estimates did not suggest a consistent trend of association between varenicline and neuropsychiatric risk.
  - The study by Pasternak et al. compared risk of neuropsychiatric emergency department visits or hospitalizations between varenicline users and bupropion users; the study found a non-significant 15% lowered risk associated with
varenicline use compared with bupropion use. Given that bupropion also has been associated with psychiatric adverse events and carries a boxed warning alerting about this possibility,\textsuperscript{16} this finding does not provide reassurance of varenicline’s neuropsychiatric safety.

- In the study by Thomas et al.,\textsuperscript{8} the two analyses (Cox regression and PS matching analysis) that indicated a negative association for suicide/non-fatal self-harm risk for varenicline use both carried bias due to baseline patient selection into the treatment groups due to channeling. The third analysis (IV analysis) appeared to have reduced some of the bias in the comparison between varenicline to NRT, but not in the comparison between bupropion and NRT. The IV-based analyses suggested varenicline might have a higher risk of fatal or non-fatal self-harm than NRT. Although the risk increase was numerically small, it was likely an under-estimation of true risk because of the under-ascertainment of non-fatal self-harm. However, because the effect estimate of varenicline-associated neuropsychiatric risk was imprecise and the confidence interval crossed zero, the data are inconclusive.

- The significant reduction of neuropsychiatric risk associated with varenicline observed in the Kotz study\textsuperscript{10} needs to be interpreted cautiously, due to the fact that the severe neuropsychiatric events that lead to hospitalization or death were not captured in the study since it was solely based on general practitioner data. In addition, the study did not differentiate whether depression visits were for a new or existing condition. The fact that varenicline use significantly decreased the occurrence of a depression visit could be an adverse effect if those visits were meant for following up a pre-existing condition, rather than treatment emergent events. Despite the authors’ effort to address possible influence from unmeasured confounding, their sensitivity analyses did not examine the impact of multiple unmeasured confounders or those that are associated with the captured confounders, such as previous or concurrent use of psychotropic drugs. The potential differential patient selection at baseline could still explain the observation of a reduced risk of neuropsychiatric risk among varenicline users. Lastly, the study excluded patients who had received overlapping prescriptions for smoking cessation drugs during the follow-up period to focus the assessment on patients received single smoking cessation treatment. Because this approach also excluded patients who switched from one smoking cessation drug to another, it would likely under-estimate the risk associated with varenicline, if the reason for switching was because of neuropsychiatric adverse events.

- The self-controlled designed used by Molero et al.\textsuperscript{11} might have inadvertently introduced confounding due to the impact from nicotine withdrawal syndrome if comparison periods did not also occur during treated smoking cessation attempts. It is unclear whether the increased neuropsychiatric risk that was observed in the study was due to varenicline use, the choice of comparator periods, or both.

- Studies that examined bupropion-associated neuropsychiatric risk
  - Although all three analyses in the Thomas et al. study\textsuperscript{8} consistently found a negative association between bupropion use and suicide/non-fatal self-harm risk,
they also suggested that bupropion use was associated with a reduced 3-month all-cause mortality risk, which is unlikely. The reduced risk might be due to the bias from the potential baseline patient selection, rather than bupropion use.

- The limitations of the Kotz et al.\textsuperscript{10} study in assessing varenicline’s neuropsychiatric risk are all applicable to the assessment of bupropion-associated risk. The study may have missed more severe events that led to hospitalization or death, could not determine whether the identified outpatient depression visit was for new or existing condition. It also may have been vulnerable to residual confounding due to the differential patient selection at baseline. The exclusion of patients who switched from one smoking cessation drug to another would likely under-estimate the risk associated with bupropion, if the reason for switching was because of neuropsychiatric adverse events.

- In all reviewed studies:
  - The impact of psychiatric history on the neuropsychiatric risk associated with varenicline or bupropion use was either not examined (Thomas et al.\textsuperscript{8} and Kotz et al.\textsuperscript{10}) or could not be appropriately assessed; either due to small sample size or small observed events in the subgroup (Meyer et al.\textsuperscript{6}, VA study, and Pasternak et al.\textsuperscript{12}) or because of inappropriate study design that could not rule out confounding by nicotine withdrawal syndrome (Molero et al.\textsuperscript{11}).
  - The outcomes examined did not cover the full range of the neuropsychiatric adverse events that have been associated with varenicline in the spontaneous case reports.

### 5. CONCLUSION

The reported results with respect to varenicline- or bupropion- associated neuropsychiatric risk in the reviewed studies varied considerably. All studies had a number of study design limitations; the biases within each study complicated interpretation of the result individually, and as a whole. The inability to assess the risk among those with pre-existing psychiatric illness further restricted the generalizability of the findings. The evidence from the existing observational studies alone is of insufficient quality to either rule in or rule out an increased neuropsychiatric risk associated with either varenicline or bupropion use. Observational data alone also are inadequate to inform whether or not neuropsychiatric risk associated with varenicline or bupropion could be different between smokers with and without psychiatric history. Neuropsychiatric safety of smoking cessation products should be assessed based on the totality of data streams, including case reports, observational and clinical trial data.
Appendix I Literature search strategy and search terms
Search and screening process of identifying articles for in-depth review (Steps and number of articles left)

1. Search articles mentioned “smoking cessation drugs” AND “Neuropsychiatric adverse outcomes”, identified N 425
2. Exclude animal studies, cell studies, pharmacokinetic/pharmacodynamics studies 377
3. Excluded wrong publication or study type in title or abstract 140
4. Excluded non-English articles 127
5. Excluded 119 articles after reviewer screening 8
   - Wrong publication or study type (N=34) (e.g., case series, RCT, reviews, letter)
   - Studies that did not examine drug-related neuropsychiatric risk (N=68) (e.g., studies that examined predictors of smoking cessation drug use among smokers with mental disorders, studies that examined how existing mental disorder impacts outcomes of smoking cessation treatment)
   - Studies that did not report relative risk of neuropsychiatric events between smoking cessation drugs or studies that did not use adequate design and analytical approach to examine neuropsychiatric risk among smoking cessation products, for example: cross-sectional analyses; studies without (concurrent) comparator groups, studies that did not account for confounding when comparing risk between studied drugs (N=17)

→ 8 articles for in-depth review
Search terms

- Smoking cessation products


- Neuropsychiatric adverse outcomes


- Animal study

Cell study

Pharmacokinetics/Pharmacodynamics studies

Excluded study type or publication type
Appendix II Summary tables for study design, methods and findings of the reviewed studies

Table 1 Design and methods of the observational studies on smoking cessation product use and neuropsychiatric risk

<table>
<thead>
<tr>
<th></th>
<th>DoD study/Meyers et al.</th>
<th>VA Study</th>
<th>Pasternak et al.</th>
<th>Thomas et al.</th>
<th>Molero et al.</th>
<th>Kotz et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Retrospective cohort</td>
<td>Retrospective cohort</td>
<td>Retrospective cohort</td>
<td>Retrospective cohort</td>
<td>Retrospective cohort</td>
<td>Retrospective cohort</td>
</tr>
<tr>
<td><strong>Data sources</strong></td>
<td>Military health system data (Claims and administrative data)</td>
<td>VA health care databases (claims and administrative data)</td>
<td>Nation-wide linked health care data in Denmark including information on prescription drug use, emergency department visits, hospital admissions, neuropsychiatric diagnosis, etc.</td>
<td>UK CPRD linked to Office for National Statistics (ONS) mortality data and Health Episode Statistics (HES) data</td>
<td>Nation-wide linked health care data in Sweden including information on prescription drug use, emergency department visit, hospital admission, outpatient visit, neuropsychiatric diagnosis, mortality information, including cause of death, etc.</td>
<td>QResearch database (version 36, upload July 31, 2013), which holds anonymised health records from 753 National Health Service general practices (GPS) from across England.</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td>Varenicline or NRT</td>
<td>Varenicline or NRT</td>
<td>Varenicline or bupropion</td>
<td>Varenicline, bupropion, or NRT</td>
<td>Varenicline-exposed period: 12-weeks after the first observed varenicline dispensing.</td>
<td>Varenicline, bupropion, or NRT</td>
</tr>
<tr>
<td><strong>Reference group</strong></td>
<td>NRT</td>
<td>NRT</td>
<td>Bupropion</td>
<td>NRT</td>
<td>Unexposed period</td>
<td>NRT</td>
</tr>
<tr>
<td><strong>Main Outcomes</strong></td>
<td>30-day Neuropsychiatric hospitalizations • Primary definition:</td>
<td>30-day Neuropsychiatric hospitalizations • hospitalization with</td>
<td>30-day Neuropsychiatric emergency department visits or hospitalizations with</td>
<td>90-day Suicide, non-fatal self-harm, depression, all-cause mortality • Suicide was</td>
<td>New psychiatric conditions Inpatient or outpatient diagnosis of psychiatric</td>
<td>6-month GP visits for depression or self-harm identified using READ codes</td>
</tr>
<tr>
<td>Condition</td>
<td>Condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization with a primary discharge diagnosis from among the ICD-9 codes of the following conditions:</td>
<td>A primary diagnosis of the following diagnoses identified using ICD-10 codes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-induced mental disorders (292.xx)</td>
<td>Mood disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient mental disorders (293.xx)</td>
<td>Psychotic disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia (295.xx)</td>
<td>Substance abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodic and mood disorders (296.xx)</td>
<td>Neurotic, stress-related or somatoform disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delusional disorders (297.xx)</td>
<td>Behavioral syndromes associated with physiological disturbances and physical factors, disorders of adult personality and behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other nonorganic psychoses (298.xx)</td>
<td>Unspecified mental disorder, confusion, hallucinations,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorders (300.xx)</td>
<td>Symptoms and signs involving emotional state and symptoms and signs involving appearance and behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personality disorders (301.xx)</td>
<td>defined as death from suicide in the ONS mortality database, using ICD-10 codes of intentional self-harm and undetermined deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Depression (296.3, 300.4, 311) |
- Schizophrenia (295.xx) |
- Bipolar disorder (296.xx) |
- Suicide attempt (E950-E959, E980-E982) |
- Psychosis excluding bipolar, depression and schizophrenia (292.xx, 293.xx, 294.xx, 297.xx, 298.xx, 299.xx) |

- Angina (296.3, 300.4, 311) |
- Schizophrenia (295.xx) |
- Bipolar disorder (296.xx) |
- Suicide attempt (E950-E959, E980-E982) |
- Psychosis excluding bipolar, depression and schizophrenia (292.xx, 293.xx, 294.xx, 297.xx, 298.xx, 299.xx) |

- Depression (296.3, 300.4, 311) |
- Schizophrenia (295.xx) |
- Bipolar disorder (296.xx) |
- Suicide attempt (E950-E959, E980-E982) |
- Psychosis excluding bipolar, depression and schizophrenia (292.xx, 293.xx, 294.xx, 297.xx, 298.xx, 299.xx) |

- Angina (296.3, 300.4, 311) |
- Schizophrenia (295.xx) |
- Bipolar disorder (296.xx) |
- Suicide attempt (E950-E959, E980-E982) |
- Psychosis excluding bipolar, depression and schizophrenia (292.xx, 293.xx, 294.xx, 297.xx, 298.xx, 299.xx) |

Suicidal behavior Suicide and suicide attempt defined as emergency inpatients or outpatient hospital visits or death due to intentional self-harm (ICD-10: X60-X84)
- Posttraumatic stress disorder (PTSD) (309.81)
- Depressive disorders (311.xx)
- Suicide attempt (E950-E959).
- Secondary definition: hospitalization with a neuropsychiatric condition in any discharge diagnoses, or, any neuropsychiatric diagnoses in outpatient records that occurred twice on different days.

| Study population | New users (17+ years-old) of varenicline and NRT patch (no smoking cessation medicine for 6 months) during the study time frame | Primary: New users of varenicline or NRT (no smoking cessation medicine for 12 months) during the study | New users (18+ years-old) of varenicline and bupropion during the study time frame and matched 1:1 by propensity scores | Primary: New users (18+ years-old) of varenicline, bupropion, and NRT (no smoking cessation medicine) during the study time frame | Primary (Within person comparison): Users (15+ years-old) of varenicline, bupropion, and NRT during the study time frame | New users (18-100 years-old) of varenicline, bupropion, and NRT (no smoking cessation medicine for 12 months) |
and matched 1:1 by propensity scores and matched in a 1:1 ratio by propensity scores

Secondary: Prevalent users of NRT who initiated varenicline or continue on NRT during the study timeframe, matched on 1:2 ratio by propensity score for 12 months) during the study timeframe

Secondary (Between person comparison): Overall population in Sweden who were over 15+ years-old during the study time frame
during the study timeframe, and did not use combination of the studied smoking cessation drugs during the 6 months after the first identified prescription

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Cox proportional-hazards regression</th>
<th>Cox proportional-hazards regression</th>
<th>Cox proportional-hazards regression</th>
<th>Cox proportional-hazards regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up continued for 30 days after this prescription with censoring for deployment, stationing overseas, loss of MHS eligibility, death or event, whichever came first</td>
<td>Follow-up started from the date when the first prescription was filled and censored at the respective date of death, disappearance, immigration, end of study (31 December 2010), switching to the other study drug or psychiatric adverse event, whichever occurred first</td>
<td>Follow-up continued for 90 days after first prescription with censoring for death, left the practice, primary event (suicide or non-fatal self-harm), end of study period, whichever came first</td>
<td>The observed time period was censored at outcome event, or end of study period or death, whichever happened first The time abroad, in prison or in hospital was also removed from the analyses</td>
<td>Follow-up continued for 6 months after first prescription with censoring for death, left the practice, primary event, end of study period, whichever came first</td>
</tr>
</tbody>
</table>

Main Analyses

Cox proportional-hazards regression

Cox proportional-hazards regression

Cox proportional-hazards regression

Stratified cox proportional-hazards regression adjusted for age as a time-varying covariate

Cox proportional-hazards regression

Propensity score matching and Cox proportional-hazards regression Instrumental variable analysis

Cox proportional-hazards regression
<table>
<thead>
<tr>
<th>Stratified analyses by psychiatric history</th>
<th>Yes</th>
<th>Psychiatric history was defined as having the diagnostic codes that were used to identify the outcome events within a year prior to the initiation of varenicline or NRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>Patients with a history of psychiatric illness were defined as having been hospitalized with an inpatient diagnosis for mental health disorders (identified by the same as the outcome events) within the 24 months prior to the initiation of varenicline or NRT. Patients with no psychiatric history were defined as having no mental health diagnoses, as in inpatient and outpatient records, and no prescriptions for medications used to treat mental health disorders within the 24 months prior to the initiation of varenicline or NRT.</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>The history of psychiatric disorder was defined as any psychiatric diagnosis listed in &quot;main outcomes&quot;, or antidepressant or antipsychotic drug use within the year before varenicline or bupropion initiation.</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Psychiatric history was defined as having the following diagnostic codes before November 1, 2006: ICD-9: 295-302, 307-316; ICD-10: F20-F48, F50-F69, F90-F98.</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*Non-fatal self-harm: suicide attempt that did not result in death
Table 2-1 Main study findings of the observational studies on smoking cessation products neuropsychiatric risk (statistically significant findings [p<0.05] are bolded)

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Varenicline (N event/total/IR)</th>
<th>Bupropion (N event/total/IR)</th>
<th>Varenicline Fully-adjusted Hazard Ratio</th>
<th>Bupropion Fully-adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer et al. 2013</td>
<td>30-day NPS hospitalization (primary diagnosis)</td>
<td>16/10,814/16 per 1,000 person-years</td>
<td>-</td>
<td>NRT 14/10,814/16 per 1,000 person-years</td>
<td>1.14 (0.56-2.34)</td>
</tr>
<tr>
<td>Meyer et al. 2013</td>
<td>30-day NPS hospitalization (any diagnosis)</td>
<td>34/10,710/39 per 1,000 person-years</td>
<td>-</td>
<td>NRT 43/10,710/49 per 1,000 person-years</td>
<td>0.79 (0.50-1.24)</td>
</tr>
<tr>
<td>Meyer et al. 2013</td>
<td>30-day NPS outpatient visits</td>
<td>234/10,710/269 per 1,000 person-years</td>
<td>-</td>
<td>NRT 327/10,710/378 per 1,000 person-years</td>
<td>0.71 (0.60-0.84)</td>
</tr>
<tr>
<td>VA study</td>
<td>30-day NPS hospitalization</td>
<td>16/14,131/16 per 1,000 person-years</td>
<td>-</td>
<td>NRT 21/14,131/21 per 1,000 person-years</td>
<td>0.76 (0.40-1.46)</td>
</tr>
<tr>
<td>VA study</td>
<td>30-day hospitalization for depression</td>
<td>8/14,131/12 per 1,000 person-years</td>
<td>-</td>
<td>NRT 7/14,131/7 per 1,000 person-years</td>
<td>1.14 (0.41-3.15)</td>
</tr>
<tr>
<td>VA study</td>
<td>30-day hospitalization for bipolar disorder</td>
<td>1/14,131/1 per 1,000 person-years</td>
<td>-</td>
<td>NRT 2/14,131/2 per 1,000 person-years</td>
<td>0.50 (0.05-5.51)</td>
</tr>
<tr>
<td>VA study</td>
<td>30-day hospitalization for schizophrenia</td>
<td>3/14,131/3 per 1,000 person-years</td>
<td>-</td>
<td>NRT 8/14,131/8 per 1,000 person-years</td>
<td>0.37 (0.10-1.41)</td>
</tr>
<tr>
<td>Pasternak et al. 2013</td>
<td>30-day NPS emergency room visit or hospitalization</td>
<td>39/17,935/27 per 1,000 person-years</td>
<td>-</td>
<td>Bupropion 46/17,935/31 per 1,000 person-years</td>
<td>0.85 (0.55-1.30)</td>
</tr>
<tr>
<td>Molero et al. 2015</td>
<td>New NPS inpatient or outpatient visit during exposed period</td>
<td>3,213/69,757/NA</td>
<td>-</td>
<td>Unexposed time NA/NA/NA</td>
<td>1.18 (1.05-1.31)</td>
</tr>
<tr>
<td>Kotz et al. 2015</td>
<td>180-day outpatient visits for depression</td>
<td>2,395/51,450/95.9 per 1,000 person-years</td>
<td>357/6,557/112.9 per 1,000 person-years</td>
<td>NRT 8,274/106,759/163.7 per 1,000 person-years</td>
<td>0.66 (0.63-0.69)</td>
</tr>
<tr>
<td>Thomas et al. 2013</td>
<td>90-day Suicide or non-fatal self-harm</td>
<td>19/31,260/3 per 1,000 person-years</td>
<td>4/6,741/2.5 per 1,000 person-years</td>
<td>NRT 69/81,545/4 per 1,000 person-years</td>
<td>0.88 (0.52-1.49)</td>
</tr>
<tr>
<td>Kotz et al. 2015</td>
<td>180-day Outpatient suicide or non-fatal self-harm</td>
<td>119/51,450/4.7 per 1,000 person-years</td>
<td>20/6,557/6.1 per 1,000 person-years</td>
<td>NRT 540/106,759/10.2 per 1,000 person-years</td>
<td>0.56 (0.46-0.68)</td>
</tr>
<tr>
<td>Molero et al. 2015</td>
<td>Suicide or non-fatal self-harm during exposed period</td>
<td>657/69,757/NA</td>
<td>-</td>
<td>Unexposed time NA/NA/NA</td>
<td>1.00 (0.72-1.37)</td>
</tr>
</tbody>
</table>
NRT: Nicotine replacement therapy; IR: Incidence Rate; NPS: neurologic/psychiatric; PS: propensity score; PTSD: post-traumatic stress disorder

Hazard Ratios calculated using Cox proportional hazards regression model

Based on propensity score-matched cohort

Adjusted for age; sex; socioeconomic status, relevant comorbidities from the Charlson Index (i.e. chronic obstructive pulmonary disease, diabetes, peptic ulcer disease, renal disease, rheumatological disease, cancer) and alcohol misuse, previous diagnosis of ischemic heart disease, cerebral infarction, heart failure, peripheral vascular disease, arrhythmia, depression and self-harm; previous suicide related event; previous smoking cessation therapy; psychiatric consultation; date of initial exposure to product, number of general practice visits per year, index of multiple deprivation, UK region.

Adjusted for sex; age; previous psychiatric illness or consultation; previous use of psychotropic drugs such as hypnotics, antipsychotics and antidepressants; previous self-harm; socioeconomic position; major chronic illness; number of general practice consultations in the year before the prescription; exposure to the drug before or after 2008; year of first prescription; and previous use of a smoking cessation product.
Appendix III Calculation of the risk differences of study outcomes based on the hazard ratios of the Cox regression and propensity score matching analyses of the Thomas et al. study

Fatal and non-fatal self-harm (varenicline versus NRT)

1. Calculate the crude outcome rates from event counts and follow-up person-time in population used for COX regression
   - NRT group: 69/19196*1000 = 3.59 per 1,000 patient-year
   - Varenicline group: 19/7363*1000 = 2.58 per 1,000 patient-year

2. Calculate the adjusted outcome rates from the crude outcome rates and risk ratios of COX regression or PS matching
   - Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression
     - NRT group: 3.59 * 1 = 3.59
     - Varenicline group: 3.59 * (0.88) = 3.16
   - Adjusted outcome rates calculated based on the crude rate of varenicline or bupropion group and the HR of COX regression
     - Varenicline group: 2.58 * 1 = 2.58
     - NRT group: 2.58 / 0.88 = 2.93
   - Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching
     - NRT group: 3.58 * 1 = 3.58
     - Varenicline group: 3.58 * (0.87) = 3.11
   - Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching
     - Varenicline group: 2.62 * 1 = 2.62
     - NRT group: 2.62 / 0.87 = 3.01

3. Calculate the adjusted risk differences between varenicline and NRT reflected by the risk ratio of COX regression or PS matching
   - Adjusted risk differences based on risk ratio of COX regression:
     - 3.16-3.59 = -0.43 (per 1,000 patient-year) = ~-0.1 (per 1,000 patients per 3 months)
     - 2.58-2.93 = -0.35 (per 1,000 patient-year) = ~-0.1 (per 1,000 patients per 3 months)
   - Adjusted risk differences based on risk ratio of PS matching regression:
     - 3.11-3.58 = -0.47 (per 1,000 patient-year) = ~-0.1 (per 1,000 patients per 3 months)
     - 2.62-3.01 = -0.39 (per 1,000 patient-year) = ~-0.1 (per 1,000 patients per 3 months)

Mortality (varenicline versus NRT)
1. **Calculate the crude outcome rates** from event counts and follow-up person-time in population used for COX regression

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Count</th>
<th>Person-Time</th>
<th>Rate per 1,000 Patient-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT group</td>
<td>292/19947</td>
<td>1000</td>
<td>14.64</td>
</tr>
<tr>
<td>Varenicline group</td>
<td>33/7575</td>
<td>1000</td>
<td>4.36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Count</th>
<th>Person-Time</th>
<th>Rate per 1,000 Patient-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT group</td>
<td>260/17715</td>
<td>1000</td>
<td>14.68</td>
</tr>
<tr>
<td>Varenicline group</td>
<td>33/7447</td>
<td>1000</td>
<td>4.43</td>
</tr>
</tbody>
</table>

2. **Calculate the adjusted outcome rates** from the crude outcome rates and risk ratios of COX regression or PS matching

- Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Count</th>
<th>Person-Time</th>
<th>Rate per 1,000 Patient-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT group</td>
<td>14.64 * 1</td>
<td>1</td>
<td>14.64</td>
</tr>
<tr>
<td>Varenicline group</td>
<td>4.36 * 0.44</td>
<td>1</td>
<td>6.44</td>
</tr>
</tbody>
</table>

- Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of COX regression

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Count</th>
<th>Person-Time</th>
<th>Rate per 1,000 Patient-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline group</td>
<td>4.36 * 1</td>
<td>1</td>
<td>4.36</td>
</tr>
<tr>
<td>NRT group</td>
<td>4.36 / 0.44</td>
<td>1</td>
<td>9.90</td>
</tr>
</tbody>
</table>

- Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Count</th>
<th>Person-Time</th>
<th>Rate per 1,000 Patient-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT group</td>
<td>14.68 * 1</td>
<td>1</td>
<td>14.68</td>
</tr>
<tr>
<td>Varenicline group</td>
<td>4.36 * 0.37</td>
<td>1</td>
<td>5.43</td>
</tr>
</tbody>
</table>

- Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Count</th>
<th>Person-Time</th>
<th>Rate per 1,000 Patient-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline group</td>
<td>4.43 * 1</td>
<td>1</td>
<td>4.43</td>
</tr>
<tr>
<td>NRT group</td>
<td>4.43 / 0.37</td>
<td>1</td>
<td>11.97</td>
</tr>
</tbody>
</table>

3. **Calculate the adjusted risk differences** between varenicline and NRT reflected by the risk ratio of COX regression or PS matching

- Adjusted risk differences based on risk ratio of COX regression= 6.44-14.64= -8.2 (per 1,000 patient-year)= ~-2.1 (per 1,000 patients per 3 months) OR 4.36-9.90= -5.5 (per 1,000 patient-year)= ~-1.4 (per 1,000 patients per 3 months)

- Adjusted risk differences based on risk ratio of PS matching= 5.43-14.68= -9.3 (per 1,000 patient-year)= ~-2.3 (per 1,000 patients per 3 months) OR 4.36-11.78= -7.5 (per 1,000 patient-year)= ~-1.9 (per 1,000 patients per 3 months)

**Fatal and non-fatal self-harm (bupropion versus NRT)**

1. **Calculate the crude outcome rates** from event counts and follow-up person-time in population used in COX regression

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Count</th>
<th>Person-Time</th>
<th>Rate per 1,000 Patient-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT group</td>
<td>69/19196</td>
<td>1000</td>
<td>3.59</td>
</tr>
<tr>
<td>Bupropion group</td>
<td>4/1662</td>
<td>1000</td>
<td>2.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Count</th>
<th>Person-Time</th>
<th>Rate per 1,000 Patient-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT group</td>
<td>69/18806</td>
<td>1000</td>
<td>3.66</td>
</tr>
</tbody>
</table>
2. Calculate the adjusted outcome rates from the crude outcome rates and risk ratios of COX regression or PS matching

-Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression
  NRT group = 3.59 * 1 = 3.59
  Bupropion group = 3.59 * (0.83) = 2.98

-Adjusted outcome rates calculated based on the crude rate of varenicline or bupropion group and the HR of COX regression
  Bupropion group = 2.4 * 1 = 2.4
  NRT group = 2.4 / 0.83 = 2.89

-Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching
  NRT group = 3.66 * 1 = 3.66
  Bupropion group = 3.66 * (0.87) = 3.18

-Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching
  Bupropion group = 2.55 * 1 = 2.55
  NRT group = 2.55 / 0.87 = 2.93

3. Calculate the adjusted risk differences between varenicline and NRT reflected by the risk ratio of COX regression or PS matching

-Adjusted risk differences based on risk ratio of COX regression=
  2.98-3.59= -0.61 (per 1,000 patient-year)= ~0.015 (per 1,000 patients per 3 months) OR
  2.4-2.89= -0.49 (per 1,000 patient-year)= ~0.12 (per 1,000 patients per 3 months)

-Adjusted risk differences based on risk ratio of PS matching regression=
  3.18-3.66= -0.48 (per 1,000 patient-year)= ~0.12 (per 1,000 patients per 3 months) OR
  2.55-2.93= -0.36 (per 1,000 patient-year)= ~0.1 (per 1,000 patients per 3 months)

Mortality (bupropion versus NRT)
1. Calculate the crude outcome rates from event counts and follow-up person-time in population used for COX regression

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Counts</th>
<th>Person-Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT group</td>
<td>292/19947*1000</td>
<td>14.64</td>
</tr>
<tr>
<td>Bupropion group</td>
<td>5/1665*1000</td>
<td>3</td>
</tr>
</tbody>
</table>

in population used for PS matching

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Counts</th>
<th>Person-Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT group</td>
<td>292/19543*1000</td>
<td>14.94</td>
</tr>
<tr>
<td>Bupropion group</td>
<td>5/1612*1000</td>
<td>3.1</td>
</tr>
</tbody>
</table>

2. Calculate the adjusted outcome rates from the crude outcome rates and risk ratios of COX regression or PS matching

-Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression
NRT group  =14.64 * 1 = 14.64
Bupropion group  =14.64 * (0.39)= 5.71

-Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of COX regression
Bupropion group  =3 * 1  = 3
NRT group  =3 / 0.39 = 7.69

-Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching
NRT group  =14.94 * 1 = 14.94
Bupropion group  =14.94 * (0.34)= 5.08

-Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching
Bupropion group  =3.1 * 1  = 3.1
NRT group  =3.1 / 0.34 = 9.12

3. Calculate the adjusted risk differences between varenicline and NRT reflected by the risk ratio of COX regression or PS matching
-Adjusted risk differences based on risk ratio of COX regression=
5.71 -14.64= -8.93 (per 1,000 patient-year)= ~-2.2 (per 1,000 patients per 3 months) OR
3 -7.69= -4.69 (per 1,000 patient-year)= ~-1.2 (per 1,000 patients per 3 months)
-Adjusted risk differences based on risk ratio of PS matching=
5.08-14.94= -9.86 (per 1,000 patient-year)= ~-2.5 (per 1,000 patients per 3 months) OR
3.1 -9.12= -6.02(per 1,000 patient-year)= ~-1.5 (per 1,000 patients per 3 months)
6. REFERENCES


# Statistical Review and Evaluation

Published Observational Studies

<table>
<thead>
<tr>
<th>NDA</th>
<th>21928</th>
</tr>
</thead>
<tbody>
<tr>
<td>Document Number/eCTD</td>
<td>N/A</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Chantix® (Varenicline)</td>
</tr>
<tr>
<td>Indication</td>
<td>Aid to smoking cessation</td>
</tr>
<tr>
<td>Applicant</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Safety Issue(s)</td>
<td>Neuropsychiatric risk</td>
</tr>
</tbody>
</table>
| Dates           | Consult Request: December 28, 2015  
                  | Review Completion: July 1, 2016 |
| Biometrics Division | Division of Biometrics VII, Office of Biostatistics |
| Primary Reviewer | Rongmei Zhang, Ph.D. |
| Secondary Reviewer | Rima Izem, Ph.D. |
| Tertiary Reviewer | Mark Levenson, Ph.D. |
| Consulting Division | Division of Epidemiology II (DEPI-II) |
| Consult Request Team | Chih-Ying (Natasha) Chen, Ph.D.  
                         | Tamra Meyer, Ph.D, MPH, Team Leader, DEPI-II |

Keywords: smoking cessation, observational studies, retrospective cohort, self-control.
1 Executive Summary

This review provides statistical evaluation on two recently published observational studies regarding varenicline and neuropsychiatric risk, in response to a consult request from Division of Epidemiology II (DEPI-II) in the Office of Surveillance and Epidemiology (OSE).

Varenicline was approved in the United States in 2006 as an aid for smoking cessation treatment. A Boxed Warning has been added to the varenicline labeling for serious neuropsychiatric adverse events (AEs) since 2009, based on spontaneous postmarketing reports. In 2014, Pfizer submitted a labeling change request to remove the boxed warning, and a joint Advisor Committee (AC) Meeting was held regarding this issue. DEPI-II reviewed five observational studies which were identified by the sponsor as part of the supporting evidence for the labeling change request, and concluded that those studies did not adequately measure the effect of varenicline on the neuropsychiatric risk. In February 2016, Pfizer submitted a labeling change request, based on the results for a completed randomized controlled trial of neuropsychiatric effects of Chantix (addressing FDA’s postmarketing request in 2008). DEPI-II identified three new observational studies published after the 2014 AC and requested Division of Biometrics VII (DB VII) to review two of them.

Kotz et al. 2015 is a new user retrospective cohort study using data from the National Health Service general practices across England. A total of 164,746 patients aged 18 to 100 who received a prescription of either nicotine replacement treatment (NRT; reference group), bupropion, or varenicline alone between 2007 and 2012 were identified and followed up for 6 months. The incidences of the neuropsychiatric outcomes for varenicline were 95.9 per 1000 patient years for depression and 4.7 per 1000 patient years for self-harm, respectively. After trimming and 1:1 matching of patients by propensity score, there were 100,326 patients for the comparison of varenicline with NRT and 12,786 patients for that of bupropion with NRT. Neither varenicline nor bupropion showed an increased risk of any neuropsychiatric events compared with NRT. More specifically, varenicline was associated with a reduced risk of depression [Hazard Ratio (HR) and 95% confidence interval (CI) was 0.65 (0.61, 0.68)] and self-harm [HR and 95% CI was 0.60 (0.48, 0.76)]

The strength of Kotz et al. study is the size of the database and the detailed protocol published prior to conducting the study. However, some potential confounders such as previous or present levels of tobacco exposure were not available in the study, which may result in biased risk estimates. Propensity score trimming and matching was used to balance measured confounding between treatment groups in the study. However, the impact of matching is unclear since no diagnostic results were provided. The study excluded patients receiving a combination of smoking cessation drugs or another smoking cessation drug during the 6-month follow-up, for the purpose of “singling out adverse events of the three distinct drugs”. However, this introduced selection bias since patients who failed the treatment were less likely to be selected into the study. Another limitation is that the study was not stratified by the pre-existing psychiatric disorders, which appears to be an effect modifier according to the results from the clinical trials (see details in the statistical review by Dr.Andraca-Carrera). Additionally, the study outcomes were not validated and there was no linkage to assess mortality.
Molero et al. 2015 is a self-control study for patients aged 15 and over and prescribed with varenicline in Sweden. A total of 69,757 patients receiving varenicline between 2006 and 2009 were identified. During this time period, 4.6% of the varenicline patients were diagnosed as having a new psychiatric condition and 0.9% received medical care for suicidal behaviors. Comparing varenicline use to non-use, results showed that varenicline was associated with an increased risk of new psychiatric conditions [HR and 95% CI was 1.18 (1.05, 1.31)]. A further assessment for varenicline and certain new psychiatric conditions found that varenicline was associated with an increased risk of anxiety conditions [HR and 95% CI was 1.23 (1.01, 1.51)] and mood conditions [HR and 95% CI was 1.31 (1.06 to 1.63)], which was only seen in overall and people with pre-existing psychiatric disorders.

The strength of Molero et al. study is the adjustment for measured and unmeasured time-invariant confounders by using a self-control study, the stratification by pre-existing psychiatric disorders, and the abilities to link the database to several registers such as migrations and deaths. However, the self-control analysis did not take into account time-varying confounders and the study lacked information on time-varying covariates. In addition, it is unclear how exposed and unexposed periods were defined and how Cox proportional hazards regression was used for the self-control study. Another limitation is that if the effect of stopping smoking may itself lead to neuropsychiatric events, then the risk estimate from the self-control study is biased. In contrast, using an active comparator like Kotz et al. study may be better if that is the case. Similarly to Kotz et al. study, the present tobacco exposure was not available and the outcomes were not validated in Molero et al. study.

Based on these two reviewed observational studies, Division of Biometrics VII concludes that the evidence for increased neuropsychiatric risk with varenicline is inconclusive.

2 Background

Varenicline (Chantix®) was approved by the FDA in May 2006 “as an aid for smoking cession treatment”. In January 2008, based on the data from spontaneous postmarketing reports of serious neuropsychiatric adverse events (AEs), FDA determined that varenicline was associated with serious neuropsychiatric adverse events and added a warning of neuropsychiatric AEs into the WARINGS section of the varenicline labeling. In May 2008, FDA issued a postmarketing requirement (PMR) to Pfizer to conduct a randomized controlled trial to assess the risk of serious neuropsychiatric AEs with varenicline. In July 2009, a Boxed Warning was added to the varenicline labeling about the serious neuropsychiatric AEs including, but not limited to, depression, suicidal ideation and behavior. In April 2014, Pfizer submitted a labeling supplement for varenicline including a meta-analysis of clinical trial data, a literature review of observational studies, and proposed labeling revisions including removing the Boxed Warning. The sponsor identified five observational studies on varenicline and neuropsychiatric risk. DEP-II reviewed these studies¹ and concluded that these studies did not adequately measure the effect of varenicline on

¹ Dr. Chin-Ying Chen, Epidemiology review of labeling supplement regarding neuropsychiatric events associated with varenicline, FDA briefing document for the joint meeting of the psychopharmacologic drugs advisory
the risk of neuropsychiatric AEs and therefore could not be interpreted as no increased risk associated with varenicline. In October 2014, a joint meeting of the psychopharmacologic drugs advisory committee and drug safety and risk management advisory committee meeting was held to consider Pfizer’s request to remove the Boxed Warning. The Committee voted to wait until randomized trial results were available.

In February 2016, Pfizer submitted a labeling change request based on the results for a completed randomized controlled trial of neuropsychiatric effects of Chantix (addressing FDA’s postmarketing request in 2008). Pfizer’s conclusion is that the study demonstrates no increased risk of neuropsychiatric adverse events associated with Chantix and therefore the boxed warning should be deleted.

DEPI-II identified three new observational studies published after the 2014 AC and requested Division of Biometrics VII (DB VII) to review two of them. The third study used a cross-sectional design, which DEPI-II concluded that it cannot be used to inference causality. Therefore DEPI-II did not request DB VII to review it. This review is largely based on information in the two published papers and their supporting documentation (publically available protocol and published supplemental results). To better understand the methods in the Molero et al study, we sent clarifying questions and received answers from the authors.

3 Study Design, Methods and Results

3.1 Kotz et al. study, 2015

The authors performed a retrospective cohort study to assess the safety of varenicline using data from QResearch general practice (GP) database. QResearch is a large, validated electronic GP databases including data from the anonymized health records of over 13 million patients from 753 GPs across England that use the EMIS software system. The study included all adult patients from QResearch who received prescriptions for varenicline, bupropion, or nicotine replacement therapy (NRT) between the committee and drug safety and risk management advisory committee meeting, October 16, 2014.

http://www.fda.gov/AdvisoryCommittees/Calendar/ucm394876.htm

2 A joint meeting of the psychopharmacologic drugs advisory committee and drug safety and risk management advisory committee meeting, October 16, 2014.

http://www.fda.gov/AdvisoryCommittees/Calendar/ucm394876.htm

3 Kotz et al., Cardiovascular and neuropsychiatric risk of varenicline, Lancet Respiratory Medicine 2015, Vol 3: 761-768.


5 Shewale et al., Mental health status of varenicline and bupropion users during a quit attempt compared to current smokers, other quitters, and non-smokers, Drug and Alcohol Dependence, 2015 September 1; 154: 132-8.
January 1, 2007 and June 30, 2012. The study excluded patients receiving a combination of smoking cessation drugs or another smoking cessation drug during the 6-month follow-up, for the purpose of “singling out adverse events of the three distinct drugs”. The study protocol including details of study design was independently published in 2014\(^6\). The key elements for the study design are summarized in Appendix I.

The flow chart for the cohort creation is shown in Figure 1. There were 164,766 eligible patients included in the study. Patients were classified into three exposure groups, i.e., bupropion alone, varenicline alone, or NRT (reference group) alone, based on the first drug they were prescribed. Patients were excluded if they had used one of the study drugs during the 12 months before the start date of the study (i.e., between January 1, 2006 and December 31, 2006). There were 6,557 bupropion patients, 51,450 varenicline patients and 106,759 NRT patients before matching. After 1:1 propensity score matching and trimming for two pair-wise comparisons (bupropion vs. NRT and NRT vs. varenicline respectively), there were 6,393 bupropion patients and the corresponding matched NRT patients, and 50,163 varenicline patients and the corresponding matched NRT patients.

Start of follow-up began for each patient on the date of the 1\(^{st}\) prescription and ended after 6 months of follow-up or outcome occurrence. Patients who left the practice or died were censored in the follow-up.

There were 2 neuropsychiatric outcomes of interest: depression and fatal or non-fatal intentional self-harm. These outcomes were not validated in the study. The authors cited two external validation studies\(^7,8\) showing that studies using this database yield similar results as those using other databases such as the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN) database.

Cox proportional hazard regression models were used to compare the risk of each outcome of interest in the two pairwise comparisons. The authors conducted three analyses: (1) Unadjusted Cox regression with all eligible patients (2) Cox regression with all eligible patients, adjusted for all observed covariates, and (3) Cox regression with 1:1 PS matched patients.

In all three analyses, neither varenicline nor bupropion showed an increased risk of any neuropsychiatric events compared with NRT (Table 1). The adjusted Cox regression and the Cox regression for PS

\(^6\) Kotz et al., Cardiovascular and neuropsychiatric safety of varenicline and bupropion compared with nicotine replacement therapy for smoking cessation: study protocol of a retrospective cohort study using the QResearch general practice database. BMJ Open 2014; 4: e005281.

\(^7\) Reeves et al., Can analyses of electronic patient records be independently and externally validated? The effect of statins on the mortality of patients with ischemic heart disease: a cohort study with nested case-control analysis. BMJ Open 2014; 4: e004952.

\(^8\) Vinogradova et al., Exposure to bisphosphonates and risk of gastrointestinal cancers: series of nested case-control studies with QResearch and CPRD data. BMJ 2013; 346; f114.
matching patients led to similar results. More specifically, in the analysis using Cox regression with 1:1 PS matched patients, varenicline was associated with a reduced risk of depression [HR and 95% CI was 0.65 (0.61, 0.68)] and self-harm [HR and 95% CI was 0.60 (0.48, 0.76)].

---

**Figure 1 Study cohort creation (Author’s figure)**

**Table 1 Incidence rates and hazard ratios of drug groups for all events during 6 month follow-up**

<table>
<thead>
<tr>
<th>Source: Reviewer’s table based on author’s analyses results</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Depression</th>
<th>No. Events</th>
<th>Incidence of event per 1000 PYs</th>
<th>Hazard Ratio and 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted^1</td>
<td>Adjusted^1</td>
</tr>
<tr>
<td>NRT(ref.)</td>
<td>8,274</td>
<td>163.7</td>
<td>0.69 (0.62, 0.77)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>357</td>
<td>112.9</td>
<td>0.59 (0.56, 0.61)</td>
</tr>
<tr>
<td>Varenicline</td>
<td>2,395</td>
<td>95.9</td>
<td>0.46 (0.37, 0.56)</td>
</tr>
<tr>
<td>Self-harm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRT(ref.)</td>
<td>540</td>
<td>10.2</td>
<td>0.60 (0.38, 0.94)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>20</td>
<td>6.1</td>
<td>0.46 (0.37, 0.56)</td>
</tr>
<tr>
<td>Varenicline</td>
<td>119</td>
<td>4.7</td>
<td>0.46 (0.37, 0.56)</td>
</tr>
</tbody>
</table>

^1 based on all eligible patients (6,557 bupropion patients, 51,450 varenicline patients and 106,759 NRT patients).
3.2 Molero et al. study, 2015

The authors used a self-control (or within person) study to examine the associations between varenicline and psychiatric conditions, suicidal behavior, transport accidents and traffic offences, and substance abuse, using the data from whole population of Sweden. The study outcomes were not validated. The key elements for the study design are summarized in Appendix I.

In the total population of Sweden aged 15 and over (n=7,917,436), 69,757 people were prescribed with varenicline between November 22, 2006 and December 31, 2009. Treatment period was defined as starting at the date of the 1st prescription and ending 12 weeks later. Prescriptions within 12 weeks of the 1st prescription were considered to be part of the same treatment period. Prescriptions occurring more than 12 weeks after a previous collection were considered to be a new treatment period. One person could have multiple treatment periods and multiple non-treatment (control) periods.

Stratified Cox proportional hazard regression were used for the within person analysis, with each person entering as a separate stratum in the analysis and serving as his/her own control. The control periods were defined as pre-exposure, between exposed periods, and after the last observed exposure periods. Age was added as a time-varying covariate. Additional adjusted covariates for treatment and non-treatment periods included migration, imprisonment, institutional youth care, hospital admission, and death. Migrations and deaths were identified by linking people to the Migration and Cause of Death Registries. Imprison was identified by linking people to the Prison Register. Institutional youth care was estimated by periods in hospital using the Patient Register. A further assessment was conducted for three psychiatric conditions (outcomes): mood conditions, anxiety conditions, and psychoses, and stratified by pre-existing psychiatric disorders.

Between person analyses were also conducted by Cox regression to compare each outcome during varenicline treatment with non-treatment periods for all patients, where treatment was considered as a time-varying covariate in cox regression model.

In the within person analyses, among 69,757 varenicline users, varenicline was associated with a significantly increased risk for one of the 7 outcomes, i.e. incidence of new psychiatric conditions [HR and 95% CI was 1.18 (1.05, 1.31)] (Table 2). In contrast, in the between person analyses, varenicline users were associated with significantly increased risks for ALL 7 outcomes (Table 2). A further assessment for varenicline and certain new psychiatric conditions found that varenicline was associated with an increased risk of anxiety conditions [HR and 95% CI was 1.23 (1.01, 1.51)] and mood conditions [HR and 95% CI was 1.31 (1.06 to 1.63)], which was only seen in overall and people with pre-existing psychiatric disorders (Table 3).
Table 2 Varenicline use vs. no use for different outcomes from within person and between person analyses.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of events at within person level/ No of events at between person level</th>
<th>Hazard ratio (95% CI) Between person, unadjusted</th>
<th>Hazard ratio (95% CI) Between person, adjusted for sex and age</th>
<th>Within person*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of new psychiatric conditions</td>
<td>6910/337 393</td>
<td>3.29 (2.99 to 3.63)</td>
<td>2.78 (2.63 to 2.93)</td>
<td>1.18 (1.05 to 1.31)</td>
</tr>
<tr>
<td>Suicidal behaviour</td>
<td>1077/40 595</td>
<td>3.44 (2.64 to 4.47)</td>
<td>4.06 (3.12 to 5.28)</td>
<td>1.00 (0.72 to 1.37)</td>
</tr>
<tr>
<td>Suspected of any crime</td>
<td>6873/507 823</td>
<td>1.45 (1.30 to 1.62)</td>
<td>2.33 (2.08 to 2.60)</td>
<td>1.10 (0.97 to 1.24)</td>
</tr>
<tr>
<td>Convicted of any crime</td>
<td>3252/338 608</td>
<td>1.18 (1.05 to 1.32)</td>
<td>1.88 (1.68 to 2.11)</td>
<td>0.96 (0.79 to 1.16)</td>
</tr>
<tr>
<td>Transport accidents</td>
<td>1129/124 445</td>
<td>1.05 (0.87 to 1.28)</td>
<td>1.46 (1.20 to 1.78)</td>
<td>1.01 (0.69 to 1.47)</td>
</tr>
<tr>
<td>Suspected of traffic offence</td>
<td>772/99 895</td>
<td>1.17 (0.88 to 1.55)</td>
<td>1.74 (1.31 to 2.32)</td>
<td>1.24 (0.84 to 1.84)</td>
</tr>
<tr>
<td>Convicted of traffic offence</td>
<td>483/57 068</td>
<td>1.13 (0.84 to 1.52)</td>
<td>1.81 (1.34 to 2.44)</td>
<td>1.30 (0.77 to 2.20)</td>
</tr>
</tbody>
</table>

*Within person model compares rate of adverse events when person is prescribed varenicline with rate when same person is not prescribed varenicline.

Source: Author’s table

Table 3 Varenicline use vs. no use for three psychiatric conditions stratified by pre-existing psychiatric disorders.

<table>
<thead>
<tr>
<th>Psychiatric condition</th>
<th>No of events</th>
<th>Hazard ratio (95% CI) All people</th>
<th>Hazard ratio (95% CI) People with pre-existing psychiatric disorders</th>
<th>Hazard ratio (95% CI) People without pre-existing psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety conditions</td>
<td>3128</td>
<td>1.27 (1.06 to 1.51)</td>
<td>1.23 (1.01 to 1.51)</td>
<td>1.41 (0.99 to 2.00)</td>
</tr>
<tr>
<td>Mood conditions</td>
<td>3166</td>
<td>1.28 (1.07 to 1.52)</td>
<td>1.31 (1.06 to 1.63)</td>
<td>1.17 (0.86 to 1.60)</td>
</tr>
<tr>
<td>Psychoses</td>
<td>1129</td>
<td>0.94 (0.73 to 1.20)</td>
<td>0.90 (0.70 to 1.16)</td>
<td>3.52 (0.81 to 15.27)</td>
</tr>
</tbody>
</table>

*Within person models compare rate of adverse events when person is prescribed varenicline with rate when same person is not prescribed varenicline.

Source: Author’s table

4 Statistical Comments

The strengths and limitations for the two studies are summarized in Table 4. Based on the two reviewed studies, Division of Biometrics VII concludes that the evidence for increased neuropsychiatric risk with varenicline is inconclusive.

Table 4 Strengths and Limitations for two studies.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strengths</strong></td>
<td>• A large observational study with detailed protocol published separately</td>
<td>• By design, within person analysis controls for time-invariant measured and unmeasured confounding</td>
</tr>
<tr>
<td></td>
<td>• Generalizability of the results because of use of a large GP database.</td>
<td>• Stratified analysis by pre-existing psychiatric disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Abilities to link the dataset to several registers to access mortality, migration, imprisonment, and institutional youth care.</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>• Unmeasured confounding issue - potential confounders such as previous or present levels of tobacco exposure</td>
<td>• Unclear definition of exposure period for within person study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unknown present tobacco exposure</td>
</tr>
</tbody>
</table>
are not available.

- Impact of PS matching in balancing the covariates is unclear as no diagnostics were reported
- Selection bias issue – patients who failed the treatment were less likely to be included in the study due to exclusion of patients having a combination drugs or switching drugs during follow-up
- Unable to link the dataset to other datasets to assess mortality.
- Not stratified by the pre-existing psychiatric disorders in the neuropsychiatric outcome assessment
- Non-validated outcomes

- Potential biased risk estimate if stopping smoking itself leads to neuropsychiatric events
- Unclear definition of start and end follow-up in the Cox proportional hazard regression
- Lack of information on time varying covariates (within person analyses only accounted for invariant measured and unmeasured confounding)
- Non-validated outcomes

5 Appendix I

Table 1 The key elements for the study design and analysis for Kotz et al, 2015 and Molero et al, 2015.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Source</td>
<td>QResearch database (753 National health service general practices across England)</td>
<td>Whole population of Sweden</td>
</tr>
<tr>
<td>Design</td>
<td>New user retrospective cohort study</td>
<td>Self-control (within person analyses)</td>
</tr>
<tr>
<td>Study Period</td>
<td>January 1, 2007 to June 30, 2012</td>
<td>November 22, 2006 to December 31, 2009</td>
</tr>
<tr>
<td>Study Drugs</td>
<td>Varenicline, bupropion, and Nicotine replacement treatment (reference group)</td>
<td>Varenicline (use vs. non use)</td>
</tr>
<tr>
<td>Population</td>
<td>&lt;Inclusion criteria&gt;</td>
<td>&lt;Inclusion criteria&gt;</td>
</tr>
<tr>
<td></td>
<td>• Aged 18-100 years</td>
<td>• Aged 15 and over</td>
</tr>
<tr>
<td></td>
<td>• Registered for &gt; 12 months before data extraction</td>
<td>• Receiving at least one Rx of varenicline between November 22, 2007 and December 31, 2009.</td>
</tr>
<tr>
<td></td>
<td>• Receiving any study drug between January 1, 2007 and June 30, 2012.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;Exclusion criteria&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Having &lt; 1 year of QResearch records before the 1st Rx</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Having one of the study drugs during 12 months before start date of the study (i.e., between Jan 1, 2006 and Dec 31, 2006)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Receiving a Rx of a combination of the study drugs during the 6 months follow-up period</td>
<td></td>
</tr>
</tbody>
</table>
Temporary residents

**Follow-up**

Follow-up started on the date of the 1\textsuperscript{st} Rx of the study drug (i.e. index date) and ended after 6-month follow-up or when reaching the outcome of interest (CV and/or neurpsychiatric). Censoring criteria included:

- Lost to follow-up because of leaving the practice
- Dead
- Reaching the end of the follow-up period

Treatment period starts on the date of the 1\textsuperscript{st} Rx of the study drug (i.e. index date) and ends 12 weeks later.

The Rx occurring more than 12 weeks after a previous Rx was considered as a new treatment period, starting at the date of the next collected Rx.

**Exposure**

- Varenicline alone
- Bupropion alone
- NRT Rx alone (=reference group)

Varenicline users (treatment vs. non-treatment periods were compared within the same person)

**Outcomes**

Neuropsychiatric outcomes: (1) depression and (2) fatal or non-fatal intentional self-harm.

Neuropsychiatric outcomes: (1) Incidence of new psychiatric conditions and (2) suicidal behavior

**Covariates**

In main analysis: age, sex, Townsend index of multiple deprivation, Strategic Health Authority of the GP practice, relevant comorbidities from the Charlson Index (i.e., COPD, diabetes, peptic ulcer disease, renal disease, rheumatological disease or cancer) and alcohol misuse, outcomes occurred prior to index date.

Additional covariates in the subgroup analysis for smokers with COPD: MRC dyspnea score (as a marker for COPD severity)

- Covariates at baseline: sex, age, psychiatric diagnoses (pre-existing psychiatric diagnosis, lifetime alcohol misuse diagnosis, lifetime nicotine dependence diagnosis)

**Analysis and Results**

Pairwise comparison between varenicline vs. NRT and bupropion vs. NRT Cox PH regression, (1) crude (2) adjusted for all measured confounding factors (3) 1:1 PS matching by using the nearest neighbor algorithm (also trimming the sample by excluding patients with PS <2.5 percentile in the treatment group and >97.5 percentile in the reference group.) (Two PS models were fit separately for the pairwise comparisons.)

- Primary cohort was 106,759 NRT users, 6,557 bupropion users, and 51,450 varenicline users. In crude and

- **Primary Analysis:** Within person stratified Cox with each person entering as a separate stratum and serving as his/her own control, age was added as a time-varying covariate, others adjusted variables included periods of treatment and non-treatment for migration, imprisonment, institutional youth care, hospital admission, and death. Among 69,757 users, results showed that varenicline users had a significantly increased risk of one of the 7 outcomes (incidence of new psychiatric conditions).
adjusted analysis, neither bupropion nor varenicline showed an increased risk of any neuropsychiatric events compared with NRT (all HRs <1).
Estimated HRs for varenicline vs. NRT were 0.66 with 95% CI (0.63, 0.69) for the risk of depression, and 0.56 with 95% CI (0.46, 0.68) for the risk of self-harm.

- After trimming and matching, two matched samples: 6,393 bupropion users with 1:1 matched NRT users, and 50,163 varenicline users with 1:1 matched NRT users. Varenicline didn’t show an increased risk of any CV or neuropsychiatric events compared with NRT (all HRs <1); bupropion showed an increased risk for peripheral vascular disease (HR >1 but not significant).
Estimated HRs for varenicline vs. NRT were 0.65 with 95% CI (0.61, 0.68) for the risk of depression, and 0.60 with 95% CI (0.48, 0.76) for the risk of self-harm.

- Secondary analysis for 3 months of follow up yielded very similar results as the main analysis

- Sensitivity analysis for unmeasured confounding (using a modelling approach and assumption of prevalence and strength of association) showed that an increased risk of CV and neuropsychiatric events assessed in varenicline users was unlikely.

- Further examination between varenicline and incidence of certain psychiatric conditions stratified by pre-existing illness. Results showed that varenicline was associated with increased risk of anxiety and mood conditions for people with pre-existing psychiatric disorders.

- Between person Cox with treatment as a time varying covariate (separate follow-up into the period before the first outcome, periods between outcomes, and the period after the last outcome) 69,757 users and 7,847,679 never-users. Result of adjusted analysis for sex and age showed significantly increased risk of all outcomes.

Source: Reviewer’s table.
Pharmacovigilance Review

Date: August 4, 2016

Reviewer: Martin Pollock, PharmD, Safety Evaluator
Division of Pharmacovigilance II (DPV II)

Team Leader: Sara Camilli, PharmD, BCPS, Safety Evaluator Team Leader
DPV II

Acting Division Director: S. Christopher Jones, PharmD, MS, MPH, Acting Director
DPV II

Product Names: Smoking cessation products: varenicline, bupropion, nicotine replacement therapy

Subject: Neuropsychiatric Adverse Event Update: 2011-2015

Application Type/Number: Multiple

Applicant/Sponsor: Multiple

OSE RCM #: 2016-989

TSI #: 260
TABLE OF CONTENTS

Executive Summary ........................................................................................................................ 3
1 Introduction ............................................................................................................................. 4
   1.1 Background .................................................................................................................. 4
   1.2 Regulatory History ................................................................................................. 5
   1.3 Product Labeling ..................................................................................................... 6
2 Methods and materials ............................................................................................................ 6
   2.1 Case Definition ......................................................................................................... 6
   2.2 FAERS Search Strategy ........................................................................................... 6
   2.3 FAERS Data Presentation ......................................................................................... 7
3 Results ..................................................................................................................................... 8
   3.1 All Smoking Cessation Drugs ................................................................................. 8
   3.2 Varenicline (N=2,864) .......................................................................................... 10
   3.3 Bupropion Smoking Cessation (N=99) ................................................................. 12
   3.4 Bupropion All Indications (N=1,864) .................................................................. 15
   3.5 Nicotine Replacement Therapy (N=893) ............................................................. 16
4 Discussion ............................................................................................................................. 18
5 Conclusions ........................................................................................................................... 19
6 Appendices ............................................................................................................................ 21
   6.1 Appendix A. FAERS Data Presented at the 2014 Chantix NPS Advisory Committee Meeting .................................................................................................................. 21
   6.2 Appendix B. FDA Adverse Event Reporting System (FAERS) .............................. 22
   6.3 Appendix C. Selected SOC Full Names and Abbreviations Used in This Review .... 23
   6.4 Appendix D. Harm PTs for All Smoking Cessation Drugs .................................... 24
EXECUTIVE SUMMARY

This DPV II review provides an update on neuropsychiatric (NPS) adverse events reported with use of smoking cessation drugs to FDA’s Adverse Event Reporting System (FAERS). We conducted this review in response to a consult request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). The purpose of this review is to provide an update of the FAERS adverse event profile, with specific interest in NPS events, for varenicline, bupropion, and nicotine replacement therapy (NRT) from 2011-2015.

FDA has received the results of the Post Marketing Requirement (referred to as the EAGLES trial) that assessed NPS events in patients on smoking cessation drug therapy (varenicline, bupropion, or nicotine replacement therapy). As a result of the EAGLES trial, Pfizer submitted a labeling supplement that proposes removal of the Boxed Warning for NPS events in the varenicline labeling; the supplement is under review by DAAAP. A September 14, 2016 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee is planned to discuss the results of the EAGLES trial and relevant published observational studies to determine whether the findings support changes to product labeling of smoking cessation drugs.

We retrieved 5,542 serious, domestic FAERS reports for smoking cessation drugs (varenicline, n=2,864; bupropion, n=1,864; nicotine replacement therapy, n=893) with an event year between 2011 and 2015. Of the 1,864 bupropion reports, 99 reported use for smoking cessation. We characterized the adverse event profile for all three smoking cessation products, with a focus on NPS events.

About 70% of varenicline and bupropion (all indications or smoking cessation) reports included at least one event from the Psychiatric or Nervous System Organ Classes (SOCs). The top 4 NPS events for both varenicline and bupropion for smoking cessation were depression, anxiety, feeling abnormal and suicidal ideation; however, we also identified reports of suicide attempt, completed suicide, and homicidal ideation for both products. For NRT, a smaller proportion of the reports included at least one event from the Psychiatric and Nervous SOCs, and there was not a preponderance of NPS events in the top reported events.

Although there was an overall decrease in the number of FAERS reports for varenicline over the five year period (2011-2015), the SOCs Psychiatric disorders and Nervous system disorders consistently accounted for most reported adverse events. Similar to varenicline, the Psychiatric and Nervous SOCs were also the most common for bupropion for smoking cessation throughout the time period of 2011 to 2015.

Serious NPS events continue to be reported in spontaneous postmarket data for both varenicline and bupropion. These data are consistent with current product labeling for varenicline and bupropion.
1 INTRODUCTION

1.1 BACKGROUND

This DPV II review provides an update on neuropsychiatric (NPS) adverse events reported with use of smoking cessation drugs to FDA’s Adverse Event Reporting System (FAERS). We conducted this review in response to a consult request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). The purpose of this review is to provide an update of the FAERS adverse event profile, with specific interest in NPS events, for varenicline, bupropion, and nicotine replacement products (NRT) from 2011-2015.

FDA has received the results of the Post Marketing Requirement (referred to as the EAGLES trial¹) that assessed NPS events in patients on smoking cessation drug therapy (varenicline, bupropion or nicotine replacement). The EAGLES trial has been published² and the authors concluded:

The study did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo. Varenicline was more effective than placebo, nicotine patch, and bupropion in helping smokers achieve abstinence, whereas bupropion and nicotine patch were more effective than placebo.³

As a result of the EAGLES trial, Pfizer submitted a labeling supplement that proposes removal of the Boxed Warning for NPS events in the varenicline labeling; the supplement is under review by DAAAP. A September 14, 2016 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee is planned to discuss the results of the EAGLES trial and relevant published observational studies to determine whether the findings support changes to product labeling of smoking cessation therapy.

NPS adverse events associated with varenicline were previously discussed at an AC meeting on October 16, 2014. This AC discussed safety data from observational studies and a meta-analysis of randomized controlled clinical trials that were conducted since the original signal of serious NPS adverse events with varenicline emerged. The committee members recommended retaining the current Boxed Warning for varenicline and reassessing the data once the EAGLES trial was complete.³ DPV II provided an update on cases reported to FAERS spanning the years 2013-2014, which found 105 NPS cases, grouped as suicidality, psychosis/mania, aggression or

¹A phase 4, randomized, double blind, active and placebo controlled, multicenter study evaluating the neuropsychiatric safety and efficacy of 12 weeks varenicline tartrate 1 mg bid and bupropion hydrochloride 150 mg bid for smoking cessation in subjects with and without a history of psychiatric disorders. The last subject completed this trial on 1/1/15.
³Minutes for the October 16, 2014 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. Approved November 12, 2014. Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisor yCommittee/ucm394880.htm
miscellaneous NPS events. These 105 cases were similar to our findings in 2008 which provided support for the Boxed Warning for serious NPS events that was added to varenicline and bupropion labeling in 2009. DPV II also prepared FAERS data showing overall counts of varenicline adverse events from 2006 to 2013 grouped by the four most common MedDRA System Organ Classes (SOCs), refer to Appendix A. Although there was an overall decrease in the number of FAERS reports for varenicline over the eight year period, the SOCs Psychiatric disorders and Nervous system disorders consistently accounted for most reported adverse events.

1.2 REGULATORY HISTORY

Information on approval, dosage forms and indication for the smoking cessation drugs is shown in Table 1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>NDA; Sponsor; Approval Date</th>
<th>Dosage Form and Strength</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chantix (varenicline)</td>
<td>21928; Pfizer; 5/10/06</td>
<td>0.5, 1, 2 mg tablets</td>
<td>Aid to smoking cessation treatment</td>
</tr>
<tr>
<td>Zyban (bupropion)†</td>
<td>020711; GlaxoSmithKline; 5/14/97</td>
<td>150 mg tablets</td>
<td>Aid to smoking cessation treatment</td>
</tr>
<tr>
<td>Nicotrol (nicotine)</td>
<td>20385; Pfizer; 3/22/96 20714; Pharmacia and Upjohn Co; 5/2/97</td>
<td>Spray; metered dose = 0.5 mg Inhalation; 4 mg/cartridge</td>
<td>Aid to smoking cessation</td>
</tr>
<tr>
<td>Other nicotine replacement products</td>
<td>Multiple OTC products</td>
<td>Gum, lozenge, patch</td>
<td>Stop smoking aid</td>
</tr>
</tbody>
</table>

†Bupropion’s original approval was for depression on 12/30/85 (Wellbutrin NDA 18644, GlaxoSmithKline).

4Pollock M. Neuropsychiatric events associated with varenicline. OSE RCM #2914-1620. September 4, 2014. The most common event for ‘miscellaneous’ was depression.
5Pollock M, Mosholder A, Lee J, Governale L. Suicidality associated with varenicline, bupropion, and nicotine transdermal patch. 7/16/08; OSE RCM #2007-2425.
6Pollock M, Mosholder A, Ju J. Psychiatric events (including suicides) associated with varenicline and bupropion. 12/8/08; OSE RCM# 2008-1291.
1.3 PRODUCT LABELING

Varenicline and bupropion product labeling include a Boxed Warning for serious NPS events.\(^7\,8\) The approved highlight Boxed Warnings for Chantix (varenicline) and Zyban (bupropion HCl) are found below.

**Chantix (varenicline)**

```
WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS
See full prescribing information for complete boxed warning.

- Serious neuropsychiatric events have been reported in patients taking CHANTIX. (5.1 and 6.2)
- Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior while taking CHANTIX or shortly after discontinuing CHANTIX. (5.1 and 6.2)
- Weigh the risks of CHANTIX against benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (5.1 and 6.2)
```

**Zyban (bupropion HCl)**

```
WARNING: NEUROPSYCHIATRIC REACTIONS; AND SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- Serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation. (5.1)
- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.2)
- Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.2)
```

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

We retrieved and categorized serious, domestic adverse event reports for varenicline, bupropion, and nicotine replacement therapy with events between January 1, 2011 and December 31, 2015.

2.2 FAERS SEARCH STRATEGY

We searched the FAERS database with the strategy in Table 2.

---

\(^7\) Chantix (varenicline) product labeling. NDA 21928. Pfizer. Revised 10/2014.

Table 2. FAERS Search Strategy*

<table>
<thead>
<tr>
<th><strong>Date of search</strong></th>
<th>June 9, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time period of search (as event date)</strong></td>
<td>January 1, 2011 – December 31, 2015</td>
</tr>
<tr>
<td><strong>Search type</strong></td>
<td>FBIS Quick query</td>
</tr>
<tr>
<td><strong>Drug name terms (active moiety)</strong></td>
<td>Varenicline, Bupropion, Nicotine</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Serious†</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>United States</td>
</tr>
</tbody>
</table>

* See Appendix B for a description of the FAERS database.
† Death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, other serious important medical events.

The overall counts presented in this document have not been de-duplicated, as we did not analyze all reports at the case level. In some situations, we performed individual report review when data was inconsistent, disproportionate, or outlying.

2.3 FAERS DATA PRESENTATION

DPV II has characterized the FAERS adverse event data using select MedDRA terminology. We use System Organ Class (SOC) and Preferred Terms (PTs). SOCs are broad MedDRA groupings of terms by etiology, manifestation site, or purpose. PTs are distinct descriptors (single medical concepts) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic.

Since MedDRA SOCs can be several characters long, and difficult to include on a small chart, we use abbreviations for SOCs in this review (Appendix C).

We present FAERS data for the three smoking cessation drugs in two formats: graphical and tabular. We also present data for all event years and for each individual event year.

2.3.1 Graphical display

Stacked bar graphs represent reported MedDRA PTs by SOC. Some PTs have MedDRA coding in more than one SOC. These ‘multi SOC PTs’ are counted in each of the coded SOCs. We determine the top 5 SOCs for all event years (2011-2015) and for each individual event year. The stacked bar graphs are normalized to 100% of the top 5 SOCs (left Y axis) for the particular time period. We use a consistent coloration scheme in the stacked bar graphs to indicate different SOCs, shown in Table 3.

---

<table>
<thead>
<tr>
<th>SOC</th>
<th>Color</th>
<th>SOC</th>
<th>Color</th>
<th>SOC</th>
<th>Color</th>
<th>SOC</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Green</td>
<td>Injury/poisoning</td>
<td>Orange</td>
<td>Product</td>
<td>Black</td>
<td>Skin</td>
<td>Yellow</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Purple</td>
<td>Nervous</td>
<td>Red</td>
<td>Psychiatric</td>
<td>Blue</td>
<td>Vascular</td>
<td>Orange</td>
</tr>
<tr>
<td>General</td>
<td>Green</td>
<td>Pregnancy</td>
<td>Pink</td>
<td>Respiratory</td>
<td>Green</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

On the *individual* smoking agent stacked bar graphs, we also display the number of FAERS reports for each event year as a grey shaded plot with a secondary (right) Y axis.

### 2.3.2 Tabular display

We use tables for ranked PTs (top 25) for each smoking cessation drug. If there are more than one PT for rank number 25, we display them all. Therefore a top 25 PT list can have more than 25 rows. We refer to these lists as ‘Top PTs’.

Among the top 25 PTs, we identify NPS events. We do *not* include sleep-related events, such as *abnormal dreams* or *insomnia*, because they are not included in the current Boxed Warning for NPS events for varenicline or bupropion and have not been a focus of our past reviews for NPS events.  

### 3 RESULTS

#### 3.1 All Smoking Cessation Drugs

We retrieved 5,542 FAERS reports for the three smoking cessation drugs as shown in Table 5.

| Table 5. Number of Serious, Domestic FAERS Reports for Smoking Cessation Drugs with an Event Year of 2011-2015 |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| All Reports | Varenicline | Bupropion | NRT |
| 5,542† | 2,864 | 1,864 | 893 |

†Not mutually exclusive; 79 reports include more than one smoking cessation drug.

The top 5, or most frequently reported, SOC for each smoking cessation drug for all event years (2011-2015) is shown in Figure 1.

---

10 Sleep-related events have been labeled from the time of approval in *Adverse Reactions/Clinical Trials Experience. Chantix (varenicline) labeling*, last revised on 10/15/14.
For the five year period, *Psychiatric* and *Nervous* SOCs were the most common for varenicline and bupropion (smoking cessation and all indications) representing 62%, 60% and 57% of the top 5 SOCs reported, respectively. The adverse event profile for NRT is different as *Psychiatric* and *Nervous* SOCs were not the most common and represent only about a third (35%) of the top 5 SOCs reported to FAERS.

Figure 2 shows FAERS data at the individual report level for the *Psychiatric* and *Nervous* SOCs.
Approximately 70% of varenicline and bupropion reports include at least one event from the *Psychiatric/Nervous* SOCs, and we consider these proportions to be comparable. NRT has the lowest percentage (56%) of reports with at least one event from the *Psychiatric/Nervous* SOCs.

3.2 **Varenicline** (N=2,864)

The top 5 SOC profile for individual event years (2011-2015) for varenicline is in Figure 3.
Overall, the number of FAERS reports decreased by 82% (1,129 reports in 2011 to 200 reports in 2015). However, Psychiatric and Nervous SOCs were consistently the two most common SOCs reported over the five year period, varying between 59-68% of the Top 5 SOCs reported.\(^{11}\)

Table 6 lists the top 25 PTs reported for varenicline by event year (2011-2015).

\(^{11}\)For all 5 years, Psychiatric and Nervous SOCs were 62% of the Top 5 SOCs (Figure 1).
<table>
<thead>
<tr>
<th>Index</th>
<th>Year</th>
<th>N=2,864</th>
<th>N=1,129</th>
<th>N=836</th>
<th>N=388</th>
<th>N=311</th>
<th>N=200</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>2011</td>
<td>2012</td>
<td>2013</td>
<td>2014</td>
<td>2015</td>
</tr>
<tr>
<td>1</td>
<td>Depression†</td>
<td>413</td>
<td>183</td>
<td>124</td>
<td>44</td>
<td>44</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>Nausea</td>
<td>322</td>
<td>143</td>
<td>104</td>
<td>29</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Anxiety</td>
<td>282</td>
<td>125</td>
<td>87</td>
<td>27</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>Feeling abnormal</td>
<td>253</td>
<td>94</td>
<td>89</td>
<td>31</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>Abnormal dreams</td>
<td>232</td>
<td>96</td>
<td>67</td>
<td>23</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>Suicidal ideation</td>
<td>211</td>
<td>86</td>
<td>51</td>
<td>27</td>
<td>32</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>Anger</td>
<td>188</td>
<td>84</td>
<td>51</td>
<td>23</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>Insomnia</td>
<td>188</td>
<td>80</td>
<td>52</td>
<td>22</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>Dyspnoea</td>
<td>187</td>
<td>83</td>
<td>57</td>
<td>23</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>Agitation</td>
<td>183</td>
<td>73</td>
<td>57</td>
<td>19</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>11</td>
<td>Malaise</td>
<td>177</td>
<td>75</td>
<td>53</td>
<td>24</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>Aggression</td>
<td>162</td>
<td>64</td>
<td>44</td>
<td>19</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>13</td>
<td>Drug ineffective</td>
<td>156</td>
<td>62</td>
<td>53</td>
<td>22</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>14</td>
<td>Headache</td>
<td>139</td>
<td>47</td>
<td>49</td>
<td>14</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>15</td>
<td>Irritability</td>
<td>139</td>
<td>65</td>
<td>44</td>
<td>12</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>16</td>
<td>Vomiting</td>
<td>124</td>
<td>43</td>
<td>41</td>
<td>15</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>17</td>
<td>Abnormal behavior</td>
<td>120</td>
<td>39</td>
<td>39</td>
<td>16</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>18</td>
<td>Dizziness</td>
<td>118</td>
<td>46</td>
<td>36</td>
<td>18</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>19</td>
<td>Nightmare</td>
<td>118</td>
<td>45</td>
<td>33</td>
<td>17</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>20</td>
<td>Hallucination</td>
<td>109</td>
<td>38</td>
<td>38</td>
<td>9</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>21</td>
<td>Rash</td>
<td>102</td>
<td>54</td>
<td>24</td>
<td>11</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>22</td>
<td>Chest pain</td>
<td>89</td>
<td>26</td>
<td>37</td>
<td>10</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>23</td>
<td>Depressed mood</td>
<td>89</td>
<td>59</td>
<td>22</td>
<td>0</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>24</td>
<td>Stress</td>
<td>87</td>
<td>32</td>
<td>30</td>
<td>10</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>25</td>
<td>Fatigue</td>
<td>80</td>
<td>38</td>
<td>28</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>26</td>
<td>Weight increased</td>
<td>80</td>
<td>39</td>
<td>19</td>
<td>12</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Total Reported PTs</td>
<td>4348</td>
<td>1819</td>
<td>1329</td>
<td>481</td>
<td>421</td>
<td>298</td>
</tr>
</tbody>
</table>

†NPS events are bolded.

The NPS event *depression* is rank number 1 in Table 6 for all years combined. In addition, there are 11 other NPS PTs (bolded) and together account for almost half (12/26; 46%) of the top PTs reported. Within the top 5 PTs, three are NPS events (*depression*, *anxiety* and *feeling abnormal*).

There are 14 other ‘harm’ events that rank below the top 25 (Appendix F). The three most common PTs are *suicide attempt* (n=76), *completed suicide* (n=58) and *homicidal ideation* (n=39).

### 3.3 BUPROPION SMOKING CESSATION (N=99)

We found 99 reports for bupropion smoking cessation.13

---

12‘Harm’ events means harm to self (e.g., *suicide*) or to another person (e.g., *homicide, assault*).
13We analyzed the bupropion all data set (n=1,864; Table 5) for smoking cessation-related terms in the indication and narrative fields.
Figure 4 shows the top 5 SOC profile for individual event years (2011-2015) for bupropion smoking cessation.

Figure 4. Bupropion Smoking Cessation, Serious, Domestic FAERS Reports (n=99): Top 5 SOCs and Number of Reports by Event Year (2011-2015)

Psychiatric and Nervous SOCs were consistently the two most common SOCs reported over the 5 year period, varying between 56-69% of the Top 5 SOCs reported.

Table 7 lists the top events reported for bupropion for smoking cessation by event year (2011-2015).
### Table 7. Top PTs for Bupropion for Smoking Cessation (n=99)

<table>
<thead>
<tr>
<th>Index</th>
<th>Year</th>
<th>All</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Seizure</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Fall</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>Pain</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Feeling abnormal‡</td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Weight decreased</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>Suicidal ideation</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Vomiting</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Drug interaction</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>Serotonin syndrome</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>Nausea</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>Blindness transient</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>Insomnia</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>Headache</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Depression</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>Anxiety</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>Crying</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>Decreased appetite</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>Hallucination</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>Agitation</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>Screaming</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>21</td>
<td>Pollakiuria</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>22</td>
<td>Retching</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>23</td>
<td>Drug ineffective</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>24</td>
<td>Dizziness</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>Chills</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>26</td>
<td>Chest pain</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

| Total Reported PTs | 162 | 18  | 31  | 16  | 19  | 78  |

‡NPS events are bolded.

Overall, eight NPS events are listed and represent almost a third (47/162; 29%) of the top PTs reported. This small (n=99) data set does not allow for a more discrete separation of rankings as seen with varenicline (Table 6) as there are multiple rows in Table 7 that have the same number of counts. With this caveat in mind, three of the NPS events (feeling abnormal, suicidal ideation, and depression) have counts within the top 5 rank of Table 7.

One disparity in Table 7 is in the year 2015. There are a large number of total reported PTs (n=78) compared to the number of reports (n=18). This is because almost two-fifths (7/18) of the reports contribute almost four-fifths (177/225) of the all reported PTs for 2015.14

14One report was a 'triplicate' with 38 PTs, each. Four other reports had between 13 and 19 PTs, each.
There are six other harm events that ranked below the top 25 in Table 7 (Appendix D). The two most common are *completed suicide* and *suicide attempt*, each reported twice.

### 3.4 BUPROPION ALL INDICATIONS (N=1,864)

The top 5 SOC profile for individual event years (2011-2015) for bupropion is in Figure 5.

![Figure 5. Bupropion All Indications Serious, Domestic FAERS Reports (n=1864): Top 5 SCOS and Number of Reports by Event Year (2011-2015)](image)

*Psychiatric* and *Nervous* SCOS are the most common reported for years 2011 and 2015 (accounting for 50% and 56%, respectively). From 2012 to 2014, the *Psychiatric* SOC is the number one rank and the *Nervous* SOC ranks third. The number of overall FAERS reports (any event) increased from 2011 to 2012, then leveled off from 2013 to 2015. This did not appear to affect the overall *Psychiatric* and *Nervous* SOC event-profile which remained between 53% and 60% over the 5 year period.

Table 8 lists the top events reported for bupropion for all indications by event year (2011-2015).

<table>
<thead>
<tr>
<th>Table 8. Top PTs for Bupropion for All Indications (n=1,864)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
</tbody>
</table>

Reference ID: 3967915
Table 8. Top PTs for Bupropion for All Indications (n=1,864)

<table>
<thead>
<tr>
<th>Index</th>
<th>Year</th>
<th>All</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Product substitution issue</td>
<td>187</td>
<td>40</td>
<td>24</td>
<td>39</td>
<td>56</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>Seizure</td>
<td>168</td>
<td>29</td>
<td>27</td>
<td>32</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Drug ineffective</td>
<td>163</td>
<td>33</td>
<td>34</td>
<td>31</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>Anxiety</td>
<td>133</td>
<td>19</td>
<td>24</td>
<td>21</td>
<td>42</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>Suicidal ideation</td>
<td>121</td>
<td>19</td>
<td>22</td>
<td>21</td>
<td>42</td>
<td>17</td>
</tr>
<tr>
<td>8</td>
<td>Nausea</td>
<td>116</td>
<td>15</td>
<td>22</td>
<td>12</td>
<td>27</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>Death</td>
<td>106</td>
<td>0</td>
<td>8</td>
<td>59</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>Toxicity to various agents</td>
<td>106</td>
<td>2</td>
<td>68</td>
<td>10</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>Headache</td>
<td>95</td>
<td>12</td>
<td>19</td>
<td>13</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>Feeling abnormal</td>
<td>89</td>
<td>13</td>
<td>22</td>
<td>13</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>Dizziness</td>
<td>88</td>
<td>13</td>
<td>16</td>
<td>13</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>14</td>
<td>Product quality issue</td>
<td>87</td>
<td>9</td>
<td>13</td>
<td>12</td>
<td>40</td>
<td>13</td>
</tr>
<tr>
<td>15</td>
<td>Exposure via ingestion</td>
<td>85</td>
<td>0</td>
<td>78</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>Drug abuse</td>
<td>82</td>
<td>1</td>
<td>54</td>
<td>25</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>Poisoning</td>
<td>77</td>
<td>0</td>
<td>59</td>
<td>12</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>Fall</td>
<td>75</td>
<td>11</td>
<td>14</td>
<td>13</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>19</td>
<td>Insomnia</td>
<td>75</td>
<td>15</td>
<td>22</td>
<td>11</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>20</td>
<td>Tremor</td>
<td>70</td>
<td>14</td>
<td>9</td>
<td>16</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>21</td>
<td>Fatigue</td>
<td>68</td>
<td>12</td>
<td>16</td>
<td>13</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>22</td>
<td>Agitation</td>
<td>61</td>
<td>14</td>
<td>13</td>
<td>8</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>23</td>
<td>Vomiting</td>
<td>57</td>
<td>9</td>
<td>10</td>
<td>5</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>24</td>
<td>Drug interaction</td>
<td>49</td>
<td>13</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>25</td>
<td>Urticaria</td>
<td>48</td>
<td>7</td>
<td>9</td>
<td>6</td>
<td>8</td>
<td>18</td>
</tr>
</tbody>
</table>

Total Reported PTs | 2689 | 350 | 768 | 498 | 630 | 443 |

*1NPS events are bolded.

The top 2 PTs in Table 8 (completed suicide<sup>15</sup> and depression) are NPS events. These two PTs along with the other four NPS events agitation, anxiety, feeling abnormal and suicidal ideation represent one-third (n=887) of all the top reported PTs.

There are 10 harm events that rank below the top PTs in Table 8. The most common event is suicide attempt (n=30); complete listing is in Appendix D.

### 3.5 Nicotine Replacement Therapy (N=893)

<sup>1</sup>Most (236/270; 87%) of the completed suicide reports were from the American Association of Poison Control Centers annual reports (http://www.aapcc.org/; accessed 7/13/15). These involved suicides described ‘intentional’, ‘suspected’ or not otherwise specified and involved multiple drug ingestions. The four most common co-reported PTs for the 236 completed suicide Poison Control reports were death (n=63), exposure via ingestion (n=61), toxicity to various agents (n=47), and poisoning (n=45). In contrast, bupropion for smoking cessation (Section 3.3) had no Poison Control Center reports, varenicline (Section 3.2) had two (both completed suicides). Nicotine replacement (Section 3.5) had eight (completed suicide, n=3; cardiac arrest, n=5). After deduplication, these eight nicotine reports amounted to one completed suicide and three cardiac arrests.
The top 5 SOC profile for individual event years (2011-2015) for NRT is in Figure 6.

From 2011 to 2014, the *Psychiatric* and *Nervous* SOCs generally ranked between third and fifth, accounting for about 40% of the top 5 SOCs.\(^{16}\) However, in 2015, the *Psychiatric* and *Nervous* SOCs accounted for about 50% of the top 5 SOCs.\(^{17}\)

Table 9 lists the top events reported for NRT.

\(^{16}\)The year 2013 in Figure 6 only shows Psychiatric (third rank), but not Nervous. This is because Nervous ranked sixth with 118 counts.

\(^{17}\)There is a decreasing trend of total FAERS reports starting with 2012. In 2015 there were 81 reports, which is 9.1% of all 893 reports for the 5 years. Caution must be used in interpreting proportional SOC changes for a yearly subclass with relatively few reports.
<table>
<thead>
<tr>
<th>Index</th>
<th>Year</th>
<th>n=893</th>
<th>n=192</th>
<th>n=261</th>
<th>n=212</th>
<th>n=147</th>
<th>n=81</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>2011</td>
<td>2012</td>
<td>2013</td>
<td>2014</td>
<td>2015</td>
</tr>
<tr>
<td>1</td>
<td>Foetal exposure during pregnancy</td>
<td>142</td>
<td>28</td>
<td>58</td>
<td>29</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Drug withdrawal syndrome neonatal</td>
<td>93</td>
<td>13</td>
<td>42</td>
<td>17</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>Dyspnoea</td>
<td>72</td>
<td>12</td>
<td>22</td>
<td>23</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Exposure during breast feeding</td>
<td>65</td>
<td>13</td>
<td>26</td>
<td>14</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Overdose</td>
<td>64</td>
<td>13</td>
<td>20</td>
<td>23</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>Malaise</td>
<td>59</td>
<td>8</td>
<td>22</td>
<td>10</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Drug ineffective</td>
<td>53</td>
<td>11</td>
<td>17</td>
<td>7</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>Feeling abnormal†</td>
<td>52</td>
<td>7</td>
<td>23</td>
<td>5</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>Treatment noncompliance</td>
<td>49</td>
<td>13</td>
<td>17</td>
<td>16</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>Nausea</td>
<td>48</td>
<td>14</td>
<td>18</td>
<td>5</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>Dizziness</td>
<td>47</td>
<td>12</td>
<td>17</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>Headache</td>
<td>46</td>
<td>10</td>
<td>12</td>
<td>15</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>Premature baby</td>
<td>43</td>
<td>10</td>
<td>15</td>
<td>8</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Anxiety</td>
<td>39</td>
<td>6</td>
<td>12</td>
<td>8</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>Low birth weight baby</td>
<td>36</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>Pneumonia</td>
<td>35</td>
<td>1</td>
<td>14</td>
<td>7</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>Vomiting</td>
<td>35</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>18</td>
<td>Maternal drugs affecting fetus</td>
<td>34</td>
<td>5</td>
<td>14</td>
<td>8</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>19</td>
<td>Incorrect drug administration</td>
<td>32</td>
<td>4</td>
<td>12</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>Nicotine dependence</td>
<td>32</td>
<td>10</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>21</td>
<td>Asthenia</td>
<td>31</td>
<td>8</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>22</td>
<td>Chest pain</td>
<td>31</td>
<td>6</td>
<td>5</td>
<td>13</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23</td>
<td>Seizure</td>
<td>31</td>
<td>9</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>24</td>
<td>Cough</td>
<td>30</td>
<td>11</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>25</td>
<td>Exposure during pregnancy</td>
<td>30</td>
<td>5</td>
<td>16</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>26</td>
<td>Insomnia</td>
<td>30</td>
<td>6</td>
<td>12</td>
<td>8</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>27</td>
<td>Pain</td>
<td>30</td>
<td>7</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1289</td>
<td>261</td>
<td>448</td>
<td>278</td>
<td>206</td>
<td>96</td>
</tr>
</tbody>
</table>

†NPS events are bolded.

There are two NPS PTs in Table 9: feeling abnormal and anxiety. These two PTs constitute less than a tenth (7%) of the 27 PTs in Table 10.

There is no report of ‘harm to self or other person’ events in Table 9. However, there are six other harm events that ranked below the top PTs in Table 9. The two most common are homicidal ideation and suicidal ideation (both n=10 each; Appendix D).

### 4 DISCUSSION

We retrieved and characterized 5,542 serious, domestic FAERS reports associated with smoking cessation therapy with an event year of 2011 to 2015. We characterized the reports by the top 5 SOCs and top PTs, with an emphasis on NPS events. We used event year, rather than report receive year, in our analysis to enable our data to be relatable to patient drug exposure patterns.
Drug use data are available in a separate document from the Division of Epidemiology II (DEPI II).

The top 5 SOCs and top PT profile for varenicline and bupropion for smoking cessation are similar. Overall, we identified a small number of reports for bupropion for smoking cessation therapy compared to varenicline. This is consistent with prior OSE/DEPI II drug usage analyses for smoking cessation drugs that have indicated that varenicline is used much more than Zyban (brand and generics) for smoking cessation.18

Varenicline FAERS reports (for any event) trended downward over the 5 year period; however, the Psychiatric and Nervous SOCs were consistently the most common (top 2 rank) representing almost two-thirds (63%) of the top 5 SOCs. When we combine 2011-2015 data with data in Appendix A, the 9-year period of 2006 to 2015 shows an overall trend of a consistently large proportion of Psychiatric and Nervous events despite overall decreases in FAERS reports for varenicline. Similar to varenicline, the Psychiatric and Nervous SOCs were also the most common for bupropion for smoking cessation throughout the time period of 2011 to 2015.

At the PT level, NPS events account for 46% of the top PTs for varenicline and 29% of the top PTs for bupropion for smoking cessation. The PTs depression, anxiety, feeling abnormal and suicidal ideation are the top NPS events for both varenicline and bupropion for smoking cessation, and are consistent with current product labeling.

There is ongoing concern for self- and other-harm events (e.g., suicidality, aggression, violent behavior) with varenicline and bupropion.19,20 Suicidal ideation is the only self- or other-harm term reported in the top PTs for varenicline and bupropion for smoking cessation. However, we looked beyond the top PTs and found that other self- and other-harm events continue to be reported for both varenicline and bupropion. The reported harm events are consistent with current product labeling.

Most NRT is available OTC (with the exception of Nicotrol, Table 1). The OTC NRT product labeling does not list NPS events.21 Regarding the FAERS data for NRT, Psychiatric and Nervous SOCs are not the most common SOCs across the years, and there is not a preponderance of NPS events in the top PTs.

5 CONCLUSIONS

We retrieved 5,542 serious, domestic FAERS reports for smoking cessation drugs (varenicline, n=2,864; bupropion, n=1,864; NRT, n=893) with an event year between 2011 and 2015. Of the

---

18Gill R. Chantix (varenicline) Drug Utilization Review. 9/3/14; OSE RCM# 2014-749. In 2013, approximately 49,000 patients received a prescription for Zyban (brand and generic) versus 1.15 million patients for varenicline.19Pollock M, Mosholder A, Lee J. Governale L. Suicidality associated with varenicline, bupropion, and nicotine transdermal patch. 7/16/08; OSE RCM #2007-2425.
20Pollock M, Mosholder A, Ju J. Psychiatric events (including suicides) associated with varenicline and bupropion. 12/8/08; OSE RCM# 2008-1291.
21 The prescription nicotine spray (Nicotrol NS) labeling mentions some NPS events in the context of tobacco withdrawal symptoms.
1,864 bupropion reports, 99 reported use for smoking cessation. We characterized the adverse event profile for all three smoking cessation products, with a focus on NPS events.

About 70% of varenicline and bupropion (all indications or smoking cessation) reports include at least one event from the *Psychiatric* or *Nervous* SOCs. The top 4 NPS events for both varenicline and bupropion for smoking cessation are *depression, anxiety, feeling abnormal and suicidal ideation*; we also identified reports of *suicide attempt, completed suicide, and homicidal ideation* for both products. For NRT, a smaller proportion of the reports include one or more events from the *Psychiatric* and *Nervous* SOCs, and there is not a preponderance of NPS events in the top reported events.

Although there was an overall decrease in the number of FAERS reports for varenicline over the five year period (2011-2015), the SOCs *Psychiatric disorders* and *Nervous system disorders* consistently accounted for most reported adverse events. Similar to varenicline, the *Psychiatric* and *Nervous* SOCs were also the most common for bupropion for smoking cessation throughout the time period of 2011 to 2015.

Serious NPS events continue to be reported in spontaneous postmarket data for both varenicline and bupropion. These data are consistent with current product labeling for varenicline and bupropion.
6 APPENDICES

6.1 APPENDIX A. FAERS DATA PRESENTED AT THE 2014 CHANTIX NPS ADVISORY COMMITTEE MEETING

Figure A1. Varenicline Serious, Domestic FAERS Reports: Top 4 SOCs and Number of Reports by Event Year (2006-2013)
6.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

**FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.
### 6.3 Appendix C. Selected SOC Full Names and Abbreviations Used in This Review

<table>
<thead>
<tr>
<th>SOC Full Name</th>
<th>SOC Abbreviation Used In This Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIAC DISORDERS</td>
<td>Cardiac</td>
</tr>
<tr>
<td>GASTROINTESTINAL DISORDERS</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</td>
<td>General</td>
</tr>
<tr>
<td>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</td>
<td>Injury/poisoning</td>
</tr>
<tr>
<td>NERVOUS SYSTEM DISORDERS</td>
<td>Nervous</td>
</tr>
<tr>
<td>PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>PRODUCT ISSUES</td>
<td>Product</td>
</tr>
<tr>
<td>PSYCHIATRIC DISORDERS</td>
<td>Psychiatric</td>
</tr>
<tr>
<td>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</td>
<td>Respiratory</td>
</tr>
<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</td>
<td>Skin</td>
</tr>
<tr>
<td>VASCULAR DISORDERS</td>
<td>Vascular</td>
</tr>
</tbody>
</table>
### 6.4 APPENDIX D. HARM PTs FOR ALL SMOKING CESSATION DRUGS FOR EVENT YEARS 2011-2015

<table>
<thead>
<tr>
<th>PT</th>
<th>Varenicline</th>
<th>Bupropion (all indications)</th>
<th>Bupropion (smoking cessation)</th>
<th>Nicotine replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed suicide</td>
<td>58</td>
<td>270 (in top PTs)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Depression suicidal</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gun shot wound</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Homicidal ideation</td>
<td>39</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Homicide</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intentional self-injury</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Physical assault</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Self injurious behaviour</td>
<td>9</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Self-injurious ideation</td>
<td>12</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Spousal abuse</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal behaviour</td>
<td>15</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>211 (in top PTs)</td>
<td>121 (in top PTs)</td>
<td>8 (in top PTs)</td>
<td>10</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>76</td>
<td>30</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Verbal abuse</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Victim of homicide</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total Reported PTs</strong></td>
<td>457</td>
<td>460</td>
<td>14</td>
<td>27</td>
</tr>
</tbody>
</table>
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Utilization Review

Date: 08/02/2016

Reviewers: Nabila Sadiq, Pharm.D.
Division of Epidemiology II

Team Leader: Rajdeep Gill, Pharm.D.
Division of Epidemiology II

Deputy Director for Drug Utilization: LCDR Grace Chai, Pharm.D.
Division of Epidemiology II

Drug Name(s): Chantix (varenicline) tablets,
Zyban (bupropion) tablets,
Nicotine Replacement Therapy

Application Type/Number: Multiple

Applicant/Sponsor: Multiple

OSE RCM #: 2016-976

**This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.**
# Table of Contents

EXECUTIVE SUMMARY ...................................................................................................................... 3

1 Introduction ....................................................................................................................................... 4
  1.1 Background ............................................................................................................................................. 4
  1.2 Product Information ................................................................................................................................ 4

2 Methods and Materials ...................................................................................................................... 4
  2.1 Determining Setting of Care ................................................................................................................... 4
  2.1 Data Sources Used .................................................................................................................................. 5

3 Results ............................................................................................................................................... 5
  3.1 Sales Data................................................................................................................................................ 5
  3.2 Prescription Data ..................................................................................................................................... 6
  3.3 Patient Data ............................................................................................................................................. 7
  3.4 Estimated Utilization Of Bupropion Products (excluding Zyban) .......................................................... 8

4 Discussion ......................................................................................................................................... 8

5 Conclusions ....................................................................................................................................... 9

6 Appendix 1: Tables ........................................................................................................................ 11

7 Appendix 2: Database Descriptions ............................................................................................... 13
EXECUTIVE SUMMARY

In preparation for the joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to be held on September 14, 2016, this review provides an analysis of drug utilization patterns for smoking cessation products. Utilization of Chantix (varenicline), Zyban (brand and generics for Zyban), Nicotrol inhaler, Nicotrol nasal spray and over-the-counter (OTC) nicotine replacement products, as well as an analysis of other bupropion products (e.g. Wellbutrin products) was analyzed to provide context and background.

The overall sales of prescription (Rx) and over-the-counter (OTC) smoking cessation products from manufacturers to various settings of care increased by 11% from approximately 6.9 million bottles/packets sold in 2011 to 7.7 million sold in 2015. In 2015, OTC products accounted for approximately 61% and Rx products accounted for approximately 39% of the total sales of smoking cessation products. However, the market share and trends in OTC sales across time should be interpreted with caution due to the limitations of data resources available. The OTC sales data shown are likely an underestimation of total OTC sales.

Analysis of outpatient retail prescription utilization data show a total 2.4 million prescriptions were dispensed from the outpatient retail setting for smoking cessation products, of which approximately 90% were for Chantix (varenicline) in 2015. Chantix (varenicline) prescriptions decreased by 17% from approximately 2.6 million dispensed prescriptions in 2011 to 2.1 million dispensed prescriptions in 2015. Zyban prescriptions increased by 57% from approximately 100,000 to 158,000 prescriptions whereas Nicotrol inhaler and Nicotrol nasal spray prescriptions decreased by 28% (95,000 to 68,000 prescriptions) and 15% (25,000 to 22,000 prescriptions) respectively, from 2011 to 2015.

The number of patients who received dispensed prescriptions for Chantix (varenicline) increased from approximately 573,000 patients in 2006 to a peak of 3.9 million patients in 2007, before declining to 1.2 million patients in 2012 and remaining relatively steady thereafter. Patient utilization of Zyban increased and Nicotrol inhaler and Nicotrol nasal spray decreased from 2006 through 2015.

Although other bupropion products1 such as Wellbutrin and generic equivalents are not indicated for smoking cessation, these products contain the same active ingredient as Zyban, which is approved for smoking cessation.2 To ascertain the possible extent of utilization of other bupropion products for smoking cessation, excluding Zyban, we analyzed both dispensed prescription data and indication data as reported by U.S. office-based physician survey database. Approximately 3% of the total diagnoses associated with other bupropion products, (excluding Zyban and its generics), were for “Nicotine dependence, unspecified, uncomplicated” (ICD-10 code F17200) in 2015. Therefore, of the total 28 million prescriptions dispensed for other bupropion products (excluding Zyban and its generics), an estimated 3% or 850,000 prescriptions may have been prescribed for smoking cessation in 2015 from U.S. outpatient retail pharmacies.

---

1 Other bupropion products including Wellbutrin, Forfivo, Aplenzin, budeprion, and generics equivalents

2 http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018644s050,020358s057lbl.pdf- Section 17 of Wellbutrin Label.
1 INTRODUCTION

In preparation for the joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to be held on September 14, 2016, this review provides an analysis of drug utilization patterns for smoking cessation products. Utilization of Chantix (varenicline), Zyban (brand and generics), Nicotrol inhaler, Nicotrol nasal spray and over-the-counter (OTC) nicotine replacement products, as well as an analysis of other bupropion products (e.g. Wellbutrin) was included to provide context and background to the meeting discussion.

1.1 BACKGROUND

The purpose of the joint meeting to be held on September 14, 2016 is to discuss the safety data from a post-marketing requirement, randomized placebo-controlled trial and published observational studies to determine the neuropsychiatric effects of Chantix (varenicline), Zyban (bupropion), and nicotine replacement therapy. The committee will also discuss whether these data support removal of the box warning for serious neuropsychiatric adverse events and additional changes to the product labeling for the studied products.

1.2 Product Information

Table 1 shows all smoking cessation products included in our utilization analysis.

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage form</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline (Chantix)</td>
<td>0.5 &amp; 1 mg tablets</td>
<td>Nicotinic receptor partial agonist</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin &amp; Zyban)</td>
<td>50, 75, 100, 150, 300 mg tablets</td>
<td>Amino ketone agent</td>
</tr>
<tr>
<td>Nicotine Products</td>
<td>Inhaler, Nasal sprays, Gum, Lozenges</td>
<td>Nicotine replacement therapy</td>
</tr>
</tbody>
</table>

Although other bupropion products such as Wellbutrin are not indicated for smoking cessation treatment, it contains the same active ingredient as Zyban, which is approved for smoking cessation.

2 METHODS AND MATERIALS

This analysis was conducted using proprietary drug utilization databases available to the Agency (see Appendix 2 for full database descriptions). Time periods assessed in this review were varied based on data availability for each data source used.

2.1 DETERMINING SETTING OF CARE

The IMS Health, IMS National Sales Perspective™ was used to determine the various retail and non-retail channels of distribution for Chantix (varenicline), Zyban (bupropion) and Nicotine Replacement Therapy (NRTs) products. Sales data for 2015 indicated that approximately 91% of Chantix and 81% of bupropion bottles/packages were distributed to the outpatient retail pharmacy setting. As a result, only the outpatient retail pharmacy utilization patterns were examined in this review. Retail pharmacies include chain stores, independent pharmacies, and food store pharmacies. Non-retail pharmacy and mail-order/specialty pharmacy settings data were not included in this analysis.

3 Information obtained from Drugs@FDA, available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
4 Information obtained from Drugs@FDA, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018644s050,020358s057lbl.pdf
5 IMS Health, National Sales Perspectives (NSP), Data extracted June 2016. File: NSPC 2016-796 Chantix channels 06.01.2016.xlsx
### 2.2 Data Sources Used

The IMS Health, National Sales Perspectives™ database was used to provide the nationally estimated number of bottles/packages of prescription (Rx) smoking cessation products and over-the-counter (OTC) nicotine replacement products sold from manufacturers to retail and non-retail channels of distribution in the U.S. from 2011 through 2015, annually. These sales data represent the amount of product being sold from manufacturers into the “back door” of various drug distribution outlets such as retail pharmacies, hospitals, clinics, etc.; it does not reflect what is being sold to or administered to patients directly. Of note, sales of OTC products shown in this review are an underestimation of total OTC sales. IMS estimates their projections of OTC products to be approximately 50% of the total U.S. OTC market.

The IMS Health, National Prescription Audit (NPA) was used to obtain the nationally estimated number of prescriptions dispensed for Chantix (varenicline) as well as Zyban products (brand and generics for Zyban), Nicotrol inhaler, and Nicotrol nasal spray (Smoking Deterrents USC Class 69000) through U.S. outpatient retail pharmacies from 2011 through 2015, annually.

The IMS Health, Total Patient Tracker (TPT) was used to obtain the nationally estimated number of patients who received a dispensed prescription Chantix (varenicline) as well as Zyban (brand and generics for Zyban), Nicotrol inhaler, and Nicotrol nasal spray from U.S. outpatient retail pharmacies for years 2006 through 2015.

Although other bupropion products, such as Wellbutrin are not indicated for smoking cessation treatment, the NPA database was also used to obtain the nationally estimated number of prescriptions dispensed for other bupropion products because they contain the same active ingredient as Zyban. To ascertain the possible extent of other bupropion products used for smoking cessation, excluding Zyban, a physician survey database was utilized to provide insight into the prescriber’s intent for indication for use.

Encuity Research, LLC. Treatment Answers™ with Pain Panel, a U.S. office-based physician survey database, was used to examine diagnoses reported to be associated with the use of other bupropion products such as Wellbutrin and generic equivalents (Antidepressants USC Class 64300) focused on diagnoses codes associated with smoking cessation for year 2015. Physician diagnoses were coded according to the International Classification of Disease (ICD-10 codes) and 95% confidence intervals were applied to the estimates. We used these results to estimate the number of prescriptions dispensed for other bupropion products (excluding Zyban) that may be associated with smoking cessation.

### 3 Results

#### 3.1 Sales Data

Figure 1 below and Table 2 in Appendix 1 provide the nationally estimated number of bottles/packages of prescription (Rx) and OTC smoking cessation products sold from manufacturers to all channels of distribution in the U.S. from 2011 through 2015. The overall sales captured increased by 11% from approximately 6.9 million in 2011 to 7.7 million bottles/packages sold in 2015.

In 2015, Rx products accounted for 39% (3.0 million bottles/packages) and OTC products accounted for 61% (4.7 million bottles/packages) of the total sales of smoking cessation products. Sales of prescription smoking cessation products remained stable and sales of OTC smoking cessation products increased by 24% from 3.8 million packages/bottles in 2011 to 4.7 million in 2015. There was an approximately 25% decrease in the sales of OTC smoking cessation products in 2012 and 2013.
However, the market share and trends in OTC sales across time should be interpreted with caution due to the limitations of data resources available. The OTC sales data shown are likely an underestimation of total OTC sales.

**Figure 1:**

Sales of smoking cessation products* in packages/bottles sold by prescription status (OTC vs Rx) sold from manufacturers to all U.S. channels of distribution, 2011-2015

![Graph showing sales trends from 2011 to 2015.]

*These data only includes products labelled for smoking cessation and do not include products that may be used off label, as other bupropion products such as Wellbutrin brand and generic equivalents


3.2 Prescription Data

Figure 2 below and Table 3 in Appendix 1 provide the nationally estimated number of dispensed prescriptions for Chantix (varenicline), Zyban products, Nicotrol inhaler, and Nicotrol nasal spray from U.S. outpatient retail pharmacies from 2011 through 2015. Of the total 2.4 million prescriptions, 90% of prescriptions were dispensed for Chantix in 2015. Overall, the number of prescriptions dispensed for Chantix decreased by 17% from approximately 2.6 million to 2.1 million prescriptions dispensed from 2011 through 2015. Although, the total number of prescriptions dispensed for Zyban products increased by 57% from approximately 100,000 to 158,000 prescriptions dispensed during the examined time period, Zyban only accounted for 7% of all prescription smoking cessation products in 2015. Nicotrol inhaler and Nicotrol nasal spray utilization decreased by 28% (95,000 to 68,000 prescriptions) and 15% (25,000 to 22,000 prescriptions) respectively from 2011 through 2015.
### Figure 2:

Nationally estimated number of prescriptions for smoking cessation products* dispensed through U.S. outpatient retail pharmacies, 2011-2015

![Prescriptions Graph](image)

*Only includes products labelled for smoking cessation. Does not include products that may be used off label, such as Wellbutrin (buproprion) SR and XL and generic equivalents.

---

3.3 **PATIENT DATA**

**Figure 3 below and Table 4 in Appendix 1** provide the nationally estimated number of unique patients who received a dispensed prescription for Chantix (varenicline), Zyban and its generics, Nicotrol inhaler, and Nicotrol nasal spray from U.S. outpatient retail pharmacies from 2006 through 2015.

The number of unique patients who received dispensed prescriptions for Chantix increased from approximately 573,000 patients in 2006 to a peak of 3.9 million patients in 2007, before declining to 1.2 million patients in 2012 and remaining relatively steady thereafter.

The number of patients who received a dispensed prescription for Zyban products increased by 35% from 64,000 patients in 2006 to 87,000 patients in 2015. The number of patients who received a dispensed prescription of Nicotrol inhaler decreased by 65% (144,000 to 49,000 patients) and Nicotrol nasal spray by 32% (10,000 to 7,000 patients) from 2006 to 2015.
3.4 ESTIMATED UTILIZATION OF BUPROPION PRODUCTS (EXCLUDING ZYBAN) FOR SMOKING CESSATION

Using dispensed prescription claims data, we found that approximately 28 million prescriptions were dispensed for all other bupropion products (excluding Zyban) such as Wellbutrin and generic equivalents (Antidepressants USC Class 64300) from outpatient retail pharmacies in 2015. Based on U.S. office-based physician surveys data for 2015, approximately 3% of the total number of drug use mentions for bupropion products (excluding Zyban) was reported to be associated with a diagnosis for “Nicotine dependence, unspecified, uncomplicated” (ICD-10 code F17200). Therefore, we estimate that of the total 28 million prescriptions dispensed for other bupropion products (excluding Zyban) in 2015, approximately 3% or 850,000 prescriptions may have been prescribed for smoking cessation.

4 DISCUSSION

Tobacco use has been quoted as the chief preventable cause of sickness and death in our society and

---

6 The term "drug uses" to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.
accounts for more than 435,000 deaths each year in the United States. Epidemiologic data suggests that more than 70% of the 45 million smokers in the United States report that they want to quit, and approximately 44% report that they try to quit each year. However, the success rate for quit smoking is extremely low.

Findings from our analysis show that the overall sales of Rx and OTC smoking cessation products from manufacturers to various settings of care increased by 11% from 2006 to 2015. The sales of OTC smoking cessation products accounted for nearly 61% and prescription smoking cessation products accounted for 39% of the total sales in 2015. However, the OTC sales data shown are likely an underestimation of total OTC sales of smoking cessation products. IMS estimates their projections of all OTC products to be representative of approximately 50% of the total U.S. OTC product market. Therefore, the market share and trends in OTC sales across time should be interpreted with caution due to the limitations of data resources available. Sales distribution data do not provide a direct estimate of use, they represent the amount of product being sold from manufacturers into the “back door” of various drug distribution outlets (e.g. retail pharmacies, hospitals, clinics, etc.) – it does not reflect what is being sold to or administered to patients directly.

In terms of outpatient utilization of the prescriptions products labeled for smoking cessation, the majority of the utilization was observed for Chantix (varenicline). Chantix (varenicline) prescriptions dispensed slightly decreased by 17% from approximately 2.6 million in 2011 to 2.1 million in 2013 and remained stable thereafter. Zyban prescriptions dispensed increased by 57% whereas Nicotrol inhaler and Nicotrol nasal spray prescriptions dispensed decreased by 28% and 15%, respectively, from 2011 through 2015. The number of patients who received dispensed prescriptions for Chantix (varenicline) increased from approximately 573,000 patients in 2006 (year of approval) to a peak of 3.9 million patients in 2007, before declining to 1.2 million patients in 2012 and remaining relatively steady thereafter. Patients who received dispensed prescriptions for Zyban increased whereas for Nicotrol inhaler and Nicotrol nasal spray decreased from 2006 through 2015.

To ascertain the possible extent of utilization of other bupropion products for smoking cessation, excluding Zyban, we analyzed both dispensed prescription claim data and indication data as reported by U.S. office-based physician survey database. According to the physician survey database, approximately 3% of the other bupropion products (excluding Zyban) were mentioned in association with a smoking cessation indication, which may translate to an estimated 850,000 bupropion prescriptions dispensed in 2015. This finding is suggestive that utilization of other bupropion products may be higher than the use of Zyban and its generics for smoking cessation indication. However, because dispensed prescription and indication data are not directly linked and due to the multiple indications associated with bupropion products (excluding Zyban) utilization, it is difficult to access the true patient exposure of these products for the indication of smoking cessation alone.

5 CONCLUSIONS

Chantix appears to be the most commonly utilized product for smoking cessation in the U.S. market. From approval in 2006, utilization of Chantix increased to a peak of 3.9 million patients in 2007, before declining to 1.2 million patients in 2012 and remaining relatively steady thereafter. Although


other bupropion products such as Wellbutrin and generic equivalents are not approved for smoking cessation, data are suggestive that bupropion products are also widely used for smoking cessation in the U.S.
### Table 2
Sales of smoking cessation products* in packages/bottles, by prescription status (OTC vs Rx), sold from manufacturers to all U.S. channels of distribution, years 2011-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Eacles (N)</th>
<th>Share (%)</th>
<th>Eacles (N)</th>
<th>Share (%)</th>
<th>Eacles (N)</th>
<th>Share (%)</th>
<th>Eacles (N)</th>
<th>Share (%)</th>
<th>Eacles (N)</th>
<th>Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Grand Total</td>
<td>6,989,040</td>
<td>100.0%</td>
<td>6,077,156</td>
<td>100.0%</td>
<td>5,960,600</td>
<td>100.0%</td>
<td>6,951,456</td>
<td>100.0%</td>
<td>7,722,956</td>
</tr>
<tr>
<td>OTC</td>
<td>3,801,497</td>
<td>54.4%</td>
<td>2,832,815</td>
<td>46.6%</td>
<td>2,849,428</td>
<td>47.8%</td>
<td>3,892,245</td>
<td>56.0%</td>
<td>4,706,097</td>
<td>60.9%</td>
</tr>
<tr>
<td>Rx</td>
<td>3,187,543</td>
<td>45.6%</td>
<td>3,244,341</td>
<td>53.4%</td>
<td>3,111,172</td>
<td>52.2%</td>
<td>3,059,210</td>
<td>44.0%</td>
<td>3,016,859</td>
<td>39.1%</td>
</tr>
</tbody>
</table>

*Only includes products labelled for smoking cessation. Does not include products that may be used off label, as other bupropion products such as Wellbutrin and generic equivalents.


### Table 3
Nationally estimated number of prescriptions for smoking cessation products* dispensed through U.S. outpatient retail pharmacies, years 2011-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Rx (Rx)</th>
<th>Share (%)</th>
<th>Rx (Rx)</th>
<th>Share (%)</th>
<th>Rx (Rx)</th>
<th>Share (%)</th>
<th>Rx (Rx)</th>
<th>Share (%)</th>
<th>Rx (Rx)</th>
<th>Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>69000 SMOKING DETERRENTS</td>
<td>2,827,704</td>
<td>100.0%</td>
<td>2,541,465</td>
<td>100.0%</td>
<td>2,324,887</td>
<td>100.0%</td>
<td>2,327,230</td>
<td>100.0%</td>
<td>2,401,217</td>
</tr>
<tr>
<td>Chantix</td>
<td>2,606,991</td>
<td>92.2%</td>
<td>2,305,384</td>
<td>90.7%</td>
<td>2,110,987</td>
<td>90.8%</td>
<td>2,118,633</td>
<td>91.0%</td>
<td>2,153,511</td>
<td>89.7%</td>
</tr>
<tr>
<td>Zyban (brand and generics)</td>
<td>100,401</td>
<td>3.6%</td>
<td>116,508</td>
<td>4.6%</td>
<td>113,480</td>
<td>4.9%</td>
<td>118,878</td>
<td>5.1%</td>
<td>157,902</td>
<td>6.6%</td>
</tr>
<tr>
<td>Nicotrol Inhaler</td>
<td>94,931</td>
<td>3.4%</td>
<td>94,282</td>
<td>3.7%</td>
<td>77,031</td>
<td>3.3%</td>
<td>66,873</td>
<td>2.9%</td>
<td>68,255</td>
<td>2.8%</td>
</tr>
<tr>
<td>Nicotrol Nasal</td>
<td>25,381</td>
<td>0.9%</td>
<td>25,291</td>
<td>1.0%</td>
<td>23,389</td>
<td>1.0%</td>
<td>22,846</td>
<td>1.0%</td>
<td>21,549</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

*Only includes products labelled for smoking cessation. Does not include products that may be used off label, as other bupropion products such as Wellbutrin and generic equivalents.


### Table 4
Nationally estimated number of unique patients who received dispensed prescriptions for smoking cessation products* from U.S. outpatient retail pharmacies, years 2006-2015

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Grand Total</td>
<td>775,004</td>
<td>100.0%</td>
<td>2,878,335</td>
<td>100.0%</td>
<td>2,883,931</td>
<td>100.0%</td>
<td>5,735,383</td>
<td>100.0%</td>
<td>3,499,889</td>
</tr>
<tr>
<td>Chantix</td>
<td>573,213</td>
<td>74%</td>
<td>2,806,737</td>
<td>98%</td>
<td>1,900,783</td>
<td>95%</td>
<td>1,622,684</td>
<td>94%</td>
<td>1,385,902</td>
<td>93.0%</td>
</tr>
<tr>
<td>Zyban (brand and generics)</td>
<td>64,404</td>
<td>8%</td>
<td>24,975</td>
<td>1%</td>
<td>35,008</td>
<td>2%</td>
<td>49,824</td>
<td>3%</td>
<td>46,621</td>
<td>3.1%</td>
</tr>
<tr>
<td>Nicotrol Inhaler</td>
<td>143,593</td>
<td>19%</td>
<td>55,339</td>
<td>2%</td>
<td>73,694</td>
<td>4%</td>
<td>69,164</td>
<td>4%</td>
<td>62,116</td>
<td>4.2%</td>
</tr>
<tr>
<td>Nicotrol Nasal Spray</td>
<td>10,245</td>
<td>1%</td>
<td>9,182</td>
<td>&lt;1%</td>
<td>8,875</td>
<td>&lt;1%</td>
<td>7,281</td>
<td>&lt;1%</td>
<td>6,747</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

*Only includes products labelled for smoking cessation. Does not include products that may be used off label, as other bupropion products such as Wellbutrin and generic equivalents.

*Summing patients across time periods and products will result in double counting and overestimates of patient counts.

Table 5
Top diagnoses associated with the use of bupropion products (excluding Zyban)* as reported by U.S. office-based physician surveys, year 2015

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Uses N (000)</th>
<th>Share %</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>bupropion hydrochloride*</td>
<td>6,291</td>
<td>100.0%</td>
<td>5,875-6,706</td>
</tr>
<tr>
<td>F17200 Nicotine dependence, unspecified, uncomplicated</td>
<td>194</td>
<td>3.1%</td>
<td>121-268</td>
</tr>
<tr>
<td>150 MG</td>
<td>178</td>
<td>91.6%</td>
<td>108-248</td>
</tr>
<tr>
<td>twice a day (BID)</td>
<td>97</td>
<td>54.7%</td>
<td>46-149</td>
</tr>
<tr>
<td>once a day (QD)</td>
<td>81</td>
<td>45.3%</td>
<td>34-128</td>
</tr>
<tr>
<td>75 MG</td>
<td>12</td>
<td>6.4%</td>
<td>&lt;0.5-31</td>
</tr>
<tr>
<td>2 twice a day</td>
<td>12</td>
<td>100.0%</td>
<td>&lt;0.5-31</td>
</tr>
<tr>
<td>300 MG</td>
<td>4</td>
<td>2.1%</td>
<td>&lt;0.5-15</td>
</tr>
<tr>
<td>once a day (QD)</td>
<td>4</td>
<td>100.0%</td>
<td>&lt;0.5-15</td>
</tr>
<tr>
<td>All Others diagnoses</td>
<td>6,094</td>
<td>96.9%</td>
<td>18,477-21,575</td>
</tr>
</tbody>
</table>

* includes other bupropion products such as Wellbutrin SR and XL and generic equivalents (excluding Zyban)


Encuity Research LLC, recommends caution interpreting projected annual uses or mentions below 100,000, as the sample size is very small with correspondingly large confidence
7 APPENDIX 2: DATABASE DESCRIPTIONS

**IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that smoking cessation products were distributed primarily to the outpatient retail setting, based on the IMS Health, IMS National Sales Perspectives™ database. As such, we focused our analysis only on the outpatient retail pharmacy settings. Therefore, the patient exposure estimates reported in this review may not apply to other settings of care in which these products may be used. All of the estimates provided in this review are projected national estimates, but no statistical tests were performed to determine statistical significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

**IMS Health, National Prescription Audit**

The National Prescription Audit (NPA™) has been the industry standard source of national prescription activity since 1952. NPA measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

**IMS, Vector One®: Total Patient Tracker (TPT)**

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database, which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year. The patient estimates focus on only outpatient retail pharmacies; therefore, they may not be representative of utilization in other settings of care such as mail-order/specialty and non-retail settings.

**Encuity Research, LLC, Treatment Answers™**

Encuity Research, LLC, Treatment Answers™ and Treatment Answers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of
diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing.

Drug use mentions and associated diagnoses were obtained using a monthly survey of 3,200 office-based physicians representing 30 specialties across the United States who report on all patient activity during one typical workday a month. These data are helpful to understand how physicians prescribe drug products. However, the small sample size may limit our ability to identify trends in the data. In general, this physician survey database is most appropriate to identify the typical uses for a product in office-based physician’s clinical practice; the sample may not represent the care from specialty clinics or inpatient settings. Encuity Research LLC, recommends caution interpreting projected annual uses or mentions below 100,000, as the sample size is very small with correspondingly large confidence intervals.
16.1 Study Information
16.1.1 Protocol and Protocol Amendments

Copies of the following documents are included:

- Final Protocol Amendment 7, Dated 07 Nov 2012
- Interventional Clinical Protocol Approval Form, Final Protocol Amendment 7, Dated 07 Nov 2012
- Final Protocol Amendment 8 Bulgaria, Denmark, Finland, France, Germany, Slovakia and Spain; Dated 07 Nov 2012
- Interventional Clinical Protocol Approval Form, Final Protocol Amendment 8 Bulgaria, Denmark, Finland, France, Germany, Slovakia and Spain; Dated 07 Nov 2012
A PHASE 4, RANDOMIZED, DOUBLE-BLIND, ACTIVE AND PLACEBO-
CONTROLLED, MULTICENTER STUDY EVALUATING THE
NEUROPSYCHIATRIC SAFETY AND EFFICACY OF 12 WEEKS VARENICLINE
TARTRATE 1 MG BID AND BUPROPION HYDROCHLORIDE 150 MG BID FOR
SMOKING CESSATION IN SUBJECTS WITH AND WITHOUT A HISTORY OF
PSYCHIATRIC DISORDERS

Compound: CP-526,555
Compound Name (if applicable): Varenicline Tartrate
US IND Number (if applicable): 58,994
EudraCT Number: 2010-022914-15
Protocol Number: A3051123
Phase: Phase 4
Amendment 7, 07 November 2012

This document contains confidential information belonging to Pfizer. Except as otherwise agreed to in writing,
by accepting or reviewing this document, you agree to hold this information in confidence and not copy or
disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event
of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

APPROVED BY PFIZER FOR PUBLIC DISCLOSURE
## Document History

<table>
<thead>
<tr>
<th>Document</th>
<th>Version Date</th>
<th>Summary of Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 7</td>
<td>07 November 2012</td>
<td>This is being amended to incorporate changes based on the updated bupropion Global Data Sheet dated 18 Sep 2012.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sections 6.2.2 Clinic Visits (Week 1 to 6 Visits, Weeks, 8, 10, 12 and ET12) and 6.3.1 Clinic Visits (Weeks 13, 16, 20, 24 and ET24 Visit): Added pregnancy testing to Visit Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 6.4.1 Subject Withdrawal is updated to include:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Study drug will be discontinued immediately for any female subject who becomes pregnant during the treatment period of the study.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 7.1.14 Laboratory was updated to include the additional pregnancy testing at clinic visits</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 8.9 Exposure During Pregnancy was updated to match the most recent protocol template and Pfizer SOPs</td>
</tr>
<tr>
<td>Amendment 6*</td>
<td>30 May 2012</td>
<td>This is being amended to incorporate changes based on feedback from the FDA and regulatory agencies in the EU.</td>
</tr>
<tr>
<td><strong>Country Specific:</strong> Bulgaria, Denmark, Finland, France, Germany, Slovakia and Spain</td>
<td></td>
<td>• Vital signs (PR and BP) are added to all clinic visits.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ECG is added to Week 12 and ET12 visit.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 4.2 Exclusion Criteria #9 is being changed from Subjects with a seizure disorder to Subjects with a current seizure disorder or any history of seizures. This change is to be consistent with EU SMPC for bupropion.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 4.2 Exclusion Criteria #23 is added to exclude subjects with skin conditions which would hinder the use of NRT placement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 6. (Study Procedures) is updated to include additional vital signs at every clinic visit and ECG at Wk 12 or ET12.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 6.4. (Subject Withdrawal) is updated to include information for Off Treatment in Study (OTIS) subjects and all subjects will be followed until final visit unless they withdraw consent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 7.1.14. (Physical Examination, Vital Signs and Electrocardiogram) is updated to include vital signs at every clinic visit and ECG as Wk 12 or ET12.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 7.1.15 (Cardiovascular Events of Interest) is changed from: Hospitalization for angina pectoris or chest pain to: Hospitalization for unstable angina. Also wording was added to further clarify how events of interest will be identified, reviewed and adjudicated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In addition the following changes/updates are made:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Remove Czech Republic from header and title page as this protocol is no longer being submitted to this country.</td>
</tr>
<tr>
<td>Amendment 5</td>
<td>30 May 2012</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>This is being amended to incorporate changes based on feedback from the US FDA and regulatory agencies in the EU.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Vital signs (PR and BP) are added to all clinic visits.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ECG is added to Week 12 and ET12 visit.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Section 4.2 Exclusion Criteria #22 is added to exclude subjects with skin conditions which would hinder the use of NRT placement.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Section 6 (Study Procedures) is updated to include additional vital signs at every clinic visit and ECG at Wk 12 or ET12.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Section 6.4 (Subject Withdrawal) is updated to include information for Off Treatment in Study (OTIS) subjects and all subjects will be followed until final visit unless they withdraw consent.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Section 7.1.12 (Physical Examination, Vital Signs and Electrocardiogram) is updated to include vital signs at every clinic visit and ECG as Wk 12 or ET12.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Section 7.1.15 (Cardiovascular Events of Interest) is changed from: Hospitalization for angina pectoris or chest pain to: Hospitalization for unstable angina. Also wording was added to further clarify how events of interest will be identified, reviewed and adjudicated. In addition the following changes/updates are made:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Section 4.2 Exclusion Criteria #5 is updated to clarify intent. It was changed from: “Subjects with a positive urine drug screen at screening or baseline”. To: Subjects with a positive urine drug screen at screening or baseline for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Section 5.3.3 Study Drug Administration- additional instructions for clarity are added to perform dose reduction of study drugs and if drug needs to be permanently discontinued. Section also updated to add information on medication error reporting.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Section 5.5 Concomitant Medication: Milnacipran (Scavella) is added to any use prohibited.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Section 7.1.10 Typographical error is corrected.**

- Section 8 Updated various Adverse Event sections to match the most recent protocol template and Pfizer SOPs.
- Section 15 Publication of Study Results updated to match the most recent protocol template and Pfizer SOPs.

<table>
<thead>
<tr>
<th>Amendment</th>
<th>Date</th>
<th>Details</th>
</tr>
</thead>
</table>
| 4*        | 10 October 2011 | This protocol is being amended to incorporate changes requested by the EMA.  
- Subjects with Bipolar I and II disorders will be excluded from the study.  
The Mental Health Professional (MHP) will be defined as a psychiatrist only. |
| 3         | 04 Oct 2011  | This protocol is being amended to incorporate changes requested by the US FDA.  
The protocol is being amended to include detailed cardiovascular medical history, collection of cardiovascular events of interest during the study, and a Cardiovascular Event Adjudication Committee. The protocol was also updated to be consistent with updated SOP CT 02 in regards to Section 15.1, Communication of Results by Pfizer. |
| 2         | 28 June 2011 | The protocol is being amended to incorporate changes requested by the US FDA and the EMA. In addition, bupropion has been added to the title, objectives and endpoints as an active comparator. The amendment also incorporates changes to the Neuropsychiatric Adverse Events Interview (NAEI) based on the outcome of the pilot in a similar patient population. In addition, the amendment provides updates to be in compliance with Pfizer SOPs, clarifies certain protocol aspects and corrects inconsistencies/typographical errors.  
- Updates safety and efficacy endpoints to include bupropion as active comparator;  
- Defines current and past diagnosis of a psychiatric history for the Inclusion Criteria;  
- Clarification of the exclusion criteria for which bupropion is not appropriate;  
- Clarification of the randomization criteria within the cohort for a psychiatric disorder;  
- Additional information of re-screening of subjects;  
- Additional verbiage for subjects lost to follow up during the study;  
- Clarification of the Clinical Global Impression of Improvement (CGI-I) and how to rate the severity for those subjects with a psychiatric history; |
Clarification of when the lack of efficacy should be reported as an adverse event;

- Updates to the statistical sections to include bupropion in the analyses;
- Changes to the Nicotine Use Inventory (NUI) to comply with US FDA requests and ensure proper data collection
- Changes to the NAEI based on the outcome of the NAEI pilot study.
- Updates to include language on potential cases of drug induced liver injury.
- Updates Appendix 9, and Appendix 10 (C-SSRS Baseline and Since Last Visit) to January 14, 2009 version).

<table>
<thead>
<tr>
<th>Amendment</th>
<th>Date</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 1</td>
<td>17 June 2010</td>
<td>See Appendix 13</td>
</tr>
<tr>
<td>Original protocol</td>
<td>17 May 2010</td>
<td>N/A</td>
</tr>
</tbody>
</table>

For Amendments: This amendment incorporates all revisions to date except those in the amendment(s) indicated with an (*). The sites following the amendment(s) marked with an (*) above must use the specific region/country/site amendments as well as the current amendment.
**SCHEDULE OF ACTIVITIES- Study Treatment Period**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screen</th>
<th>BL (Day 8)</th>
<th>Wk 2</th>
<th>Wk 3</th>
<th>Wk 4</th>
<th>Wk 5</th>
<th>Wk 6</th>
<th>Wk 7*</th>
<th>Wk 8</th>
<th>Wk 9*</th>
<th>Wk 10</th>
<th>Wk 11*</th>
<th>Wk 12</th>
<th>ET* 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent(^b)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History, Cardiovascular Medical History, Demography, Smoking history/height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs (PR, BP)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SCID I and II</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Volunteered reporting</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HADS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Aggression Questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview (NAEI)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBQ-R</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagerström Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exhaled CO</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense Study Drugs</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC, Blood Chemistry</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy Test(^c) (urine or serum)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Drug Screen(^d) (dipstick at site)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Emergency Contact Information Card</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric Evaluation(^e)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect cardiovascular events of interest</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Designates telephone visit
\(^b\) If ET is before the Week 12 visit.
\(^c\) Must be signed prior to any protocol procedures being performed.
\(^d\) All females unless surgically sterilized or at least 2 years postmenopausal.
\(^e\) May be performed at other visits at investigator’s discretion.
\(^f\) If deemed needed per protocol section 7.1.10.
## SCHEDULE OF ACTIVITIES- Post - Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Wk 13</th>
<th>Wk 14*</th>
<th>Wk 15*</th>
<th>Wk 16</th>
<th>Wk 17*</th>
<th>Wk 18*</th>
<th>Wk 19*</th>
<th>Wk 20</th>
<th>Wk 21*</th>
<th>Wk 22*</th>
<th>Wk 23*</th>
<th>Wk 24</th>
<th>ET* 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital Signs (PR, BP)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Volunteered reporting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HADS</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NUI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exhaled CO</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Psychiatric Evaluation</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Collect cardiovascular events of interest</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy Testc (urine or serum)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

* Designates telephone visit.

a If ET is after Week 12 visit and before Week 24 visit.

b If deemed needed per protocol section 7.1.10.

c All females unless surgically sterilized or at least 2 years postmenopausal.
TABLE OF CONTENTS

1. INTRODUCTION .....................................................................................................................12
   1.1. Indication .......................................................................................................................12
   1.2. Background and Rationale ............................................................................................12

2. STUDY OBJECTIVES AND ENDPOINTS.............................................................................15
   2.1. Objectives ......................................................................................................................15
       2.1.1. Safety ................................................................................................................15
       2.1.2. Efficacy: Abstinence from Smoking ................................................................16
   2.2. Endpoints .......................................................................................................................16
       2.2.1. Safety ................................................................................................................16
       2.2.2. Efficacy .............................................................................................................17

3. STUDY DESIGN.......................................................................................................................17

4. SUBJECT SELECTION............................................................................................................19
   4.1. Inclusion Criteria ...........................................................................................................19
       4.1.1. Additional Inclusion Criteria for Neuropsychiatric Cohort..............................20
   4.2. Exclusion Criteria ..........................................................................................................21
   4.3. Randomization Criteria .................................................................................................25
   4.4. Life Style Guidelines .....................................................................................................25

5. STUDY TREATMENTS...........................................................................................................26
   5.1. Allocation to Treatment ................................................................................................27
   5.2. Breaking the Blind ........................................................................................................27
   5.3. Drug Supplies ................................................................................................................27
       5.3.1. Formulation and Packaging ..............................................................................27
       5.3.2. Preparation and Dispensing ..............................................................................27
       5.3.3. Administration ..................................................................................................28
       5.3.4. Compliance .......................................................................................................29
   5.4. Drug Storage and Drug Accountability.........................................................................29
   5.5. Concomitant Medication(s) ...........................................................................................29

6. STUDY PROCEDURES ...........................................................................................................31
   6.1. Screening .......................................................................................................................31
   6.2. Study Period ..................................................................................................................33
       6.2.1. Baseline Visit (Randomization).................................................................33
6.2.2. Clinic Visits (Week 1 to 6 Visits, Weeks, 8, 10, 12 and ET12 Visit) ...............34
6.2.3. Telephone Visits (Weeks 7, 9, 11) .................................................................35
6.3. Nontreatment Follow-up Period (Weeks 13 through 24) .............................35
6.3.1. Clinic Visits (Weeks 13, 16, 20, 24 and ET24 Visit) .................................35
6.3.2. Telephone Visits (Weeks 14, 15, 17, 18, 19, 21, 22, and 23) .................36
6.4. Subject Withdrawal ..........................................................................................36
6.4.1. Individual Subject Dosing Stopping Criteria .............................................37

7. ASSESSMENTS .................................................................................................................38
7.1. Safety ..........................................................................................................................38
7.1.1. Adverse Events ........................................................................................................38
7.1.1.1. Primary Neuropsychiatric Safety Endpoint ..............................................38
7.1.1.2. Actively Solicited Neuropsychiatric Adverse Events .........................39
7.1.2. Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 10, and the Suicidal Behaviors Questionnaire (SBQ-R) Appendix 3 .................39
7.1.3. Hospital Anxiety and Depression Scale (HADS) Appendix 2 .................40
7.1.4. Clinical Global Impression of Severity (CGI-S) Appendix 7 .................40
7.1.5. Clinical Global Impression of Improvement (CGI-I) Appendix 8 ..........41
7.1.6. Aggression Questionnaire (AQ) Appendix 5 .............................................41
7.1.7. Nicotine Use Inventory (NUI) Appendix 4 ...............................................41
7.1.8. End-Expiratory Exhaled Carbon Monoxide (Exhaled CO) ....................41
7.1.9. Fagerström Test for Nicotine Dependence ..............................................41
7.1.10. Psychiatric Evaluations/Risk Assessments ..............................................41
7.1.11. Psychiatric Treatment Monitoring ...............................................................42
7.1.12. Physical Examination, Vital Signs and Electrocardiogram .................43
7.1.13. Medical History ..............................................................................................43
7.1.14. Laboratory ........................................................................................................43
7.1.15. Cardiovascular (CV) Events of Interest ...................................................43
7.1.15.1. Serious Cardiac Arrhythmias ..............................................................44
7.2. Efficacy .....................................................................................................................45
7.2.1. Measures of Abstinence from Smoking ....................................................45

8. ADVERSE EVENT REPORTING .........................................................................................45
8.1. Adverse Events ..........................................................................................................45
8.2. Reporting Period ...........................................................................................................46
8.3. Definition of an Adverse Event .....................................................................................46
8.4. Abnormal Test Findings .................................................................................................47
8.5. Serious Adverse Events .................................................................................................47
8.5.1. Potential Cases of Drug-Induced Liver Injury .........................................................48
8.6. Hospitalization ..............................................................................................................49
8.7. Severity Assessment ......................................................................................................50
8.8. Causality Assessment ....................................................................................................50
8.9. Exposure During Pregnancy ........................................................................................51
8.10. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal) ...........52
8.11. Eliciting Adverse Event Information ...........................................................................52
8.12. Reporting Requirements ..............................................................................................52
8.12.1. Serious Adverse Event Reporting Requirements .....................................................52
8.12.2. Non-Serious Adverse Event Reporting Requirements .............................................53
8.12.3. Sponsor Reporting Requirements to Regulatory Authorities ..................................53
9. DATA ANALYSIS/STATISTICAL METHODS ..................................................................53
9.1. Analysis Sets .................................................................................................................53
9.2. Sample Size Determination ...........................................................................................54
9.3. Safety Objective Analysis ..............................................................................................54
9.4. Efficacy Objective Analysis ..........................................................................................55
9.5. Methods and Analysis ...................................................................................................56
9.6. Interim Analysis ............................................................................................................56
9.7. Independent Data Monitoring Committee .....................................................................57
9.8. Cardiovascular Event Adjudication Committee (CEAC) ..............................................57
10. QUALITY CONTROL AND QUALITY ASSURANCE ....................................................61
11. DATA HANDLING AND RECORD KEEPING ...............................................................61
11.1. Case Report Forms/Electronic Data Record .................................................................61
11.2. Record Retention .........................................................................................................62
12. ETHICS ..............................................................................................................................62
12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) ......................62
12.2. Ethical Conduct of the Study .......................................................................................63
12.3. Subject Information and Consent ..............................................................63
12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP ...........................................................................................................63

13. DEFINITION OF END OF TRIAL ........................................................................64

13.1. End of Trial in all Participating Countries ...................................................64

14. SPONSOR DISCONTINUATION CRITERIA ......................................................64

15. PUBLICATION OF STUDY RESULTS ............................................................64

15.1. Communication of Results by Pfizer .........................................................64

15.2. Publications by Investigators ....................................................................65

16. REFERENCES ....................................................................................................66

APPENDICES

Appendix 1. Fagerström Test for Nicotine Dependence ........................................67
Appendix 2. Hospital Anxiety and Depression Scale (HADS) ..................................68
Appendix 3. Suicide Behaviors Questionnaire-Revised (SBQ-R)............................69
Appendix 4. Nicotine Use Inventory (NUI) ..............................................................70
Appendix 5. Aggression Questionnaire (AQ) .........................................................71
Appendix 6. Neuropsychiatric Adverse Events Interview (NAEI) ............................73
Appendix 7. Clinical Global Impression of Severity (CGI-S) ....................................80
Appendix 8. Clinical Global Impression of Improvement (CGI-I) .............................81
Appendix 9. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) Baseline ......................................................................................................82
Appendix 10. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) Since Last Visit ..........................................................................................85
Appendix 11. List of Abbreviations .......................................................................88
Appendix 12. CV Required Documents ..................................................................89
Appendix 13. CLINICAL PROTOCOL AMENDMENT 1 .........................................93
1. INTRODUCTION

1.1. Indication

Aid to smoking cessation treatment.

1.2. Background and Rationale

**Varenicline**

Varenicline was approved as Chantix® by the US FDA in May 2006, and as Champix® by the EMEA in September 2006, and is now approved in more than 90 countries worldwide for smoking cessation in adults. The approved dose regimen is 1-mg twice daily (1 mg BID) for 12 weeks starting with a 1-week titration.

Protocol A3051123 is a Phase 4 study being conducted to assess varenicline as an aid to smoking cessation treatment in subjects with and without an established diagnosis of major psychiatric disorder and to characterize the neuropsychiatric safety profile in both of these cohorts. This study qualifies as a Post-Authorization Safety Study (PASS) and it is a US Post-Marketing Requirement and an EU Post-Approval Commitment. The population will be characterized by presence or absence of an established and stable diagnosis of major psychiatric disorder, current or past, Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision DSM IV TR-defined. This is described as “diagnosis of psychiatric disorder” throughout the protocol.

Literature has shown that subjects with a current Axis I disorder were more likely to experience tobacco withdrawal symptoms and withdrawal-related discomfort and relapse. Subjects with Axis I disorders may need more intensive and/or longer treatments to help them cope with withdrawal symptoms and prevent relapse.11

In Phase 3, subjects with psychiatric disorders were not included per protocol by the use of the following exclusion criteria: “Subjects currently or within the past 12 months requiring treatment for depression. Subjects with current or prior history of panic disorder, psychosis, or bipolar disorder”. In this study, recruitment will be balanced equally with respect to subjects with and without a diagnosis of major psychiatric disorder to allow for the assessment of neuropsychiatric events in each of the cohorts and each of the treatment groups. Subjects will be randomized to receive varenicline, placebo, bupropion hydrochloride or transdermal nicotine patch (NRT), the latter two being included as active controls.

Varenicline is a selective nicotinic acetylcholine receptor (nAChR) partial agonist designed to have specific and potent binding at the α4β2 receptor subtype, which mediates the reinforcing effects of nicotine. Because of its mixed agonist-antagonist properties, varenicline offers the therapeutic benefit of relieving symptoms of nicotine withdrawal and cigarette craving during abstinence while blocking the reinforcing effects of chronic nicotine. Because of its high selectivity for α4β2 nicotinic receptors, at therapeutic levels,3 varenicline does not bind to other neurotransmitter receptors and transporters,9 including those implicated in mental disorders.2
Phase 2 to Phase 4 placebo controlled clinical trials have demonstrated the efficacy and tolerability of varenicline 1 mg BID in more than 3000 cigarette smokers, increasing the odds of quitting approximately 4-fold compared with placebo at end of treatment, and nearly 2-fold compared with bupropion at end of treatment. The most frequently reported treatment-emergent adverse events associated with varenicline were nausea, sleep disturbance, constipation, flatulence and vomiting. Nausea was reported by approximately 30% of patients treated with varenicline 1 mg BID after an initial week of dose titration compared with 10% in patients taking placebo. In patients taking 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient.

Post Marketing Experience

There have been post-marketing reports of neuropsychiatric symptoms, some serious, including changes in mood, agitation, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, changes in behavior, anxiety, panic, suicidal ideation, suicide attempt and completed suicide in patients attempting to quit smoking with varenicline. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish causal relationship to drug exposure or smoking status. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of varenicline in these reports is not known. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness.

There have also been reports of serious skin reactions and hypersensitivity reactions, including angioedema.

Bupropion

Bupropion was first approved for the treatment of depression (as Wellbutrin™) on 30 December 1985 in the USA. The first approval for smoking cessation (as Zyban™) was in 1996, also in the USA. Bupropion has been approved for depression in approximately 70 countries worldwide and for smoking cessation in almost 90 countries. Post-marketing exposure is estimated to be 90 million patient exposures for all bupropion formulations and indications, of which approximately 24 million are for use in smoking cessation.

Zyban™ was the first non-nicotine treatment for nicotine dependence as an aid to smoking cessation. Zyban™ is chemically unrelated to nicotine or other agents currently used in the treatment of nicotine addiction. Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and does not inhibit monoamine oxidase. The mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms. Bupropion increases dopamine concentrations in the nucleus accumbens in rats. While the clinical significance is unknown, this action may mimic the effects of nicotine and reduce cravings associated with nicotine addiction. Bupropion also reduces noradrenergic neuron
firing in the locus ceruleus of rats. While this may explain the reduction in nicotine withdrawal symptoms, the clinical significance is unknown. In clinical trials, treatment with bupropion reduced withdrawal symptoms compared to placebo and also showed evidence of reduction in craving for cigarettes or urge to smoke compared to placebo.

The efficacy of bupropion for the treatment of nicotine dependence as an aid to smoking cessation was evaluated in clinical studies of 1,508 non-depressed, chronic cigarette smokers. Two randomized, placebo-controlled trials were conducted:

- A dose-response trial of Zyban™ 100 mg/day (50 mg BID), 150 mg/day, 300 mg/day (150 mg BID), and placebo;
- A comparative trial of Zyban™, Habitrol® (nicotine transdermal system – NTS; also marketed as Nicotinell® by Novartis in some countries), the combination of Zyban™ and NTS, and placebo.

In both clinical trials, patients treated with Zyban™ achieved a higher four-week continuous quit rate than placebo-treated patients. In addition, Zyban™ was more effective than NTS in the comparative study. The combination of Zyban™ and NTS produced the highest rates of continuous abstinence, although not statistically significantly different from Zyban™ alone. In the dose-response trial, patients treated with Zyban™ 300 mg/day (150 mg BID) maintained a significantly higher abstinence rate than those treated with placebo through the end of six months.

Zyban™ was generally well tolerated by chronic cigarette smokers enrolled in the clinical trials. The most common adverse events consistently observed with Zyban™ were dry mouth and insomnia. Both of these events may be dose related. Bupropion is likely to have a low potential for abuse, and there was no evidence of withdrawal phenomena upon abrupt cessation of Zyban™.

Placebo-controlled Phase 3 and Phase 4 studies of bupropion for smoking cessation generally excluded patients who had a psychiatric disorder (eg, major depressive episode, bipolar disorder, panic disorder, psychosis) or who were taking psychoactive drugs. This study qualifies as a Post-Authorization Safety Study (PASS) and it is a US Post-Marketing Requirement.

Post Marketing Experience

Seizure is the most medically-significant dose-related adverse reaction associated with bupropion. A postmarketing surveillance study and pooling of clinical trial data have shown the incidence for the sustained-release tablet to be approximately 0.1% in therapeutic doses. Hypersensitivity reactions are also important adverse events that occur with bupropion.

Neuropsychiatric symptoms have been reported. In particular, psychotic and manic symptomatology has been observed, mainly in patients with a known history of psychiatric illness. The following neuropsychiatric reactions are listed in the Adverse Reactions section of the bupropion Core Data Sheet (CDS), the frequency of which have been estimated from
integrated placebo-controlled smoking cessation studies or postmarketing reports: insomnia, depression, confusion, delusions, paranoid ideation, hallucinations, agitation, restlessness, anxiety, irritability, hostility, aggression, depersonalisation, abnormal dreams, concentration disturbance and dizziness.

Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported during bupropion treatment, and generally occurred during the early stages of treatment.

Bupropion is indicated for the treatment of depression in some countries. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adults with major depressive disorder and other psychiatric disorders showed an increased risk of suicidal thinking and behavior associated with antidepressant use compared to placebo in patients less than 25 years old.

Clinicians should be aware of the possible emergence of significant depressive symptoms or suicidal ideation in patients being treated with bupropion, and should advise and monitor patients accordingly.

**Single Reference Safety Document**

The Single Reference Safety Document for varenicline is the Core Data Sheet. The Single Reference Safety Documents for Bupropion and NRT are the respective Core Data Sheets (CDS).

### 2. STUDY OBJECTIVES AND ENDPOINTS

#### 2.1. Objectives

#### 2.1.1. Safety

**Primary Safety Objectives:**

1. To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo in the incidence of the primary neuropsychiatric AE endpoint for subjects:
   a. With a diagnosis of psychiatric disorder;
   b. Without a diagnosis of psychiatric disorder.

2. To characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).
2.1.2. Efficacy: Abstinence from Smoking

Main Efficacy Objective: To compare smoking abstinence rates of varenicline and bupropion relative to placebo for the last 4 weeks of treatment and continuously through Week 24, as measured by CO-confirmed continuous abstinence rate (CAR) CAR9-12 and CAR9-24, respectively, separately for subjects with and without a diagnosis of psychiatric disorder.

Secondary Objective:

To assess if there is a difference between cohorts in the placebo adjusted relative abstinence rates (CAR 9 12 and CAR 9 24) of varenicline and bupropion, separately.

Another secondary objective of the study is to perform the following comparisons with respect to the primary safety and efficacy endpoints:

1. NRT vs. Placebo;
2. Varenicline vs. Bupropion;
3. Varenicline vs. NRT;
4. Bupropion vs NRT.

2.2. Endpoints

2.2.1. Safety

The primary safety endpoint is the occurrence of at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. This endpoint is referred to as the Neuropsychiatric (NPS) AE endpoint.

Secondary Safety Endpoints:

- Occurrence of the components of the primary safety endpoint;
- Individual item responses, along with subscale scores and overall score (when applicable; specifics are stated in the Statistical Analysis Plan), for the following questionnaires:
  - Hospital Anxiety and Depression Scale (HADS) Appendix 2;
  - Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 10;
  - Clinical Global Impression of Improvement (CGI-I) Appendix 8.
2.2.2. Efficacy

The main efficacy endpoint is 4-week CO-confirmed continuous abstinence for Weeks 9 through 12.

Secondary Efficacy Endpoints:

The secondary efficacy endpoint is CO-confirmed continuous abstinence from Week 9 through Week 24.

An additional secondary efficacy endpoint is the 7-day point prevalence of abstinence at each assessment visit.

3. STUDY DESIGN

This is a 24-week, double-blind, NRT and placebo-controlled, multi-center, parallel group study designed to assess the safety and efficacy of varenicline 1 mg BID and bupropion hydrochloride 150 mg BID for smoking cessation. The primary comparisons will be varenicline vs. placebo and bupropion vs. placebo. NRT is included as active control and study medications will be given via a triple-dummy design. The duration of active treatment is 12 weeks followed by a non-treatment follow-up phase for an additional 12 weeks (see diagram below). The study will randomize approximately 2000 subjects in each of 4 treatment arms, for a total of 8000 subjects at approximately 200 sites.

Subjects will be classified into one of the two cohorts—those with an established and stable diagnosis of psychiatric disorder, confirmed by the Structured Clinical Interview for DSM-IV Axis 1 and 2 Disorders (SCID I and II) conducted at screening; and those without a diagnosis of psychiatric disorder. An equal number of subjects with or without a diagnosis of a psychiatric disorder will be enrolled and randomized among the 4 treatment arms (varenicline, bupropion, NRT, and placebo) in 1:1:1:1 ratio. All clinic visits are in an outpatient clinic setting.
Screening Phase: The screening period will be approximately 3-14 days in duration. Results of screening laboratory evaluations and the electrocardiogram will be reviewed during this period to assure subject eligibility. Determination if there is a diagnosis of a psychiatric disorder for each subject will be confirmed at screening using DSM IV TR based on clinical assessment and confirmed by SCID I and II.

A subject who meets all inclusion criteria at the screening visit will progress to the baseline visit. At the baseline visit only those subjects who continue to meet all other criteria will be randomized.

Treatment Phase: The 12-week placebo controlled treatment period has periodic clinic visits for safety and efficacy assessments and smoking cessation counseling. There will be weekly clinic visits up to and including Week 6 and then biweekly clinic visits between Week 6 and Week 12. On weeks with no scheduled clinic visits, telephone contact visits will occur to collect smoking status. During the active treatment phase, varenicline and bupropion dosing will begin on the Baseline day with a one-week titration followed by 11 weeks of 1 mg BID and 150 mg BID respectively. NRT dosing will begin at the Week 1 visit with a 21 mg patch per day for 7 weeks, followed by a 14 mg patch per day for 2 weeks, and then a 7 mg patch for 2 weeks. All subjects will set a target quit date (TQD) to coincide with the Week 1 visit. The Week 1 visit occurs at the end of the first week of the treatment phase (Day 8). Smoking cessation counseling up to 10 min duration will be provided at each clinic visit consistent with the Agency for Healthcare Research and Quality (AHRQ) guidelines beginning at Baseline.
Non-Treatment Phase: Study drug will be discontinued at the Week 12 visit and subjects will continue into the non-treatment follow-up period. Clinic visits will occur at Weeks 13, 16, 20 and 24. On weeks with no scheduled clinic visits, telephone contact visits will occur to collect smoking status. Smoking cessation counseling up to 10 min duration will be provided at each clinic visit consistent with the Agency for Healthcare Research and Quality (AHRQ) guidelines.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by the Investigator before subjects are included in the study. Subjects both with and without a diagnosis of a major psychiatric disorder will be eligible for this study. Subjects without a diagnosis of a psychiatric disorder that meet all other study criteria are eligible to be included in the non-psychiatric stratum. To be included in the non-psychiatric stratum, the subject must not have ANY previous diagnosis of a psychiatric disorder confirmed by SCID I and II.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the psychiatric or non-psychiatric arm of the study:

1. Male or female cigarette smokers, 18-75 years, motivated to stop smoking and considered suitable for a smoking cessation attempt.

2. Smoked an average of at least 10 cigarettes per day during past year and during the month prior to the screening visit, and exhaled carbon monoxide (CO) >10 ppm at screening.

3. Females who are not of childbearing potential (ie, who are surgically sterilized or at least 2 years postmenopausal) and who are not nursing may be included. Females who are of childbearing potential may be included provided that they are not pregnant, not nursing, and meet all of the following criteria:
   - Are instructed and agree to avoid pregnancy through 30 days after the last dose of study medication;
   - Have a negative pregnancy test (β-hCG) at Screening and Baseline and
   - Agree to use at least one of the birth control methods listed below:
An oral contraceptive agent, an intrauterine device (IUD), an implantable contraceptive (eg, Norplant), or an injectable contraceptive (eg, Depo Provera) for at least 1 month prior to entering the study and will continue its use through at least 30 days after the last dose of study medication or;

- A double barrier method of contraception, eg, condom and diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study medication or abstinence.

4. A personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

5. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.1.1. Additional Inclusion Criteria for Neuropsychiatric Cohort

In addition to the criteria above, subjects to be included in the Neuropsychiatric cohort must also meet the following:

All subjects will be screened for Axis I and II diagnosis (current and/or past) using DSM IV TR criteria based on clinical assessment and confirmed by SCID (administered by a clinician1 or a qualified person trained in clinical mental health, ie; a PhD level clinical psychologist, or an individual with master level training in related areas [masters level psychologist, social work] who have been trained to use the SCID2). A “current” diagnosis is defined as the subject meeting the established criteria in the prior month. A “past” diagnosis is also the same as a “lifetime” diagnosis where applicable. A past diagnosis can have occurred anytime in the past medical history. The four major diagnostic groups comprising the neuropsychiatric cohort are: Psychotic, Affective, Anxiety and Personality Disorders. The four diagnostic groups are further described below. Subjects will be included in the psychiatric cohort, if they are considered clinically stable and meet criteria, either current or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and have met diagnostic criteria before the initiation of study treatment.

a. Psychotic Disorders limited to:
   - Schizophrenia;
   - Schizoaffective.

b. Affective Disorders limited to:
   - Major Depression;

---

1 Clinician is defined as someone licensed to practice medicine according to existing regulations.
2 Documentation of training will be kept at the clinical site.
- Bipolar-I;
- Bipolar-II.

c. Anxiety Disorders limited to:
   - Panic Disorder with or without Agoraphobia;
   - Post-Traumatic Stress Disorder;
   - Obsessive-Compulsive Disorder;
   - Social Phobia;
   - Generalized Anxiety Disorder.

d. Personality Disorders limited to past history of:
   - Borderline Personality Disorder.

All subjects with an Axis I or II diagnosis must be judged to be clinically stable including the following:
- No acute exacerbation of their condition in the preceding 6 months;
- If on treatment for their condition, must have been on stable treatment for a minimum of 3 months (e.g., stable drug and dose ≥3 months);
- No change in treatment is anticipated for the duration of the study;
- In the opinion of the Investigator, the patient is not at high risk of self-injury or suicidal behavior;
- In the event the Investigator is not a mental health professional (MHP), the subject should be evaluated by a MHP to confirm the SCID I or II diagnosis and determine if the subject is stable. A MHP must be a psychiatrist or licensed PhD level clinical psychologist. A subject who requires new treatment or is judged not to be clinically stable cannot be randomized.

Subjects who did not meet study inclusion criteria may be re-screened if deemed clinically stable at a later date and the case has been reviewed and approved by the Pfizer clinician.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects with a past or current diagnosis of one of the following disorders:
a. Psychotic Disorders:
   - Schizophreniform;
   - Delusional Disorder;
   - Psychotic Disorder NOS.

b. All Delirium, Dementia, and Amnestic and Other Cognitive Disorders;

c. All Substance-Induced Disorders (Other than nicotine);

d. All Factitious Disorders;

e. All Dissociative Disorders;

f. All Impulse Control Disorders;

g. Evidence of substance abuse/misuse or dependence severe enough to compromise the subject’s ability to comply with the study requirements;

h. Subjects with antisocial, schizotypal, or any other personality disorder severe enough to compromise the subject’s ability to comply with the study requirements.

Subjects with a past history of a comorbid condition listed in the above Exclusion Criteria may be included in the study and placed in the “psychiatric stratum” if A) the subject is concurrently diagnosed with an inclusionary diagnosis, B) the subject is able to comply with study requirements, and C) for substance abuse/misuse, the subject is considered to be in sustained full remission (no criteria for abuse or dependency being met in the last 12 months), and D) the patient is not taking agonists or partial agonists (ie, methadone, buprenorphine).

If the subjects described above (exclusionary co-morbid psychiatric condition) do not meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, they are not eligible for the study. Subjects who meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, and who have a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) may be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent condition is stable and does not prevent the subject from safely complying with study procedures. In such cases, please consult with the medical monitor.

2. Subjects with an Axis I diagnosis according to DSM IV TR criteria who have a rating of 5 or higher on the Clinical Global Impression- Severity (CGI-S). Appendix 7.
3. Subjects who are believed to have a suicidal risk at screening, baseline, or after assessment by a qualified MHP-(Psychiatrist or licensed PhD level clinical psychologist) if a risk assessment interview was required after screening or baseline using the Columbia Suicide Severity Rating Scale (C-SSRS). See section 7.1.2 (Appendix 10).

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS. Appendix 10.
- Previous history of suicide behaviors in the past year.


5. Subjects with a positive urine drug screen at screening or baseline for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition.

6. Subjects taking an investigational drug within 30 days before the Baseline visit and at anytime during the study period.

7. Subjects who have taken varenicline, bupropion, or NRT within 30 days prior to Baseline visit.

8. Only one subject per household may participate.

9. Subjects for whom treatment with bupropion is not appropriate:

- Subjects with seizure disorder;
- Subjects undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines);
- Subjects with current or prior diagnosis of anorexia or bulimia nervosa;
- Subjects who have taken a monoamine oxidase (MAO) inhibitor within the past fourteen days (prior to the Baseline visit);
- Subjects who are taking the following narrow therapeutic range medications which are metabolized by CYP2D6; desipramine, nortriptyline, Type 1C antiarrhythmics (eg, propafenone, flecainide), thioridazine.

Specific information regarding warnings, precautions, contraindications, adverse events and other pertinent information on bupropion that may impact subject eligibility is provided in the Core Data Sheets. In particular, bupropion should be administered with extreme caution to patients with risk factors for seizures, eg, a history of seizure, cranial trauma, or concomitant medications that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic steroids, etc.).
10. Subjects who intend to donate blood or blood components while receiving study drug or within 1 month of the completion of the treatment phase of the study.

11. Subjects with severe chronic obstructive pulmonary disease (COPD) defined as any subject who fulfills any of the following criteria:

- History of repeated exacerbations of COPD (greater than or equal to 3 in 3 years);
- Requires systemic corticosteroid maintenance (eg, oral prednisolone) for management of chronic symptoms;
- Is maintained on oxygen therapy for management of chronic symptoms.

12. Subjects with a recent (<5 years) history of cancer. Subjects with a remote (>5 years) history of cancer may be considered pending discussion with the study clinician. Subjects with cured basal cell or squamous cell carcinoma of the skin are allowed.

13. Subjects with evidence or history of clinically significant allergic reactions to drugs (eg, severe cutaneous and/or systemic allergic reactions).

14. Any subject at screening with an SGOT (AST) or SGPT (ALT) greater than 3 times the upper limit of normal (ULN) or total bilirubin greater than 2 times the ULN.

15. Subjects with clinically significant cardiovascular disease in the past 2 months. Examples of clinically significant cardiovascular disease include:

- Myocardial infarction;
- Coronary artery bypass graft (CABG);
- Percutaneous transluminal coronary angioplasty (PTCA);
- Severe or unstable angina;
- A serious arrhythmia;
- Clinically significant ECG conduction abnormalities;
- Hospitalizations for heart failure.

16. Subjects with clinically significant cerebrovascular disease in the past 2 months. Examples of clinically significant cerebrovascular disease include:

- Cerebrovascular accident (CVA), stroke;
- Documented transient ischemic attack (TIA).
17. Subjects who do not agree to abstain from using non-cigarette tobacco products (including, eg, pipe tobacco, cigars, snuff, chewing tobacco, hookah, etc.) or marijuana during study participation.

18. Subjects who do not agree to abstain from using nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during study participation (both the treatment phase and the post-treatment follow-up).

19. Subjects who have previously experienced an adverse drug reaction that the investigator considers potentially due to treatment with any of the active drugs in this study and of sufficient concern that further exposure to this medication would be inadvisable.

20. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

21. Subjects taking a concomitant medication that is prohibited by this protocol (See Section 5.5).

22. Subjects with skin conditions resulting in red, broken or irritated skin that may hinder the use of the nicotine replacement therapy (NRT) patch.

4.3. Randomization Criteria

Subjects who meet inclusion and exclusion criteria may be randomized. A computer-generated randomization schedule will be used to assign subjects to treatment, with two-level stratification by the presence or absence of a diagnosis of psychiatric disorder. An equal number of smokers will be enrolled in each of the two cohorts. When the planned enrollment has been achieved in one of the cohorts, enrollment will continue only into the other cohort until recruitment goals have been reached.

Within the cohort with a diagnosis of a psychiatric disorder, treatment assignment will be stratified with respect to the four major diagnosis groups (Psychotic, Affective, Anxiety and Personality Disorders).

4.4. Life Style Guidelines

Participants are expected to abstain from the use of tobacco products such as pipe tobacco, cigars, snuff, chewing tobacco, hookah, and the use of marijuana. Subjects will be expected to refrain from using any form of nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during both the treatment and non treatment follow-up phases.
Females of childbearing potential (not surgically sterilized or <2 years postmenopausal) must agree to practice a form of effective contraception, such as an oral contraceptive agent, an intrauterine device (IUD), an implantable contraceptive (eg, Norplant), or an injectable contraceptive (eg, Depo Provera) for at least 1 month prior to entering the study and will continue its use through at least 30 days after the last dose of study medication. Alternatively they may use double barrier contraception (ie, condom plus spermicide in combination with a female condom, diaphragm, cervical cap or intrauterine device), or sexual abstinence prior to entering into the study and for at least 30 days following the last dose of study drug.

5. STUDY TREATMENTS

This study utilizes a triple-dummy design as shown in the table below. Subjects randomized to one of the three active dosing groups will take that active medication and the other 2 medications in matching placebo form. And subjects randomized to placebo will receive matching placebo for varenicline, bupropion, and NRT, and follow the same titration and dosing schedules as those randomized to each of the active medication groups.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Day 1-3</th>
<th>Day 4-7</th>
<th>Week 1*-8</th>
<th>Week 8-10</th>
<th>Week 10-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline (V)</td>
<td>0.5 mg V QD</td>
<td>0.5 mg V BID</td>
<td>1 mg V BID</td>
<td>1 mg V BID</td>
<td>1 mg V BID</td>
</tr>
<tr>
<td></td>
<td>1 placebo B QD</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
</tr>
<tr>
<td></td>
<td>B QD</td>
<td>BID</td>
<td>BID</td>
<td>BID</td>
<td>BID</td>
</tr>
<tr>
<td>Bupropion (B)</td>
<td>150 mg B QD</td>
<td>150 mg B BID</td>
<td>150 mg B BID</td>
<td>150 mg B BID</td>
<td>150 mg B BID</td>
</tr>
<tr>
<td></td>
<td>1 placebo V QD</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
</tr>
<tr>
<td></td>
<td>150 mg B QD</td>
<td>150 mg B BID</td>
<td>150 mg B BID</td>
<td>150 mg B BID</td>
<td>150 mg B BID</td>
</tr>
<tr>
<td>NRT patch</td>
<td>1 placebo V QD</td>
<td>1 placebo B QD</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
</tr>
<tr>
<td></td>
<td>1 placebo V BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
</tr>
<tr>
<td></td>
<td>14 mg NRT QD</td>
<td>14 mg NRT QD</td>
<td>14 mg NRT QD</td>
<td>14 mg NRT QD</td>
<td>14 mg NRT QD</td>
</tr>
<tr>
<td></td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
</tr>
<tr>
<td></td>
<td>7 mg NRT QD</td>
<td>7 mg NRT QD</td>
<td>7 mg NRT QD</td>
<td>7 mg NRT QD</td>
<td>7 mg NRT QD</td>
</tr>
<tr>
<td></td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
</tr>
<tr>
<td></td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
</tr>
<tr>
<td></td>
<td>1 placebo NRT QD</td>
<td>1 placebo NRT QD</td>
<td>1 placebo NRT QD</td>
<td>1 placebo NRT QD</td>
<td>1 placebo NRT QD</td>
</tr>
<tr>
<td></td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
</tr>
<tr>
<td></td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
</tr>
<tr>
<td></td>
<td>1 placebo NRT QD</td>
<td>1 placebo NRT QD</td>
<td>1 placebo NRT QD</td>
<td>1 placebo NRT QD</td>
<td>1 placebo NRT QD</td>
</tr>
</tbody>
</table>

*On day of Week 1 visit, the varenicline dose will be taken as 2-0.5 mg tablets (or 2 placebo varenicline tablets) in the AM and 1 mg tablet (or 1 placebo varenicline tablet) in the PM.

All subjects randomized to varenicline will be titrated to the full dose during the first week in the following manner: 0.5 mg QD x 3 days, 0.5 mg BID x 4 days, then 1 mg BID for 11 weeks. Subjects randomized to bupropion will receive 150 mg QD x 3 days and then will take 150 mg BID for the remainder of the treatment period (11 weeks and 4 days). Subjects randomized to NRT will start active dosing the morning of the Week 1 visit and will receive a 21 mg transdermal patch per day x 7 weeks, followed by a 14 mg transdermal patch per day x 2 weeks, and then a 7 mg transdermal patch x 2 weeks for a total of 11 weeks of treatment.

Dosing will continue until the Week 12 visit. All subjects will then be followed for an additional 12 weeks in the non-treatment phase of the protocol.
Smoking cessation counseling of up to 10 minutes will be given at each clinic visit during the treatment and non-treatment periods. The counseling will be 1:1, individually tailored to each subject’s needs, and consistent with AHRQ guidelines. Whenever possible, counseling should be conducted by the same counselor throughout, so that the relationship builds and brings additional value to the sessions.

5.1. Allocation to Treatment

This is a double-blind, parallel group study. Subjects will be stratified by diagnosis of psychiatric disorder or lack thereof and then randomized to varenicline, bupropion, NRT or placebo in a 1:1:1:1 ratio. Overall enrollment will be equal for the two cohorts (and within the cohort with a diagnosis of psychiatric disorder, treatment will be balanced with respect to the major diagnosis groups, per Section 4.3). Investigators will obtain subject identification numbers and study drug assignments utilizing a web-based or telephone call-in drug management system as directed by the sponsor. Identification numbers for the subjects will be provided at the screening visit.

5.2. Breaking the Blind

The study will be subject, investigator, and sponsor blinded.

At the initiation of the study, the study site will be instructed on the method for breaking the blind of an individual subject. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented.

5.3. Drug Supplies

5.3.1. Formulation and Packaging

Blinded tablets (varenicline, bupropion, or placebo) will be supplied in bottles containing sufficient tablets to dose daily between visits during the treatment period. Varenicline will be supplied as 0.5 mg tablets for the first week and 1.0 mg tablets for the remaining 11 weeks of the study treatment period. Bupropion will be supplied as 150 mg tablets. Blinded NRT (active and placebo) will be supplied in cartons containing sufficient transdermal patches to cover each study visit schedule, 21 mg patch for Weeks 1 to 8, 14 mg patch for Weeks 8 to 10, and 7 mg patch for Weeks 10 to 12. New bottles and cartons will be dispensed at each clinic visit to provide sufficient study drug until the next scheduled clinic visit.

5.3.2. Preparation and Dispensing

Study drug is to be dispensed to subjects by qualified site study staff at each scheduled clinic visit from the Baseline visit to the Week 10 visit (according to the study flowchart). Subjects will be given their first supply of bottles at the Baseline visit and first supply of patches at the Week 1 visit and will receive new supplies at each clinic visit through the Week 10 visit.
Subjects will be instructed to store the study drug at room temperature (20-25°C or 69-77°F) and out of the reach of children.

All empty or unused study medication (bottles and patches) must be returned by each subject at each clinic visit through Week 12. Unused medication will be catalogued by site staff to verify data reported by the subjects.

5.3.3. Administration

Varenicline (or placebo) administration will begin with a titration period. Treatment will begin from the Week 1 bottle on the evening of the Baseline visit day. For the first 3 days of the Week 1 dosing period subjects will take one 0.5 mg tablet per day in the evening. For the next 4 days this will increase to two 0.5 mg tablets per day, 1 in the morning and 1 in the evening. On the day of the Week 1 visit (Day 8), subjects will increase their dose to two 0.5 mg tablets in the morning. At the Week 1 visit and subsequent clinic visits through the Week 10 visit subjects will receive new bottles and will take two 1 mg tablets daily, one in the evening and one in the morning.

Bupropion (or placebo) administration will begin with a titration period. Treatment will begin from the Week 1 bottle on the evening of the Baseline visit day. For the first 3 days of the Week 1 dosing period subjects will take one 150 mg bupropion in the evening. On Day 4 they increase dosing to one 150 mg bupropion BID (one in the morning and one in the evening) and dosing remains unchanged until Week 12.

Dosing should occur with 240 ml of water and it is recommended that subjects eat prior to dosing. It is recommended that there be at least 8 hours between the morning and evening dosing.

At the discretion of the Investigator, dosing with blinded tablet medications (varenicline, bupropion, matching placebos) may be reduced, temporarily discontinued or stopped for subjects who have intolerable adverse events (eg, nausea); or for subjects who in the opinion of the Investigator require a dose reduction due to use of concurrent medications. A dose reduction is performed by decreasing both blinded tablet medications to once per day dosing. If a dose reduction is required, both blinded tablet medications should be reduced at the same time.

NRT (or placebo) administration starts on the day of the Week 1 visit and subjects will receive a 21 mg transdermal patch per day for 7 weeks, followed by a 14 mg transdermal patch per day for 2 weeks, and then a 7 mg transdermal patch for 2 weeks for a total of 11 weeks of treatment.

At the discretion of the Investigator, dosing with blinded NRT (NRT or matching placebo) may be temporarily discontinued or stopped for subjects who have intolerable adverse events. It is not possible to reduce the dose of blinded NRT.
If any of the study drugs need to be permanently discontinued then all 3 blinded study medications (varenicline/placebo, bupropion/placebo, and NRT/placebo) must be permanently discontinued.

Medication errors may result in this study from the administration or consumption of the wrong study drug or by the wrong study subject. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRF and on the SAE form when appropriate. In the event of a medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page (refer to ADVERSE EVENT REPORTING section for further details).

### 5.3.4. Compliance

Subjects will return bottles and cartons at each clinic visit and a drug accountability form will be completed. Missed doses should be discussed to try to ascertain the reason(s). Reasons for missed doses and/or patterns of missed doses should be incorporated into the smoking cessation counseling and every effort should be made to ensure proper subject dosing.

### 5.4. Drug Storage and Drug Accountability

The investigator or an approved representative (eg, pharmacist), will ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Store at room temperature as indicated on the label.

To ensure adequate records, all study drug will be accounted for in drug accountability inventory forms as instructed by Pfizer. Subjects must return all bottles and cartons to the investigator. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies must be returned to Pfizer or its designated agent.

### 5.5. Concomitant Medication(s)

While medications with narrow therapeutic index that are metabolized by CYP 2D6 are excluded (please refer to Any Use Prohibited, below), there is the potential for increased blood levels of certain antipsychotic and antidepressant medications. Therefore, investigators should pay attention to signs and symptoms of increased blood levels, and if noted, call the medical monitor for advice on how to manage the subject. These signs and symptoms should be recorded as adverse events.
If investigators have questions on any drugs not listed here they should be discussed with the study clinician.

**Episodic Use Only Permitted:**

- Acetaminophen;
- Antihistamines;
- Aspirin (chronic use also permitted);
- Bronchodilators (chronic use also permitted);
- Inhaled steroids (chronic use also permitted);
- Oral and injectable steroids;
- Nitroglycerin;
- COX-2 selective and non-selective NSAIDs (chronic use also permitted);
- Over the counter medications (excluding stimulants, Kava Kava, St. John’s Wort).

**Chronic Use Permitted:**

- Anti-anginal agents;
- Antihypertensive agents;
- Antidepressants, Antipsychotics, Anxiolytics, and Mood stabilizer treatments prescribed for an Axis I disorder (Except for Tricyclic antidepressants, Thioridazine and Bupropion as described below);
- Aspirin;
- Bronchodilators;
- Hormone Replacement Therapy;
- Inhaled steroids;
- Lipid-lowering agents;
- Multivitamins;
- COX-2 selective and non-selective NSAIDs;
• Oral and depot contraceptives;
• Thyroid replacement;
• Oral diabetes medications.

Any Use Prohibited:
• Drugs containing bupropion;
• Varenicline (Chantix®/Champix®);
• Nicotine replacement therapy and other aids to smoking cessation;
• Naltrexone;
• Insulin;
• Theophylline;
• Warfarin;
• Monoamine oxidase (MAO) inhibitors;
• Over the counter and prescribed stimulants and anorectic agents;
• Narrow therapeutic range medications which are metabolized by CYP2D6; desipramine, nortriptyline, Type 1C antiarrhythmics (eg, propafenone, flecainide), thioridazine;
• Milnacipran (Scavella).

6. STUDY PROCEDURES

6.1. Screening

The Screening visit will occur 3 to 14 days prior to the baseline/randomization. The following procedures will be conducted during screening:

• Obtain informed consent for the clinical trial (must be signed prior to the initiation of any study related activities);
• Record demography, medical history, cardiovascular medical history, and smoking history (including questions regarding past attempts to quit smoking, cigarette use, assessment of past and present illicit drug use, an assessment of past and present alcohol use, and past use of NRT, bupropion and varenicline);
• Physical examination;

• Measure and record height;

• Complete the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID I and II). The SCID II consists of a subject-completed Personality Questionnaire and follow up Interview-based questions;

• In the event the Investigator is not a mental health professional (MHP), the subject should be evaluated by a MHP to confirm the SCID I or II diagnosis and determine if the subject is stable. A MHP must be a psychiatrist or licensed PhD level clinical psychologist. **A subject who requires new treatment or is judged not to be clinically stable cannot be randomized;**

• Complete the Clinical Global Impression- Severity (CGI-S) Appendix 7;

• Subject completes the Suicidal Behaviors Questionnaire-Revised (SBQ-R Appendix 3;

• Complete the Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 10;

• Record concomitant medications and non-drug treatment;

• Subject completes the Fagerström Test for Nicotine Dependence Appendix 1;

• Measure the end-expiratory exhaled carbon monoxide (exhaled CO);

• Record a 12-lead electrocardiogram (ECG);

• Collect blood samples for CBC and blood chemistry;

• Perform urine or serum pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal;

• Perform urine drug screen (dipstick at site);

• Verify trial eligibility by checking and documenting Inclusion/Exclusion criteria; 4.1, 4.2.

• Psychiatric evaluation if warranted (See Section 7.1.10).

Subjects who did not meet study inclusion criteria may be re-screened if deemed clinically stable at a later date and the case has been reviewed and approved by the Pfizer clinician.
6.2. Study Period

6.2.1. Baseline Visit (Randomization)

The following procedures will be conducted at the Baseline visit:

- Record sitting blood pressure, pulse rate and weight;
- Review cardiovascular medical history and update as needed;
- Record volunteered adverse events;
- Complete CGI-S Appendix 7;
- Subject completes the Hospital Anxiety and Depression Scale (HADS) Appendix 2;
- Complete Aggression Questionnaire Appendix 5;
- Conduct Neuropsychiatric Adverse Events Interview and record solicited adverse events Appendix 6;
- Record concomitant medications and non-drug treatment;
- Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) Appendix 10 and record suicide-related adverse events;
- Complete the Nicotine Use Inventory (NUI) Appendix 4;
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Perform urine drug screen (dipstick at site);
- Perform pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal (dipstick at site);
- Provide subject with study specific Emergency Contact Information Card;
- Smoking Cessation counselling 1:1 ≤10 minutes;
- Re-check and document Inclusion/Exclusion criteria; see Section 4.1, 4.2;
- Randomize to treatment;
- Dispense study drug: Baseline bottles of study drug;
- Psychiatric evaluation if warranted (See Section 7.1.10).
6.2.2. Clinic Visits (Week 1 to 6 Visits, Weeks, 8, 10, 12 and ET_{12} Visit)

One week after their Baseline visit the subject will return for the Week 1 visit. The Week 1 visit should occur on study Day 8 and will be planned to coincide with the day on which the subject will attempt to quit, called the target quit date (TQD). The subject’s last cigarette prior to the quit attempt will be before midnight prior to the Week 1 visit.

Following the Week 1 visit, clinic visits will be conducted weekly at Weeks 2, 3, 4, 5, 6 and then bi-weekly at Weeks 8, 10, and 12. Every effort should be made to have the subject return on the same day of the week for the clinic visits, thereby keeping visits on time. To accommodate unforeseen circumstances a visit window of ±3 days can be allowed throughout the study as long as proper dosing is maintained in the dosing period. The visit window should be used with discretion and all subjects should remain on original visit schedule throughout study participation (ie, If weekly visits were previously conducted on Wednesdays, the visits should return to Wednesdays after the window is utilized). If an early termination occurs before the end of Week 12, an early termination visit (ET_{12}) will be conducted. It should be noted that these ET visits relate only to early termination in the study not early stopping of treatment, which is a situation where the subject should be encouraged to continue study participation to complete the remaining scheduled visits through Week 24. At each of these visits, the following procedures will be conducted:

- Record sitting blood pressure and pulse rate;
- Record volunteered adverse events;
- Complete CGI-I Appendix 8;
- Subject completes the HADS Appendix 2;
- Conduct Neuropsychiatric Adverse Events Interview and record solicited adverse events Appendix 6;
- Record concomitant medications and non-drug treatment and update existing concomitant medications as needed;
- Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) Appendix 10 and record suicide-related adverse events;
- Complete the Nicotine Use Inventory (NUI) Appendix 4;
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Perform pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal;
- Smoking Cessation counseling 1:1 ≤10 minutes;
- Dispense drug bottles and patches sufficient until next clinic visit (not at Week 12 or ET<sub>12</sub>);

- Subjects who report severe neuropsychiatric AEs or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) or answer "yes" to items 4, 5 or any suicidal behavioural question on C-SSRS appendix 10 will receive a psychiatric evaluation by a qualified mental health professional (MHP: psychiatrist or licensed PhD level clinical psychologist).

- Collect and forward records on cardiovascular events of interest or hospitalizations as defined in Appendix 12 for adjudication, if applicable.

**Additional procedures at Week 12 visit or ET<sub>12</sub> visit.**

- Record a 12-lead electrocardiogram (ECG);
- Record sitting blood pressure and pulse rate;
- Measure and record weight;
- CBC, blood chemistry.

**6.2.3. Telephone Visits (Weeks 7, 9, 11)**

Complete the Nicotine Use Inventory (NUI). Appendix 4.

**6.3. Nontreatment Follow-up Period (Weeks 13 through 24)**

Following completion of the Week 12 visit, subjects will continue into the non-treatment follow-up phase of the protocol. If a subject discontinues study drug prior to the Week 12 visit, the subject should be encouraged to continue study participation to complete the remaining scheduled visits through Week 24.

**6.3.1. Clinic Visits (Weeks 13, 16, 20, 24 and ET<sub>24</sub> Visit)**

Subjects will return for visits to the clinic at the end of Weeks 13, 16, 20, and 24. If an early termination occurs after the Week 12 visit and before the Week 24 visit, an early termination visit (ET<sub>24</sub>) will be conducted. At these visits, the following procedures will be conducted:

- Record sitting blood pressure and pulse rate;
- Record Body Weight (Week 24 and ET<sub>24</sub> only);
- Record volunteered adverse events;
- Complete CGI-I; Appendix 8
- Subject completes the HADS; Appendix 2;

- Conduct Neuropsychiatric Adverse Events Interview (NAEI) and record solicited adverse events Appendix 6;

- Record concomitant medications and non-drug treatment and update existing concomitant medications as needed;

- Complete the Columbia Suicide-Severity Rating Scale (CSSRS) Appendix 10 and record suicide-related adverse events;

- Complete the Nicotine Use Inventory (NUI) Appendix 4;

- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);

- Perform pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal at Week 16;

- Smoking Cessation counseling 1:1 ≤10 minutes;

- Subjects who report severe neuropsychiatric AEs or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) or who answer "yes" to items 4, 5 or any behavioural question on CSSRS Appendix 10 will receive a psychiatric evaluation by a qualified mental health professional (MHP: psychiatrist or licensed PhD level clinical psychologist).

- Collect and forward records on cardiovascular events of interest or hospitalizations as defined in Appendix 12 for adjudication, if applicable.

6.3.2. Telephone Visits (Weeks 14, 15, 17, 18, 19, 21, 22, and 23)

- Complete the Nicotine Use Inventory (NUI). Appendix 4.

6.4. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

Subjects who discontinue treatment will be encouraged to continue participation in the study and all planned assessments/evaluations. Specifically, they will maintain the visit schedule and should continue participation through the non-treatment follow-up phase of the study.
All subjects who permanently discontinue study drugs for any reason should remain in the study as Off Treatment and In Study (OTIS). Every effort should be made to keep the subject in the study until the final visit and all planned assessments/evaluations should be performed. Specifically, the subject will maintain the visit schedule and continue participation through the non-treatment follow-up phase of the study.

If a subject withdraws from the study, but does not withdraw consent, he/she should be contacted at the end of the trial to assess vital status/cardiovascular events. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. All reasonable efforts should be made to contact subjects who are lost to follow up to ascertain their reason(s) for not continuing in the study. A determination needs to be made that they are truly lost to follow up and not withdrawing for another reason (eg, adverse event or lack of efficacy).

6.4.1. Individual Subject Dosing Stopping Criteria

During the double-blind, active treatment phase subjects will be monitored on a regular basis for any clinically significant symptomatic changes, including any changes in neuropsychiatric symptoms. The following individual dosing stopping criteria will be followed:

Dosing with blinded tablet medications (varenicline, bupropion, matching placebos) may be reduced, temporarily discontinued or stopped for intolerable adverse events, or if the Investigator believes that continuing dosing will be detrimental to the subject’s mental or physical health.

Dosing with blinded NRT (NRT or matching placebo) may be temporarily discontinued or stopped for intolerable adverse events or if the Investigator believes that continuing dosing will be detrimental to the subject’s mental or physical health. It is not possible to reduce the dose of blinded NRT.

- If a subject answers “yes” on items 4, 5 or to any behavioral question on the CSSRS, Appendix 10 the subject must have a risk assessment by a qualified mental health professional (MHP: Psychiatrist or licensed PhD level clinical psychologist) to determine whether it is safe to continue active dosing in trial. In the event the risk assessment can not be immediately performed, it will be at the discretion of the Investigator to determine if study drug should be discontinued (temporarily or permanently) until the risk assessment is completed.

- Study drug will be discontinued immediately for any female subject who becomes pregnant during the treatment period of the study. These subjects should continue to attend study visits OTIS as noted in Section 6.4
7. ASSESSMENTS

7.1. Safety

7.1.1. Adverse Events

All adverse events (AEs) volunteered, observed, or solicited (of all severities) will be recorded in the AE CRF from the time the subject signs the informed consent up to and including Week 24.

Solicited neuropsychiatric adverse events will be collected by use of the Neuropsychiatric Adverse Event Interview (NAEI) at each clinic visit (starting from baseline) up to and including Week 24. The voluntarily reported AEs will be assessed first at each study visit followed by the NAEI Appendix 6 and then the CSSRS Appendix 10.

When reporting an adverse event, verbatim text will also be recorded on a supplemental adverse event reporting page. Reported events by a household member of the subject or personal physician, which are deemed to be adverse events by the Investigator, will be captured as adverse events and the reporters’ verbatim text of these events will also be captured.

Suicide related adverse events will be solicited by completion of the C-SSRS at each clinic visit up to and including Week 24. Any severe neuropsychiatric adverse event(s) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) recorded will require the subject to receive a psychiatric evaluation by a qualified mental health professional MHP (Psychiatrist or licensed PhD level clinical psychologist) (Section 7.1.10) and a narrative will be constructed for each event. In the event the investigator meets the requirements of the MHP, he/she may complete this evaluation.

Subjects will be provided with study specific Emergency Contact Information cards at the baseline visit. The card will state that the subject has made a commitment to stop smoking and has joined the study and seeks the help and support of the family at home. It will state the list of neuropsychiatric events of concern and encourage the family to call the site to report such events if the subject himself/herself seems unaware. If the subject consents, an additional card will be provided for the subject’s PCP. In this manner, household members and PCPs will be alerted to the possibility of adverse events and provided with direct contact information for study site personnel.

7.1.1.1. Primary Neuropsychiatric Safety Endpoint

The primary safety endpoint is the occurrence of at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal or hostility and/or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide.
Thus, the adverse event database will include items having been captured by any of the following means:

- Volunteered adverse event reporting;

- Actively solicited neuropsychiatric adverse events through the conduct of the Neuropsychiatric Adverse Event Interview (NAEI) Appendix 6 deemed to be adverse events by the Investigator;

- Items captured from proxy report (ie, PCP, family member) judged to be adverse events by the Investigator;

- Suicide related events solicited by completion of the C-SSRS Appendix 10 and deemed to be an adverse event by the Investigator.

The primary safety endpoint encompasses events reported (via the AE CRF page) through any of the above means of assessments. Additionally, the MedDRA version and Preferred Terms to be included in the primary safety endpoint will be described in the Statistical Analysis Plan.

Secondary safety endpoint related to adverse events is the occurrence of the components of the primary safety endpoint.

7.1.1.2. Actively Solicited Neuropsychiatric Adverse Events

The Neuropsychiatric Adverse Event Interview (NAEI) Appendix 6, will actively inquire about the following type of adverse events: aggression, anxiety, agitation, depression, delusions, dissociative states, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, paranoia, panic, and psychosis. The NAEI, developed by Pfizer, was piloted in a similar population to the one to be included in this study (patients with and without a history of psychiatric disease enrolled in a smoking cessation program) to evaluate patient understanding of all questions. The results of the study support use of the NAEI for neuropsychiatric adverse events solicitation.

If a subject has a positive response to any item on the NAEI, a determination will be made by the investigator as to whether this meets criteria for an adverse event. If it does meet criteria as an adverse event it will be recorded on the adverse event pages of the Case Report Form.

7.1.2. Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 10, and the Suicidal Behaviors Questionnaire (SBQ-R) Appendix 3

The C-SSRS will be completed by trained site personnel at screening and at each subsequent clinic visit up to and including Week 24. The Suicidal Behaviors Questionnaire- Revised (SBQ-R) will be completed by the subject at the screening visit.
At the screening visit, to detect possible suicidality, the C-SSRS and SBQ-R are completed. A risk assessment will be done by a qualified mental health professional (MHP: Psychiatrist or licensed PhD level clinical psychologist) if the subject’s responses on either of these screening instruments indicate:

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS; Appendix 10.
- Previous history of suicide behaviors in the past year;
- In the investigators judgment a risk assessment is required.

At post-baseline visits during the study if subject answers “yes” on items 4, 5 or on any suicidal behavioral question on C-SSRS (Appendix 10) a risk assessment will be done by a qualified MHP to determine whether it is safe to continue active dosing in trial.

7.1.3. Hospital Anxiety and Depression Scale (HADS) Appendix 2

The HADS is a subject self-report scale and contains 14 items rated on 4-point Likert-type scales. Two subscales assess depression and anxiety.

If a subject scores ≥11 on the Depression subscale of the HADS at baseline or any time during the study, the subject should receive an evaluation by a MHP (see section 7.1.10).

Subjects’ self report via the HADS is aimed to more fully characterize potential depression and anxiety related events. These additional measurements will be collected and evaluated in a different manner than the observed or volunteered adverse events. No attempt will be made to resolve any apparent discrepancies between observed or volunteered adverse events and the additional data collected from subjects using the HADS self-report. These additional data will be presented in separate tables, separate figures, and separate data listings, and will be reviewed in the final study report.

7.1.4. Clinical Global Impression of Severity (CGI-S) Appendix 7

The CGI-S is a clinician rated instrument measuring the severity of a subject’s psychiatric condition on a 7 point scale at time of assessment, relative to clinician's past experience in patients with same diagnosis. The scores are: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; or 7=extremely ill. The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician’s experience with the psychiatric population to which the subject belongs. This scale should be administered by the same rater throughout the study whenever possible.
7.1.5. Clinical Global Impression of Improvement (CGI-I) Appendix 8

The CGI-I is a clinician rated instrument that measures change in subject’s psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale ranging from 1 (very much improved) to 7 (very much worse). The ratings will be applicable even to those without psychiatric diagnoses (e.g., those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician’s experience with the psychiatric population to which the subject belongs. This scale should be administered by the same rater throughout the study whenever possible.

7.1.6. Aggression Questionnaire (AQ) Appendix 5

The Aggression Questionnaire is a subject self-reported scale and consists of 4 factors, Physical Aggression (PA), Verbal Aggression (VA), Anger (A) and Hostility (H), measured only at baseline for use as an historical benchmark. The total score for Aggression is the sum of the factor scores.

7.1.7. Nicotine Use Inventory (NUI) Appendix 4

The Nicotine Use Inventory (NUI) is a questionnaire regarding use of cigarettes and other nicotine-containing products during the treatment period or tobacco products during non-treatment follow-up period. The NUI was designed for and applied in previous varenicline studies. The NUI will be completed weekly at all clinical visits and telephone contacts.

7.1.8. End-Expiratory Exhaled Carbon Monoxide (Exhaled CO)

In order to confirm the smoking abstinence reported in the NUI, an end-expiratory exhaled carbon monoxide (exhaled CO) will be measured at each clinic visit using a breath CO monitor. An exhaled CO ≤10 ppm is required to claim successful smoking cessation.

7.1.9. Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence provides a short, self-reported measure of dependency on nicotine. This test will be completed at screening only. The test’s questions and scale are shown in Appendix 1.

7.1.10. Psychiatric Evaluations/Risk Assessments

A risk assessment should be done by a qualified mental health professional (MHP: a psychiatrist or licensed PhD level clinical psychologist) if any of the following conditions are met:
If a subject reports a severe neuropsychiatric adverse event (as detailed in Section 2.2.1) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) the subject will be referred for a psychiatric evaluation;

- Subject answers “yes” on item 5, on C-SSRS during the screening visit or subject answers “yes” on item 4, 5 or on any suicidal behavioral question on C-SSRS Appendix 10 during the study;

- Previous history of suicide behaviors in the past year (prior to randomization);

- The subject scores $\geq 11$ on the Depression subscale of the HADS Appendix 2 at baseline or at any time during the study.

The investigator may also refer a subject for a psychiatric evaluation if they have concerns over their subject’s psychiatric condition at any other stage during the study.

The following items will be addressed in each evaluation:

- Is a therapeutic intervention required for the subject?

- Arrangement for treatment and follow-up as appropriate if a therapeutic intervention is required;

- Is this a new DSM IV diagnosis for this subject or an exacerbation of a pre-existing condition?

The evaluation will be done by a qualified mental health professional (MHP: Psychiatrist or licensed PhD level clinical psychologist). In the event the Investigator is also qualified as a MHP, he or she may conduct this evaluation. A written copy of the risk assessment should be included in the subject’s clinical record as source document and will be recorded in the case report form. Subjects who have a “yes” response on items 4, 5 or on any suicidal behavioral question on C-SSRS on more than one occasion during a study must have their potential suicidality managed appropriately by the Investigator together with a qualified MHP (or the Investigator alone if the Investigator is a qualified MHP). The subjects can continue dosing while being evaluated, at the Investigator’s discretion. In addition, the Investigator should consult with the Pfizer clinician to determine whether the subject can continue in the study.

7.1.11. Psychiatric Treatment Monitoring

At each clinic visit up to and including Week 24, any requirement for either a change in treatment or an initiation of treatment for an Axis I or II disorder (either drug therapy or psychotherapy) will be recorded.
7.1.12. Physical Examination, Vital Signs and Electrocardiogram

A physical examination will be performed at the screening visit. Abnormal changes from screening deemed clinically significant by the Investigator should be recorded as adverse events.

Body weight will be measured at the baseline visit and Wk 12 or ET\textsubscript{12} and Wk 24 or ET\textsubscript{24}. Height will be measured at the Screening visit. Both will be measured in indoor clothing without shoes.

Sitting blood pressure and pulse rate will be measured at the baseline visit, Wks 1, 2, 3, 4, 5, 6, 8, 10, Wk 12 or ET\textsubscript{12}, and Wks 13, 16, 20 and 24 or ET\textsubscript{24}. Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest mmHg. All blood pressure measurements are to be taken in the dominant arm with the appropriate size cuff. Pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

A 12-lead electrocardiogram will be obtained at screening and at the end of treatment study visit (Wk 12 or ET\textsubscript{12}).

7.1.13. Medical History

Medical history, which comprises all past and present diseases or syndromes that in the Investigator's judgment are considered to be clinically significant, will be recorded in the CRF. This includes recording any significant cardiovascular, respiratory, endocrine/metabolic, gastrointestinal, genitourinary, musculoskeletal, hematological, neurological, neoplastic disease, drug abuse, or other relevant conditions. Medical history will be collected at screening visit only.

7.1.14. Laboratory

Blood chemistry, complete blood count with differential and platelet count will be completed at the Screening visit and at Week 12/ET\textsubscript{12}. A minimum of 8 hour fast is needed prior to blood collection for the chemistry panel. A urine drug screen will be performed at the Screening and Baseline visits (dipstick at site) and at other visits at the investigator’s discretion. Pregnancy test for all women, unless surgically sterilized or at least 2 years postmenopausal will be completed at Screening and Baseline, Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16 (dipstick at site or serum).

7.1.15. Cardiovascular (CV) Events of Interest

Cardiovascular adverse events will be prospectively reviewed and adjudicated by an independent Cardiovascular Event Adjudication Committee. The committee will be blinded to study treatment allocation. The committee will confirm diagnosis for cardiovascular events of interest based on review of documentation provided by investigators. All deaths will be reviewed by the adjudication committee who will make a determination of whether a death is cardiovascular or non-cardiovascular.
Clinically significant cardiac events of interest include:

- Non-fatal myocardial infarction;
- Resuscitated cardiac arrest;
- Need for coronary revascularization;
- Hospitalization for unstable angina;
- Hospitalization for congestive heart failure;
- Fatal, non-fatal stroke or transient ischemic attack (TIA);
- Any new diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any procedure for the treatment of PVD (or any peripheral vascular intervention);
- Cardiovascular death.

In order to ensure that no potential SAEs of interest are missed, in addition to the events above any hospitalization for angina, chest pain, loss of consciousness, cardiac or vascular procedures, respiratory diseases (excluding infections and cancer), and generalized edema will be sent for adjudication as described in Section 9.8. The sponsor will periodically review adverse event lists to identify additional cases for adjudication, irrespective of the diagnosis as described in Section 9.8.

7.1.15.1. Serious Cardiac Arrhythmias

In addition to cardiac events of interest serious cardiac arrhythmias will be reviewed and adjudicated by the independent adjudication committee. Serious cardiac arrhythmias are defined as the presence of a sustained cardiac rhythm disturbance lasting more than 1 minute which results in either hemodynamic compromise, syncope, cardiac arrest, a cerebral vascular event, or altered mental status, and requires urgent intervention with cardiac monitoring, drug therapy, cardioversion, or placement of a temporary pacemaker.

Examples include:

- Ventricular tachycardia;
- Torsade de Pointes;
- Ventricular fibrillation;
- AICD discharge (must state the underlying initiating rhythm);
- Bradycardia;
- Complete heart block;
- Atrial fibrillation / flutter;
- Supraventricular tachycardia;
- Sick sinus syndrome;
- Second degree heart block (type 2).

7.2. Efficacy

7.2.1. Measures of Abstinence from Smoking

Information for the calculation of abstinence parameters will be obtained at each clinic visit or telephone contact from a set of questions about cigarette and other nicotine use since the last visit/contact (Nicotine Use Inventory). At clinic visits, subject reports of smoking status will be confirmed by measurement of end expiratory exhaled carbon monoxide (CO) concentration, with a result ≤10 ppm indicating abstinence.

The main efficacy endpoint for the study is CO-confirmed 4-week continuous abstinence for Weeks 9 through 12, as determined by their answers to questions on the Nicotine Use Inventory and confirmation of their exhaled CO.

The secondary efficacy endpoint for the study is CO-confirmed continuous abstinence for Weeks 9 through 24, as determined by their answers to questions on the Nicotine Use Inventory and confirmation of their exhaled CO.

Additionally, other secondary endpoints arise from the NUI assessment:

Seven-day point prevalence of abstinence: CO-confirmed 7-day continuous abstinence for each NUI assessment visit (separately), as determined by their answers to the ‘last 7 days’ questions on the Nicotine Use Inventory (NUI) and confirmation of their exhaled CO.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed, volunteered or solicited adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.
As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

8.2. Reporting Period

For serious adverse events, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject’s participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Should an investigator be made aware of any serious adverse event occurring any time after the active reporting period, it must be promptly reported.

Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject provides informed consent through last subject visit.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
• Drug interactions;
• Extravasation;
• Exposure during pregnancy;
• Exposure via breast feeding;
• Medication error.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

• Test result is associated with accompanying symptoms, and/or
• Test result requires additional diagnostic testing or medical/surgical intervention, and/or
• Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
• Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

• Results in death;
• Is life-threatening (immediate risk of death);
• Requires inpatient hospitalization or prolongation of existing hospitalization;
• Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
• Results in congenital anomaly/birth defect;
• Lack of efficacy should be reported as an adverse event when it is associated with a serious adverse event.
Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5.1. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy’s Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT $\geq$ 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin $\geq$ 2 X ULN with no evidence of hemolysis and an alkaline phosphatase $\leq$ 2 X ULN or not available.

- For subjects with preexisting ALT OR AST OR total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
  - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT $\geq$ 2 times the baseline values and $\geq$ 3 X ULN, or $\geq$ 8 X ULN (whichever is smaller).

- **Concurrent with**
  - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal or $\geq$ 3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct
and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting criteria a or b, with no other cause for LFT abnormalities identified at the time should be considered potential Hy’s Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy’s Law cases should be reported as serious adverse events. All study drug treatments should be discontinued in these events.

8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;

- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

### 8.7. Severity Assessment

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>Does not interfere with subject's usual function.</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Interferes to some extent with subject's usual function.</td>
</tr>
<tr>
<td>SEVERE</td>
<td>Interferes significantly with subject's usual function.</td>
</tr>
</tbody>
</table>

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

### 8.8. Causality Assessment

The investigator’s assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not investigational product caused the event, then the event will be handled as “related to investigational product” for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.
8.9. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero (EIU)) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product;

2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner’s pregnancy

If a study subject or study subject’s partner becomes or is found to be pregnant during the study subject’s treatment with the investigational product, the investigator must submit this information to Pfizer on an EIU Form (this is a specific version of the Serious Adverse Event Form). In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.
Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the EIU Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the EIU Form that the subject was given this letter to provide to his partner.

8.10. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.11. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events voluntarily reported by the study subject. In addition, each study subject will be questioned about adverse events as described in Section 7.1.1.

8.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.12.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breast feeding cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a
description of the adverse event in sufficient detail to allow for a complete medical
assessment of the case and independent determination of possible causality. Information on
other possible causes of the event, such as concomitant medications and illnesses must be
provided. In the case of a subject death, a summary of available autopsy findings must be
submitted as soon as possible to Pfizer or its designated representative.

8.12.2. Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be
noted that the form for collection of serious adverse event information is not the same as the
adverse event CRF. Where the same data are collected, the forms must be completed in a
consistent manner. For example, the same adverse event term should be used on both forms.
Adverse events should be reported using concise medical terminology on the CRFs as well as
on the form for collection of serious adverse event information.

8.12.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse events reporting, including suspected serious unexpected adverse reactions, will be
carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study
will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor.
This document may modify the plans outlined in the protocol; however, any major
modifications of the primary endpoint definition and/or its analysis will also be reflected in a
protocol amendment.

This study serves as the parent study to A3051148, the later representing an extended
cardiovascular adverse event surveillance period. The endpoints for A3051123 focus on
neuro-psychiatric adverse events. Hence, all other adverse events (including those
cardiovascular in nature) that occur during study conduct will be reported according to Pfizer
safety standards. Subsequently, all data from this parent study deemed necessary to properly
summarize and report cardiovascular safety, including the derivation of composite endpoints
for cardiovascular adverse events, will be incorporated into the overall evaluation of
A3051148.

9.1. Analysis Sets

The Safety analysis population contains all treated subjects.

The full analysis set (FAS) is defined under the intent-to-treat principle, namely as all
randomized subjects.

Treatment misallocation rules will be specified in the Statistical Analysis Plan.
9.2. Sample Size Determination

The study is sized to attain an adequate level of precision in the estimation of the treatment difference for varenicline and bupropion versus placebo in the incidence of the primary neuropsychiatric safety endpoint within each cohort.

For the subjects in the cohort without a diagnosis of psychiatric disorder, considering both the available data from the varenicline randomized double-blind placebo-controlled clinical trials as well as the planned usage of the NAEI to aid in data collection, the incidence estimate for placebo is assumed to be approximately 3.5% for volunteered neuropsychiatric adverse events included in the primary safety endpoint. If there were an attributable risk difference of 2.63% (which translates to a 75% increase in the relative risk scale), a sample size of 1,000 per treatment group will provide sufficient precision with an expected 95% confidence interval of (0.75% to 4.50%), ie, a margin of error of ±1.87%.

For the subjects in the cohort with a diagnosis of psychiatric disorder, there are no sufficient data available and a 7.0% incidence for the placebo group is hypothesized. If there were a similar relative risk increase, an attributable risk difference of 5.25%, the sample size of 1,000 per treatment group will provide sufficient precision with an expected 95% confidence interval of (2.68% to 7.82 %), ie, a margin of error of ±2.57%.

The preceding assumptions, when taken together to produce a stratified pooled estimate of risk difference, suggests that a sample size of 2,000 per treatment group will provide sufficient precision with an expected 95% confidence interval of (2.34% to 5.52%), ie, a margin of error of ±1.59%.

The main abstinence (efficacy) superiority analyses are adequately powered. Given a placebo rate of 10% and 1,000 subjects per treatment group per cohort, an odds ratio of 2.0 can be detected at a 5% level with at least 80% power.

9.3. Safety Objective Analysis

Primary Safety Objectives:

1. To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo with a pre-specified level of precision in the incidence of the primary neuropsychiatric AE endpoint for subjects:

   a. With a diagnosis of psychiatric disorder;

   b. Without a diagnosis of psychiatric disorder.

2. To characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).

Secondary safety objectives include an assessment of the above two objectives with respect to each of the remaining pairwise treatment comparisons.
The primary safety analyses will provide model-based estimates and associated 95% confidence intervals for the difference in the incidence of the primary neuropsychiatric safety endpoint between varenicline and placebo and between bupropion and placebo for subjects in each cohort. Further, an interaction involving treatment and cohort will be tested at a 10% level and, lacking evidence of significant interaction, pooled estimates of these risk differences and their associated 95% confidence intervals will be computed.

The preceding primary safety analysis will be repeated for each of the components of the composite safety endpoint.

Adverse event, laboratory, and other safety data (eg, Hospital Anxiety and Depression Scale (HADS) and the Clinical Global Impression of Improvement (CGI-I) will be summarized by frequencies of events and or mean changes from baseline to each assessment period, as appropriate.

Additional adverse event summaries will be done for the post treatment follow up period.

The safety summaries will include:

- A summary of neuropsychiatric adverse events of interest leading to treatment and/or study discontinuations.
- A summary of neuropsychiatric adverse events of interest resulting in an intervention.

Adverse event frequencies and other safety data on the active control drug (NRT) will be summarized and tabulated.

9.4. Efficacy Objective Analysis

Main Efficacy Objective: To compare smoking abstinence rates of varenicline and bupropion relative to placebo for the last 4 weeks of treatment and continuously through Week 24, as measured by CO-confirmed CAR9-12 and CAR9-24, respectively, separately for subjects with and without a diagnosis of psychiatric disorder.

Secondary Objective: To assess if there is a difference between cohorts in the placebo adjusted relative abstinence rates (CAR9-12 and CAR9-24) of varenicline and bupropion, separately.

Hypotheses and Decision Rules

The main and secondary abstinence hypotheses are to test the superiority of varenicline versus placebo (and, separately, bupropion versus placebo), with respect to CAR9-12 and CAR9-24. Each cohort is to be tested individually at a 5% level, without any multiplicity adjustment. Furthermore, in the event that the Statistical Analysis Plan declares an interaction term(s) within the construct of a statistical model, assessment for significance of any such interaction term is to be done individually at a 10% level.
Other secondary efficacy objectives include an assessment of the above two objectives with respect to each of the remaining four pairwise treatment comparisons.

9.5. Methods and Analysis

The primary and secondary safety and abstinence endpoints are binary in nature. Appropriate descriptive statistics will be provided for these endpoints.

The statistical model used in the safety and abstinence analyses will be a logistic regression model that controls for the effects due to treatment, cohort and pooled site (the latter defined explicitly in the SAP).

Logistic regression analyses will be based on a binomial distribution with either an identity link function (risk difference for safety endpoints) or a logit link function (odds ratios for abstinence endpoints). Contrasts will be constructed for the primary and secondary pairwise treatment comparisons, both per cohort as well as for the pooled cohorts. For each contrast, the risk difference (or odds ratio) estimate and respective 95% confidence interval will be produced. There is no adjustment for multiplicity. Furthermore, any interaction assessment will be conducted at a 10% level. If warranted, the computation of estimates arising from the pooling of cohorts will not involve any model reduction.

Analyses for abstinence endpoints will be based on the FAS. Analyses for safety endpoints will be based on the Safety population. Adverse event data and the primary neuropsychiatric safety endpoint will be summarized and respectively analyzed using Pfizer Safety Standards and a 30-day lag following the end of 12 weeks of treatment for treatment-emergent all causality adverse events. Non-treatment-emergent adverse events (ie, from 30 days following the end of treatment through week 24) will also be summarized.

For those subjects in the “with diagnosis of psychiatric disorder” cohort, the investigator will record the primary major diagnosis group (psychotic disorders, affective disorders, anxiety disorders or borderline personality disorders) on the CRF, in effect defining a sub-cohort for each of these subjects. It is noted that with respect to analyses, cohort has two levels: (1) without diagnosis of psychiatric disorder and (2) with diagnosis of psychiatric disorder. Any secondary analysis that focuses on partitioning the “with diagnosis of psychiatric disorder” cohort will utilize the primary major diagnosis group as indicated on the CRF. Further analysis details will be presented in the SAP.

9.6. Interim Analysis

The unblinded primary endpoint rate (along with all AE reporting and other safety data) will be monitored at the periodic meetings of the Independent Data Monitoring Committee (IDMC). Recommendations by the IDMC to the sponsor based on the primary endpoint rate can occur throughout the study following any of the IDMC meetings. These recommendations could be related to emerging risk in one of the treatment arms or a lower primary endpoint rate than planned for in the protocol.
The sponsor will also request that the IDMC provide the blinded (pooled across both treatment and cohort) primary endpoint rate after 50% of the subjects have completed the study. If this endpoint rate is below 3.5%, then the sponsor will notify the regulators of the lower than planned endpoint rate and, if needed, request a meeting to discuss the potential implications for the study sample size and number of investigator sites.

An unblinded interim statistical analysis will be conducted and reported to the IDMC after 75% of the subjects have completed the study. This unblinded interim analysis will consist of all pair-wise treatment comparisons within and combined over the two cohorts of subjects with and without a history of psychiatric illness. Also, an upper 1-sided 95% confidence interval for the placebo primary endpoint rate in the no history cohort will be computed and projected to the planned study size. If this projected upper bound is less than 3.5%, then a sample size re-estimation will be performed. Further details will be specified within the formal Interim Analysis Plan. The sponsor will remain blinded to the interim results. The unblinded interim analysis at the 75% point is considered optimum because it will provide sufficient data (both in terms of precision and improved balance in randomization) to make recommendations regarding the possible increase in sample size as well as give sufficient time for the sponsor to implement the recommendations. Furthermore, any sample size re-estimation would apply to all treatment groups in both cohorts (ie, all treatment allocation ratios remain unchanged) and no treatment group in either cohort would stop enrollment. Any recommendations made by the IDMC as a result of the unblinded interim analysis will be communicated to the regulators before implementation.

9.7. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to assess safety data at regular intervals for the duration of the trial and make recommendations to the Executive Steering Committee on whether to continue, modify or stop the study. An IDMC charter authored a priori and governed by the IDMC will be completed.

The committee will be responsible for ongoing monitoring of the safety of subjects in the study. Any recommendation made by the committee to alter the conduct of the study will be forwarded to the Sponsor for final decision. The Sponsor will forward such decisions, which may include summaries of aggregate analyses of safety endpoint events, to regulatory authorities, as appropriate.

9.8. Cardiovascular Event Adjudication Committee (CEAC)

An independent adjudication committee will review documentation provided by investigators during study conduct to identify cardiovascular events of interest (primary and secondary CV safety endpoints). Investigators will collect and submit documentation to the CEAC for all adverse events related to:

- Non-fatal myocardial infarction;
- Any hospital admission for chest pain;
- Hospitalization for angina pectoris/unstable angina;
- Need for coronary revascularization or any cardiac or vascular intervention;
- Resuscitated cardiac arrest;
- Hospitalization for congestive heart failure;
- Fatal, non-fatal stroke or transient ischemic attack (TIA);
- Any diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any procedure for the treatment of PVD;
- Cardiovascular Death;
- Death from any cause:
  - Hospitalization for loss of consciousness:
  - Respiratory diseases (excluding infections and cancer),
- Generalized edema

To ensure that all possible cardiovascular adverse events of interest (primary and secondary endpoints) are referred to the CEAC for review, a listing of all adverse events (serious and non-serious) from the following SOCs, HLGTS, HLTS, LLTS and PTs will be prepared monthly and sent to the CEAC.

1. All Deaths.
2. SOCs:
   - Cardiac Disorders;
   - General Disorders and Administration Site Conditions;
   - Injury, Poisoning, and Procedural Complications;
   - Investigations;
   - Musculoskeletal and Connective Tissue Disorders;
   - Nervous System Disorders;
   - Respiratory, Thoracic, and Mediastinal Disorders;
   - Surgical and Medical Procedures;
• Vascular Disorders.

3. HLGT:
• Tissue disorders NEC.

4. HLT:
• Necrosis, NEC.

5. LLTs:
• Cerebral Revascularization Synangiosis (search value: revascularization);
• Coronary Revascularization (search value: revascularization);
• Peripheral Revascularization (search value: revascularization);
• Renal Revascularization (search value: revascularization);
• Transmyocardial Revascularization (search value: revascularization);
• Acute myocardial ischemia (search value: myocardial ischemia);
• ECG signs of myocardial ischemia (search value: myocardial ischemia);
• Myocardial ischemia (search value: myocardial ischemia);
• Myocardial ischemia recurrent (search value: myocardial ischemia);
• Silent myocardial ischemia (search value: myocardial ischemia).

6. PTs:
• Acute Myocardial Infarction (search value: myocardial infarction);
• Myocardial Infarction (search value: myocardial infarction);
• Post Procedural Myocardial Infarction (search value: myocardial infarction);
• Silent Myocardial Infarction (search value: myocardial infarction);
• Cell Death.

These searches will be complemented by a quarterly standardized Medra query for other possible CV events that may also require adjudication.
- Myocardial Infarction;
- Ischemic Heart Disease;
- Cardiac Arrhythmias;
- Cardiac Failure;
- Embolic and Thrombotic Events;
- Shock;
- Torsade de pointes/QT prolongation;
- Cerebrovascular Disorders;
- Central Nervous System Haemorrhages and Cerebrovascular Accidents;
- Vasculitis;
- Cardiomyopathy;
- Hemodynamic edema, effusions, and fluid overload;
- Hypertension;
- Pulmonary Hypertension;
- Renovascular Disorders;
- Shock.

The events will be adjudicated using a standard events manual under blinded conditions. The adjudication committee will make the determination of whether a death is cardiac or non-cardiac.

The independent adjudication committee will also review serious cardiac arrhythmias. Serious cardiac arrhythmias are defined as the presence of a sustained cardiac rhythm disturbance lasting more than 1 minute which results in either hemodynamic compromise, syncope, cardiac arrest, a cerebral vascular event, or altered mental status, and requires urgent intervention with cardiac monitoring, drug therapy, cardioversion, or placement of a temporary pacemaker.

Examples include:
- Ventricular tachycardia;
• Torsade de Pointes;
• Ventricular fibrillation;
• AICD discharge (must state the underlying initiating rhythm);
• Bradycardia;
• Complete heart block;
• Atrial fibrillation / flutter;
• Supraventricular tachycardia;
• Sick sinus syndrome;
• Second degree heart block (type 2).

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.
The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry”.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, Molecular Profiling Supplement, informed consent forms, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.
The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.
13. DEFINITION OF END OF TRIAL

13.1. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as last subject’s last visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of varenicline at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose the clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer posts the results of all studies that it has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products. Pfizer posts results within one year of the primary outcome completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV).

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).
Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.
16. REFERENCES


10. Study Report: Assessing the Content Validity of the Neuropsychiatric Adverse Events Interview (NAEI), 12 Jan 2011 http://gdms.pfizer.com/gdms/drl/objectId090177e181ba217d

# Appendix 1. Fagerström Test for Nicotine Dependence

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answers</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How soon after you wake up do you smoke your first cigarette?</td>
<td>Within 5 minutes</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6-30 minutes</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31-60 minutes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>After 60 minutes</td>
<td>0</td>
</tr>
<tr>
<td>2. Do you find it difficult to refrain from smoking in places where it is forbidden eg, in church, at the library, in the cinema, etc.?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>3. Which cigarette would you hate most to give up?</td>
<td>The first one in the morning</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any other</td>
<td>0</td>
</tr>
<tr>
<td>4. How many cigarettes/day do you smoke?</td>
<td>10 or less</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21-30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31 or more</td>
<td>3</td>
</tr>
<tr>
<td>5. Do you smoke more frequently during the first hours after waking than during the rest of the day?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>6. Do you smoke if you are so ill that you are in bed most of the day?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>
Appendix 2. Hospital Anxiety and Depression Scale (HADS)

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and Check (✓) the reply which comes closest to how you have been feeling in the past week. Ignore the numbers printed beside each response. Don’t take too long over your replies, your immediate reaction to each item will probably be more accurate than a long thought-out response.

HADS copyright R.P. Snaith and A.S. Zigmond 1983, 1992, 1994. Record from items originally published in Acta Psychiatria Scandinavica, 67, 361–70, copyright © Munksgaard International Publishers Ltd, Copenhagen, 1983. Published by GL Assessment Limited, The Chiswick Centre, 414 Chiswick High Road, London W4 5TF, UK. All rights reserved. GL Assessment is part of the Granada Learning Group. This work may not be photocopied or otherwise reproduced by any means, even within the terms of a Photocopying Licence, without the written permission of the Publishers.
Appendix 3. Suicide Behaviors Questionnaire-Revised (SBQ-R)

Instructions: Please check the number beside the statement or phrase that best applies to you.

1. Have you ever thought about or attempted to kill yourself? (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Never</td>
</tr>
<tr>
<td>2.</td>
<td>It was just a brief passing thought</td>
</tr>
<tr>
<td>3a.</td>
<td>I have had a plan at least once to kill myself but did not try to do it</td>
</tr>
<tr>
<td>3b.</td>
<td>I have had a plan at least once to kill myself and really wanted to die</td>
</tr>
<tr>
<td>4a.</td>
<td>I have attempted to kill myself, but did not want to die</td>
</tr>
<tr>
<td>4b.</td>
<td>I have attempted to kill myself, and really hoped to die</td>
</tr>
</tbody>
</table>

2. How often have you thought about killing yourself in the past year? (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Never</td>
</tr>
<tr>
<td>2.</td>
<td>Rarely (1 time)</td>
</tr>
<tr>
<td>3.</td>
<td>Sometimes (2 times)</td>
</tr>
<tr>
<td>4.</td>
<td>Often (3-4 times)</td>
</tr>
<tr>
<td>5.</td>
<td>Very Often (5 or more times)</td>
</tr>
</tbody>
</table>

3. Have you ever told someone that you were going to commit suicide, or that you might do it? (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>No</td>
</tr>
<tr>
<td>2a.</td>
<td>Yes, at one time, but did not really want to die</td>
</tr>
<tr>
<td>2b.</td>
<td>Yes, at one time, and really wanted to die</td>
</tr>
<tr>
<td>3a.</td>
<td>Yes, more than once, but did not want to do it</td>
</tr>
<tr>
<td>3b.</td>
<td>Yes, more than once, and really wanted to do it</td>
</tr>
</tbody>
</table>

4. How likely is it that you will attempt suicide someday? (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.</td>
<td>Never</td>
</tr>
<tr>
<td>1.</td>
<td>No chance at all</td>
</tr>
<tr>
<td>2.</td>
<td>Rather unlikely</td>
</tr>
<tr>
<td>3.</td>
<td>Unlikely</td>
</tr>
<tr>
<td>4.</td>
<td>Likely</td>
</tr>
<tr>
<td>5.</td>
<td>Rather likely</td>
</tr>
<tr>
<td>6.</td>
<td>Very likely</td>
</tr>
</tbody>
</table>

Appendix 4. Nicotine Use Inventory (NUI)

Asked at the Baseline through the Week 12 visit

- Has the subject smoked any cigarettes (even a puff) since the last site visit / telephone contact?

- Has the subject used any other nicotine-containing products* (e.g., nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) since the last site visit / telephone contact?

- Has the subject smoked any cigarettes (even a puff) in the last 7 days?

- If the subject smoked in the last 7 days, has the subject had any days on which no cigarettes were smoked, and if so, how many days?

- If the subject smoked in the last 7 days, how many cigarettes did the subject smoke per day, on average for the days on which smoking occurred?

- Has the subject used any other nicotine-containing products* (e.g., nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) in the last 7 days?

* This question refers to any unauthorized nicotine containing products and not the NRT patch which was provided during study treatment phase.

Asked at the Week 13 visit through the Week 24 visit:

- Has the subject smoked any cigarettes (even a puff) since the last site visit / telephone contact?

- Has the subject used any other tobacco products (eg, pipe, cigars, chew, snuff) since the last site visit / telephone contact?

- Has the subject smoked any cigarettes (even a puff) in the last 7 days?

- If the subject smoked in the last 7 days, has the subject had any days on which no cigarettes were smoked, and if so, how many days?

- If the subject smoked in the last 7 days, how many cigarettes did the subject smoke per day, on average for the days on which smoking occurred?

- Has the subject used any other tobacco products (eg, pipe, cigars, chew, snuff) in the last 7 days?

- Nicotine replacement therapy and/or other smoking cessation medications should be recorded in the concomitant medicine pages in the case report form.

PFIZER CONFIDENTIAL
Page 70
272 of 564
Page 72
Appendix 5. Aggression Questionnaire (AQ)

Instructions:

Using the 5 point scale shown below, indicate how uncharacteristic or characteristic each of the following statements is in describing you. Place your rating in the box to the right of the statement.

1 = extremely uncharacteristic of me
2 = somewhat uncharacteristic of me
3 = neither uncharacteristic nor characteristic of me
4 = somewhat characteristic of me
5 = extremely characteristic of me

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Some of my friends think I am a hothead.</td>
</tr>
<tr>
<td>2</td>
<td>If I have to resort to violence to protect my rights, I will.</td>
</tr>
<tr>
<td>3</td>
<td>When people are especially nice to me, I wonder what they want.</td>
</tr>
<tr>
<td>4</td>
<td>I tell my friends openly when I disagree with them.</td>
</tr>
<tr>
<td>5</td>
<td>I have become so mad that I have broken things.</td>
</tr>
<tr>
<td>6</td>
<td>I can’t help getting into arguments when people disagree with me.</td>
</tr>
<tr>
<td>7</td>
<td>I wonder why sometimes I feel so bitter about things.</td>
</tr>
<tr>
<td>8</td>
<td>Once in a while, I can’t control the urge to strike another person.</td>
</tr>
<tr>
<td>9</td>
<td>I am an even-tempered person.</td>
</tr>
<tr>
<td>10</td>
<td>I am suspicious of overly friendly strangers.</td>
</tr>
<tr>
<td>11</td>
<td>I have threatened people I know.</td>
</tr>
<tr>
<td>12</td>
<td>I flare up quickly but get over it quickly.</td>
</tr>
<tr>
<td>13</td>
<td>Given enough provocation, I may hit another person.</td>
</tr>
<tr>
<td>14</td>
<td>When people annoy me, I may tell them what I think of them.</td>
</tr>
<tr>
<td>15</td>
<td>I am sometimes eaten up with jealousy.</td>
</tr>
<tr>
<td>16</td>
<td>I can think of no good reason for ever hitting a person.</td>
</tr>
<tr>
<td>17</td>
<td>At times I feel I have gotten a raw deal out of life.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>18.</td>
<td>I have trouble controlling my temper.</td>
</tr>
<tr>
<td>19.</td>
<td>When frustrated, I let my irritation show.</td>
</tr>
<tr>
<td>20.</td>
<td>I sometimes feel that people are laughing at me behind my back.</td>
</tr>
<tr>
<td>21.</td>
<td>I often find myself disagreeing with people.</td>
</tr>
<tr>
<td>22.</td>
<td>If somebody hits me, I hit back.</td>
</tr>
<tr>
<td>23.</td>
<td>I sometimes feel like a powder keg ready to explode.</td>
</tr>
<tr>
<td>24.</td>
<td>Other people always seem to get the breaks.</td>
</tr>
<tr>
<td>25.</td>
<td>There are people who pushed me so far that we came to blows.</td>
</tr>
<tr>
<td>26.</td>
<td>I know that “friends” talk about me behind my back</td>
</tr>
<tr>
<td>27.</td>
<td>My friends say that I am somewhat argumentative</td>
</tr>
<tr>
<td>28.</td>
<td>Sometimes I fly off the handle for no good reason.</td>
</tr>
<tr>
<td>29.</td>
<td>I get into flights a little more than the average person.</td>
</tr>
</tbody>
</table>

References

## Appendix 6. Neuropsychiatric Adverse Events Interview (NAEI)

<table>
<thead>
<tr>
<th>Neuropsychiatric Adverse Events Interview Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Have you felt depressed (sad, blue, down, empty, as if you didn’t care)?</td>
</tr>
<tr>
<td>• Do you find that you have lost interest in things or get less pleasure from things that you used to enjoy?</td>
</tr>
<tr>
<td>• Have you cried or felt like crying?</td>
</tr>
<tr>
<td>• Have you been worried or scared?</td>
</tr>
<tr>
<td>• Have you been nervous or anxious?</td>
</tr>
<tr>
<td>• Have you felt panicky at all?</td>
</tr>
<tr>
<td>• Some people have panic attacks when they suddenly feel very frightened and have physical symptoms like heart palpitations (your heart is pounding and/or beating rapidly), shortness of breath and chest pains. Have you had this?</td>
</tr>
<tr>
<td>• Have you had times when you felt extremely agitated?</td>
</tr>
<tr>
<td>• Have you had times when you felt like you had to be always moving or even pacing?</td>
</tr>
<tr>
<td>• Have you felt unusually cheerful, or happy, not just your normal self, so that other people noticed?</td>
</tr>
<tr>
<td>• Have you had much more energy than usual to do things?</td>
</tr>
<tr>
<td>• Have you needed less sleep than usual to feel rested?</td>
</tr>
<tr>
<td>• Have you felt hostile towards others?</td>
</tr>
<tr>
<td>• Have you been involved in any serious arguments or fights?</td>
</tr>
<tr>
<td>• Have you had the urge to injure or harm someone?</td>
</tr>
<tr>
<td>• Have you felt that people have been talking about you?</td>
</tr>
<tr>
<td>• Have you felt that someone may be after you, or trying to harm you in some way?</td>
</tr>
<tr>
<td>• Has there been anything unusual about the way things look or sound or smell?</td>
</tr>
<tr>
<td>• Have you heard things that other people couldn’t hear, like noises or voices of people talking when there was no one around?</td>
</tr>
<tr>
<td>• Have you seen things that other people couldn’t see?</td>
</tr>
<tr>
<td>• Has your mind been playing tricks on you in any way?</td>
</tr>
<tr>
<td>• Have you had any ideas that other people might not understand or might find strange?</td>
</tr>
<tr>
<td>• Have things seemed unreal to you?</td>
</tr>
<tr>
<td>• Have you felt that you are detached from or have trouble connecting with other people?</td>
</tr>
<tr>
<td>• Have you felt strange or unnatural in any other way?</td>
</tr>
</tbody>
</table>
Neuropsychiatric Adverse Events Interview (NAEI) Guidelines

General Overview & Background on the NAEI

The NAEI has been designed as a semi-structured interview to systematically assess the presence and severity of specific neuropsychiatric symptoms as part of the adverse event data collection process. The NAEI is used at Baseline to detect symptoms that are present at the time of the subject’s entry into this clinical trial and at follow-up visits to prospectively monitor emergent symptoms. The goal is to facilitate the collection of information relevant to specific neuropsychiatric events of interest in a standardized manner. Standardizing the way in which such information is collected in a clinical trial optimizes reliability and validity across sites and clinicians.

The NAEI is intended to guide the interviewer in determining whether a symptom is present, and then, if it is, clinically significant. In assessing whether a symptom's “clinical significant”, it is important to examine the:

7. Frequency and duration of the symptom.

8. Severity of the symptom.

If the patient responds affirmatively to questions about a specific NAEI symptom, the symptom then must be evaluated by the investigator for clinical presentation and severity and recorded as an adverse event (AE) or serious adverse event (SAE) if warranted. AEs are graded according to their intensity (mild, moderate, or severe) by examining the degree of functional impairment associated with them as per instructions in the protocol. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. Refer to Protocol Section 8 for more information on both AE and SAE reporting.

The determination whether a symptom is an adverse event and therefore warrants an AE report should always be based on the steps outlined in the figure below:
These administration instructions are intended to help interviewers use the NAEI correctly. Sites are responsible for following these guidelines throughout the course of the study. Sites should keep a copy of these guidelines handy to refer to as needed.

A worksheet for the NAEI interview has been developed and made available to sites to facilitate its use. The worksheet is used for both the baseline and follow-up visits. The interviewer should take notes on the worksheet to assist with AE reporting if needed and to refer to during future visits.

**INTERVIEWER QUALIFICATIONS**

The NAEI interview should be conducted by a staff person at the site who has completed training on the NAEI. Only interviewers who have completed the formal training on the NAEI to Pfizer’s standards can administer it for this trial.

If a site needs additional training for a new interviewer, they must contact Pfizer to make arrangements for the necessary training. No interviewer should administer the NAEI without the appropriate training. Refresher training will be required during the study.

Note that where possible, sites are strongly encouraged to have the same individual conduct the volunteered AE collection, the NAEI interview, the C-SSRS, and any other clinical ratings scales included in the protocol.
Sites should make every effort to keep the same interviewer for each subject over the course of the trial.

**Time Period to be Rated**

At Baseline, symptoms should be assessed for the past two (2) weeks. At follow-up visits, the time period to be rated is since the last clinic visit.

The interviewer should be careful when asking questions to make sure the subject is clear on the time period being rated. It may be helpful to frame questions by frequently reminding the subject of the time frame “In past 2 weeks” (at baseline) or “Since your last visit” (at follow-up) and by probing to make sure the symptoms described did occur during the time period in question (eg, at baseline asking, “Was that during the past 2 weeks?”).

**Materials Needed to Complete the NAEI**

The NAEI guidelines should always be available for reference.

In addition, at all visits after the baseline visit, the interviewer should have at hand:

- The subject’s AE log worksheet;
- Previously completed NAEI worksheets.

**Order of Assessment**

The assessment sequence for this trial must be followed carefully. Assessments should be done in the following order:

1. Volunteered AE report – opening question on how the subject has been feeling in general;
2. Follow up on previously reported AEs that are still ongoing;
3. Clinical rating scales as specified in the protocol;
4. NAEI;
5. Columbia Suicide Severity Rating Scale.

**Volunteered AE report**: The collection of volunteered AE reports should follow the site’s usual procedures. Generally this is done by asking the subject how s/he has been feeling in general. During the collection of volunteered AE information, the interviewer should be careful to ask sufficient follow-up questions to determine the clinical significance of the reported event and therefore whether an AE report is warranted.
Follow-up of any previously reported AEs: At all visits after the baseline visit, the interviewer then follows up on any previously reported AEs that, according to the AE log worksheet, are still ongoing (i.e., do not have a stop date) to see if resolved. AEs on the AE log worksheet may have been volunteered or solicited at previous visits.

NAEI: The NAEI is designed to guide the interviewer through a series of questions probing for neuropsychiatric symptoms using a semi-structured interview approach (see detailed administration instructions below). In most cases, the interviewer will need to ask all of the NAEI questions. However, some symptoms that are addressed by the NAEI questions may already have been volunteered during the volunteered AE discussion. In such situations, if the interviewer has already gained enough information to fully assess the question, it is not necessary to repeat the respective question(s) during NAEI administration.

BASELINE NAEI

TO BEGIN THE INTERVIEW: The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had during the past two (2) weeks.

The NAEI questions have been grouped into symptom categories and all questions in each group should be asked before making a determination about a potential adverse event.

The interviewer will have to add their own follow-up questions to the written NAEI questions to obtain necessary information. Follow-up questions should be used as needed for clarification on symptoms and to assess the frequency/duration, severity, and degree of functional impairment related to the symptom. Sample follow-up questions are provided in this document. The interviewer should probe as needed to assess the subject’s experiences and to make an appropriate assessment. The interviewer should be careful to clarify the time period (past 2 weeks) the questions refer to.

As noted before, once a symptom has been identified as present, its clinical significance must be ascertained.

NAEI Item Example:

During the past 2 weeks:

1. Have you been feeling sad, unhappy, worthless, or depressed?

IF YES, SAMPLE FOLLOW-UP QUESTIONS:

How often have you been bothered by this in the past 2 weeks?

Was it a little bit of the time, some of the time or most of the time?

Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people in the past 2 weeks?
IF YES: How hard? Can you give me an example?

FOLLOW-UP VISITS NAEI

The purpose of this assessment is to identify symptoms that have been present since the subject’s last visit and if this represents a change from their last visit. Follow-up questions are provided to help make these ratings.

To begin the follow-up interview: The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had since their last visit.

The same interview flow should be followed as at the baseline visit. In addition, for any symptom that is reported, follow up questions should assess whether this is a change from the last visit.

Follow-up NAEI Item Example:

Since your last clinic visit:

1. Have you been feeling sad, unhappy, worthless, or depressed?

Sample Follow-up Questions:

How often have you been bothered by this since your last clinic visit?

Was it a little bit of the time, some of the time or most of the time?

Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people since your last clinic visit?

IF YES: How hard? Can you give me an example?

Has this been a change from the last time you were here?

IF YES: How much of a change?

AFTER COMPLETING THE NAEI AT BASELINE AND FOLLOW-UP VISITS

The interviewer should review the responses to the questions on the NAEI and notes taken during the interview, to determine whether, in his/her clinical judgment, any neuropsychiatric event reported warrants classification as an AE. Both the subject’s answers to the questions and observations made during the interview should serve as the basis for making this determination.
For each solicited adverse event, the interviewer must determine the maximum level of intensity of the symptom as either:

<table>
<thead>
<tr>
<th>MILD</th>
<th>Does not interfere with subject's usual functioning.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODERATE</td>
<td>Interferes to some extent with subject's usual functioning.</td>
</tr>
<tr>
<td>SEVERE</td>
<td>Interferes significantly with subject's usual functioning.</td>
</tr>
</tbody>
</table>

AEs should be added to the subject’s AE log worksheet. This, together with the completed NAEI worksheet should be filed with the subject’s other documents so that they are available for future visits. The site staff should follow Pfizer’s instructions to complete the AE Case Report Form page.
Appendix 7. Clinical Global Impression of Severity (CGI-S)

SEVERITY OF ILLNESS: Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?

<table>
<thead>
<tr>
<th>(Check (X) ONE only):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT ASSESSED</td>
<td>NORMAL, NOT AT ALL ILL</td>
</tr>
<tr>
<td>BORDERLINE, MENTALLY ILL</td>
<td>MARKEDLY ILL</td>
</tr>
<tr>
<td>MILDLY ILL</td>
<td>SEVERELY ILL</td>
</tr>
<tr>
<td></td>
<td>AMONG THE MOST EXTREMELY ILL PATIENTS</td>
</tr>
</tbody>
</table>

Note: The ratings will be applicable even to those without psychiatric diagnoses (e.g., those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician’s experience with the psychiatric population to which the subject belongs.
Appendix 8. Clinical Global Impression of Improvement (CGI-I)

GLOBAL IMPRESSION OF CHANGE: Rate total impression of change whether or not, in your judgment, it is due entirely to drug treatment.

Compared to his/her condition at the Week 0 Visit, how much has the patient changed?

<table>
<thead>
<tr>
<th>(Check (X) ONE only):</th>
<th>VERY MUCH IMPROVED</th>
<th>NO CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT ASSESSED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MINIMALLY IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH WORSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VERY MUCH WORSE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician’s experience with the psychiatric population to which the subject belongs.
Appendix 9. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) Baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE
(C-SSRS)

Baseline
Version 1/14/09


Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J. Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu
© 2008 The Research Foundation for Mental Hygiene, Inc.
## SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes”, ask questions 3, 4, and 5. If the answer to question 1 and/or 2 is “yes”, complete “Intensity of Ideation” section below.

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
<th>Most Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Wish to be Dead</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Non-Specific Active Suicidal Thoughts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Active Suicidal Ideation with Specific Plan and Intent</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-6 from above, with 1 being the least severe and 6 being the most severe). Ask about time before she was feeling the most suicidal.

<table>
<thead>
<tr>
<th>Type # (1-6)</th>
<th>Description of Ideation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency</th>
<th>How many times have you had these thoughts?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1) Less than once a week, (2) Once a week, (3) 2-3 times a week, (4) Daily or almost daily, (5) Many times each day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration</th>
<th>When you have these thoughts, how long do they last?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1) Fleeting: no seconds or minutes, (2) Lasts more than</td>
</tr>
<tr>
<td></td>
<td>1 hour some of the time, (4) 4-8 hours/most of the day,</td>
</tr>
<tr>
<td></td>
<td>(5) More than 8 hours/continuous, (6) 1-6 hours a lot of</td>
</tr>
<tr>
<td></td>
<td>time</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Controllability</th>
<th>Could you stop thinking about killing yourself or wanting to die if you wanted to?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1) Usually able to control thoughts, (2) Can control thoughts with a lot of difficulty,</td>
</tr>
<tr>
<td></td>
<td>(3) Can control thoughts with little difficulty, (4) Unable to control thoughts,</td>
</tr>
<tr>
<td></td>
<td>(5) Can control thoughts with some difficulty, (6) Does not attempt to control thoughts,</td>
</tr>
</tbody>
</table>

### Deterrents

<table>
<thead>
<tr>
<th>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Deterrent definitely stopped you from attempting suicide, (2) Deterrent might have stopped you,</td>
</tr>
<tr>
<td>(3) Deterrent definitely did not stop you, (4) Deterrent definitely did not stop you,</td>
</tr>
<tr>
<td>(5) Deterrent definitely did not stop you, (6) Deterrent definitely did not stop you,</td>
</tr>
</tbody>
</table>

### Reasons for Ideation

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn’t go on living with this pain or how you were feeling) or was it to get attention, revenge, or a reaction from others? Or both?

(1) Completely to get attention, revenge, or a reaction from others, (2) Mostly to get attention, revenge or a reaction from others, (3) Equally to get attention, revenge or a reaction from others, (4) Mostly to end or stop the pain you couldn’t go on living with the pain or how you were feeling, (5) Equally to end or stop the pain you couldn’t go on living with the pain or how you were feeling, (6) Mostly to end or stop the pain you couldn’t go on living with the pain or how you were feeling, (7) Mostly to end or stop the pain you couldn’t go on living with the pain or how you were feeling, (8) Does not apply.
### SUICIDAL BEHAVIOR

(Valid for all subjects until 90 days from the date of the last known follow-up visit, unless otherwise noted.)

<table>
<thead>
<tr>
<th>Actual Attempt</th>
<th>Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**A potentially lethal attempt committed with the intent to die.**

- A potentially serious attempt committed with the intent to die. Intent does not have to be 100%.
- If there is any attempt to die, it is considered an actual suicide attempt.
- If the attempt is successful, it is considered an actual suicide attempt.

**Inferior Intent:** Even if an individual expresses a desire to die, it may be inferred clinically from their behavior or circumstances. For example, a highly lethal act that is clearly not an accident, even if an individual expresses a desire to die, may be inferred clinically from their behavior or circumstances.

**Has Subject Engaged in Non-Suicidal Self-Injurious Behavior?**

<table>
<thead>
<tr>
<th>Interrupted Attempt</th>
<th>Total # of Interrupted Attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

When the individual is interrupted by an outside circumstance, this is considered an interrupted attempt.

- Overdose: A person has taken any pills, this becomes an attempt rather than an interrupted attempt. Example: An individual takes a pill, is interrupted by a phone call, and then returns to the pill. This is considered an attempt rather than an interrupted attempt.
- Self-Directed: An individual has taken a pill and then is interrupted by a phone call, and then returns to the pill. This is considered an attempt rather than an interrupted attempt.

**Aborted Attempt:**

- When a person begins to take steps toward making a suicidal attempt, but stops themselves before actually harming themselves in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops themselves instead of being stopped by something else.

**Preparatory Acts or Behavior:**

- Acts or preparation towards imminent making a suicidal attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, preparing to kill oneself). Examples of self-destructive behavior include collecting pills, getting a gun, giving valuables away or writing a suicide note.

<table>
<thead>
<tr>
<th>Suicidal Behavior</th>
<th>Most Recent Attempt Date</th>
<th>Most Lethal Attempt Date</th>
<th>Intact/First Attempt Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Enter Code</td>
<td>Enter Code</td>
</tr>
</tbody>
</table>

**Actual Lethality/Medical Damage:**

1. No physical damage or very minor physical damage (e.g., scratches)
2. Moderate physical damage (e.g., broken bones, minor bleeding, sprains)
3. Severe physical damage (e.g., severe bleeding, major surgery, loss of major body part)
4. Death

**Potential Lethality:** Only answer if actual lethality is known.

- Behavior not likely to result in injury
- Behavior likely to result in injury but not likely to cause death
- Behavior likely to result in death despite available medical care
Appendix 10. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09


Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD. Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Holberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103-130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@chilfpsych.columbia.edu
© 2008 The Research Foundation for Mental Hygiene, Inc.
**SUICIDAL IDEATION**

Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes,” ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is “yes,” complete “Intensity of Ideation” section below.

<table>
<thead>
<tr>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

1. Wish to be Dead
   Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
   *Have you wished you were dead or did you want to go to sleep and not wake up?*
   
   If yes, describe:

2. Non-Specific Active Suicidal Thoughts
   General, non-specific thoughts of wanting to end one’s life/commit suicide (e.g., “I’ve thought about killing myself”) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
   *Have you actually had any thoughts of killing yourself?*
   
   If yes, describe:

3. Active Suicidal Ideation with Any Method (Not Plan) without Intent to Act
   Subject endorses thoughts of suicide and has thoughts of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, “I thought about taking an overdose or I would make a specific plan as to when, where, and how I would actually do it... and I would never go through with it.”
   *Have you been thinking about how you might do this?*
   
   If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
   Active suicidal thoughts of killing oneself and thoughts of one method without intent to act on such thoughts, as opposed to “I have the thoughts but I definitely will not do anything about them.”
   *Have you had these thoughts and had some intention of acting on them?*
   
   If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
   Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
   *Have you worked out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*
   
   If yes, describe:

**INTENSITY OF IDEATION**

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 the most severe).

<table>
<thead>
<tr>
<th>Type (1-5)</th>
<th>Description of Ideation</th>
</tr>
</thead>
</table>

**Most Severe Ideation:**

**Frequency**

- (1) Less than once a week
- (2) Once a week
- (3) 2-5 times a week
- (4) Daily or almost daily
- (5) Many times each day

**Duration**

- (1) Feeling, few seconds or minutes
- (2) Less than 1 hour some of the time
- (3) 1-4 hours most of the time
- (4) 4-8 hours most of the time
- (5) More than 8 hours or persistent

**Controllability**

- (1) Easily able to control thoughts
- (2) Can control thoughts with a lot of difficulty
- (3) Can control thoughts with little difficulty
- (4) Unable to control thoughts
- (5) Does not attempt to control thoughts

**Deterrents**

- (1) Deterrents definitely stopped you from attempting suicide
- (2) Deterrents probably stopped you
- (3) Unclear if deterrents stopped you
- (4) Deterrents most likely did not stop you
- (5) Deterrents definitely did not stop you

**Reasons for Ideation**

- (1) Completely to get attention, revenge or a reaction from others
- (2) Mostly to get attention, revenge or a reaction from others
- (3) Equally to get attention, revenge or a reaction from others and to end the pain

---

**PFIZER CONFIDENTIAL**

Page 86

288 of 564
Page 88
<table>
<thead>
<tr>
<th><strong>SUICIDAL BEHAVIOR</strong></th>
<th><strong>Since Last Visit</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Actual Attempt:</strong></td>
<td></td>
</tr>
<tr>
<td>A successful behavior act committed with at least some wish to die, or a result of one. Behavior was in part thought of as helpful to kill oneself. Intent does not have to be 100%. If there is any intent to die associated with the act, then it can be considered an actual suicide attempt. <strong>There does not have to be any injury or harm, just the potential for injury or harm.</strong> If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.</td>
<td></td>
</tr>
<tr>
<td><strong>Inferior Intent:</strong></td>
<td></td>
</tr>
<tr>
<td>Even if an individual desires to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from a window of a high floor/structure). Also, if someone desires to die, but they thought that what they did could be lethal, intent may be inferred.</td>
<td></td>
</tr>
<tr>
<td><strong>Have you made a suicide attempt?</strong></td>
<td>Yes No</td>
</tr>
<tr>
<td><strong>Have you done anything to harm yourself?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Have you done anything dangerous where you could have died?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>What did you do?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Did you...</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Did you want to die (even a little) when you...?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Were you trying to end your life when you...?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Or did you think it was possible you could have died from...?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Or did you do it purely for other reasons (without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen))? (Self-Injurious Behavior without suicidal intent)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>If yes, describe:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</strong></td>
<td>Yes No</td>
</tr>
<tr>
<td><strong>Interrupted Attempt:</strong></td>
<td></td>
</tr>
<tr>
<td>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if yes, list, what occurred)</td>
<td></td>
</tr>
<tr>
<td><strong>Overdose:</strong> Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.</td>
<td></td>
</tr>
<tr>
<td><strong>Shooting:</strong> Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is pointed to jump, is grabbed and taken down from ledge. Hanging: Person has nooses around neck, but has not yet started to hang, is stopped from doing so.</td>
<td></td>
</tr>
<tr>
<td><strong>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>If yes, describe:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Aborted Attempt:</strong></td>
<td></td>
</tr>
<tr>
<td>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually engage in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.</td>
<td></td>
</tr>
<tr>
<td><strong>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>If yes, describe:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Preparatory Acts or Behavior:</strong></td>
<td></td>
</tr>
<tr>
<td>Acts or preparation towards imminent making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying a rope, properly tying it, or wrapping it around one's neck, etc., buying a gun, writing a suicide note, etc.).</td>
<td></td>
</tr>
<tr>
<td><strong>Have you obtained any steps toward making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>If yes, describe:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Suicidal Behavior:</strong></td>
<td></td>
</tr>
<tr>
<td>Suicidal behavior was present during the assessment period?</td>
<td></td>
</tr>
<tr>
<td><strong>Completed Suicide:</strong></td>
<td>Yes No</td>
</tr>
<tr>
<td><strong>Answer for Actual Attempts Only</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Actual Lethality/Medical Damage:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Minor physical damage (e.g., lacerations, scalding, burns, etc.).</td>
<td></td>
</tr>
<tr>
<td>2. Moderate physical damage; medical attention needed; conscious but sleepy; somewhat responsive; second-degree burn; bleeding of major vessel.</td>
<td></td>
</tr>
<tr>
<td>3. Minimal severe physical damage; medical hospitalization and limited intensive care required (e.g., amputation with reflex intact; third-degree burn less than 30% of body; extensive blood loss but can recover; major fractures).</td>
<td></td>
</tr>
<tr>
<td>4. Severe physical damage; medical hospitalization with intensive care required (e.g., amputation without reflexes; third-degree burn over 30% of body; extensive blood loss with unstable vital signs; major damage to a vital organ).</td>
<td></td>
</tr>
<tr>
<td>5. Death</td>
<td></td>
</tr>
<tr>
<td><strong>Potential Lethality:</strong> Only Answer if Actual Lethality ≠ 0</td>
<td></td>
</tr>
<tr>
<td>Likely lethality of actual attempt if no medical damage (i.e., potential for very serious lethality; gun in mouth and pulled the trigger but gun fails to fire so no medical damage, lay on train tracks with coming train but pulled away before train ran over).</td>
<td></td>
</tr>
<tr>
<td><strong>Enter Code</strong></td>
<td></td>
</tr>
<tr>
<td><strong>If behavior is not likely to result in injury:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Behavior is not likely to result in injury but not likely to cause death</td>
<td></td>
</tr>
<tr>
<td>2. Behavior is likely to result in death despite available medical care</td>
<td></td>
</tr>
</tbody>
</table>
# Appendix 11. List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AHRQ</td>
<td>Agency Healthcare Research and Quality</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ARISg</td>
<td>Global Adverse Reaction Information System</td>
</tr>
<tr>
<td>AQ</td>
<td>Aggression Questionnaire</td>
</tr>
<tr>
<td>BID</td>
<td>twice daily</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CAR</td>
<td>continuous abstinence rate</td>
</tr>
<tr>
<td>C-CASA</td>
<td>Columbia Classification Algorithm of Suicide Assessment</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Columbia Suicide Severity Rating Scale</td>
</tr>
<tr>
<td>CO</td>
<td>carbon monoxide</td>
</tr>
<tr>
<td>CQR</td>
<td>continuous quit rate</td>
</tr>
<tr>
<td>CGI-I</td>
<td>Clinical Global Impression-Improvement</td>
</tr>
<tr>
<td>CGI-S</td>
<td>Clinical Global Impression- Severity</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
</tr>
<tr>
<td>DSMC</td>
<td>Data Safety Monitoring Committee</td>
</tr>
<tr>
<td>DSM-IV TR</td>
<td>Diagnostic and Statistic Manual of Mental Disorders 4th Edition Text Revision</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ET</td>
<td>early termination</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>intent to treat</td>
</tr>
<tr>
<td>MHP</td>
<td>mental health professional (psychiatrist or licensed PhD level clinical psychologist)</td>
</tr>
<tr>
<td>mm</td>
<td>millimeter</td>
</tr>
<tr>
<td>mmHg</td>
<td>millimeters of mercury</td>
</tr>
<tr>
<td>NAEI</td>
<td>Neuropsychiatric Adverse Event Interview</td>
</tr>
<tr>
<td>NUI</td>
<td>Nicotine Use Inventory</td>
</tr>
<tr>
<td>PDS</td>
<td>Pfizer Data Standards</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PR</td>
<td>pulse rate</td>
</tr>
<tr>
<td>QD</td>
<td>once daily</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SBQ-R</td>
<td>Suicide Behaviors Questionnaire-Revised</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM Disorders</td>
</tr>
<tr>
<td>TQD</td>
<td>target quit day</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
</tbody>
</table>
Appendix 12. CV Required Documents

Deaths and cardiovascular events of interest will be reviewed and adjudicated by an independent events committee. The committee will review all pertinent information for each reported case.

Clinical sites will forward all the available records with the appropriate routing form for adjudication.

Any Hospitalization for loss of consciousness, cardiac or vascular procedures, respiratory diseases (excluding infections and cancer) and generalized edema:

- Admission notes;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Laboratory imaging and ancillary examinations.

Hospitalization for Chest Pain or Angina Pectoris/Unstable angina:

- Admission notes;
- Discharge summary;
- ECG tracing(s) (include eRT ECG);
- Stress test or Thallium scan;
- Angiography report;
- Summary of Event in English (signed by an MD);
- Other (for example, MUGA scan, Holter);
- Cardiac enzymes:
  - CK;
  - CK-MB;
  - LDH;
  - Troponin I;
  - Troponin T;
Hospitalization for Congestive Heart Failure:

- Admission notes;
- Physician notes/progress reports supporting typical CHF symptoms and signs or other diagnostic test results;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Chest x-ray;
- ECG tracings;
- Ejections fraction by echocardiogram, MUGA scans, etc.;
- Brain natriuretic peptide (BNP) and NT-proBNP results should be submitted, if available;
- Other.

Coronary Revascularization Procedure (CABG, PTCA, Atherectomy, Transplant, Other)

- Admission notes;
- Physician notes/progress reports;
- Operative report;
- Catheterization report;
- PTCA operative reports;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Other.

Non-fatal Myocardial Infarction or Resuscitated Cardiac Arrest

- Discharge Summary;
- Clinical Notes;
- Summary of Event in English (signed by an MD);
• Cardiac imaging data (if available);

• ECG tracing(s) (include eRT ECG);

• Cardiac enzymes:
  • CK;
  • CK-MB;
  • LDH Troponin I;
  • Troponin I;
  • Other.

**Non-fatal Stroke, TIA**

• Admission and/or physician progress notes, including neurological exam;

• Discharge summary;

• Summary of Event in English (signed by MD);

• Operative Report;

• CT;

• MRI;

• Angiography Report;

• Spinal Fluid Analysis;

• Other.

**First Diagnosis of PVD or Procedure for PVD**

• Physician Notes;

• Summary of Event in English (signed by an MD);

• Diagnostic Tests (angiograms, Dopplers, etc.);

• PVD procedure;

• Percutaneous Revascularization (ie, atherectomy, PTA);
- Amputation;
- Other.

**Serious Cardiac Arrhythmias**

- Physician Notes;
- Summary of Event in English (signed by an MD);
- Diagnostic Tests;
- Admission notes if applicable;
- Discharge summary;
- ECG tracing(s) (include eRT ECG);
- Other (for example, Holter).

**Deaths**

- Physician Notes;
- Summary of Event in English (signed by an MD);
- Admission and/or physician progress notes;
- Diagnostic tests if applicable;
- Discharge summary if applicable;
- Autopsy Report (if performed);
- Other.
Appendix 13. CLINICAL PROTOCOL AMENDMENT 1

Current Amendment: 1

<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Date</th>
<th>Country (ies)</th>
<th>Site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 June 2010</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Previous Amendments:

<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Date</th>
<th>Country (ies)</th>
<th>Site(s)</th>
</tr>
</thead>
</table>

SUMMARY

Reason(s) for Amendment

The protocol is being amended to incorporate changes requested by the US FDA (Agency), to clarify certain protocol aspects and to correct inconsistencies/typographical errors. The changes requested by FDA were to use a different guidance for suicide risk, clarifying that primary focus of suicide risk assessment is the presence or absence of current significant suicidality. The Agency asked that the following wording was added to the protocol: training and background requirements for administering the SCID; narratives for all moderate events included in the composite primary endpoint; instructions to record all AEs irrespective of the mechanism for ascertainment in the AE CRF; description of AE collection using the NAEI, including guidelines to the investigator in the appendix; instructions in the appendices and text to instruct investigators that CGI-S and CGI-I ratings are in reference to psychiatric diagnoses; revision to the additional inclusion criteria for the neuropsychiatric cohort to specify that both a current condition and a lifetime diagnosis are eligible for inclusion; reference to the pilot study to test the NAEI; and correction on schedule of activities to include C-SSRS assessment at Week 10. Minor corrections for inconsistencies were performed as detailed below.

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

The “change from” section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, text) is used to show the deletion of information from the current text.

The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.

Section <Insert section number>, <Insert section title>, Page <Insert page number as appropriate>

Change From

Change To
1. Section, SCHEDULE OF ACTIVITIES - Study Treatment period and Post Treatment Period

Change From

SCHEDULE OF ACTIVITIES- Study Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screen</th>
<th>BL (Day 8)</th>
<th>Wk 2</th>
<th>Wk 3</th>
<th>Wk 4</th>
<th>Wk 5</th>
<th>Wk 6</th>
<th>Wk 7*</th>
<th>Wk 8</th>
<th>Wk 9*</th>
<th>Wk 10</th>
<th>Wk 11*</th>
<th>Wk 12</th>
<th>ET*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent b</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History, Demography, Smoking history/ height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs (HR, BP)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCID I and II</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Volunteered reporting (NAEI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression Questionnaire</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview (NAEI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBQ-R</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagerström Test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled CO</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense Study Drugs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, Blood Chemistry</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test c (urine or serum)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Drug Screen d (dipstick at site)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Contact Information Card</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### SCHEDULE OF ACTIVITIES - Post - Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Wk 13</th>
<th>Wk 14*</th>
<th>Wk 15*</th>
<th>Wk 16</th>
<th>Wk 17*</th>
<th>Wk 18*</th>
<th>Wk 19*</th>
<th>Wk 20</th>
<th>Wk 21*</th>
<th>Wk 22*</th>
<th>Wk 23*</th>
<th>Wk 24</th>
<th>ET*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volunteered reporting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interview</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled CO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Change To

### SCHEDULE OF ACTIVITIES - Study Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screen</th>
<th>BL (Day 8)</th>
<th>Wk 1</th>
<th>Wk 2</th>
<th>Wk 3</th>
<th>Wk 4</th>
<th>Wk 5</th>
<th>Wk 6</th>
<th>Wk 7*</th>
<th>Wk 8</th>
<th>Wk 9*</th>
<th>Wk 10</th>
<th>Wk 11*</th>
<th>Wk 12</th>
<th>ET*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent^b</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History, Demography, Smoking history/ height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs (HR, BP)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCID I and II</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volunteered reporting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression Questionnaire</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interview (NAEI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBQ-R</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaledström Test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense Study Drugs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>Screen</td>
<td>BL (Day 8)</td>
<td>Wk 1</td>
<td>Wk 2</td>
<td>Wk 3</td>
<td>Wk 4</td>
<td>Wk 5</td>
<td>Wk 6</td>
<td>Wk 7*</td>
<td>Wk 8</td>
<td>Wk 9*</td>
<td>Wk 10</td>
<td>Wk 11*</td>
<td>Wk 12</td>
<td>ET a</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------</td>
<td>------------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
<td>------</td>
<td>-------</td>
<td>-------</td>
<td>--------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>EKG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, Blood Chemistry</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test c</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Drug Screen d</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Contact Information Card</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**SCHEDULE OF ACTIVITIES- Post - Treatment Period**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Wk 13</th>
<th>Wk 14*</th>
<th>Wk 15*</th>
<th>Wk 16</th>
<th>Wk 17*</th>
<th>Wk 18*</th>
<th>Wk 19*</th>
<th>Wk 20</th>
<th>Wk 21*</th>
<th>Wk 22*</th>
<th>Wk 23*</th>
<th>Wk 24</th>
<th>ET a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Volunteered reporting</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled CO</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Section 4. SUBJECT SELECTION, 4.1. Inclusion Criteria, 5th bullet**

**Change From**

- A double barrier method of contraception, eg, condom and/or diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study medication or abstinence.

**Change To**

- A double barrier method of contraception, eg, condom and diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study medication or abstinence.
3. Section 4. SUBJECT SELECTION, 4.1.1. Additional Inclusion Criteria for Neuropsychiatric Cohort, 2nd paragraph and 2 footnotes

Change From

All subjects will be screened for Axis I and II diagnosis (current and/or past) using DSM IV TR criteria based on clinical assessment and confirmed by SCID (administered by a clinician or trained mental health professional, ie; a PhD level clinical psychologist, or an individual with master level training in related areas [masters level psychologist, social work] who have been trained to use the SCID). Subjects will be included in the psychiatric cohort, if they are considered clinically stable by the Investigator and currently meet criteria, either current or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and have met diagnostic criteria before the initiation of study treatment. If the Investigator is not a psychiatrist or licensed PhD level clinical psychologist, he/she should consult with a mental health professional (MHP) to determine if the subject is stable.

1Clinician is defined as someone licensed to practice medicine according to existing regulations
2Documentation of training will be kept at the clinical site.

Change To

All subjects will be screened for Axis I and II diagnosis (current and/or past) using DSM IV TR criteria based on clinical assessment and confirmed by SCID (administered by a clinician or trained mental health professional, ie; a PhD level clinical psychologist, or an individual with master level training in related areas [masters level psychologist, social work] who have been trained to use the SCID). Subjects will be included in the psychiatric cohort, if they are considered clinically stable by the Investigator and meet criteria, either current or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and have met diagnostic criteria before the initiation of study treatment. If the Investigator is not a psychiatrist or licensed PhD level clinical psychologist, he/she should consult with a mental health professional (MHP) to determine if the subject is stable.

1Clinician is defined as someone licensed to practice medicine according to existing regulations
2Documentation of training will be kept at the clinical site.

4. Section 4. SUBJECT SELECTION, 4.2 Exclusion Criteria, 3rd paragraph, number 3, 4th - 7th bullets

Change From

If the subjects described above (exclusionary co-morbid psychiatric condition) do not meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, they are not eligible for the study. Subjects who meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, and who have a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) may be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent
condition is stable and does not prevent the subject from safely complying with study procedures. In such cases, please consult with the medical monitor.

3. Subjects who are believed to have a suicidal risk at screening, baseline, or after assessment by a qualified mental health professional (Psychiatrist or licensed PhD level clinical psychologist) if a risk assessment interview was required after screening or baseline using the Suicidal Behaviors Questionnaire Revised (SBQ-R) Appendix 3 and Columbia Suicide Severity Rating Scale (C-SSRS). Appendix 9:

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on items 4, 5 or any suicidal behavioral questions of the C-SSRS. Appendix 9.
- Previous history of suicide behaviors in the past 10 years.
- Any lifetime history of serious or recurrent suicidal behavior,
- SBQ-R total score $\geq 8$.

Change To

If the subjects described above (exclusionary co-morbid psychiatric condition) do not meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, they are not eligible for the study. Subjects who meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, and who have a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) may be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent condition is stable and does not prevent the subject from safely complying with study procedures. In such cases, please consult with the medical monitor.

3. Subjects who are believed to have a suicidal risk at screening, baseline, or after assessment by a qualified mental health professional (Psychiatrist or licensed PhD level clinical psychologist) if a risk assessment interview was required after screening or baseline using the Columbia Suicide Severity Rating Scale (C-SSRS). Appendix 9:

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS. Appendix 9.
- Previous history of suicide behaviors in the past year,

5. Section 6. STUDY PROCEDURES, 6.1. Screening, 4th and 19th bullets

Change From

- Measure and record height and weight;
- Psychiatric evaluation if warranted (See Section 7.1.10 7.1.7).
Change To

- Measure and record height;

- Psychiatric evaluation if warranted (See Section 7.1.10).

6. **Section 6. STUDY PROCEDURES, 6.2.1. Baseline Visit (Randomization), 1st and 18th bullets**

Change From

- Record sitting blood pressure, pulse rate and weight;

- Psychiatric evaluation if warranted (See Section 7.1.10 7.1.7).

Change To

- Record sitting blood pressure, pulse rate and weight;

- Psychiatric evaluation if warranted (See Section 7.1.10).

7. **Section 6. STUDY PROCEDURES, 6.3.1. Clinic Visits (Weeks 13, 16, 20, 24 and ET24 Visit), 1st bullet**

Addition

Record Body Weight (Week 24 and ET24 only);

8. **Section 7. ASSESSMENTS, 7.1.1. Adverse Events, 1st, 2nd and 4th paragraphs**

Change From

All adverse events (AEs) volunteered, spontaneously observed, or solicited (of all severities) or reported will be recorded in the AE CRF up to and including Week 24.

In addition, actively solicited neuropsychiatric adverse events will be collected by use of the Neuropsychiatric Adverse Event Interview (NAEI) at each clinic visit (starting from baseline) up to and including Week 24. The voluntarily reported AEs will be assessed first at each study visit followed by the NAEI and then the C-SSRS.

Suicide related adverse events will be solicited by completion of the C-SSRS at each clinic visit up to and including Week 24. Any severe neuropsychiatric adverse event(s) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) recorded will require the subject to be referred for a psychiatric evaluation by a qualified mental health professional MHP (Psychiatrist or licensed PhD level clinical psychologist) (Section 7.1.10 7.1.9) and a narrative will be
constructed for each severe event. In the event the investigator meets the requirements of the MHP, he/she may complete this evaluation.

**Change To**

All adverse events (AEs) volunteered, observed, or solicited (of all severities) will be recorded in the AE CRF up to and including Week 24.

Solicited neuropsychiatric adverse events will be collected by use of the Neuropsychiatric Adverse Event Interview (NAEI) at each clinic visit (starting from baseline) up to and including Week 24. The voluntarily reported AEs will be assessed first at each study visit followed by the NAEI and then the C-SSRS.

Suicide related adverse events will be solicited by completion of the C-SSRS at each clinic visit up to and including Week 24. Any severe neuropsychiatric adverse event(s) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) recorded will require the subject to be referred for a psychiatric evaluation by a qualified mental health professional MHP (Psychiatrist or licensed PhD level clinical psychologist) (Section 7.1.10) and a narrative will be constructed for each event. In the event the investigator meets the requirements of the MHP, he/she may complete this evaluation.

9. **Section 7. ASSESSMENTS, 7.1.1.1. Primary Neuropsychiatric Safety Endpoint, 5th and 7th paragraphs**

**Change From**

Items captured from proxy report (ie, PCP, family member) judged to be adverse events by the Investigator;

The primary safety endpoint encompasses events reported (via the AE CRF page) through any of the above three means of assessments. Additionally, the MedDRA version and Preferred Terms to be included in the primary safety endpoint will be described in the Statistical Analysis Plan.

**Change To**

Items captured from proxy report (ie, PCP, family member) judged to be adverse events by the Investigator;

The primary safety endpoint encompasses events reported (via the AE CRF page) through any of the above means of assessments. Additionally, the MedDRA version and Preferred Terms to be included in the primary safety endpoint will be described in the Statistical Analysis Plan.
10. Section 7. ASSESSMENTS, 7.1.1.2. Actively Solicited Neuropsychiatric Adverse Events

Change From

The Neuropsychiatric Adverse Event Interview (NAEI) Appendix 6, will actively inquire about the following type of adverse events: aggression, anxiety, agitation, depression, delusions, dissociative states, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, paranoia, panic, and psychosis. If a subject has a positive response to any item on the NAEI, a determination will be made by the investigator as to whether this meets criteria for an adverse event. If it does meet criteria as an adverse event it will be recorded on the adverse event pages of the Case Report Form.

Change To

The Neuropsychiatric Adverse Event Interview (NAEI) Appendix 6, will actively inquire about the following type of adverse events: aggression, anxiety, agitation, depression, delusions, dissociative states, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, paranoia, panic, and psychosis. If a subject has a positive response to any item on the NAEI, a determination will be made by the investigator as to whether this meets criteria for an adverse event. If it does meet criteria as an adverse event it will be recorded on the adverse event pages of the Case Report Form. A pilot study is being conducted to test the NAEI in a similar population to the one to be included in this study (patients with and without a history of psychiatric disease enrolled in a smoking cessation program).

11. Section 7. ASSESSMENTS, 7.1.2. Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 9, Appendix 10 and the Suicidal Behaviors Questionnaire (SBQ-R) Appendix 3, 1st- 3rd bullets

Change From

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on items 4, 5 or any suicidal behavioral questions of the C-SSRS; Appendix 9;
- Previous history of suicide behaviors in the past 10 years;
- Any lifetime history of serious or recurrent suicidal behavior;
- SBQ-R total score ≥8;

Change To

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS; Appendix 9;
● Previous history of suicide behaviors in the past year;


Change From

The CGI-S is a clinician rated instrument measuring the severity of a subject’s psychiatric condition on a 7 point scale at time of assessment, relative to clinician's past experience in patients with same diagnosis. The scores are: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; or 7=extremely ill. The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). This scale should be administered by the same rater throughout the study whenever possible.

Change To

The CGI-S is a clinician rated instrument measuring the severity of a subject’s psychiatric condition on a 7 point scale at time of assessment, relative to clinician's past experience in patients with same diagnosis. The scores are: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; or 7=extremely ill. The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). This scale should be administered by the same rater throughout the study whenever possible.

13. Section 7. ASSESSMENTS, 7.1.5. Clinical Global Impression of Improvement (CGI-I) Appendix 8

Change From

The CGI-I is a clinician rated instrument that measures change in subject’s psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale ranging from 1 (very much improved) to 7 (very much worse). The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). This scale should be administered by the same rater throughout the study whenever possible.

Change To

The CGI-I is a clinician rated instrument that measures change in subject’s psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale
ranging from 1 (very much improved) to 7 (very much worse). The ratings will be applicable even to those without psychiatric diagnoses (e.g., those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). This scale should be administered by the same rater throughout the study whenever possible.


Change From

- Subject answers “yes” on items 4, 5 or on any suicidal behavioral question on C-SSRS during the screening visit or subject answers “yes” on item 4, 5 or on any suicidal behavioral question on C-SSRS during the study;
- Previous history of suicide behaviors in the past 10 years (prior to randomization);
- Any lifetime history of serious or recurrent suicidal behavior (prior to randomization);
- SBQ-R total score ≥ 8 at screening.

Change To

- Subject answers “yes” on item 5, on C-SSRS during the screening visit or subject answers “yes” on item 4, 5 or on any suicidal behavioral question on C-SSRS during the study;
- Previous history of suicide behaviors in the past year (prior to randomization);

15. Section 7. ASSESSMENTS, 7.1.12. Physical Examination, Vital Signs and Electrocardiogram, 3rd paragraph

Change From

Sitting blood pressure and pulse rate will be measured at the screening and baseline visits and Wk 12 or ET12. Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest mmHg. All blood pressure measurements are to be taken in the dominant arm with the appropriate size cuff. Pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

Change To

Sitting blood pressure and pulse rate will be measured at the screening and baseline visits and Wk 12 or ET12. Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest mmHg.
mmHg. All blood pressure measurements are to be taken in the dominant arm with the appropriate size cuff. Pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

16. Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.3. Safety Objectives Analysis, 7th paragraph and last 2 bullets

Addition

The safety summaries will also be expanded to specifically include:

- A summary of neuropsychiatric adverse events of interest leading to treatment and/or study discontinuations.

- A summary of neuropsychiatric adverse events of interest resulting in an intervention.

17. Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.5. Methods and Analysis, last paragraph

Addition

The investigator will record the primary major diagnosis group (the sub-stratification of the psychiatric disorder cohort) in the CRF. Secondary analyses involving this primary major diagnosis group will utilize this classification and be completed. Further analysis details will be presented in the SAP.

18. Section, APPENDICES, Appendix 5. Aggression Questionnaire (AQ), title

Change From

Appendix 5. Aggression Questionnaire (AQ)

Change To

Appendix 5. Aggression Questionnaire (AQ)

19. Section, APPENDICES, Appendix 6. Neuropsychiatric Adverse Events Interview (NAEI), after 1st page

Addition

General Overview & Background on the NAEI

The NAEI has been designed as a semi-structured interview to systematically assess the presence and severity of specific neuropsychiatric symptoms as part of the adverse event data collection process. The NAEI is used at Baseline to detect symptoms that are present at the time of the subject’s entry into this clinical trial and at follow-up visits to
prospectively monitor emergent symptoms. The goal is to facilitate the collection of information relevant to specific neuropsychiatric events of interest in a standardized manner. Standardizing the way in which such information is collected in a clinical trial optimizes reliability and validity across sites and clinicians.

The NAEI is intended to guide the interviewer in determining whether a symptom is present, and then, if it is, clinical significance. In assessing whether a symptom's “clinical significant”, it is important to examine the

(1) frequency and duration of the symptom.

(2) severity of the symptom

If the patient responds affirmatively to questions about a specific NAEI symptom, the symptom then must be evaluated by the investigator for clinical presentation and severity and recorded as an adverse event (AE) or serious adverse event (SAE) if warranted. AEs are graded according to their intensity (mild, moderate, or severe) by examining the degree of functional impairment associated with them as per instructions in the protocol. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. Refer to Protocol Section 8 for more information on both AE and SAE reporting.

The determination whether a symptom is an adverse event and therefore warrants an AE report should always be based on the steps outlined in the figure below:

These administration instructions are intended to help interviewers use the NAEI correctly. Sites are responsible for following these guidelines throughout the course of the study. Sites should keep a copy of these guidelines handy to refer to as needed.

A worksheet for the NAEI interview has been developed and made available to sites to facilitate its use. The worksheet is used for both the baseline and follow-up visits. The interviewer should take notes on the worksheet to assist with AE reporting if needed and to refer to during future visits.

INTERVIEWER QUALIFICATIONS

The NAEI interview should be conducted by a staff person at the site who has completed training on the NAEI. Only interviewers who have completed the formal training on the NAEI to Pfizer’s standards can administer it for this trial.
If a site needs additional training for a new interviewer, they must contact Pfizer to make arrangements for the necessary training. No interviewer should administer the NAEI without the appropriate training. Refresher training will be required during the study.

Note that where possible, sites are strongly encouraged to have the same individual conduct the volunteered AE collection, the NAEI interview, the C-SSRS, and any other clinical ratings scales included in the protocol.

Sites should make every effort to keep the same interviewer for each subject over the course of the trial.

**Time Period to be Rated**

At Baseline, symptoms should be assessed for the past two (2) weeks. At follow-up visits, the time period to be rated is since the last clinic visit.

The interviewer should be careful when asking questions to make sure the subject is clear on the time period being rated. It may be helpful to frame questions by frequently reminding the subject of the time frame “In past 2 weeks” (at baseline) or “Since your last visit” (at follow-up) and by probing to make sure the symptoms described did occur during the time period in question (e.g., at baseline asking, “Was that during the past 2 weeks?”).

**Materials Needed to Complete the NAEI**

The NAEI guidelines should always be available for reference.

In addition, at all visits after the baseline visit, the interviewer should have at hand
- the subject’s AE log worksheet
- previously completed NAEI worksheets

**Order of Assessment**

The assessment sequence for this trial must be followed carefully. Assessments should be done in the following order:

6. Volunteered AE report – opening question on how the subject has been feeling in general

7. Follow up on previously reported AEs that are still ongoing

8. Clinical rating scales as specified in the protocol

9. NAEI
10. Columbia Suicide Severity Rating Scale

Volunteered AE report: The collection of volunteered AE reports should follow the site’s usual procedures. Generally this is done by asking the subject how s/he has been feeling in general. During the collection of volunteered AE information, the interviewer should be careful to ask sufficient follow-up questions to determine the clinical significance of the reported event and therefore whether an AE report is warranted.

Follow-up of any previously reported AEs: At all visits after the baseline visit, the interviewer then follows up on any previously reported AEs that, according to the AE log worksheet, are still ongoing (i.e., do not have a stop date) to see if resolved. AEs on the AE log worksheet may have been volunteered or solicited at previous visits.

NAEI: The NAEI is designed to guide the interviewer through a series of questions probing for neuropsychiatric symptoms using a semi-structured interview approach (see detailed administration instructions below). In most cases, the interviewer will need to ask all of the NAEI questions. However, some symptoms that are addressed by the NAEI questions may already have been volunteered during the volunteered AE discussion. In such situations, if the interviewer has already gained enough information to fully assess the question, it is not necessary to repeat the respective question(s) during NAEI administration.

BASELINE NAEI

TO BEGIN THE INTERVIEW: The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had during the past two (2) weeks.

The NAEI questions have been grouped into symptom clusters and all questions in each group should be asked before making a determination about a potential adverse event.

The interviewer will have to add their own follow-up questions to the written NAEI questions to obtain necessary information. Follow-up questions should be used as needed for clarification on symptoms and to assess the frequency/duration, severity, and degree of functional impairment related to the symptom. Sample follow-up questions are provided in this document. The interviewer should probe as needed to assess the subject’s experiences and to make an appropriate assessment. The interviewer should be careful to clarify the time period (past 2 weeks) the questions refer to.

As noted before, once a symptom has been identified as present, its clinical significance must be ascertained.

NAEI Item Example:

During the past 2 weeks:
1. Have you been feeling sad, unhappy, worthless, or depressed?

IF YES, SAMPLE FOLLOW-UP QUESTIONS:

- How often have you been bothered by this in the past 2 weeks?

  Was it a little bit of the time, some of the time or most of the time?

  Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people in the past 2 weeks?

  IF YES: How hard? Can you give me an example?

FOLLOW-UP VISITS NAEI

The purpose of this assessment is to identify symptoms that have been present since the subject’s last visit and if this represents a change from their last visit. Follow-up questions are provided to help make these ratings.

To begin the follow-up interview: The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had since their last visit.

The same interview flow should be followed as at the baseline visit. In addition, for any symptom that is reported, follow up questions should assess whether this is a change from the last visit.

Follow-up NAEI Item Example:

Since your last clinic visit:

1. Have you been feeling sad, unhappy, worthless, or depressed?

Sample Follow-up Questions:

  How often have you been bothered by this since your last clinic visit?

  Was it a little bit of the time, some of the time or most of the time?

  Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people since your last clinic visit?

  IF YES: How hard? Can you give me an example?

  Has this been a change from the last time you were here?

  IF YES: How much of a change?

AFTER COMPLETING THE NAEI AT BASELINE AND FOLLOW-UP VISITS
The interviewer should review the responses to the questions on the NAEI and notes taken during the interview, to determine whether, in his/her clinical judgment, any neuropsychiatric event reported warrants classification as an AE. Both the subject’s answers to the questions and observations made during the interview should serve as the basis for making this determination.

For each solicited adverse event, the interviewer must determine the maximum level of intensity of the symptom as either:

<table>
<thead>
<tr>
<th>MILD</th>
<th>Does not interfere with subject's usual functioning.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODERATE</td>
<td>Interferes to some extent with subject's usual functioning.</td>
</tr>
<tr>
<td>SEVERE</td>
<td>Interferes significantly with subject's usual functioning.</td>
</tr>
</tbody>
</table>

AEs should be added to the subject’s AE log worksheet. This, together with the completed NAEI worksheet should be filed with the subject’s other documents so that they are available for future visits. The site staff should follow Pfizer’s instructions to complete the AE Case Report Form page.

20. Section, APPENDICES, Appendix 7. Global Clinical Impression of Severity (CGI-S), last paragraph

Addition

Note: The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits).
21. Section, APPENDICES, Appendix 8. Global Clinical Impression of Improvement (CGI-I), table and last paragraph

Change From

<table>
<thead>
<tr>
<th>(Check (X) ONE only):</th>
<th>VERY MUCH IMPROVED</th>
<th>NO CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT ASSESSED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MINIMALLY IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH WORSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MINIMALLY IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VERY MUCH WORSE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(Check (X) ONE only):</th>
<th>NORMAL, NOT AT ALL ILL</th>
<th>MODERATELY ILL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT ASSESSED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BORDERLINE, MENTALLY ILL</td>
<td></td>
<td>MARKEDLY ILL</td>
</tr>
<tr>
<td>MILDLY ILL</td>
<td></td>
<td>SEVERELY ILL</td>
</tr>
<tr>
<td>AMONG THE MOST EXTREMELY ILL PATIENTS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits.

Change To

<table>
<thead>
<tr>
<th>(Check (X) ONE only):</th>
<th>VERY MUCH IMPROVED</th>
<th>NO CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT ASSESSED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MINIMALLY IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH WORSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MINIMALLY IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VERY MUCH WORSE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Note: The ratings will be applicable even to those without psychiatric diagnoses (e.g., those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits.

22. Section, APPENDICES, Appendix 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS), (Baseline), 1st page after Disclaimer

Deletion

(Choose (X) ONE only):

<table>
<thead>
<tr>
<th>NOT ASSESSED</th>
<th>VERY MUCH IMPROVED</th>
<th>NO CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MUCH IMPROVED</td>
<td>MINIMALLY WORSE</td>
</tr>
<tr>
<td></td>
<td>MINIMALLY IMPROVED</td>
<td>MUCH WORSE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VERY MUCH WORSE</td>
</tr>
</tbody>
</table>

23. Section, APPENDICES, Appendix 10. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) (Since Last Visit)

Change From


Disclaimer: This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of Suicidality depends on clinical judgement.

**SUICIDAL IDEATION**
Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes,” ask questions 3, 4 and 5.

1. Wish To Be Dead
   Have you wished you were dead or wished you could go to sleep and not wake up?  
   Frequency of ideation _____  
   If yes, describe  
   Yes/No

2. Non-Specific Active Suicidal Thoughts
   Have you actually had any thoughts of killing yourself?  Frequency of ideation _____  
   If yes, describe  
   Yes/No

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
   Have you been thinking about how you might do this?  Frequency of ideation _____  
   If yes, describe  
   Yes/No
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Have you had these thoughts and had some intention of acting on them? Frequency of ideation ______ Yes/No
If yes, describe.
5. Active Suicidal Ideation with Specific Plan and Intent
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan? Frequency of ideation ______ Yes/No
If yes, describe.

INTENSITY OF IDEATION
The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he/she was feeling the most suicidal. Only rate most common if most severe and most common are different.

<table>
<thead>
<tr>
<th>Ideation Type</th>
<th>Type # (1-5)</th>
<th>Most Common</th>
<th>Most Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Common Ideation:</td>
<td></td>
<td>Most Common</td>
<td>Most Severe</td>
</tr>
<tr>
<td>Most Severe Ideation:</td>
<td></td>
<td>Most Common</td>
<td>Most Severe</td>
</tr>
</tbody>
</table>

Frequency
How many times have you had these thoughts?
1. Less than once a week
2. Once a week
3. 2-5 times in week
4. Daily or almost daily
5. Many times each day

Duration
When you have the thoughts how long do they last?
1. Fleeting – few seconds or minutes
2. Less than 1 hour/some of the time
3. 1-4 hours/a lot of time
4. 4-8 hours/most of day
5. More than 8 hours/persistent or continuous

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
1. Easily able to control thoughts
2. Can control thoughts with little difficulty
3. Can control thoughts with some difficulty
4. Can control thoughts with a lot of difficulty
5. Unable to control thoughts
0. Does not attempt to control thoughts

Deterrents
Are there things – anyone or anything (eg family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?
1. Deterrents definitely stopped you from attempting suicide
2. Deterrents probably stopped you
3. Uncertain that deterrents stopped you
4. Deterrents most likely did not stop you
0. Does not apply; wish to die only
Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end pain or stop the way you were feeling (in other words you couldn’t go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
1. Completely to get attention, revenge or a reaction from others
2. Mostly to get attention, revenge or a reaction from others
3. Equally to get attention, revenge or a reaction from others and to end/stop the pain
4. Mostly to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
5. Completely to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).

SUICIDAL BEHAVIOR
(Check all that apply, so long as these are separate events; must ask about all types)

Actual Attempt:
Have you made a suicide attempt? Yes/No
Have you done anything to harm yourself?
Have you done anything dangerous where you could have died?
   What did you do? Total # of attempts
   Did you _____ as a way to end your life?
   Did you want to die (even a little) when you _____?
   Were you trying to end your life when you _____?
   Or did you think it was possible you could have died from _____?
Or did you do it purely for other reasons / without any intention of killing yourself (like to relieve stress, feel better, get sympathy, or to get something else to happen)? (Self-injurious behavior without suicidal intent)
If yes, describe.

Has the subject engaged in Non-Suicidal Self-Injurious Behavior?
Yes/No

Interrupted Attempt:
Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?
If yes, describe.
Total # of interrupted

Aborted Attempt:
Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?
If yes, describe.
Total # of aborted

Preparatory Acts or Behavior:
Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?
If yes, describe.
Suicidal Behavior:
Suicidal behavior was present during the assessment period?
If yes, describe.
Completed Suicide:
Yes/No
<table>
<thead>
<tr>
<th>ANSWER FOR ACTUAL ATTEMPTS ONLY</th>
<th>Most Recent Attempt Date:</th>
<th>Worst/Most Lethal Attempt Date:</th>
<th>Since Last Visit/Initial/First Attempt Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Lethality/Medical Damage:</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
</tr>
<tr>
<td>0. No physical damage or very minor physical damage (eg, surface scratches).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second degree burns; bleeding of major vessel).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Moderately severe physical damage; medical hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Severe physical damage; medical hospitalization with intensive care required (eg, comatose without reflexes; third degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Death</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
</tr>
<tr>
<td>Potential Lethality: Only Answer if Actual Lethality = 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 = Behavior not likely to result in injury</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
</tr>
<tr>
<td>1 = Behavior likely to result in injury but not likely to cause death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Behavior likely to result in death despite available medical care</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. (Oquendo M. A.; Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M. B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 – 130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu.

**Change To**


Disclaimer: This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of Suicidality depends on clinical judgement.
### SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes,” ask questions 3, 4 and 5.

<table>
<thead>
<tr>
<th>Question</th>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Wish To Be Dead</strong></td>
<td></td>
</tr>
<tr>
<td>Have you wished you were dead or wished you could go to sleep and not wake up?</td>
<td></td>
</tr>
<tr>
<td>Frequency of ideation</td>
<td>Yes/No</td>
</tr>
<tr>
<td>If yes, describe</td>
<td></td>
</tr>
<tr>
<td>2. <strong>Non-Specific Active Suicidal Thoughts</strong></td>
<td></td>
</tr>
<tr>
<td>Have you actually had any thoughts of killing yourself?</td>
<td></td>
</tr>
<tr>
<td>Frequency of ideation</td>
<td>Yes/No</td>
</tr>
<tr>
<td>If yes, describe</td>
<td></td>
</tr>
<tr>
<td>3. <strong>Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</strong></td>
<td></td>
</tr>
<tr>
<td>Have you been thinking about how you might do this?</td>
<td></td>
</tr>
<tr>
<td>Frequency of ideation</td>
<td>Yes/No</td>
</tr>
<tr>
<td>If yes, describe</td>
<td></td>
</tr>
<tr>
<td>4. <strong>Active Suicidal Ideation with Some Intent to Act, without Specific Plan</strong></td>
<td></td>
</tr>
<tr>
<td>Have you had these thoughts and had some intention of acting on them?</td>
<td></td>
</tr>
<tr>
<td>Frequency of ideation</td>
<td>Yes/No</td>
</tr>
<tr>
<td>If yes, describe</td>
<td></td>
</tr>
<tr>
<td>5. <strong>Active Suicidal Ideation with Specific Plan and Intent</strong></td>
<td></td>
</tr>
<tr>
<td>Have you started to work out or worked out the details of how to kill yourself?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Do you intend to carry out this plan?</td>
<td></td>
</tr>
<tr>
<td>If yes, describe</td>
<td></td>
</tr>
</tbody>
</table>

### INTENSITY OF IDEATION

The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he/she was feeling the most suicidal. Only rate most common if most severe and most common are different.

<table>
<thead>
<tr>
<th>Ideation Type</th>
<th>Type # (1-5)</th>
<th>Description of Ideation</th>
<th>Most Common</th>
<th>Most Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Common Ideation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Severe Ideation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How many times have you had these thoughts?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Less than once a week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Once a week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. 2-5 times in week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Daily or almost daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Many times each day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When you have the thoughts how long do they last?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Fleeting – few seconds or minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Less than 1 hour/some of the time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. 1-4 hours/a lot of time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. 4-8 hours/most of day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. More than 8 hours/persistent or continuous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Controllability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could/can you stop thinking about killing yourself or wanting to die if you want to?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Easily able to control thoughts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Can control thoughts with little difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Can control thoughts with some difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Can control thoughts with a lot of difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. Unable to control thoughts  
0. Does not attempt to control thoughts

**Deterrents**
Are there things – anyone or anything (eg family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?  
1. Deterrents definitely stopped you from attempting suicide  
2. Deterrents probably stopped you  
3. Uncertain that deterrents stopped you  
4. Deterrents most likely did not stop you  
0. Does not apply, wish to die only

**Reasons for Ideation**
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end pain or stop the way you were feeling (in other words you couldn’t go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?  
1. Completely to get attention, revenge or a reaction from others  
2. Mostly to get attention, revenge or a reaction from others  
3. Equally to get attention, revenge or a reaction from others and to end/stop the pain  
4. Mostly to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).  
5. Completely to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).

---

**SUICIDAL BEHAVIOR**
(Check all that apply, so long as these are separate events; must ask about all types)  

<table>
<thead>
<tr>
<th>Actual Attempt:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you made a suicide attempt? Yes/No</td>
</tr>
<tr>
<td>Have you done anything to harm yourself?</td>
</tr>
<tr>
<td>Have you done anything dangerous where you could have died?</td>
</tr>
<tr>
<td>What did you do?</td>
</tr>
<tr>
<td>Did you ______ as a way to end your life?</td>
</tr>
<tr>
<td>Did you want to die (even a little) when you ______?</td>
</tr>
<tr>
<td>Were you trying to end your life when you ______?</td>
</tr>
<tr>
<td>Or did you think it was possible you could have died from ______?</td>
</tr>
<tr>
<td>Total # of attempts ______</td>
</tr>
</tbody>
</table>

Or did you do it purely for other reasons / without any intention of killing your self (like to relieve stress, feel better, get sympathy, or to get something else to happen)? *(Self-injurious behavior without suicidal intent)*
If yes, describe. Yes/No

<table>
<thead>
<tr>
<th>Interrupted Attempt:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? Yes/No</td>
</tr>
<tr>
<td>Total # of interrupted ______</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aborted Attempt:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? Yes/No</td>
</tr>
<tr>
<td>Total # of aborted ______</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preparatory Acts or Behavior:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? Yes/No</td>
</tr>
</tbody>
</table>
Suicidal Behavior:
Suicidal behavior was present during the assessment period? Yes/No
If yes, describe
Completed Suicide: Yes/No

<table>
<thead>
<tr>
<th>ANSWER FOR ACTUAL ATTEMPTS ONLY</th>
<th>Most Recent Attempt Date:</th>
<th>Worst/Most Lethal Attempt Date:</th>
<th>Since Last Visit:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Lethality/Medical Damage:</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
</tr>
<tr>
<td>0. No physical damage or very minor physical damage (eg, surface scratches).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second degree burns; bleeding of major vessel).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Moderately severe physical damage; medical hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Severe physical damage; medical hospitalization with intensive care required (eg, comatose without reflexes; third degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Death</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
</tr>
</tbody>
</table>

Potential Lethality: Only Answer if Actual Lethality = 0

| 0 = Behavior not likely to result in injury | Enter Code | Enter Code |
| 1 = Behavior likely to result in injury but not likely to cause death | Enter Code | Enter Code |
| 2 = Behavior likely to result in death despite available medical care | Enter Code | Enter Code |

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. (Oquendo M. A.; Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M. B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 – 130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu.
<table>
<thead>
<tr>
<th>Identifier</th>
<th>Version</th>
<th>Title</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT02-GSOP-RF08</td>
<td>1.0</td>
<td>INTERVENTIONAL CLINICAL PROTOCOL APPROVAL FORM</td>
<td>02-APR-2012</td>
</tr>
</tbody>
</table>

A PHASE 4, RANDOMIZED, DOUBLE-BLIND, ACTIVE AND PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE NEUROPSYCHIATRIC SAFETY AND EFFICACY OF 12 WEEKS VARENICLINE TARTRATE 1 MG BID AND BUPROPION HYDROCHLORIDE 150 MG BID FOR SMOKING CESSATION IN SUBJECTS WITH AND WITHOUT A HISTORY OF PSYCHIATRIC DISORDERS.

**Compound:**
CP-526,555

**Compound Name (if applicable):**
Varenicline Tartrate

**US IND Number (if applicable):**
58,994

**Protocol Number:**
A3051123

**Phase:**
Phase 4

**Version and Date:**
Amendment 7
07 November 2012

**European Clinical Trial Database (EudraCT) Number, if applicable:**
2010-022914-15

Approval Signature indicates acknowledgement that the protocol meets all necessary requirements as described in this SOP including affirmation that the following requirements have been met:

- Where required, the protocol achieved a satisfactory Protocol Quality Score
- Clinical Operations agreement the protocol is executable
- EUQPPV review is completed for PASS protocols
- Technical and scientific QC has been performed
- Medical review has been performed, as appropriate
- Statistical review has been performed, as appropriate

**Print Name:**
Carla Yunis, MD, MPH

**Signature:**
[Signature]

**Date:**
07 November 2012

**Instructions:**
Upon completion, file official copy to Trial Master File.

This document contains confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing this document, you agree to hold this information in confidence and not to disclose it to others (except where required by applicable law) or to use it for unauthorized purposes. In the event of an actual or suspected breach of this obligation, Pfizer should be promptly notified.

Approved by Pfizer for public disclosure.
A PHASE 4, RANDOMIZED, DOUBLE-BLIND, ACTIVE AND PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE NEUROPSYCHIATRIC SAFETY AND EFFICACY OF 12 WEEKS VARENICLINE TARTRATE 1 MG BID AND BUPROPION HYDROCHLORIDE 150 MG BID FOR SMOKING CESSATION IN SUBJECTS WITH AND WITHOUT A HISTORY OF PSYCHIATRIC DISORDERS

Compound: CP-526,555
Compound Name (if applicable): Varenicline Tartrate
US IND Number (if applicable): 58,994
EudraCT Number: 2010-022914-15
Protocol Number: A3051123
Phase: Phase 4
Amendment 8
Local amendment for Bulgaria, Denmark, Finland, France, Germany, Slovakia and Spain
07 November 2012

This document contains confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing this document, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.
## Document History

<table>
<thead>
<tr>
<th>Document</th>
<th>Version Date</th>
<th>Summary of Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 8</td>
<td>07 November 2012</td>
<td>This is being amended to incorporate changes based on the updated bupropion Global Data Sheet dated 18 Sep 2012.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sections 6.2.2 Clinic Visits (Week 1 to 6 Visits, Weeks, 8, 10, 12 and ET12) and 6.3.1 Clinic Visits (Weeks 13, 16, 20, 24 and ET24 Visit): Added pregnancy testing to Visit Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 6.4.1 Subject Withdrawal is updated to include:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Study drug will be discontinued immediately for any female subject who becomes pregnant during the treatment period of the study.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 7.1.14 Laboratory was updated to include the additional pregnancy testing at clinic visits.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 8.9 Exposure During Pregnancy was updated to match the most recent protocol template and Pfizer SOPs.</td>
</tr>
<tr>
<td>Amendment 7*</td>
<td>07 November 2012 (Global)</td>
<td>This is being amended to incorporate changes based on the updated bupropion Global Data Sheet dated 18 Sep 2012.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sections 6.2 and 6.3. Study Period and Nontreatment Follow-up Period- Pregnancy testing is being added to Visit Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 6.4.1 Subject Withdrawal • Study drug will be discontinued immediately for any female subject who becomes pregnant during the treatment period of the study.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 7.1.14 Laboratory was updated to include the additional pregnancy testing at clinic visits.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 8.9 Exposure During Pregnancy was updated to match the most recent protocol template and Pfizer SOPs.</td>
</tr>
<tr>
<td>Amendment 6</td>
<td>30 May 2012</td>
<td>This is being amended to incorporate changes based on feedback from the FDA and regulatory agencies in the EU.</td>
</tr>
<tr>
<td>Country Specific: Bulgaria, Denmark, Finland, France, Germany, Slovakia and Spain</td>
<td></td>
<td>• Vital signs (PR and BP) are added to all clinic visits.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ECG is added to Week 12 and ET12 visit.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 4.2 Exclusion Criteria #9 is being changed from Subjects with a seizure disorder to Subjects with a current seizure disorder or any history of seizures. This change is to be consistent with EU SMPC for bupropion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 4.2 Exclusion Criteria #23 is added to exclude subjects with skin conditions which would hinder the use of NRT placement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 6 (Study Procedures) is updated to include additional vital signs at every clinic visit and ECG at Wk 12 or ET12.</td>
</tr>
</tbody>
</table>
- Section 6.4 (Subject Withdrawal) is updated to include information for Off Treatment in Study (OTIS) subjects and all subjects will be followed until final visit unless they withdraw consent.
- Section 7.1.12 (Physical Examination, Vital Signs and Electrocardiogram) is updated to include vital signs at every clinic visit and ECG as Wk 12 or ET12.
- Section 7.1.15 (Cardiovascular Events of Interest) is changed from: Hospitalization for angina pectoris or chest pain to: Hospitalization for unstable angina. Also wording was added to further clarify how events of interest will be identified, reviewed and adjudicated.

In addition the following changes/updates are made:
- Remove Czech Republic from header and title page as this protocol is no longer being submitted to this country.
- Section 4.2 Exclusion Criteria #5 is updated to clarify intent. It was changed from: “Subjects with a positive urine drug screen at screening or baseline”. To: Subjects with a positive urine drug screen at screening or baseline for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition.
- Section 5.3.3 Study Drug Administration- additional instructions for clarity are added to perform dose reduction of study drugs and if drug needs to be permanently discontinued. Section also updated to add information on medication error reporting.
- Section 5.5 Concomitant Medication: Milnacipran (Scavella) is added to any use prohibited.
- Section 7.1.10 Typographical error is corrected.
- Section 8 Updated various Adverse Event sections to match the most recent protocol template and Pfizer SOPs.
- Section 15 Publication of Study Results updated to match the most recent protocol template and Pfizer SOPs.

<table>
<thead>
<tr>
<th>Amendment 5*</th>
<th>30 May 2012 (Global)</th>
<th>This is being amended to incorporate changes based on feedback from the US FDA and regulatory agencies in the EU.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- Vital signs (PR and BP) are added to all clinic visits.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ECG is added to Week 12 and ET12 visit.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Section 4.2 Exclusion Criteria #22 is added to exclude subjects with skin conditions which would hinder the use of NRT placement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Section 6 (Study Procedures) is updated to include additional vital signs at every clinic visit and ECG at Wk 12 or ET12.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Section 6.4 (Subject Withdrawal) is updated to include information for Off Treatment in Study (OTIS) subjects and all subjects will be followed until final visit unless they withdraw consent.</td>
</tr>
</tbody>
</table>
- Section 7.1.1.2 (Physical Examination, Vital Signs and Electrocardiogram) is updated to include vital signs at every clinic visit and ECG as Wk 12 or ET12.
- Section 7.1.15 (Cardiovascular Events of Interest) is changed from: Hospitalization for angina pectoris or chest pain to: Hospitalization for unstable angina. Also wording was added to further clarify how events of interest will be identified, reviewed and adjudicated.

In addition the following changes/updates are made:

- Section 4.2 Exclusion Criteria #5 is updated to clarify intent. It was changed from: “Subjects with a positive urine drug screen at screening or baseline”. To: Subjects with a positive urine drug screen at screening or baseline for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition
- Section 5.3.3 Study Drug Administration- additional instructions for clarity are added to perform dose reduction of study drugs and if drug needs to be permanently discontinued. Section also updated to add information on medication error reporting.
- Section 5.5 Concomitant Medication: Milnacipran (Scavella) is added to any use prohibited.
- Section 7.1.10 Typographical error is corrected.
- Section 8. Updated various Adverse Event sections to match the most recent protocol template and Pfizer SOPs.
- Section 15 Publication of Study Results updated to match the most recent protocol template and Pfizer SOPs.

### Amendment 4

| 10 October 2011 | This protocol is being amended to incorporate changes requested by the EMA.
| Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Slovakia and Spain. | Subjects with Bipolar I and II disorders will be excluded from the study.
| | The Mental Health Professional (MHP) will be defined as a psychiatrist only.

### Amendment 3

| 04 Oct 2011 | This protocol is being amended to incorporate changes requested by the US FDA. The protocol is being amended to include detailed cardiovascular medical history, collection of cardiovascular events of interest during the study, and a Cardiovascular Event Adjudication Committee. The protocol was also updated to be consistent with updated SOP CT 02 in regards to Section 15.1, Communication of Results by Pfizer.

### Amendment 2

| 28 June 2011 | The protocol is being amended to incorporate changes requested by the US FDA and the EMA. In addition, bupropion has been added to the title, objectives and endpoints as an active comparator. The amendment also incorporates changes to the Neuropsychiatric Adverse Events Interview (NAEI) based on the outcome of the pilot in a similar patient population. In addition, the amendment provides updates to be in compliance with Pfizer SOPs, clarifies certain protocol aspects and corrects inconsistencies/typographical errors.
- Updates safety and efficacy endpoints to include bupropion as active comparator;
- Defines current and past diagnosis of a psychiatric history for the Inclusion Criteria;
- Clarification of the exclusion criteria for which bupropion is not appropriate;
- Clarification of the randomization criteria within the cohort for a psychiatric disorder;
- Additional information of re-screening of subjects;
- Additional verbiage for subjects lost to follow up during the study;
- Clarification of the Clinical Global Impression of Improvement (CGI-I) and how to rate the severity for those subjects with a psychiatric history;
- Clarification of when the lack of efficacy should be reported as an adverse event;
- Updates to the statistical sections to include bupropion in the analyses;
- Changes to the Nicotine Use Inventory (NUI) to comply with US FDA requests and ensure proper data collection;
- Changes to the NAEI based on the outcome of the NAEI pilot study.
- Updates to include language on potential cases of drug induced liver injury.
- Updates Appendix 9, and Appendix 10 (C-SSRS Baseline and Since Last Visit) to January 14, 2009 version).

<table>
<thead>
<tr>
<th>Amendment</th>
<th>Date</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 1</td>
<td>17 June 2010</td>
<td>See Appendix 13</td>
</tr>
<tr>
<td>Original protocol</td>
<td>17 May 2010</td>
<td>N/A</td>
</tr>
</tbody>
</table>

For Amendments: This amendment incorporates all revisions to date except those in the amendment(s) indicated with an (*). The sites following the amendment(s) marked with an (*) above must use the specific region/country/site amendments as well as the current amendment.
## SCHEDULE OF ACTIVITIES - Study Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screen</th>
<th>BL</th>
<th>Wk 1 (Day 8)</th>
<th>Wk 2</th>
<th>Wk 3</th>
<th>Wk 4</th>
<th>Wk 5</th>
<th>Wk 6</th>
<th>Wk 7*</th>
<th>Wk 8</th>
<th>Wk 9*</th>
<th>Wk 10</th>
<th>Wk 11*</th>
<th>Wk 12</th>
<th>ET*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent*</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History, Cardiovascular Medical History, Demography, Smoking history/height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs (PR, BP)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCID I and II</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Volunteered reporting</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression Questionnaire</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview (NAEI)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBQ-R</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagerström Test</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled CO</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense Study Drugs</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, Blood Chemistry</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (urine or serum)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Drug Screen (dipstick at site)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Contact Information Card</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric Evaluation*</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect cardiovascular events of interest</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Designates telephone visit.

a If ET is before the Week 12 visit.

b Must be signed prior to any protocol procedures being performed.

c All females unless surgically sterilized or at least 2 years postmenopausal.

d May be performed at other visits at investigator’s discretion.

e If deemed needed per protocol section 7.1.10.
## SCHEDULE OF ACTIVITIES - Post-Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Wk 13</th>
<th>Wk 14*</th>
<th>Wk 15*</th>
<th>Wk 16</th>
<th>Wk 17*</th>
<th>Wk 18*</th>
<th>Wk 19*</th>
<th>Wk 20</th>
<th>Wk 21*</th>
<th>Wk 22*</th>
<th>Wk 23*</th>
<th>Wk 24</th>
<th>ET 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital Signs (PR, BP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Volunteered reporting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
</tr>
<tr>
<td>Exhaled CO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric Evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect cardiovascular events of interest</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test^</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Designates telephone visit.

a If ET is after Week 12 visit and before Week 24 visit.

b If deemed needed per protocol section 7.1.10.

c All females unless surgically sterilized or at least 2 years postmenopausal.
TABLE OF CONTENTS

1. INTRODUCTION .....................................................................................................................12
  1.1. Indication .......................................................................................................................12
  1.2. Background and Rationale ............................................................................................12

2. STUDY OBJECTIVES AND ENDPOINTS .............................................................................15
  2.1. Objectives ......................................................................................................................15
      2.1.1. Safety ................................................................................................................15
      2.1.2. Efficacy: Abstinence from Smoking ................................................................16
  2.2. Endpoints .......................................................................................................................16
      2.2.1. Safety ................................................................................................................16
      2.2.2. Efficacy .............................................................................................................17

3. STUDY DESIGN .......................................................................................................................17

4. SUBJECT SELECTION ............................................................................................................19
  4.1. Inclusion Criteria ...........................................................................................................19
      4.1.1. Additional Inclusion Criteria for Neuropsychiatric Cohort .........................20
  4.2. Exclusion Criteria ..........................................................................................................21
  4.3. Randomization Criteria .................................................................................................25
  4.4. Life Style Guidelines .....................................................................................................25

5. STUDY TREATMENTS ...........................................................................................................26
  5.1. Allocation to Treatment ................................................................................................27
  5.2. Breaking the Blind ........................................................................................................27
  5.3. Drug Supplies ................................................................................................................27
      5.3.1. Formulation and Packaging ..............................................................................27
      5.3.2. Preparation and Dispensing ..............................................................................28
      5.3.3. Administration ..................................................................................................28
      5.3.4. Compliance .......................................................................................................29
  5.4. Drug Storage and Drug Accountability .........................................................................29
  5.5. Concomitant Medication(s) ...........................................................................................30

6. STUDY PROCEDURES ...........................................................................................................32
  6.1. Screening .......................................................................................................................32
  6.2. Study Period ..................................................................................................................33
6.2.1. Baseline Visit (Randomization) ................................................................. 33
6.2.2. Clinic Visits (Week 1 to 6 Visits, Weeks 8, 10, 12 and ET_{12} Visit) ...... 34
6.2.3. Telephone Visits (Weeks 7, 9, 11) ............................................................... 35
6.3. Nontreatment Follow-up Period (Weeks 13 through 24) ......................... 35
6.3.1. Clinic Visits (Weeks 13, 16, 20, 24 and ET_{24} Visit) .............................. 36
6.3.2. Telephone Visits (Weeks 14, 15, 17, 18, 19, 21, 22, and 23) .......... 37
6.4. Subject Withdrawal .................................................................................... 37
   6.4.1. Individual Subject Dosing Stopping Criteria ...................................... 37
7. ASSESSMENTS ............................................................................................... 38
   7.1. Safety ......................................................................................................... 38
      7.1.1. Adverse Events .................................................................................. 38
         7.1.1.1. Primary Neuropsychiatric Safety Endpoint .................................. 39
         7.1.1.2. Actively Solicited Neuropsychiatric Adverse Events .................. 39
      7.1.2. Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 10, and
            the Suicidal Behaviors Questionnaire (SBQ-R) Appendix 3 ................. 40
      7.1.3. Hospital Anxiety and Depression Scale (HADS) Appendix 2 .......... 40
      7.1.4. Clinical Global Impression of Severity (CGI-S) Appendix 7 ......... 41
      7.1.5. Clinical Global Impression of Improvement (CGI-I) Appendix 8 ... 41
      7.1.6. Aggression Questionnaire (AQ) Appendix 5 ................................. 41
      7.1.7. Nicotine Use Inventory (NUI) Appendix 4 ....................................... 41
      7.1.8. End-Expiratory Exhaled Carbon Monoxide (Exhaled CO) ............ 42
      7.1.9. Fagerström Test for Nicotine Dependence ....................................... 42
      7.1.10. Psychiatric Evaluations/Risk Assessments ..................................... 42
      7.1.11. Psychiatric Treatment Monitoring ............................................... 43
      7.1.12. Physical Examination, Vital Signs and Electrocardiogram .......... 43
      7.1.13. Medical History ............................................................................. 43
      7.1.14. Laboratory ..................................................................................... 44
      7.1.15. Cardiovascular (CV) Events of Interest ......................................... 44
         7.1.15.1. Serious Cardiac Arrhythmias ................................................. 45
    7.2. Efficacy .................................................................................................. 45
       7.2.1. Measures of Abstinence from Smoking ......................................... 45
8. ADVERSE EVENT REPORTING .................................................................... 46
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1. Adverse Events</td>
<td>46</td>
</tr>
<tr>
<td>8.2. Reporting Period</td>
<td>46</td>
</tr>
<tr>
<td>8.3. Definition of an Adverse Event</td>
<td>47</td>
</tr>
<tr>
<td>8.4. Abnormal Test Findings</td>
<td>47</td>
</tr>
<tr>
<td>8.5. Serious Adverse Events</td>
<td>48</td>
</tr>
<tr>
<td>8.5.1. Potential Cases of Drug-Induced Liver Injury</td>
<td>49</td>
</tr>
<tr>
<td>8.6. Hospitalization</td>
<td>50</td>
</tr>
<tr>
<td>8.7. Severity Assessment</td>
<td>51</td>
</tr>
<tr>
<td>8.8. Causality Assessment</td>
<td>51</td>
</tr>
<tr>
<td>8.9. Exposure During Pregnancy</td>
<td>51</td>
</tr>
<tr>
<td>8.10. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)</td>
<td>53</td>
</tr>
<tr>
<td>8.11. Eliciting Adverse Event Information</td>
<td>53</td>
</tr>
<tr>
<td>8.12. Reporting Requirements</td>
<td>53</td>
</tr>
<tr>
<td>8.12.1. Serious Adverse Event Reporting Requirements</td>
<td>53</td>
</tr>
<tr>
<td>8.12.2. Non-Serious Adverse Event Reporting Requirements</td>
<td>54</td>
</tr>
<tr>
<td>8.12.3. Sponsor Reporting Requirements to Regulatory Authorities</td>
<td>54</td>
</tr>
<tr>
<td>9. DATA ANALYSIS/STATISTICAL METHODS</td>
<td>54</td>
</tr>
<tr>
<td>9.1. Analysis Sets</td>
<td>54</td>
</tr>
<tr>
<td>9.2. Sample Size Determination</td>
<td>55</td>
</tr>
<tr>
<td>9.3. Safety Objective Analysis</td>
<td>55</td>
</tr>
<tr>
<td>9.4. Efficacy Objective Analysis</td>
<td>56</td>
</tr>
<tr>
<td>9.5. Methods and Analysis</td>
<td>57</td>
</tr>
<tr>
<td>9.6. Interim Analysis</td>
<td>58</td>
</tr>
<tr>
<td>9.7. Independent Data Monitoring Committee</td>
<td>58</td>
</tr>
<tr>
<td>9.8. Cardiovascular Event Adjudication Committee (CEAC)</td>
<td>59</td>
</tr>
<tr>
<td>10. QUALITY CONTROL AND QUALITY ASSURANCE</td>
<td>62</td>
</tr>
<tr>
<td>11. DATA HANDLING AND RECORD KEEPING</td>
<td>63</td>
</tr>
<tr>
<td>11.1. Case Report Forms/Electronic Data Record</td>
<td>63</td>
</tr>
<tr>
<td>11.2. Record Retention</td>
<td>63</td>
</tr>
<tr>
<td>12. ETHICS</td>
<td>64</td>
</tr>
<tr>
<td>12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)</td>
<td>64</td>
</tr>
</tbody>
</table>
12.2. Ethical Conduct of the Study ........................................................................................................64
12.3. Subject Information and Consent ...............................................................................................64
12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP..........................65
13. DEFINITION OF END OF TRIAL .................................................................................................65
13.1. End of Trial in all Participating Countries ....................................................................................65
14. SPONSOR DISCONTINUATION CRITERIA ....................................................................................65
15. PUBLICATION OF STUDY RESULTS .........................................................................................65
15.1. Communication of Results by Pfizer ..........................................................................................65
15.2. Publications by Investigators .......................................................................................................66
16. REFERENCES ..................................................................................................................................68

APPENDICES

Appendix 1. Fagerström Test for Nicotine Dependence ......................................................................69
Appendix 2. Hospital Anxiety and Depression Scale (HADS) ...............................................................70
Appendix 3. Suicide Behaviors Questionnaire-Revised (SBQ-R) .........................................................71
Appendix 4. Nicotine Use Inventory (NUI) ..........................................................................................72
Appendix 5. Aggression Questionnaire (AQ) .....................................................................................73
Appendix 6. Neuropsychiatric Adverse Events Interview (NAEI) ..........................................................75
Appendix 7. Clinical Global Impression of Severity (CGI-S) ...............................................................82
Appendix 8. Clinical Global Impression of Improvement (CGI-I) ..........................................................83
Appendix 9. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) Baseline........................84
Appendix 10. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) Since Last Visit..............87
Appendix 11. List of Abbreviations .....................................................................................................90
Appendix 12. CV Required Documents .............................................................................................91
Appendix 13. CLINICAL PROTOCOL AMENDMENT 1 .................................................................95
1. INTRODUCTION

1.1. Indication

Aid to smoking cessation treatment.

1.2. Background and Rationale

**Varenicline**

Varenicline was approved as Chantix® by the US FDA in May 2006, and as Champix® by the EMEA in September 2006, and is now approved in more than 90 countries worldwide for smoking cessation in adults. The approved dose regimen is 1-mg twice daily (1 mg BID) for 12 weeks starting with a 1-week titration.

Protocol A3051123 is a Phase 4 study being conducted to assess varenicline as an aid to smoking cessation treatment in subjects with and without an established diagnosis of major psychiatric disorder and to characterize the neuropsychiatric safety profile in both of these cohorts. This study qualifies as a Post-Authorization Safety Study (PASS) and it is a US Post-Marketing Requirement and an EU Post-Approval Commitment. The population will be characterized by presence or absence of an established and stable diagnosis of major psychiatric disorder, current or past, Diagnostic and Statistic Manual of Mental Disorders 4th Edition Text Revision DSM IV TR-defined. This is described as “diagnosis of psychiatric disorder” throughout the protocol.

Literature has shown that subjects with a current Axis I disorder were more likely to experience tobacco withdrawal symptoms and withdrawal-related discomfort and relapse. Subjects with Axis I disorders may need more intensive and/or longer treatments to help them cope with withdrawal symptoms and prevent relapse.\(^\text{11}\)

In Phase 3, subjects with psychiatric disorders were not included per protocol by the use of the following exclusion criteria: “Subjects currently or within the past 12 months requiring treatment for depression. Subjects with current or prior history of panic disorder, psychosis, or bipolar disorder”. In this study, recruitment will be balanced equally with respect to subjects with and without a diagnosis of major psychiatric disorder to allow for the assessment of neuropsychiatric events in each of the cohorts and each of the treatment groups. Subjects will be randomized to receive varenicline, placebo, bupropion hydrochloride or transdermal nicotine patch (NRT), the latter two being included as active controls.

Varenicline is a selective nicotinic acetylcholine receptor (nAChR) partial agonist designed to have specific and potent binding at the $\alpha 4\beta 2$ receptor subtype, which mediates the reinforcing effects of nicotine. Because of its mixed agonist-antagonist properties, varenicline offers the therapeutic benefit of relieving symptoms of nicotine withdrawal and cigarette craving during abstinence while blocking the reinforcing effects of chronic nicotine. Because of its high selectivity for $\alpha 4b2$ nicotinic receptors, at therapeutic levels,\(^\text{3}\) varenicline does not bind to other neurotransmitter receptors and transporters,\(^\text{9}\) including those implicated in mental disorders.\(^\text{2}\)
Phase 2 to Phase 4 placebo controlled clinical trials have demonstrated the efficacy and tolerability of varenicline 1 mg BID in more than 3000 cigarette smokers, increasing the odds of quitting approximately 4-fold compared with placebo at end of treatment, and nearly 2-fold compared with bupropion at end of treatment. The most frequently reported treatment-emergent adverse events associated with varenicline were nausea, sleep disturbance, constipation, flatulence and vomiting. Nausea was reported by approximately 30% of patients treated with varenicline 1 mg BID after an initial week of dose titration compared with 10% in patients taking placebo. In patients taking 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient.

**Post Marketing Experience**

There have been post-marketing reports of neuropsychiatric symptoms, some serious, including changes in mood, agitation, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, changes in behavior, anxiety, panic, suicidal ideation, suicide attempt and completed suicide in patients attempting to quit smoking with varenicline. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish causal relationship to drug exposure or smoking status. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of varenicline in these reports is not known. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness.

There have also been reports of serious skin reactions and hypersensitivity reactions, including angioedema.

**Bupropion**

Bupropion was first approved for the treatment of depression (as Wellbutrin™) on 30 December 1985 in the USA. The first approval for smoking cessation (as Zyban™) was in 1996, also in the USA. Bupropion has been approved for depression in approximately 70 countries worldwide and for smoking cessation in almost 90 countries. Post-marketing exposure is estimated to be 90 million patient exposures for all bupropion formulations and indications, of which approximately 24 million are for use in smoking cessation.

Zyban™ was the first non-nicotine treatment for nicotine dependence as an aid to smoking cessation. Zyban™ is chemically unrelated to nicotine or other agents currently used in the treatment of nicotine addiction. Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and does not inhibit monoamine oxidase. The mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms. Bupropion increases dopamine concentrations in the nucleus accumbens in rats. While the clinical significance is unknown, this action may mimic the effects of nicotine and reduce cravings associated with nicotine addiction. Bupropion also reduces noradrenergic neuron...
firing in the locus ceruleus of rats. While this may explain the reduction in nicotine withdrawal symptoms, the clinical significance is unknown. In clinical trials, treatment with bupropion reduced withdrawal symptoms compared to placebo and also showed evidence of reduction in craving for cigarettes or urge to smoke compared to placebo.

The efficacy of bupropion for the treatment of nicotine dependence as an aid to smoking cessation was evaluated in clinical studies of 1,508 non-depressed, chronic cigarette smokers. Two randomized, placebo-controlled trials were conducted:

- A dose-response trial of Zyban™ 100 mg/day (50 mg BID), 150 mg/day, 300 mg/day (150 mg BID), and placebo;
- A comparative trial of Zyban™, Habitrol® (nicotine transdermal system – NTS; also marketed as Nicotinell® by Novartis in some countries), the combination of Zyban™ and NTS, and placebo.

In both clinical trials, patients treated with Zyban™ achieved a higher four-week continuous quit rate than placebo-treated patients. In addition, Zyban™ was more effective than NTS in the comparative study. The combination of Zyban™ and NTS produced the highest rates of continuous abstinence, although not statistically significantly different from Zyban™ alone. In the dose-response trial, patients treated with Zyban™ 300 mg/day (150 mg BID) maintained a significantly higher abstinence rate than those treated with placebo through the end of six months.

Zyban™ was generally well tolerated by chronic cigarette smokers enrolled in the clinical trials. The most common adverse events consistently observed with Zyban™ were dry mouth and insomnia. Both of these events may be dose related. Bupropion is likely to have a low potential for abuse, and there was no evidence of withdrawal phenomena upon abrupt cessation of Zyban™.

Placebo-controlled Phase 3 and Phase 4 studies of bupropion for smoking cessation generally excluded patients who had a psychiatric disorder (e.g., major depressive episode, bipolar disorder, panic disorder, psychosis) or who were taking psychoactive drugs. This study qualifies as a Post-Authorization Safety Study (PASS) and it is a US Post-Marketing Requirement.

Post Marketing Experience

Seizure is the most medically-significant dose-related adverse reaction associated with bupropion. A postmarketing surveillance study and pooling of clinical trial data have shown the incidence for the sustained-release tablet to be approximately 0.1% in therapeutic doses. Hypersensitivity reactions are also important adverse events that occur with bupropion.
Neuropsychiatric symptoms have been reported. In particular, psychotic and manic symptomatology has been observed, mainly in patients with a known history of psychiatric illness. The following neuropsychiatric reactions are listed in the Adverse Reactions section of the bupropion Core Data Sheet (CDS), the frequency of which have been estimated from integrated placebo-controlled smoking cessation studies or postmarketing reports: insomnia, depression, confusion, delusions, paranoid ideation, hallucinations, agitation, restlessness, anxiety, irritability, hostility, aggression, depersonalisation, abnormal dreams, concentration disturbance and dizziness.

Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported during bupropion treatment, and generally occurred during the early stages of treatment.

Bupropion is indicated for the treatment of depression in some countries. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adults with major depressive disorder and other psychiatric disorders showed an increased risk of suicidal thinking and behavior associated with antidepressant use compared to placebo in patients less than 25 years old.

Clinicians should be aware of the possible emergence of significant depressive symptoms or suicidal ideation in patients being treated with bupropion, and should advise and monitor patients accordingly.

**Single Reference Safety Document**

The Single Reference Safety Document for varenicline is the Core Data Sheet. The Single Reference Safety Documents for Bupropion and NRT are the respective Core Data Sheets (CDS).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Safety

**Primary Safety Objectives:**

1. To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo in the incidence of the primary neuropsychiatric AE endpoint for subjects:

   a. With a diagnosis of psychiatric disorder;

   b. Without a diagnosis of psychiatric disorder.
2. To characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).

2.1.2. Efficacy: Abstinence from Smoking

Main Efficacy Objective: To compare smoking abstinence rates of varenicline and bupropion relative to placebo for the last 4 weeks of treatment and continuously through Week 24, as measured by CO-confirmed continuous abstinence rate (CAR) CAR9-12 and CAR9-24, respectively, separately for subjects with and without a diagnosis of psychiatric disorder.

Secondary Objective:

To assess if there is a difference between cohorts in the placebo adjusted relative abstinence rates (CAR9 12 and CAR9 24) of varenicline and bupropion, separately.

Another secondary objective of the study is to perform the following comparisons with respect to the primary safety and efficacy endpoints:

1. NRT vs. Placebo;
2. Varenicline vs. Bupropion;
3. Varenicline vs. NRT;
4. Bupropion vs NRT.

2.2. Endpoints

2.2.1. Safety

The primary safety endpoint is the occurrence of at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. This endpoint is referred to as the Neuropsychiatric (NPS) AE endpoint.

Secondary Safety Endpoints:

- Occurrence of the components of the primary safety endpoint;
- Individual item responses, along with subscale scores and overall score (when applicable; specifics are stated in the Statistical Analysis Plan), for the following questionnaires:
  - Hospital Anxiety and Depression Scale (HADS) Appendix 2;
  - Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 10;
• Clinical Global Impression of Improvement (CGI-I) Appendix 8.

2.2.2. Efficacy

The main efficacy endpoint is 4-week CO-confirmed continuous abstinence for Weeks 9 through 12.

Secondary Efficacy Endpoints:

The secondary efficacy endpoint is CO-confirmed continuous abstinence from Week 9 through Week 24.

An additional secondary efficacy endpoint is the 7-day point prevalence of abstinence at each assessment visit.

3. STUDY DESIGN

This is a 24-week, double-blind, NRT and placebo-controlled, multi-center, parallel group study designed to assess the safety and efficacy of varenicline 1 mg BID and bupropion hydrochloride 150 mg BID for smoking cessation. The primary comparisons will be varenicline vs. placebo and bupropion vs. placebo. NRT is included as active control and study medications will be given via a triple-dummy design. The duration of active treatment is 12 weeks followed by a non-treatment follow-up phase for an additional 12 weeks (see diagram below). The study will randomize approximately 2000 subjects in each of 4 treatment arms, for a total of 8000 subjects at approximately 200 sites.

Subjects will be classified into one of the two cohorts—those with an established and stable diagnosis of psychiatric disorder, confirmed by the Structured Clinical Interview for DSM-IV Axis 1 and 2 Disorders (SCID I and II) conducted at screening; and those without a diagnosis of psychiatric disorder. An equal number of subjects with or without a diagnosis of a psychiatric disorder will be enrolled and randomized among the 4 treatment arms (varenicline, bupropion, NRT, and placebo) in 1:1:1:1 ratio. All clinic visits are in an outpatient clinic setting.
Screening Phase: The screening period will be approximately 3-14 days in duration. Results of screening laboratory evaluations and the electrocardiogram will be reviewed during this period to assure subject eligibility. Determination if there is a diagnosis of a psychiatric disorder for each subject will be confirmed at screening using DSM IV TR based on clinical assessment and confirmed by SCID I and II.

A subject who meets all inclusion criteria at the screening visit will progress to the baseline visit. At the baseline visit only those subjects who continue to meet all other criteria will be randomized.

Treatment Phase: The 12-week placebo controlled treatment period has periodic clinic visits for safety and efficacy assessments and smoking cessation counseling. There will be weekly clinic visits up to and including Week 6 and then biweekly clinic visits between Week 6 and Week 12. On weeks with no scheduled clinic visits, telephone contact visits will occur to collect smoking status. During the active treatment phase, varenicline and bupropion dosing will begin on the Baseline day with a one-week titration followed by 11 weeks of 1 mg BID and 150 mg BID respectively. NRT dosing will begin at the Week 1 visit with a 21 mg patch per day for 7 weeks, followed by a 14 mg patch per day for 2 weeks, and then a 7 mg patch for 2 weeks. All subjects will set a target quit date (TQD) to coincide with the Week 1 visit. The Week 1 visit occurs at the end of the first week of the treatment phase (Day 8). Smoking cessation counseling up to 10 min duration will be provided at each clinic visit consistent with the Agency for Healthcare Research and Quality (AHRQ) guidelines beginning at Baseline.
Non-Treatment Phase: Study drug will be discontinued at the Week 12 visit and subjects will continue into the non-treatment follow-up period. Clinic visits will occur at Weeks 13, 16, 20 and 24. On weeks with no scheduled clinic visits, telephone contact visits will occur to collect smoking status. Smoking cessation counseling up to 10 min duration will be provided at each clinic visit consistent with the Agency for Healthcare Research and Quality (AHRQ) guidelines.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by the Investigator before subjects are included in the study. Subjects both with and without a diagnosis of a major psychiatric disorder will be eligible for this study. Subjects without a diagnosis of a psychiatric disorder that meet all other study criteria are eligible to be included in the non-psychiatric stratum. To be included in the non-psychiatric stratum, the subject must not have ANY previous diagnosis of a psychiatric disorder confirmed by SCID I and II.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the psychiatric or non-psychiatric arm of the study:

1. Male or female cigarette smokers, 18-75 years, motivated to stop smoking and considered suitable for a smoking cessation attempt.

2. Smoked an average of at least 10 cigarettes per day during past year and during the month prior to the screening visit, and exhaled carbon monoxide (CO) >10 ppm at screening.

3. Females who are not of childbearing potential (ie, who are surgically sterilized or at least 2 years postmenopausal) and who are not nursing may be included. Females who are of childbearing potential may be included provided that they are not pregnant, not nursing, and meet all of the following criteria:
   - Are instructed and agree to avoid pregnancy through 30 days after the last dose of study medication;
   - Have a negative pregnancy test (β-hCG) at Screening and Baseline and
   - Agree to use at least one of the birth control methods listed below:
• An oral contraceptive agent, an intrauterine device (IUD), an implantable contraceptive (eg, Norplant), or an injectable contraceptive (eg, Depo Provera) for at least 1 month prior to entering the study and will continue its use through at least 30 days after the last dose of study medication or;

• A double barrier method of contraception, eg, condom and diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study medication or abstinence.

4. A personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

5. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.1.1. Additional Inclusion Criteria for Neuropsychiatric Cohort

In addition to the criteria above, subjects to be included in the Neuropsychiatric cohort must also meet the following:

All subjects will be screened for Axis I and II diagnosis (current and/or past) using DSM IV TR criteria based on clinical assessment and confirmed by SCID (administered by a clinician\(^1\) or a qualified person trained in clinical mental health, ie; a PhD level clinical psychologist, or an individual with master level training in related areas [masters level psychologist, social work] who have been trained to use the SCID\(^2\)). A “current” diagnosis is defined as the subject meeting the established criteria in the prior month. A “past” diagnosis is also the same as a “lifetime” diagnosis where applicable. A past diagnosis can have occurred anytime in the past medical history. The four major diagnostic groups comprising the neuropsychiatric cohort are: Psychotic, Affective, Anxiety and Personality Disorders. The four diagnostic groups are further described below. Subjects will be included in the psychiatric cohort, if they are considered clinically stable and meet criteria, either current or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and have met diagnostic criteria before the initiation of study treatment.

a. Psychotic Disorders limited to:

• Schizophrenia;

• Schizoaffective.

b. Affective Disorders limited to:

---

\(^1\) Clinician is defined as someone licensed to practice medicine according to existing regulations.

\(^2\) Documentation of training will be kept at the clinical site.
• Major Depression;

c. Anxiety Disorders limited to:

• Panic Disorder with or without Agoraphobia;
• Post-Traumatic Stress Disorder;
• Obsessive-Compulsive Disorder;
• Social Phobia;
• Generalized Anxiety Disorder.

d. Personality Disorders limited to past history of:

• Borderline Personality Disorder.

All subjects with an Axis I or II diagnosis must be judged to be clinically stable including the following:

• No acute exacerbation of their condition in the preceding 6 months;
• If on treatment for their condition, must have been on stable treatment for a minimum of 3 months (eg, stable drug and dose ≥3 months);
• No change in treatment is anticipated for the duration of the study;
• In the opinion of the Investigator, the patient is not at high risk of self-injury or suicidal behavior;
• In the event the Investigator is not a mental health professional (MHP), the subject should be evaluated by a MHP to confirm the SCID I or II diagnosis and determine if the subject is stable. A MHP must be a psychiatrist. A subject who requires new treatment or is judged not to be clinically stable cannot be randomized.

Subjects who did not meet study inclusion criteria may be re-screened if deemed clinically stable at a later date and the case has been reviewed and approved by the Pfizer clinician.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects with a past or current diagnosis of one of the following disorders:

   a. Psychotic Disorders:
• Schizophreniform;
• Delusional Disorder;
• Psychotic Disorder NOS.

b. All Delirium, Dementia, and Amnestic and Other Cognitive Disorders;

c. All Substance-Induced Disorders (Other than nicotine);

d. All Factitious Disorders;

e. All Dissociative Disorders;

f. All Impulse Control Disorders;

g. Evidence of substance abuse/misuse or dependence severe enough to compromise the subject’s ability to comply with the study requirements;

h. Subjects with antisocial, schizotypal, or any other personality disorder severe enough to compromise the subject’s ability to comply with the study requirements.

Subjects with a past history of a comorbid condition listed in the above Exclusion Criteria may be included in the study and placed in the “psychiatric stratum” if A) the subject is concurrently diagnosed with an inclusionary diagnosis, B) the subject is able to comply with study requirements, and C) for substance abuse/misuse, the subject is considered to be in sustained full remission (no criteria for abuse or dependency being met in the last 12 months), and D) the patient is not taking agonists or partial agonists (i.e., methadone, buprenorphine).

If the subjects described above (exclusionary co-morbid psychiatric condition) do not meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, they are not eligible for the study. Subjects who meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, and who have a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) may be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent condition is stable and does not prevent the subject from safely complying with study procedures. In such cases, please consult with the medical monitor.

2. Subjects with an Axis I diagnosis according to DSM IV TR criteria who have a rating of 5 or higher on the Clinical Global Impression- Severity (CGI-S). Appendix 7.

3. Subjects who are believed to have a suicidal risk at screening, baseline, or after assessment by a qualified MHP-(Psychiatrist) if a risk assessment interview was required after screening or baseline using the Columbia Suicide Severity Rating Scale (C-SSRS). See section 7.1.2 (Appendix 10).
• Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS. Appendix 10.

• Previous history of suicide behaviors in the past year.


5. Subjects with a positive urine drug screen at screening or baseline for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition.

6. Subjects taking an investigational drug within 30 days before the Baseline visit and at anytime during the study period.

7. Subjects who have taken varenicline, bupropion, or NRT within 30 days prior to Baseline visit.

8. Only one subject per household may participate.

9. Subjects for whom treatment with bupropion is not appropriate:

   • Subjects with a current seizure disorder or any history of seizures;
   
   • Subjects undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines);
   
   • Subjects with current or prior diagnosis of anorexia or bulimia nervosa;
   
   • Subjects who have taken a monoamine oxidase (MAO) inhibitor within the past fourteen days (prior to the Baseline visit);
   
   • Subjects who are taking the following narrow therapeutic range medications which are metabolized by CYP2D6; desipramine, nortriptyline, Type 1C antiarrhythmics (eg, propafenone, flecainide), thioridazine.

Specific information regarding warnings, precautions, contraindications, adverse events and other pertinent information on bupropion that may impact subject eligibility is provided in the Core Data Sheets. In particular, bupropion should be administered with extreme caution to patients with risk factors for seizures, eg, a history of seizure, cranial trauma, or concomitant medications that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic steroids, etc.).

10. Subjects who intend to donate blood or blood components while receiving study drug or within 1 month of the completion of the treatment phase of the study.

11. Subjects with severe chronic obstructive pulmonary disease (COPD) defined as any subject who fulfills any of the following criteria:
- History of repeated exacerbations of COPD (greater than or equal to 3 in 3 years);
- Requires systemic corticosteroid maintenance (eg, oral prednisolone) for management of chronic symptoms;
- Is maintained on oxygen therapy for management of chronic symptoms.

12. Subjects with a recent (<5 years) history of cancer. Subjects with a remote (>5 years) history of cancer may be considered pending discussion with the study clinician. Subjects with cured basal cell or squamous cell carcinoma of the skin are allowed.

13. Subjects with evidence or history of clinically significant allergic reactions to drugs (eg, severe cutaneous and/or systemic allergic reactions).

14. Any subject at screening with an SGOT (AST) or SGPT (ALT) greater than 3 times the upper limit of normal (ULN) or total bilirubin greater than 2 times the ULN.

15. Subjects with clinically significant cardiovascular disease in the past 2 months. Examples of clinically significant cardiovascular disease include:
   - Myocardial infarction;
   - Coronary artery bypass graft (CABG);
   - Percutaneous transluminal coronary angioplasty (PTCA);
   - Severe or unstable angina;
   - A serious arrhythmia;
   - Clinically significant ECG conduction abnormalities;
   - Hospitalizations for heart failure.

16. Subjects with clinically significant cerebrovascular disease in the past 2 months. Examples of clinically significant cerebrovascular disease include:
   - Cerebrovascular accident (CVA), stroke;
   - Documented transient ischemic attack (TIA).

17. Subjects who do not agree to abstain from using non-cigarette tobacco products (including, eg, pipe tobacco, cigars, snuff, chewing tobacco, hookah, etc.) or marijuana during study participation.
18. Subjects who do not agree to abstain from using nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during study participation (both the treatment phase and the post-treatment follow-up).

19. Subjects who have previously experienced an adverse drug reaction that the investigator considers potentially due to treatment with any of the active drugs in this study and of sufficient concern that further exposure to this medication would be inadvisable.

20. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

21. Subjects taking a concomitant medication that is prohibited by this protocol (See Section 5.5).

22. Subjects with Bipolar I or Bipolar II disorders. These subjects are not allowed into the study even if they are concurrently diagnosed with an inclusionary diagnosis listed in Section 4.1.1.

23. Subjects with skin conditions resulting in red, broken or irritated skin that may hinder the use of the nicotine replacement therapy (NRT) patch.

4.3. Randomization Criteria

Subjects who meet inclusion and exclusion criteria may be randomized. A computer-generated randomization schedule will be used to assign subjects to treatment, with two-level stratification by the presence or absence of a diagnosis of psychiatric disorder. An equal number of smokers will be enrolled in each of the two cohorts. When the planned enrollment has been achieved in one of the cohorts, enrollment will continue only into the other cohort until recruitment goals have been reached.

Within the cohort with a diagnosis of a psychiatric disorder, treatment assignment will be stratified with respect to the four major diagnosis groups (Psychotic, Affective, Anxiety and Personality Disorders).

4.4. Life Style Guidelines

Participants are expected to abstain from the use of tobacco products such as pipe tobacco, cigars, snuff, chewing tobacco, hookah, and the use of marijuana. Subjects will be expected to refrain from using any form of nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during both the treatment and non treatment follow-up phases.
Females of childbearing potential (not surgically sterilized or <2 years postmenopausal) must agree to practice a form of effective contraception, such as an oral contraceptive agent, an intrauterine device (IUD), an implantable contraceptive (eg, Norplant), or an injectable contraceptive (eg, Depo Provera) for at least 1 month prior to entering the study and will continue its use through at least 30 days after the last dose of study medication. Alternatively they may use double barrier contraception (ie, condom plus spermicide in combination with a female condom, diaphragm, cervical cap or intrauterine device), or sexual abstinence prior to entering into the study and for at least 30 days following the last dose of study drug.

5. STUDY TREATMENTS

This study utilizes a triple-dummy design as shown in the table below. Subjects randomized to one of the three active dosing groups will take that active medication and the other 2 medications in matching placebo form. And subjects randomized to placebo will receive matching placebo for varenicline, bupropion, and NRT, and follow the same titration and dosing schedules as those randomized to each of the active medication groups.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Day 1-3</th>
<th>Day 4-7</th>
<th>Week 1*-8</th>
<th>Week 8-10</th>
<th>Week 10-12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Varenicline (V)</strong></td>
<td>0.5 mg V QD</td>
<td>0.5 mg V BID</td>
<td>1 mg V BID</td>
<td>1 mg V BID</td>
<td>1 mg V BID</td>
</tr>
<tr>
<td>1 placebo B QD</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
</tr>
<tr>
<td><strong>Bupropion (B)</strong></td>
<td>150 mg B QD</td>
<td>150 mg B BID</td>
<td>150 mg B BID</td>
<td>150 mg B BID</td>
<td>150 mg B BID</td>
</tr>
<tr>
<td>1 placebo V QD</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
</tr>
<tr>
<td><strong>NRT patch</strong></td>
<td>1 placebo V QD</td>
<td>1 placebo V BID</td>
<td>21 mg NRT QD</td>
<td>14 mg NRT QD</td>
<td>7 mg NRT QD</td>
</tr>
<tr>
<td>1 placebo B QD</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>1 placebo V QD</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
<td>1 placebo V BID</td>
</tr>
<tr>
<td>1 placebo B QD</td>
<td>1 placebo B BID</td>
<td>1 placebo B BID</td>
<td>1 placebo NRT QD</td>
<td>1 placebo NRT QD</td>
<td>1 placebo NRT QD</td>
</tr>
</tbody>
</table>

*On day of Week 1 visit, the varenicline dose will be taken as 2-0.5mg tablets (or 2 placebo varenicline tablets) in the AM and 1 mg tablet (or 1 placebo varenicline tablet) in the PM.

All subjects randomized to varenicline will be titrated to the full dose during the first week in the following manner: 0.5 mg QD x 3 days, 0.5 mg BID x 4 days, then 1 mg BID for 11 weeks. Subjects randomized to bupropion will receive 150 mg QD x 3 days and then will take 150 mg BID for the remainder of the treatment period (11 weeks and 4 days). Subjects randomized to NRT will start active dosing the morning of the Week 1 visit and will receive a 21 mg transdermal patch per day x 7 weeks, followed by a 14 mg transdermal patch per day x 2 weeks, and then a 7 mg transdermal patch x 2 weeks for a total of 11 weeks of treatment.
Dosing will continue until the Week 12 visit. All subjects will then be followed for an additional 12 weeks in the non-treatment phase of the protocol.

Smoking cessation counseling of up to 10 minutes will be given at each clinic visit during the treatment and non-treatment periods. The counseling will be 1:1, individually tailored to each subject’s needs, and consistent with AHRQ guidelines. Whenever possible, counseling should be conducted by the same counselor throughout, so that the relationship builds and brings additional value to the sessions.

5.1. Allocation to Treatment

This is a double-blind, parallel group study. Subjects will be stratified by diagnosis of psychiatric disorder or lack thereof and then randomized to varenicline, bupropion, NRT or placebo in a 1:1:1:1 ratio. Overall enrollment will be equal for the two cohorts (and within the cohort with a diagnosis of psychiatric disorder, treatment will be balanced with respect to the major diagnosis groups, per Section 4.3). Investigators will obtain subject identification numbers and study drug assignments utilizing a web-based or telephone call-in drug management system as directed by the sponsor. Identification numbers for the subjects will be provided at the screening visit.

5.2. Breaking the Blind

The study will be subject, investigator, and sponsor blinded.

At the initiation of the study, the study site will be instructed on the method for breaking the blind of an individual subject. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented.

5.3. Drug Supplies

5.3.1. Formulation and Packaging

Blinded tablets (varenicline, bupropion, or placebo) will be supplied in bottles containing sufficient tablets to dose daily between visits during the treatment period. Varenicline will be supplied as 0.5 mg tablets for the first week and 1.0 mg tablets for the remaining 11 weeks of the study treatment period. Bupropion will be supplied as 150 mg tablets. Blinded NRT (active and placebo) will be supplied in cartons containing sufficient transdermal patches to cover each study visit schedule, 21 mg patch for Weeks 1 to 8, 14 mg patch for Weeks 8 to 10, and 7 mg patch for Weeks 10 to 12. New bottles and cartons will be dispensed at each clinic visit to provide sufficient study drug until the next scheduled clinic visit.
5.3.2. Preparation and Dispensing

Study drug is to be dispensed to subjects by qualified site study staff at each scheduled clinic visit from the Baseline visit to the Week 10 visit (according to the study flowchart). Subjects will be given their first supply of bottles at the Baseline visit and first supply of patches at the Week 1 visit and will receive new supplies at each clinic visit through the Week 10 visit. Subjects will be instructed to store the study drug at room temperature (20-25°C or 69-77°F) and out of the reach of children.

All empty or unused study medication (bottles and patches) must be returned by each subject at each clinic visit through Week 12. Unused medication will be catalogued by site staff to verify data reported by the subjects.

5.3.3. Administration

Varenicline (or placebo) administration will begin with a titration period. Treatment will begin from the Week 1 bottle on the evening of the Baseline visit day. For the first 3 days of the Week 1 dosing period subjects will take one 0.5 mg tablet per day in the evening. For the next 4 days this will increase to two 0.5 mg tablets per day, 1 in the morning and 1 in the evening. On the day of the Week 1 visit (Day 8), subjects will increase their dose to two 0.5 mg tablets in the morning. At the Week 1 visit and subsequent clinic visits through the Week 10 visit subjects will receive new bottles and will take two 1 mg tablets daily, one in the evening and one in the morning.

Bupropion (or placebo) administration will begin with a titration period. Treatment will begin from the Week 1 bottle on the evening of the Baseline visit day. For the first 3 days of the Week 1 dosing period subjects will take one 150 mg bupropion in the evening. On Day 4 they increase dosing to one 150 mg bupropion BID (one in the morning and one in the evening) and dosing remains unchanged until Week 12.

Dosing should occur with 240 ml of water and it is recommended that subjects eat prior to dosing. It is recommended that there be at least 8 hours between the morning and evening dosing.

At the discretion of the Investigator, dosing with blinded tablet medications (varenicline, bupropion, matching placebos) may be reduced, temporarily discontinued or stopped for subjects who have intolerable adverse events (eg, nausea); or for subjects who in the opinion of the Investigator require a dose reduction due to use of concurrent medications. A dose reduction is performed by decreasing both blinded tablet medications to once per day dosing. If a dose reduction is required, both blinded tablet medications should be reduced at the same time.

NRT (or placebo) administration starts on the day of the Week 1 visit and subjects will receive a 21 mg transdermal patch per day for 7 weeks, followed by a 14 mg transdermal patch per day for 2 weeks, and then a 7 mg transdermal patch for 2 weeks for a total of 11 weeks of treatment.
At the discretion of the Investigator, dosing with blinded NRT (NRT or matching placebo) may be temporarily discontinued or stopped for subjects who have intolerable adverse events. It is not possible to reduce the dose of blinded NRT.

If any of the study drugs need to be permanently discontinued then all 3 blinded study medications (varenicline/placebo, bupropion/placebo, and NRT/placebo) must be permanently discontinued.

Medication errors may result in this study from the administration or consumption of the wrong study drug or by the wrong study subject. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRF and on the SAE form when appropriate. In the event of a medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the product.

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page (refer to ADVERSE EVENT REPORTING section for further details).

5.3.4. Compliance

Subjects will return bottles and cartons at each clinic visit and a drug accountability form will be completed. Missed doses should be discussed to try to ascertain the reason(s). Reasons for missed doses and/or patterns of missed doses should be incorporated into the smoking cessation counseling and every effort should be made to ensure proper subject dosing.

5.4. Drug Storage and Drug Accountability

The investigator or an approved representative (eg, pharmacist), will ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Store at room temperature as indicated on the label.

To ensure adequate records, all study drug will be accounted for in drug accountability inventory forms as instructed by Pfizer. Subjects must return all bottles and cartons to the investigator. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies must be returned to Pfizer or its designated agent.
5.5. Concomitant Medication(s)

While medications with narrow therapeutic index that are metabolized by CYP 2D6 are excluded (please refer to Any Use Prohibited, below), there is the potential for increased blood levels of certain antipsychotic and antidepressant medications. Therefore, investigators should pay attention to signs and symptoms of increased blood levels, and if noted, call the medical monitor for advice on how to manage the subject. These signs and symptoms should be recorded as adverse events.

If investigators have question on any drugs not listed here they should be discussed with the study clinician.

Episodic Use Only Permitted:

- Acetaminophen;
- Antihistamines;
- Aspirin (chronic use also permitted);
- Bronchodilators (chronic use also permitted);
- Inhaled steroids (chronic use also permitted);
- Oral and injectable steroids;
- Nitroglycerin;
- COX-2 selective and non-selective NSAIDs (chronic use also permitted);
- Over the counter medications (excluding stimulants, Kava Kava, St. John’s Wort).

Chronic Use Permitted:

- Anti-anginal agents;
- Antihypertensive agents;
- Antidepressants, Antipsychotics, Anxiolytics, and Mood stabilizer treatments prescribed for an Axis I disorder (Except for Tricyclic antidepressants, Thioridazine and Bupropion as described below);
- Aspirin;
- Bronchodilators;
- Hormone Replacement Therapy;
- Inhaled steroids;
- Lipid-lowering agents;
- Multivitamins;
- COX-2 selective and non-selective NSAIDs;
- Oral and depot contraceptives;
- Thyroid replacement;
- Oral diabetes medications.

Any Use Prohibited:

- Drugs containing bupropion;
- Varenicline (Chantix®/Champix®);
- Nicotine replacement therapy and other aids to smoking cessation;
- Naltrexone;
- Insulin;
- Theophylline;
- Warfarin;
- Monoamine oxidase (MAO) inhibitors;
- Over the counter and prescribed stimulants and anorectic agents;
- Narrow therapeutic range medications which are metabolized by CYP2D6; desipramine, nortriptyline, Type 1C antiarrhythmics (eg, propafenone, flecainide), thioridazine;
- Milnacipran (Scavella).
6. STUDY PROCEDURES

6.1. Screening

The Screening visit will occur 3 to 14 days prior to the baseline/randomization. The following procedures will be conducted during screening:

- Obtain informed consent for the clinical trial (must be signed prior to the initiation of any study related activities);
- Record demography, medical history, cardiovascular medical history, and smoking history (including questions regarding past attempts to quit smoking, cigarette use, assessment of past and present illicit drug use, an assessment of past and present alcohol use, and past use of NRT, bupropion and varenicline);
- Physical examination;
- Measure and record height;
- Complete the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID I and II). The SCID II consists of a subject- completed Personality Questionnaire and follow up Interview-based questions;
- In the event the Investigator is not a mental health professional (MHP), the subject should be evaluated by a MHP to confirm the SCID I or II diagnosis and determine if the subject is stable. A MHP must be a psychiatrist. **A subject who requires new treatment or is judged not to be clinically stable cannot be randomized**;
- Complete the Clinical Global Impression- Severity (CGI-S) Appendix 7;
- Subject completes the Suicidal Behaviors Questionnaire-Revised (SBQ-R Appendix 3;
- Complete the Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 10;
- Record concomitant medications and non- drug treatment;
- Subject completes the Fagerström Test for Nicotine Dependence\(^6\) Appendix 1;
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Record a 12-lead electrocardiogram (ECG);
- Collect blood samples for CBC and blood chemistry;
• Perform urine or serum pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal

• Perform urine drug screen (dipstick at site);

• Verify trial eligibility by checking and documenting Inclusion/Exclusion criteria; 4.1, 4.2.

• Psychiatric evaluation if warranted (See Section 7.1.10).

Subjects who did not meet study inclusion criteria may be re-screened if deemed clinically stable at a later date and the case has been reviewed and approved by the Pfizer clinician.

6.2. Study Period

6.2.1. Baseline Visit (Randomization)

The following procedures will be conducted at the Baseline visit:

• Record sitting blood pressure, pulse rate and weight;

• Review cardiovascular medical history and update as needed;

• Record volunteered adverse events;

• Complete CGI-S Appendix 7;

• Subject completes the Hospital Anxiety and Depression Scale (HADS) Appendix 2;

• Complete Aggression Questionnaire Appendix 5;

• Conduct Neuropsychiatric Adverse Events Interview and record solicited adverse events Appendix 6;

• Record concomitant medications and non-drug treatment;

• Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) Appendix 10 and record suicide-related adverse events;

• Complete the Nicotine Use Inventory (NUI) Appendix 4;

• Measure the end-expiratory exhaled carbon monoxide (exhaled CO);

• Perform urine drug screen (dipstick at site);
• Perform pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal (dipstick at site);

• Provide subject with study specific Emergency Contact Information Card;

• Smoking Cessation counselling 1:1 ≤10 minutes;

• Re-check and document Inclusion/Exclusion criteria; see Section 4.1, 4.2;

• Randomize to treatment;

• Dispense study drug: Baseline bottles of study drug;

• Psychiatric evaluation if warranted (See Section 7.1.10).

6.2.2. Clinic Visits (Week 1 to 6 Visits, Weeks, 8, 10, 12 and ET12 Visit)

One week after their Baseline visit the subject will return for the Week 1 visit. The Week 1 visit should occur on study Day 8 and will be planned to coincide with the day on which the subject will attempt to quit, called the target quit date (TQD). The subject’s last cigarette prior to the quit attempt will be before midnight prior to the Week 1 visit.

Following the Week 1 visit, clinic visits will be conducted weekly at Weeks 2, 3, 4, 5, 6 and then bi-weekly at Weeks 8, 10, and 12. Every effort should be made to have the subject return on the same day of the week for the clinic visits, thereby keeping visits on time. To accommodate unforeseen circumstances a visit window of ±3 days can be allowed throughout the study as long as proper dosing is maintained in the dosing period. The visit window should be used with discretion and all subjects should remain on original visit schedule throughout study participation (ie, If weekly visits were previously conducted on Wednesdays, the visits should return to Wednesdays after the window is utilized). If an early termination occurs before the end of Week 12, an early termination visit (ET12) will be conducted. It should be noted that these ET visits relate only to early termination in the study not early stopping of treatment, which is a situation where the subject should be encouraged to continue study participation to complete the remaining scheduled visits through Week 24. At each of these visits, the following procedures will be conducted:

• Record sitting blood pressure and pulse rate;

• Record volunteered adverse events;

• Complete CGI-I Appendix 8;

• Subject completes the HADS Appendix 2;

• Conduct Neuropsychiatric Adverse Events Interview and record solicited adverse events Appendix 6;
- Record concomitant medications and non-drug treatment and update existing concomitant medications as needed;

- Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) Appendix 10 and record suicide-related adverse events;

- Complete the Nicotine Use Inventory (NUI) Appendix 4;

- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);

- Perform pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal;

- Smoking Cessation counseling 1:1 ≤10 minutes;

- Dispense drug bottles and patches sufficient until next clinic visit (not at Week 12 or ET12);

- Subjects who report severe neuropsychiatric AEs or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) or answer "yes" to items 4, 5 or any suicidal behavioural question on C-SSRS Appendix 10 will receive a psychiatric evaluation by a qualified mental health professional (MHP: psychiatrist).

- Collect and forward records on cardiovascular events of interest or hospitalizations as defined in Appendix 12 for adjudication, if applicable.

**Additional procedures at Week 12 visit or ET12 visit.**

- Record a 12-lead electrocardiogram (ECG);

- Record sitting blood pressure and pulse rate;

- Measure and record weight;

- CBC, blood chemistry.

**6.2.3. Telephone Visits (Weeks 7, 9, 11)**

Complete the Nicotine Use Inventory (NUI). Appendix 4.

**6.3. Nontreatment Follow-up Period (Weeks 13 through 24)**

Following completion of the Week 12 visit, subjects will continue into the non-treatment follow-up phase of the protocol. If a subject discontinues study drug prior to the Week 12 visit, the subject will continue into the same non-treatment follow-up period as all other subjects. During follow-up, subjects will be monitored for cardiovascular events of interest or hospitalizations as defined in Appendix 12 for adjudication, if applicable.
visit, the subject should be encouraged to continue study participation to complete the remaining scheduled visits through Week 24.

6.3.1. Clinic Visits (Weeks 13, 16, 20, 24 and ET\textsubscript{24} Visit)

Subjects will return for visits to the clinic at the end of Weeks 13, 16, 20, and 24. If an early termination occurs after the Week 12 visit and before the Week 24 visit, an early termination visit (ET\textsubscript{24}) will be conducted. At these visits, the following procedures will be conducted:

- Record sitting blood pressure and pulse rate;
- Record Body Weight (Week 24 and ET\textsubscript{24} only);
- Record volunteered adverse events;
- Complete CGI-I; Appendix 8;
- Subject completes the HADS; Appendix 2;
- Conduct Neuropsychiatric Adverse Events Interview (NAEI) and record solicited adverse events Appendix 6;
- Record concomitant medications and non-drug treatment and update existing concomitant medications as needed;
- Complete the Columbia Suicide-Severity Rating Scale (CSSRS) Appendix 10 and record suicide-related adverse events;
- Complete the Nicotine Use Inventory (NUI) Appendix 4;
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Perform pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal at Week 16;
- Smoking Cessation counseling 1:1 ≤10 minutes;
- Subjects who report severe neuropsychiatric AEs or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) or who answer "yes" to items 4, 5 or any behavioural question on CSSRS Appendix 10 will receive a psychiatric evaluation by a qualified mental health professional (MHP: psychiatrist).
- Collect and forward records on cardiovascular events of interest or hospitalizations as defined in Appendix 12 for adjudication, if applicable.
6.3.2. Telephone Visits (Weeks 14, 15, 17, 18, 19, 21, 22, and 23)

- Complete the Nicotine Use Inventory (NUI).  Appendix 4.

6.4. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

Subjects who discontinue treatment will be encouraged to continue participation in the study and all planned assessments/evaluations. Specifically, they will maintain the visit schedule and should continue participation through the non-treatment follow-up phase of the study.

All subjects who permanently discontinue study drugs for any reason should remain in the study as Off Treatment and In Study (OTIS). Every effort should be made to keep the subject in the study until the final visit and all planned assessments/evaluations should be performed. Specifically, the subject will maintain the visit schedule and continue participation through the non-treatment follow-up phase of the study.

If a subject withdraws from the study, but does not withdraw consent, he/she should be contacted at the end of the trial to assess vital status/cardiovascular events. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. All reasonable efforts should be made to contact subjects who are lost to follow up to ascertain their reason(s) for not continuing in the study. A determination needs to be made that they are truly lost to follow up and not withdrawing for another reason (eg, adverse event or lack of efficacy).

6.4.1. Individual Subject Dosing Stopping Criteria

During the double-blind, active treatment phase subjects will be monitored on a regular basis for any clinically significant symptomatic changes, including any changes in neuropsychiatric symptoms. The following individual dosing stopping criteria will be followed:

Dosing with blinded tablet medications (varenicline, bupropion, matching placebos) may be reduced, temporarily discontinued or stopped for intolerable adverse events, or if the Investigator believes that continuing dosing will be detrimental to the subject’s mental or physical health.
Dosing with blinded NRT (NRT or matching placebo) may be temporarily discontinued or stopped for intolerable adverse events or if the Investigator believes that continuing dosing will be detrimental to the subject’s mental or physical health. It is not possible to reduce the dose of blinded NRT.

- If a subject answers “yes” on items 4, 5 or to any behavioral question on the CSSRS, Appendix 10 the subject must have a risk assessment by a qualified mental health professional (MHP: Psychiatrist) to determine whether it is safe to continue active dosing in trial. In the event the risk assessment can not be immediately performed, it will be at the discretion of the Investigator to determine if study drug should be discontinued (temporarily or permanently) until the risk assessment is completed.

- Study drug will be discontinued immediately for any female subject who becomes pregnant during the treatment period of the study. These subjects should continue to attend study visits OTIS as noted in Section 6.4.

7. ASSESSMENTS

7.1. Safety

7.1.1. Adverse Events

All adverse events (AEs) volunteered, observed, or solicited (of all severities) will be recorded in the AE CRF from the time the subject signs the informed consent up to and including Week 24.

Solicited neuropsychiatric adverse events will be collected by use of the Neuropsychiatric Adverse Event Interview (NAEI) at each clinic visit (starting from baseline) up to and including Week 24. The voluntarily reported AEs will be assessed first at each study visit followed by the NAEI Appendix 6 and then the CSSRS Appendix 10.

When reporting an adverse event, verbatim text will also be recorded on a supplemental adverse event reporting page. Reported events by a household member of the subject or personal physician, which are deemed to be adverse events by the Investigator, will be captured as adverse events and the reporters’ verbatim text of these events will also be captured.

Suicide related adverse events will be solicited by completion of the C-SSRS at each clinic visit up to and including Week 24. Any severe neuropsychiatric adverse event(s) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) recorded will require the subject to receive a psychiatric evaluation by a qualified mental health professional MHP (Psychiatrist) (Section 7.1.10) and a narrative will be constructed for each event. In the event the investigator meets the requirements of the MHP, he/she may complete this evaluation.
Subjects will be provided with study specific Emergency Contact Information cards at the baseline visit. The card will state that the subject has made a commitment to stop smoking and has joined the study and seeks the help and support of the family at home. It will state the list of neuropsychiatric events of concern and encourage the family to call the site to report such events if the subject himself/herself seems unaware. If the subject consents, an additional card will be provided for the subject’s PCP. In this manner, household members and PCPs will be alerted to the possibility of adverse events and provided with direct contact information for study site personnel.

7.1.1.1. Primary Neuropsychiatric Safety Endpoint

The primary safety endpoint is the occurrence of at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal or hostility and/or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide.

Thus, the adverse event database will include items having been captured by any of the following means:

- Volunteered adverse event reporting;
- Actively solicited neuropsychiatric adverse events through the conduct of the Neuropsychiatric Adverse Event Interview (NAEI) Appendix 6 deemed to be adverse events by the Investigator;
- Items captured from proxy report (ie, PCP, family member) judged to be adverse events by the Investigator;
- Suicide related events solicited by completion of the C-SSRS Appendix 10 and deemed to be an adverse event by the Investigator.

The primary safety endpoint encompasses events reported (via the AE CRF page) through any of the above means of assessments. Additionally, the MedDRA version and Preferred Terms to be included in the primary safety endpoint will be described in the Statistical Analysis Plan.

Secondary safety endpoint related to adverse events is the occurrence of the components of the primary safety endpoint.

7.1.1.2. Actively Solicited Neuropsychiatric Adverse Events

The Neuropsychiatric Adverse Event Interview (NAEI) Appendix 6, will actively inquire about the following type of adverse events: aggression, anxiety, agitation, depression, delusions, dissociative states, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, paranoia, panic, and psychosis. The NAEI, developed by Pfizer, was piloted in a
similar population to the one to be included in this study (patients with and without a history of psychiatric disease enrolled in a smoking cessation program) to evaluate patient understanding of all questions. The results of the study support use of the NAEI for neuropsychiatric adverse events solicitation.

If a subject has a positive response to any item on the NAEI, a determination will be made by the investigator as to whether this meets criteria for an adverse event. If it does meet criteria as an adverse event it will be recorded on the adverse event pages of the Case Report Form.

7.1.2. Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 10, and the Suicidal Behaviors Questionnaire (SBQ-R) Appendix 3

The C-SSRS will be completed by trained site personnel at screening and at each subsequent clinic visit up to and including Week 24. The Suicidal Behaviors Questionnaire- Revised (SBQ-R) will be completed by the subject at the screening visit.

At the screening visit, to detect possible suicidality, the C-SSRS and SBQ-R are completed. A risk assessment will be done by a qualified mental health professional (MHP: Psychiatrist) if the subject’s responses on either of these screening instruments indicate:

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS; Appendix 10.
- Previous history of suicide behaviors in the past year;
- In the investigator’s judgment a risk assessment is required.

At post-baseline visits during the study if subject answers “yes” on items 4, 5 or on any suicidal behavioral question on C-SSRS (Appendix 10) a risk assessment will be done by a qualified MHP to determine whether it is safe to continue active dosing in trial.

7.1.3. Hospital Anxiety and Depression Scale (HADS) Appendix 2

The HADS is a subject self-report scale and contains 14 items rated on 4-point Likert-type scales. Two subscales assess depression and anxiety.

If a subject scores ≥11 on the Depression subscale of the HADS at baseline or any time during the study, the subject should receive an evaluation by a MHP (see section 7.1.10).

Subjects’ self report via the HADS is aimed to more fully characterize potential depression and anxiety related events. These additional measurements will be collected and evaluated in a different manner than the observed or volunteered adverse events. No attempt will be made to resolve any apparent discrepancies between observed or volunteered adverse events and the additional data collected from subjects using the HADS self-report. These additional data will be presented in separate tables, separate figures, and separate data listings, and will be reviewed in the final study report.
7.1.4. Clinical Global Impression of Severity (CGI-S) Appendix 7

The CGI-S is a clinician rated instrument measuring the severity of a subject’s psychiatric condition on a 7 point scale at time of assessment, relative to clinician's past experience in patients with same diagnosis. The scores are: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; or 7=extremely ill. The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician’s experience with the psychiatric population to which the subject belongs. This scale should be administered by the same rater throughout the study whenever possible.

7.1.5. Clinical Global Impression of Improvement (CGI-I) Appendix 8

The CGI-I is a clinician rated instrument that measures change in subject’s psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale ranging from 1 (very much improved) to 7 (very much worse). The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician’s experience with the psychiatric population to which the subject belongs. This scale should be administered by the same rater throughout the study whenever possible.

7.1.6. Aggression Questionnaire (AQ) Appendix 5

The Aggression Questionnaire is a subject self-reported scale and consists of 4 factors, Physical Aggression (PA), Verbal Aggression (VA), Anger (A) and Hostility (H), measured only at baseline for use as an historical benchmark. The total score for Aggression is the sum of the factor scores.¹

7.1.7. Nicotine Use Inventory (NUI) Appendix 4

The Nicotine Use Inventory (NUI) is a questionnaire regarding use of cigarettes and other nicotine-containing products during the treatment period or tobacco products during non-treatment follow-up period. The NUI was designed for and applied in previous varenicline studies. The NUI will be completed weekly at all clinical visits and telephone contacts.
7.1.8. End-Expiratory Exhaled Carbon Monoxide (Exhaled CO)

In order to confirm the smoking abstinence reported in the NUI, an end-expiratory exhaled carbon monoxide (exhaled CO) will be measured at each clinic visit using a breath CO monitor. An exhaled CO ≤10 ppm is required to claim successful smoking cessation.

7.1.9. Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence provides a short, self-reported measure of dependency on nicotine. This test will be completed at screening only. The test’s questions and scale are shown in Appendix 1.

7.1.10. Psychiatric Evaluations/Risk Assessments

A risk assessment should be done by a qualified mental health professional (MHP: a psychiatrist) if any of the following conditions are met:

- If a subject reports a severe neuropsychiatric adverse event (as detailed in Section 2.2.1) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) the subject will be referred for a psychiatric evaluation;
- Subject answers “yes” on item 5, on C-SSRS during the screening visit or subject answers “yes” on item 4, 5 or on any suicidal behavioral question on C-SSRS Appendix 10 during the study;
- Previous history of suicide behaviors in the past year (prior to randomization);
- The subject scores ≥11 on the Depression subscale of the HADS Appendix 2 at baseline or at any time during the study.

The investigator may also refer a subject for a psychiatric evaluation if they have concerns over their subject’s psychiatric condition at any other stage during the study.

The following items will be addressed in each evaluation:

- Is a therapeutic intervention required for the subject?
- Arrangement for treatment and follow-up as appropriate if a therapeutic intervention is required;
- Is this a new DSM IV diagnosis for this subject or an exacerbation of a pre-existing condition?
The evaluation will be done by a qualified mental health professional (MHP: Psychiatrist). In the event the Investigator is also qualified as a MHP, he or she may conduct this evaluation. A written copy of the risk assessment should be included in the subject’s clinical record as source document and will be recorded in the case report form. Subjects who have a “yes” response on items 4, 5 or on any suicidal behavioral question on C-SSRS on more than one occasion during a study must have their potential suicidality managed appropriately by the Investigator together with a qualified MHP (or the Investigator alone if the Investigator is a qualified MHP). The subjects can continue dosing while being evaluated, at the Investigator’s discretion. In addition, the Investigator should consult with the Pfizer clinician to determine whether the subject can continue in the study.

7.1.11. Psychiatric Treatment Monitoring

At each clinic visit up to and including Week 24, any requirement for either a change in treatment or an initiation of treatment for an Axis I or II disorder (either drug therapy or psychotherapy) will be recorded.

7.1.12. Physical Examination, Vital Signs and Electrocardiogram

A physical examination will be performed at the screening visit. Abnormal changes from screening deemed clinically significant by the Investigator should be recorded as adverse events.

Body weight will be measured at the baseline visit and Wk 12 or ET12 and Wk 24 or ET24. Height will be measured at the Screening visit. Both will be measured in indoor clothing without shoes.

Sitting blood pressure and pulse rate will be measured at the baseline visit Wks 1, 2, 3, 4, 5, 6, 8, 10, Wk 12 or ET12 and Wks 13, 16, 20 and 24 or ET24. Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest mmHg. All blood pressure measurements are to be taken in the dominant arm with the appropriate size cuff. Pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

A 12-lead electrocardiogram will be obtained at screening and at the end of treatment study visit (Wk 12 or ET12).

7.1.13. Medical History

Medical history, which comprises all past and present diseases or syndromes that in the Investigator's judgment are considered to be clinically significant, will be recorded in the CRF. This includes recording any significant cardiovascular, respiratory, endocrine/metabolic, gastrointestinal, genitourinary, musculoskeletal, hematological, neurological, neoplastic disease, drug abuse, or other relevant conditions. Medical history will be collected at screening visit only.
7.1.14. Laboratory

Blood chemistry, complete blood count with differential and platelet count will be completed at the Screening visit and at Week 12/ET. A minimum of 8 hour fast is needed prior to blood collection for the chemistry panel. A urine drug screen will be performed at the Screening and Baseline visits (dipstick at site) and at other visits at the investigator’s discretion. Pregnancy test for all women, unless surgically sterilized or at least 2 years postmenopausal will be completed at Screening and Baseline, Week 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 (dipstick at site or serum).

7.1.15. Cardiovascular (CV) Events of Interest

Cardiovascular adverse events will be prospectively reviewed and adjudicated by an independent Cardiovascular Event Adjudication Committee. The committee will be blinded to study treatment allocation. The committee will confirm diagnosis for cardiovascular events of interest based on review of documentation provided by investigators. All deaths will be reviewed by the adjudication committee who will make a determination of whether a death is cardiovascular or non-cardiovascular.

Clinically significant cardiac events of interest include:

- Non-fatal myocardial infarction;
- Resuscitated cardiac arrest;
- Need for coronary revascularization;
- Hospitalization for unstable angina;
- Hospitalization for congestive heart failure;
- Fatal, non-fatal stroke or transient ischemic attack (TIA);
- Any new diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any procedure for the treatment of PVD (or any peripheral vascular intervention);
- Cardiovascular death.

In order to ensure that no potential SAEs of interest are missed, in addition to the events above any hospitalization for angina, chest pain, loss of consciousness, cardiac or vascular procedures, respiratory diseases (excluding infections and cancer), and generalized edema will be sent for adjudication as described in Section 9.8. The sponsor will periodically review adverse event lists to identify additional cases for adjudication, irrespective of the diagnosis as described in Section 9.8.
7.1.15.1. Serious Cardiac Arrhythmias

In addition to cardiac events of interest serious cardiac arrhythmias will be reviewed and adjudicated by the independent adjudication committee. Serious cardiac arrhythmias are defined as the presence of a sustained cardiac rhythm disturbance lasting more than 1 minute which results in either hemodynamic compromise, syncope, cardiac arrest, a cerebral vascular event, or altered mental status, and requires urgent intervention with cardiac monitoring, drug therapy, cardioversion, or placement of a temporary pacemaker.

Examples include:

- Ventricular tachycardia;
- Torsade de Pointes;
- Ventricular fibrillation;
- AICD discharge (must state the underlying initiating rhythm);
- Bradycardia;
- Complete heart block;
- Atrial fibrillation / flutter;
- Supraventricular tachycardia;
- Sick sinus syndrome;
- Second degree heart block (type 2).

7.2. Efficacy

7.2.1. Measures of Abstinence from Smoking

Information for the calculation of abstinence parameters will be obtained at each clinic visit or telephone contact from a set of questions about cigarette and other nicotine use since the last visit/contact (Nicotine Use Inventory). At clinic visits, subject reports of smoking status will be confirmed by measurement of end expiratory exhaled carbon monoxide (CO) concentration, with a result <=10 ppm indicating abstinence.

The main efficacy endpoint for the study is CO-confirmed 4-week continuous abstinence for Weeks 9 through 12, as determined by their answers to questions on the Nicotine Use Inventory and confirmation of their exhaled CO.
The secondary efficacy endpoint for the study is CO-confirmed continuous abstinence for Weeks 9 through 24, as determined by their answers to questions on the Nicotine Use Inventory and confirmation of their exhaled CO.

Additionally, other secondary endpoints arise from the NUI assessment:

Seven-day point prevalence of abstinence: CO-confirmed 7-day continuous abstinence for each NUI assessment visit (separately), as determined by their answers to the ‘last 7 days’ questions on the Nicotine Use Inventory (NUI) and confirmation of their exhaled CO.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed, volunteered or solicited adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

8.2. Reporting Period

For serious adverse events, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject’s participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Should an investigator be made aware of any serious adverse event occurring any time after the reporting period, it must be promptly reported.

Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject provides informed consent through last subject visit.
8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breast feeding;
- Medication error.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
• Test result requires additional diagnostic testing or medical/surgical intervention, and/or

• Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

• Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

• Results in death;

• Is life-threatening (immediate risk of death);

• Requires inpatient hospitalization or prolongation of existing hospitalization;

• Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

• Results in congenital anomaly/birth defect;

• Lack of efficacy should be reported as an adverse event when it is associated with a serious adverse event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.
8.5.1. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy’s Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT $\geq 3$ times the upper limit of normal (X ULN) concurrent with a total bilirubin $\geq 2$ X ULN with no evidence of hemolysis and an alkaline phosphatase $\leq 2$ X ULN or not available.

- For subjects with preexisting ALT OR AST OR total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
  - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT $\geq 2$ times the baseline values and $\geq 3$ X ULN, or $\geq 8$ X ULN (whichever is smaller).

- Concurrent with
  - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal OR $\geq 3$ times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting criteria a or b, with no other cause for LFT abnormalities identified at the time should be considered potential Hy’s Law cases.
irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy’s Law cases should be reported as serious adverse events. All study drug treatments should be discontinued in these events.

8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;
**8.7. Severity Assessment**

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>Does not interfere with subject's usual function.</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Interferes to some extent with subject's usual function.</td>
</tr>
<tr>
<td>SEVERE</td>
<td>Interferes significantly with subject's usual function.</td>
</tr>
</tbody>
</table>

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

**8.8. Causality Assessment**

The investigator’s assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as “related to investigational product” for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

**8.9. Exposure During Pregnancy**

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product;
2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner’s pregnancy.

If a study subject or study subject’s partner becomes or is found to be pregnant during the study subject’s treatment with the investigational product, the investigator must submit this information to Pfizer on an EIU Form (this is a specific version of the Serious Adverse Event Form). In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the EIU Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the EIU Form that the subject was given this letter to provide to his partner.
8.10. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.11. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events voluntarily reported by the study subject. In addition, each study subject will be questioned about adverse events as described in Section 7.1.1.

8.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.12.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breast feeding cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.
8.12.2. Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.12.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse events reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

This study serves as the parent study to A3051148, the later representing an extended cardiovascular adverse event surveillance period. The endpoints for A3051123 focus on neuro-psychiatric adverse events. Hence, all other adverse events (including those cardiovascular in nature) that occur during study conduct will be reported according to Pfizer safety standards. Subsequently, all data from this parent study deemed necessary to properly summarize and report cardiovascular safety, including the derivation of composite endpoints for cardiovascular adverse events, will be incorporated into the overall evaluation of A3051148.

9.1. Analysis Sets

The Safety analysis population contains all treated subjects.

The full analysis set (FAS) is defined under the intent-to-treat principle, namely as all randomized subjects.

Treatment misallocation rules will be specified in the Statistical Analysis Plan.
9.2. Sample Size Determination

The study is sized to attain an adequate level of precision in the estimation of the treatment difference for varenicline and bupropion versus placebo in the incidence of the primary neuropsychiatric safety endpoint within each cohort.

For the subjects in the cohort without a diagnosis of psychiatric disorder, considering both the available data from the varenicline randomized double-blind placebo-controlled clinical trials as well as the planned usage of the NAEI to aid in data collection, the incidence estimate for placebo is assumed to be approximately 3.5% for volunteered neuropsychiatric adverse events included in the primary safety endpoint. If there were an attributable risk difference of 2.63% (which translates to a 75% increase in the relative risk scale), a sample size of 1,000 per treatment group will provide sufficient precision with an expected 95% confidence interval of (0.75% to 4.50%), ie, a margin of error of ±1.87%.

For the subjects in the cohort with a diagnosis of psychiatric disorder, there are no sufficient data available and a 7.0% incidence for the placebo group is hypothesized. If there were a similar relative risk increase, an attributable risk difference of 5.25%, the sample size of 1,000 per treatment group will provide sufficient precision with an expected 95% confidence interval of (2.68% to 7.82%), ie, a margin of error of ±2.57%.

The preceding assumptions, when taken together to produce a stratified pooled estimate of risk difference, suggests that a sample size of 2,000 per treatment group will provide sufficient precision with an expected 95% confidence interval of (2.34% to 5.52%), ie, a margin of error of ±1.59%.

The main abstinence (efficacy) superiority analyses are adequately powered. Given a placebo rate of 10% and 1,000 subjects per treatment group per cohort, an odds ratio of 2.0 can be detected at a 5% level with at least 80% power.

9.3. Safety Objective Analysis

Primary Safety Objectives:

1. To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo with a pre-specified level of precision in the incidence of the primary neuropsychiatric AE endpoint for subjects:
   a. With a diagnosis of psychiatric disorder;
   b. Without a diagnosis of psychiatric disorder.

2. To characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).
Secondary safety objectives include an assessment of the above two objectives with respect to each of the remaining pairwise treatment comparisons.

The primary safety analyses will provide model-based estimates and associated 95% confidence intervals for the difference in the incidence of the primary neuropsychiatric safety endpoint between varenicline and placebo and between bupropion and placebo for subjects in each cohort. Further, an interaction involving treatment and cohort will be tested at a 10% level and, lacking evidence of significant interaction, pooled estimates of these risk differences and their associated 95% confidence intervals will be computed.

The preceding primary safety analysis will be repeated for each of the components of the composite safety endpoint.

Adverse event, laboratory, and other safety data (e.g., Hospital Anxiety and Depression Scale (HADS) and the Clinical Global Impression of Improvement (CGI-I) will be summarized by frequencies of events and or mean changes from baseline to each assessment period, as appropriate.

Additional adverse event summaries will be done for the post treatment follow up period.

The safety summaries will include:

- A summary of neuropsychiatric adverse events of interest leading to treatment and/or study discontinuations.
- A summary of neuropsychiatric adverse events of interest resulting in an intervention.

Adverse event frequencies and other safety data on the active control drug (NRT) will be summarized and tabulated.

### 9.4. Efficacy Objective Analysis

Main Efficacy Objective: To compare smoking abstinence rates of varenicline and bupropion relative to placebo for the last 4 weeks of treatment and continuously through Week 24, as measured by CO-confirmed CAR9-12 and CAR9-24, respectively, separately for subjects with and without a diagnosis of psychiatric disorder.

Secondary Objective: To assess if there is a difference between cohorts in the placebo adjusted relative abstinence rates (CAR9 12 and CAR9 24) of varenicline and bupropion, separately.
Hypotheses and Decision Rules

The main and secondary abstinence hypotheses are to test the superiority of varenicline versus placebo (and, separately, bupropion versus placebo), with respect to CAR9-12 and CAR9-24. Each cohort is to be tested individually at a 5% level, without any multiplicity adjustment. Furthermore, in the event that the Statistical Analysis Plan declares an interaction term(s) within the construct of a statistical model, assessment for significance of any such interaction term is to be done individually at a 10% level.

Other secondary efficacy objectives include an assessment of the above two objectives with respect to each of the remaining four pairwise treatment comparisons.

9.5. Methods and Analysis

The primary and secondary safety and abstinence endpoints are binary in nature. Appropriate descriptive statistics will be provided for these endpoints.

The statistical model used in the safety and abstinence analyses will be a logistic regression model that controls for the effects due to treatment, cohort and pooled site (the latter defined explicitly in the SAP).

Logistic regression analyses will be based on a binomial distribution with either an identity link function (risk difference for safety endpoints) or a logit link function (odds ratios for abstinence endpoints). Contrasts will be constructed for the primary and secondary pairwise treatment comparisons, both per cohort as well as for the pooled cohorts. For each contrast, the risk difference (or odds ratio) estimate and respective 95% confidence interval will be produced. There is no adjustment for multiplicity. Furthermore, any interaction assessment will be conducted at a 10% level. If warranted, the computation of estimates arising from the pooling of cohorts will not involve any model reduction.

Analyses for abstinence endpoints will be based on the FAS. Analyses for safety endpoints will be based on the Safety population. Adverse event data and the primary neuropsychiatric safety endpoint will be summarized and respectively analyzed using Pfizer Safety Standards and a 30-day lag following the end of 12 weeks of treatment for treatment-emergent all causality adverse events. Non-treatment-emergent adverse events (i.e., from 30 days following the end of treatment through week 24) will also be summarized.

For those subjects in the “with diagnosis of psychiatric disorder” cohort, the investigator will record the primary major diagnosis group (psychotic disorders, affective disorders, anxiety disorders or borderline personality disorders) on the CRF, in effect defining a sub-cohort for each of these subjects. It is noted that with respect to analyses, cohort has two levels: (1) without diagnosis of psychiatric disorder and (2) with diagnosis of psychiatric disorder. Any secondary analysis that focuses on partitioning the “with diagnosis of psychiatric disorder” cohort will utilize the primary major diagnosis group as indicated on the CRF. Further analysis details will be presented in the SAP.
9.6. Interim Analysis

The unblinded primary endpoint rate (along with all AE reporting and other safety data) will be monitored at the periodic meetings of the Independent Data Monitoring Committee (IDMC). Recommendations by the IDMC to the sponsor based on the primary endpoint rate can occur throughout the study following any of the IDMC meetings. These recommendations could be related to emerging risk in one of the treatment arms or a lower primary endpoint rate than planned for in the protocol.

The sponsor will also request that the IDMC provide the blinded (pooled across both treatment and cohort) primary endpoint rate after 50% of the subjects have completed the study. If this endpoint rate is below 3.5%, then the sponsor will notify the regulators of the lower than planned endpoint rate and, if needed, request a meeting to discuss the potential implications for the study sample size and number of investigator sites.

An unblinded interim statistical analysis will be conducted and reported to the IDMC after 75% of the subjects have completed the study. This unblinded interim analysis will consist of all pair-wise treatment comparisons within and combined over the two cohorts of subjects with and without a history of psychiatric illness. Also, an upper 1-sided 95% confidence interval for the placebo primary endpoint rate in the no history cohort will be computed and projected to the planned study size. If this projected upper bound is less than 3.5%, then a sample size re-estimation will be performed. Further details will be specified within the formal Interim Analysis Plan. The sponsor will remain blinded to the interim results. The unblinded interim analysis at the 75% point is considered optimum because it will provide sufficient data (both in terms of precision and improved balance in randomization) to make recommendations regarding the possible increase in sample size as well as give sufficient time for the sponsor to implement the recommendations. Furthermore, any sample size re-estimation would apply to all treatment groups in both cohorts (ie, all treatment allocation ratios remain unchanged) and no treatment group in either cohort would stop enrollment. Any recommendations made by the IDMC as a result of the unblinded interim analysis will be communicated to the regulators before implementation.

9.7. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to assess safety data at regular intervals for the duration of the trial and make recommendations to the Executive Steering Committee on whether to continue, modify or stop the study. An IDMC charter authored a priori and governed by the IDMC will be completed.

The committee will be responsible for ongoing monitoring of the safety of subjects in the study. Any recommendation made by the committee to alter the conduct of the study will be forwarded to the Sponsor for final decision. The Sponsor will forward such decisions, which may include summaries of aggregate analyses of safety endpoint events, to regulatory authorities, as appropriate.
9.8. Cardiovascular Event Adjudication Committee (CEAC)

An independent adjudication committee will review documentation provided by investigators during study conduct to identify cardiovascular events of interest (primary and secondary CV safety endpoints). Investigators will collect and submit documentation to the CEAC for all adverse events related to:

- Non-fatal myocardial infarction;
- Any hospital admission for chest pain;
- Hospitalization for angina pectoris/unstable angina;
- Need for coronary revascularization or any cardiac or vascular intervention;
- Resuscitated cardiac arrest;
- Hospitalization for congestive heart failure;
- Fatal, non-fatal stroke or transient ischemic attack (TIA);
- Any diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any procedure for the treatment of PVD;
- Cardiovascular Death;
- Death from any cause:
- Hospitalization for loss of consciousness:
- Respiratory diseases (excluding infections and cancer),
- Generalized edema

To ensure that all possible cardiovascular adverse events of interest (primary and secondary endpoints) are referred to the CEAC for review, a listing of all adverse events (serious and non-serious) from the following SOCs, HLGT, HLT, LLT and PTs will be prepared monthly and sent to the CEAC.

1. All Deaths.
2. SOCs:
   - Cardiac Disorders;
   - General Disorders and Administration Site Conditions;
• Injury, Poisoning, and Procedural Complications;
• Investigations;
• Musculoskeletal and Connective Tissue Disorders;
• Nervous System Disorders;
• Respiratory, Thoracic, and Mediastinal Disorders;
• Surgical and Medical Procedures;
• Vascular Disorders.

3. HLGT:
• Tissue disorders NEC.

4. HLT:
• Necrosis, NEC.

5. LLTs:
• Cerebral Revascularization Synangiosis (search value: revascularization);
• Coronary Revascularization (search value: revascularization);
• Peripheral Revascularization (search value: revascularization);
• Renal Revascularization (search value: revascularization);
• Transmyocardial Revascularization (search value: revascularization);
• Acute myocardial ischemia (search value: myocardial ischemia);
• ECG signs of myocardial ischemia (search value: myocardial ischemia);
• Myocardial ischemia (search value: myocardial ischemia);
• Myocardial ischemia recurrent (search value: myocardial ischemia);
• Silent myocardial ischemia (search value: myocardial ischemia).

6. PTs:
• Acute Myocardial Infarction (search value: myocardial infarction);
• Myocardial Infarction (search value: myocardial infarction);
• Post Procedural Myocardial Infarction (search value: myocardial infarction);
• Silent Myocardial Infarction (search value: myocardial infarction);
• Cell Death.

These searches will be complemented by a quarterly standardized Medra query for other possible CV events that may also require adjudication.

• Myocardial Infarction;
• Ischemic Heart Disease;
• Cardiac Arrhythmias;
• Cardiac Failure;
• Embolic and Thrombotic Events;
• Shock;
• Torsade de pointes/QT prolongation;
• Cerebrovascular Disorders;
• Central Nervous System Haemorrhages and Cerebrovascular Accidents;
• Vasculitis;
• Cardiomyopathy;
• Hemodynamic edema, effusions, and fluid overload;
• Hypertension;
• Pulmonary Hypertension;
• Renovascular Disorders;
• Shock.

The events will be adjudicated using a standard events manual under blinded conditions. The adjudication committee will make the determination of whether a death is cardiac or non cardiac.
The independent adjudication committee will also review serious cardiac arrhythmias. Serious cardiac arrhythmias are defined as the presence of a sustained cardiac rhythm disturbance lasting more than 1 minute which results in either hemodynamic compromise, syncope, cardiac arrest, a cerebral vascular event, or altered mental status, and requires urgent intervention with cardiac monitoring, drug therapy, cardioversion, or placement of a temporary pacemaker.

Examples include:

- Ventricular tachycardia;
- Torsade de Pointes;
- Ventricular fibrillation;
- AICD discharge (must state the underlying initiating rhythm);
- Bradycardia;
- Complete heart block;
- Atrial fibrillation / flutter;
- Supraventricular tachycardia;
- Sick sinus syndrome;
- Second degree heart block (type 2).

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.
11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry”.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.
12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, Molecular Profiling Supplement, informed consent forms, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.
12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as last subject’s last visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of varenicline at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer posts the results of all studies that it has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within one year of the primary outcome completion date (PCD).
- For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV).
- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.
Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.
16. REFERENCES


10. Study Report: Assessing the Content Validity of the Neuropsychiatric Adverse Events Interview (NAEI), 12 Jan 2011 http://gdms.pfizer.com/gdms/drl/objectId090177e181ba217d

## Appendix 1. Fagerström Test for Nicotine Dependence

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answers</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How soon after you wake up do you smoke your first cigarette?</td>
<td>Within 5 minutes</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6-30 minutes</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31-60 minutes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>After 60 minutes</td>
<td>0</td>
</tr>
<tr>
<td>2. Do you find it difficult to refrain from smoking in places where it is forbidden eg, in church, at the library, in the cinema, etc.?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>3. Which cigarette would you hate most to give up?</td>
<td>The first one in the morning</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any other</td>
<td>0</td>
</tr>
<tr>
<td>4. How many cigarettes/day do you smoke?</td>
<td>10 or less</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21-30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31 or more</td>
<td>3</td>
</tr>
<tr>
<td>5. Do you smoke more frequently during the first hours after waking than during the rest of the day?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>6. Do you smoke if you are so ill that you are in bed most of the day?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>
Appendix 2. Hospital Anxiety and Depression Scale (HADS)

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and Check (✓) the reply which comes closest to how you have been feeling in the past week. Ignore the numbers printed beside each response. Don’t take too long over your replies, your immediate reaction to each item will probably be more accurate than a long thought-out response.

HADS copyright R.P. Snaith and A.S. Zigmond 1983, 1992, 1994. Record from items originally published in Acta Psychiatrica Scandinavica, 67, 361–70, copyright © Munksgaard International Publishers Ltd, Copenhagen, 1983. Published by GL Assessment Limited, The Chiswick Centre, 414 Chiswick High Road, London W4 5TF, UK. All rights reserved. GL Assessment is part of the Granada Learning Group. This work may not be photocopied or otherwise reproduced by any means, even within the terms of a Photocopying Licence, without the written permission of the Publishers.
## Appendix 3. Suicide Behaviors Questionnaire-Revised (SBQ-R)

**Instructions:** Please check the number beside the statement or phrase that best applies to you.

### 1. Have you ever thought about or attempted to kill yourself? (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Never</td>
<td></td>
</tr>
<tr>
<td>2. It was just a brief passing thought</td>
<td></td>
</tr>
<tr>
<td>3a. I have had a plan at least once to kill myself but did not try to do it</td>
<td></td>
</tr>
<tr>
<td>3b. I have had a plan at least once to kill myself and really wanted to die</td>
<td></td>
</tr>
<tr>
<td>4a. I have attempted to kill myself, but did not want to die</td>
<td></td>
</tr>
<tr>
<td>4b. I have attempted to kill myself, and really hoped to die</td>
<td></td>
</tr>
</tbody>
</table>

### 2. How often have you thought about killing yourself in the past year? (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Never</td>
<td></td>
</tr>
<tr>
<td>2. Rarely (1 time)</td>
<td></td>
</tr>
<tr>
<td>3. Sometimes (2 times)</td>
<td></td>
</tr>
<tr>
<td>4. Often (3-4 times)</td>
<td></td>
</tr>
<tr>
<td>5. Very Often (5 or more times)</td>
<td></td>
</tr>
</tbody>
</table>

### 3. Have you ever told someone that you were going to commit suicide, or that you might do it? (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No</td>
<td></td>
</tr>
<tr>
<td>2a. Yes, at one time, but did not really want to die</td>
<td></td>
</tr>
<tr>
<td>2b. Yes, at one time, and really wanted to die</td>
<td></td>
</tr>
<tr>
<td>3a. Yes, more than once, but did not want to do it</td>
<td></td>
</tr>
<tr>
<td>3b. Yes, more than once, and really wanted to do it</td>
<td></td>
</tr>
</tbody>
</table>

### 4. How likely is it that you will attempt suicide someday? (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Never</td>
<td></td>
</tr>
<tr>
<td>1. No chance at all</td>
<td></td>
</tr>
<tr>
<td>2. Rather unlikely</td>
<td></td>
</tr>
<tr>
<td>3. Unlikely</td>
<td></td>
</tr>
<tr>
<td>4. Likely</td>
<td></td>
</tr>
<tr>
<td>5. Rather likely</td>
<td></td>
</tr>
<tr>
<td>6. Very likely</td>
<td></td>
</tr>
</tbody>
</table>

Appendix 4. Nicotine Use Inventory (NUI)

As asked at the Baseline through the Week 12 visit:

- Has the subject smoked any cigarettes (even a puff) since the last site visit / telephone contact?
- Has the subject used any other nicotine-containing products* (e.g., nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) since the last site visit / telephone contact?
- Has the subject smoked any cigarettes (even a puff) in the last 7 days?
- If the subject smoked in the last 7 days, has the subject had any days on which no cigarettes were smoked, and if so, how many days?
- If the subject smoked in the last 7 days, how many cigarettes did the subject smoke per day, on average for the days on which smoking occurred?
- Has the subject used any other nicotine-containing products* (e.g., nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) in the last 7 days?

* This question refers to any unauthorized nicotine containing products and not the NRT patch which was provided during study treatment phase.

As asked at the Week 13 visit through the Week 24 visit:

- Has the subject smoked any cigarettes (even a puff) since the last site visit / telephone contact?
- Has the subject used any other tobacco products (e.g., pipe, cigars, chew, snuff) since the last site visit / telephone contact?
- Has the subject smoked any cigarettes (even a puff) in the last 7 days?
- If the subject smoked in the last 7 days, has the subject had any days on which no cigarettes were smoked, and if so, how many days?
- If the subject smoked in the last 7 days, how many cigarettes did the subject smoke per day, on average for the days on which smoking occurred?
- Has the subject used any other tobacco products (e.g., pipe, cigars, chew, snuff) in the last 7 days?
- Nicotine replacement therapy and/or other smoking cessation medications should be recorded in the concomitant medicine pages in the case report form.
Appendix 5. Aggression Questionnaire (AQ)

Instructions:

Using the 5 point scale shown below, indicate how uncharacteristic or characteristic each of the following statements is in describing you. Place your rating in the box to the right of the statement.

1 = extremely uncharacteristic of me
2 = somewhat uncharacteristic of me
3 = neither uncharacteristic nor characteristic of me
4 = somewhat characteristic of me
5 = extremely characteristic of me

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Some of my friends think I am a hothead</td>
</tr>
<tr>
<td>2.</td>
<td>If I have to resort to violence to protect my rights, I will.</td>
</tr>
<tr>
<td>3.</td>
<td>When people are especially nice to me, I wonder what they want.</td>
</tr>
<tr>
<td>4.</td>
<td>I tell my friends openly when I disagree with them.</td>
</tr>
<tr>
<td>5.</td>
<td>I have become so mad that I have broken things.</td>
</tr>
<tr>
<td>6.</td>
<td>I can’t help getting into arguments when people disagree with me.</td>
</tr>
<tr>
<td>7.</td>
<td>I wonder why sometimes I feel so bitter about things.</td>
</tr>
<tr>
<td>8.</td>
<td>Once in a while, I can’t control the urge to strike another person.</td>
</tr>
<tr>
<td>9.</td>
<td>I am an even-tempered person.</td>
</tr>
<tr>
<td>10.</td>
<td>I am suspicious of overly friendly strangers.</td>
</tr>
<tr>
<td>11.</td>
<td>I have threatened people I know.</td>
</tr>
<tr>
<td>12.</td>
<td>I flare up quickly but get over it quickly.</td>
</tr>
<tr>
<td>13.</td>
<td>Given enough provocation, I may hit another person.</td>
</tr>
<tr>
<td>14.</td>
<td>When people annoy me, I may tell them what I think of them.</td>
</tr>
<tr>
<td>15.</td>
<td>I am sometimes eaten up with jealousy.</td>
</tr>
<tr>
<td>16.</td>
<td>I can think of no good reason for ever hitting a person.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>17.</td>
<td>At times I feel I have gotten a raw deal out of life.</td>
</tr>
<tr>
<td>18.</td>
<td>I have trouble controlling my temper.</td>
</tr>
<tr>
<td>19.</td>
<td>When frustrated, I let my irritation show.</td>
</tr>
<tr>
<td>20.</td>
<td>I sometimes feel that people are laughing at me behind my back.</td>
</tr>
<tr>
<td>21.</td>
<td>I often find myself disagreeing with people.</td>
</tr>
<tr>
<td>22.</td>
<td>If somebody hits me, I hit back.</td>
</tr>
<tr>
<td>23.</td>
<td>I sometimes feel like a powder keg ready to explode.</td>
</tr>
<tr>
<td>24.</td>
<td>Other people always seem to get the breaks.</td>
</tr>
<tr>
<td>25.</td>
<td>There are people who pushed me so far that we came to blows.</td>
</tr>
<tr>
<td>26.</td>
<td>I know that &quot;friends&quot; talk about me behind my back.</td>
</tr>
<tr>
<td>27.</td>
<td>My friends say that I am somewhat argumentative.</td>
</tr>
<tr>
<td>28.</td>
<td>Sometimes I fly off the handle for no good reason.</td>
</tr>
<tr>
<td>29.</td>
<td>I get into flights a little more than the average person.</td>
</tr>
</tbody>
</table>

**References**

### Appendix 6. Neuropsychiatric Adverse Events Interview (NAEI)

<table>
<thead>
<tr>
<th>Neuropsychiatric Adverse Events Interview Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Have you felt depressed (sad, blue, down, empty, as if you didn’t care)?</td>
</tr>
<tr>
<td>• Do you find that you have lost interest in things or get less pleasure from things that you used to enjoy?</td>
</tr>
<tr>
<td>• Have you cried or felt like crying?</td>
</tr>
<tr>
<td>• Have you been worried or scared?</td>
</tr>
<tr>
<td>• Have you been nervous or anxious?</td>
</tr>
<tr>
<td>• Have you felt panicky at all?</td>
</tr>
<tr>
<td>• Some people have panic attacks when they suddenly feel very frightened and have physical symptoms like heart palpitations (your heart is pounding and/or beating rapidly), shortness of breath and chest pains. Have you had this?</td>
</tr>
<tr>
<td>• Have you had times when you felt extremely agitated?</td>
</tr>
<tr>
<td>• Have you had times when you felt like you had to be always moving or even pacing?</td>
</tr>
<tr>
<td>• Have you felt unusually cheerful, or happy, not just your normal self, so that other people noticed?</td>
</tr>
<tr>
<td>• Have you had much more energy than usual to do things?</td>
</tr>
<tr>
<td>• Have you needed less sleep than usual to feel rested?</td>
</tr>
<tr>
<td>• Have you felt hostile towards others?</td>
</tr>
<tr>
<td>• Have you been involved in any serious arguments or fights?</td>
</tr>
<tr>
<td>• Have you had the urge to injure or harm someone?</td>
</tr>
<tr>
<td>• Have you felt that people have been talking about you?</td>
</tr>
<tr>
<td>• Have you felt that someone may be after you, or trying to harm you in some way?</td>
</tr>
<tr>
<td>• Has there been anything unusual about the way things look or sound or smell?</td>
</tr>
<tr>
<td>• Have you heard things that other people couldn’t hear, like noises or voices of people talking when there was no one around?</td>
</tr>
<tr>
<td>• Have you seen things that other people couldn’t see?</td>
</tr>
<tr>
<td>• Has your mind been playing tricks on you in any way?</td>
</tr>
<tr>
<td>• Have you had any ideas that other people might not understand or might find strange?</td>
</tr>
<tr>
<td>• Have things seemed unreal to you?</td>
</tr>
<tr>
<td>• Have you felt that you are detached from or have trouble connecting with other people?</td>
</tr>
<tr>
<td>• Have you felt strange or unnatural in any other way?</td>
</tr>
</tbody>
</table>
Neuropsychiatric Adverse Events Interview (NAEI) Guidelines

General Overview & Background on the NAEI

The NAEI has been designed as a semi-structured interview to systematically assess the presence and severity of specific neuropsychiatric symptoms as part of the adverse event data collection process. The NAEI is used at Baseline to detect symptoms that are present at the time of the subject’s entry into this clinical trial and at follow-up visits to prospectively monitor emergent symptoms. The goal is to facilitate the collection of information relevant to specific neuropsychiatric events of interest in a standardized manner. Standardizing the way in which such information is collected in a clinical trial optimizes reliability and validity across sites and clinicians.

The NAEI is intended to guide the interviewer in determining whether a symptom is present, and then, if it is, clinically significant. In assessing whether a symptom’s “clinical significant”, it is important to examine the:

1. Frequency and duration of the symptom.
2. Severity of the symptom.

If the patient responds affirmatively to questions about a specific NAEI symptom, the symptom then must be evaluated by the investigator for clinical presentation and severity and recorded as an adverse event (AE) or serious adverse event (SAE) if warranted. AEs are graded according to their intensity (mild, moderate, or severe) by examining the degree of functional impairment associated with them as per instructions in the protocol. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. Refer to Protocol Section 8 for more information on both AE and SAE reporting.

The determination whether a symptom is an adverse event and therefore warrants an AE report should always be based on the steps outlined in the figure below:
These administration instructions are intended to help interviewers use the NAEI correctly. Sites are responsible for following these guidelines throughout the course of the study. Sites should keep a copy of these guidelines handy to refer to as needed.

A worksheet for the NAEI interview has been developed and made available to sites to facilitate its use. The worksheet is used for both the baseline and follow-up visits. The interviewer should take notes on the worksheet to assist with AE reporting if needed and to refer to during future visits.

**INTERVIEWER QUALIFICATIONS**

The NAEI interview should be conducted by a staff person at the site who has completed training on the NAEI. Only interviewers who have completed the formal training on the NAEI to Pfizer’s standards can administer it for this trial.

If a site needs additional training for a new interviewer, they must contact Pfizer to make arrangements for the necessary training. No interviewer should administer the NAEI without the appropriate training. Refresher training will be required during the study.
Note that where possible, sites are strongly encouraged to have the same individual conduct the volunteered AE collection, the NAEI interview, the C-SSRS, and any other clinical ratings scales included in the protocol.

Sites should make every effort to keep the same interviewer for each subject over the course of the trial.

**Time Period to be Rated**

At Baseline, symptoms should be assessed for the past two (2) weeks. At follow-up visits, the time period to be rated is since the last clinic visit.

The interviewer should be careful when asking questions to make sure the subject is clear on the time period being rated. It may be helpful to frame questions by frequently reminding the subject of the time frame “In past 2 weeks” (at baseline) or “Since your last visit” (at follow-up) and by probing to make sure the symptoms described did occur during the time period in question (eg, at baseline asking, “Was that during the past 2 weeks?”).

**Materials Needed to Complete the NAEI**

The NAEI guidelines should always be available for reference.

In addition, at all visits after the baseline visit, the interviewer should have at hand:

- The subject’s AE log worksheet;
- Previously completed NAEI worksheets.

**Order of Assessment**

The assessment sequence for this trial must be followed carefully. Assessments should be done in the following order:

1. Volunteered AE report – opening question on how the subject has been feeling in general;
2. Follow up on previously reported AEs that are still ongoing;
3. Clinical rating scales as specified in the protocol;
4. NAEI;
5. Columbia Suicide Severity Rating Scale.
Volunteered AE report: The collection of volunteered AE reports should follow the site’s usual procedures. Generally this is done by asking the subject how s/he has been feeling in general. During the collection of volunteered AE information, the interviewer should be careful to ask sufficient follow-up questions to determine the clinical significance of the reported event and therefore whether an AE report is warranted.

Follow-up of any previously reported AEs: At all visits after the baseline visit, the interviewer then follows up on any previously reported AEs that, according to the AE log worksheet, are still ongoing (i.e., do not have a stop date) to see if resolved. AEs on the AE log worksheet may have been volunteered or solicited at previous visits.

NAEI: The NAEI is designed to guide the interviewer through a series of questions probing for neuropsychiatric symptoms using a semi-structured interview approach (see detailed administration instructions below). In most cases, the interviewer will need to ask all of the NAEI questions. However, some symptoms that are addressed by the NAEI questions may already have been volunteered during the volunteered AE discussion. In such situations, if the interviewer has already gained enough information to fully assess the question, it is not necessary to repeat the respective question(s) during NAEI administration.

BASELINE NAEI

TO BEGIN THE INTERVIEW: The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had during the past two (2) weeks.

The NAEI questions have been grouped into symptom categories and all questions in each group should be asked before making a determination about a potential adverse event.

The interviewer will have to add their own follow-up questions to the written NAEI questions to obtain necessary information. Follow-up questions should be used as needed for clarification on symptoms and to assess the frequency/duration, severity, and degree of functional impairment related to the symptom. Sample follow-up questions are provided in this document. The interviewer should probe as needed to assess the subject’s experiences and to make an appropriate assessment. The interviewer should be careful to clarify the time period (past 2 weeks) the questions refer to.

As noted before, once a symptom has been identified as present, its clinical significance must be ascertained.

NAEI Item Example:

During the past 2 weeks:

1. Have you been feeling sad, unhappy, worthless, or depressed?

IF YES, SAMPLE FOLLOW-UP QUESTIONS:
How often have you been bothered by this in the past 2 weeks?

Was it a little bit of the time, some of the time or most of the time?

Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people in the past 2 weeks?

IF YES: How hard? Can you give me an example?

FOLLOW-UP VISITS NAEI

The purpose of this assessment is to identify symptoms that have been present since the subject’s last visit and if this represents a change from their last visit. Follow-up questions are provided to help make these ratings.

To begin the follow-up interview: The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had since their last visit.

The same interview flow should be followed as at the baseline visit. In addition, for any symptom that is reported, follow up questions should assess whether this is a change from the last visit.

Follow-up NAEI Item Example:

Since your last clinic visit:

1. Have you been feeling sad, unhappy, worthless, or depressed?

Sample Follow-up Questions:

How often have you been bothered by this since your last clinic visit?

Was it a little bit of the time, some of the time or most of the time?

Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people since your last clinic visit?

IF YES: How hard? Can you give me an example?

Has this been a change from the last time you were here?

IF YES: How much of a change?
AFTER COMPLETING THE NAEI AT BASELINE AND FOLLOW-UP VISITS

The interviewer should review the responses to the questions on the NAEI and notes taken during the interview, to determine whether, in his/her clinical judgment, any neuropsychiatric event reported warrants classification as an AE. Both the subject’s answers to the questions and observations made during the interview should serve as the basis for making this determination.

For each solicited adverse event, the interviewer must determine the maximum level of intensity of the symptom as either:

<table>
<thead>
<tr>
<th>INTENSITY</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>Does not interfere with subject's usual functioning.</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Interferes to some extent with subject's usual functioning.</td>
</tr>
<tr>
<td>SEVERE</td>
<td>Interferes significantly with subject's usual functioning.</td>
</tr>
</tbody>
</table>

AEs should be added to the subject’s AE log worksheet. This, together with the completed NAEI worksheet should be filed with the subject’s other documents so that they are available for future visits. The site staff should follow Pfizer’s instructions to complete the AE Case Report Form page.
Appendix 7. Clinical Global Impression of Severity (CGI-S)

SEVERITY OF ILLNESS: Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?

<table>
<thead>
<tr>
<th>(Check (X) ONE only):</th>
<th>NOT ASSESSED</th>
<th>NORMAL, NOT AT ALL ILL</th>
<th>MODERATELY ILL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BORDERLINE, MENTALLY ILL</td>
<td>MARKEDLY ILL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MILDLY ILL</td>
<td>SEVERELY ILL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMONG THE MOST EXTREMELY ILL PATIENTS</td>
<td></td>
</tr>
</tbody>
</table>

Note: The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician’s experience with the psychiatric population to which the subject belongs.
Appendix 8. Clinical Global Impression of Improvement (CGI-I)

GLOBAL IMPRESSION OF CHANGE: Rate total impression of change whether or not, in your judgment, it is due entirely to drug treatment.

Compared to his/her condition at the Week 0 Visit, how much has the patient changed?

<table>
<thead>
<tr>
<th>(Check (X) ONE only):</th>
<th>NOT ASSESSED</th>
<th>VERY MUCH IMPROVED</th>
<th>NO CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MUCH IMPROVED</td>
<td>MINIMALLY WORSE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MINIMALLY IMPROVED</td>
<td>MUCH WORSE</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VERY MUCH WORSE</td>
<td></td>
</tr>
</tbody>
</table>

Note: The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician’s experience with the psychiatric population to which the subject belongs.
Appendix 9. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) Baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE
(C-SSRS)

Baseline
Version 1/14/09


Disclaimer:
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CNMND), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M.A., Halberstam B. & Mann J. J. Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103-130. 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu
© 2008 The Research Foundation for Mental Hygiene, Inc.
<table>
<thead>
<tr>
<th>SUICIDAL IDEATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes”, ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is “yes”, complete “Intensity of Ideation” section below.</td>
</tr>
</tbody>
</table>

1. Wish to be Dead
- Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
  - Have you wished you were dead or wished you could go to sleep and not wake up?
  - If yes, describe:

2. Non-Specific Active Suicidal Thoughts
- General, non-specific thoughts of wanting to end one’s life (commit suicide, e.g., “I’ve thought about killing myself”) without thoughts of ways to kill oneself/associates with intent or plan.
  - Have you had any thoughts of killing yourself?
  - If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different from a specific plan with time, place or method details worked out (e.g., thoughts of method to kill self but not a specific plan). Includes person who would say, “I thought about taking an overdose but I never made a specific plan as to how, when, where or how I would actually do it... and I would never go through with it.”
  - Have you been thinking about how you might do this?
  - If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to “I have the thoughts but I definitely will not do anything about them.”
  - Have you had these thoughts and had some intent of acting on them?
  - If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
- Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
  - Have you started to work on or worked out the details of how to kill yourself? Do you intend to carry out this plan?
  - If yes, describe:

<table>
<thead>
<tr>
<th>Intensity of Ideation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most Severe Ideation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type # (1-5)</td>
</tr>
</tbody>
</table>

- Frequency
  - How many times have you had these thoughts?
  - (1) Less than once a week  (2) Once a week  (3) 2-5 times a week  (4) Daily or almost daily  (5) Many times each day

- Duration
  - When you have the thoughts, how long do they last?
  - (1) Flitting - few seconds or minutes  (2) Less than a hour of the time  (3) 1-2 hours of the time  (4) 4-8 hours most of the day  (5) More than 8 hours persistent or continuous

- Controllability
  - Could you stop thinking about killing yourself or wanting to die if you wanted to?
  - (1) Easily able to control thoughts  (2) Can control thoughts with little difficulty  (3) Can control thoughts with some difficulty  (4) Unable to control thoughts  (5) Does not attempt to control thoughts

- Deterrents
  - Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
  - (1) Deterrents definitely stopped you from attempting suicide  (2) Deterrents probably stopped you  (3) Deterrents definitely did not stop you  (4) Does not apply

- Reasons for Ideation
  - What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn’t go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
  - (1) Completely to get attention, revenge or a reaction from others  (2) Mostly to get attention, revenge or a reaction from others  (3) Equally to get attention, revenge or a reaction from others  (4) Mostly to stop the pain (you couldn’t go on living with the pain or how you were feeling)  (5) Completely to stop the pain (you couldn’t go on living with the pain or how you were feeling)  (6) Does not apply

<table>
<thead>
<tr>
<th>Most Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version: F14009</td>
</tr>
<tr>
<td>SUICIDAL BEHAVIOR</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Actual Attempt:</strong></td>
</tr>
<tr>
<td>A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as a method to kill oneself. Intent does not have to be 100%. If there is any intent/deed to die associated with the act, then it can be considered an actual suicide attempt. <strong>There does not have to be any injury or harm, just the potential for injury or harm.</strong> If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.</td>
</tr>
<tr>
<td><strong>Infering Intent:</strong></td>
</tr>
<tr>
<td>Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of high floor window). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.</td>
</tr>
<tr>
<td><strong>Have you made a suicide attempt?</strong></td>
</tr>
<tr>
<td><strong>Have you done anything to harm yourself?</strong></td>
</tr>
<tr>
<td><strong>Have you done anything dangerous where you could have died?</strong></td>
</tr>
<tr>
<td>What did you do?</td>
</tr>
<tr>
<td>Did you ____ as a way to end your life?</td>
</tr>
<tr>
<td>Did you want to die (even a little) when you ____?</td>
</tr>
<tr>
<td>Were you trying to end your life when you ____?</td>
</tr>
<tr>
<td>Or did you think it was possible you could have died from ____?</td>
</tr>
<tr>
<td><strong>Or did you do it partly for other reasons without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?</strong> (Self-Injurious Behavior without suicidal intent)</td>
</tr>
<tr>
<td>Yes, describe:</td>
</tr>
<tr>
<td><strong>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</strong></td>
</tr>
<tr>
<td><strong>Interrupted Attempts:</strong></td>
</tr>
<tr>
<td>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not, for that, actual attempt would have occurred).</td>
</tr>
<tr>
<td>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.</td>
</tr>
<tr>
<td>Stabbing: Person has gun pointed toward self; gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt.</td>
</tr>
<tr>
<td>Jumping: Person is poised to jump, is grabbed and taken down from ledge.</td>
</tr>
<tr>
<td>Hanging: Person has noose around neck but has not yet started to hang, is stopped from doing so.</td>
</tr>
<tr>
<td><strong>Have there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</strong></td>
</tr>
<tr>
<td>Yes, describe:</td>
</tr>
<tr>
<td><strong>Aborted Attempts:</strong></td>
</tr>
<tr>
<td>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior.</td>
</tr>
<tr>
<td>Examples are similar to interrupted attempts, except that the individual stops themselves, instead of being stopped by something else.</td>
</tr>
<tr>
<td><strong>Have there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</strong></td>
</tr>
<tr>
<td>Yes, describe:</td>
</tr>
<tr>
<td><strong>Preparatory Acts or Behavior:</strong></td>
</tr>
<tr>
<td>Acts or preparation towards immediately making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).</td>
</tr>
<tr>
<td>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</td>
</tr>
<tr>
<td>Yes, describe:</td>
</tr>
<tr>
<td><strong>Suicidal Behavior:</strong></td>
</tr>
<tr>
<td>Suicidal behavior was present during the assessment period?</td>
</tr>
<tr>
<td><strong>Answer for Actual Attempts Only</strong></td>
</tr>
<tr>
<td><strong>Actual Lethality/Medical Damage:</strong></td>
</tr>
<tr>
<td>1. Mental physical damage (e.g., lethargic speech, first-degree burns, mild bleeding, sprains).</td>
</tr>
<tr>
<td>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive, second-degree burns, bleeding of major vessels).</td>
</tr>
<tr>
<td>3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact, third-degree burns less than 20% of body, extensive blood loss but can recover, major fractures).</td>
</tr>
<tr>
<td>4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes, third-degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area).</td>
</tr>
<tr>
<td>5. Death.</td>
</tr>
<tr>
<td><strong>Potential Lethality: Only Answer if Actual Lethality ≥ 3</strong></td>
</tr>
<tr>
<td>0 = Behavior not likely to result in injury</td>
</tr>
<tr>
<td>1 = Behavior likely to result in injury but not likely to cause death</td>
</tr>
<tr>
<td>2 = Behavior likely to result in death despite available medical care</td>
</tr>
</tbody>
</table>
Appendix 10. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE
(C-SSRS)

Since Last Visit

Version 1/14/09


Disclaimer:
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Hollister B. & Mann J. J. Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@chilpsych.columbia.edu
© 2008 The Research Foundation for Mental Hygiene, Inc.
### SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes”, ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is “yes”, complete “Intensity of Ideation” section below.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Wish to be Dead</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. Have you wished you were dead or wished you could go to sleep and not wake up?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Non-Specific Active Suicidal Thoughts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject endorses thoughts of wanting to end one’s life (commit suicide, e.g., “I’ve thought about killing myself”) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. Have you actually had any thoughts of killing yourself?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Active Suicidal Ideation with Any Method (Not Plan) without Intent to Act</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thoughts of how to kill self but not a specific plan). Include person who would say, “I thought about taking an overdose but I never made a specific plan as to where, or how I would actually do it, and I wouldn’t ever go through with it.” Have you been thinking about how you might do this?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to “I have the thoughts but I definitely will not do anything about them.” Have you had these thoughts and had some intention of acting on them?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Active Suicidal Ideation with Specific Plan and Intent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

<table>
<thead>
<tr>
<th>Most Severe Ideation</th>
<th>Most Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type # (1-5)</td>
<td>Description of Ideation</td>
</tr>
<tr>
<td>Frequency</td>
<td>How many times have you had these thoughts?</td>
</tr>
<tr>
<td></td>
<td>(1) Less than once a week</td>
</tr>
<tr>
<td>Duration</td>
<td>When you have the thoughts, how long do they last?</td>
</tr>
<tr>
<td></td>
<td>(1) Flashing, few seconds or minutes</td>
</tr>
<tr>
<td>Controllability</td>
<td>Could you stop thinking about killing yourself or wanting to die if you wanted to?</td>
</tr>
<tr>
<td></td>
<td>(1) Easily able to control thoughts</td>
</tr>
<tr>
<td>Deterrents</td>
<td>Are there things anyone or anything (e.g., family, religion, pain of death) that stopped you from wanting to die or acting on thoughts of committing suicide?</td>
</tr>
<tr>
<td></td>
<td>(1) Emotions definitely stopped you from attempting suicide</td>
</tr>
<tr>
<td>Reasons for Ideation</td>
<td>Why you were feeling the way you were feeling (or why you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</td>
</tr>
<tr>
<td></td>
<td>(1) Completely to get attention, revenge or a reaction from others</td>
</tr>
<tr>
<td></td>
<td>(6) Mostly to end or stop the pain you couldn’t go on</td>
</tr>
</tbody>
</table>
SUICIDAL BEHAVIOR

*Check all that apply, so long as these are separate events; must ask about all types.*

<table>
<thead>
<tr>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Actual Attempt:**
A suicidal self-injurious act committed with the intent to die. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

**Inferring Intent:** Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/subject). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

**Have you made a suicide attempt?**

<table>
<thead>
<tr>
<th>Have you done anything to harm yourself?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Have you done anything dangerous where you could have died?**

<table>
<thead>
<tr>
<th>Did you</th>
<th>Did you want to die (even a little) when you did?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Or did you do it purely for other reasons? (without ANY intention of killing yourself (to relieve stress, feel better, get sympathy, or get something else to happen))?** (Self-Injurious Behavior without suicidal intent)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

**Has subject engaged in Non-Suicidal Self-Injurious Behavior?**

<table>
<thead>
<tr>
<th>Interrupted Attempt:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Overshoot:** Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.

**Shooting:** Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is jumped to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck, but stops hanging (e.g., by pulling string). Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

**Aborted Attempt:**

<table>
<thead>
<tr>
<th>Preparatory Acts or Behavior:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Acts or preparations towards intentionally making a suicide attempt.** This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one’s death by suicide (e.g., giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

**Suicidal Behavior:**

<table>
<thead>
<tr>
<th>Suicidal behavior was present during the assessment period?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

**Completed Suicide:**

<table>
<thead>
<tr>
<th>Completed Suicide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

**Answer for Actual Attempts Only**

**Actual Lethality/Medical Damage:**

<table>
<thead>
<tr>
<th>No physical damage or very minor physical damage (e.g., surface scratch).</th>
</tr>
</thead>
</table>

**1. Minor physical damage (e.g., laceration, superficial wound, minor bleeding, splinter).**

**2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessels).**

**3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).**

**4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).**

**5. Death:**

<table>
<thead>
<tr>
<th>Potential Lethality: Only Answer If Actual Lethality = 0</th>
</tr>
</thead>
</table>

**Likely lethality of actual attempt (If medical damage for following examples, while having no actual medical damage, had potential for very serious lethality, yet gun in mouth and pulled the trigger but gun fails to fire so no medical damage, hanging on tree trunk with winning in string but pulled away before run over).**

<table>
<thead>
<tr>
<th>Behavior likely to result in injury</th>
<th>Behavior likely to result but not likely to cause death</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 = Behavior likely to result in injury</td>
<td>1 = Behavior likely to result but not likely to cause death</td>
</tr>
<tr>
<td>2 = Behavior likely to result in death if no available medical care</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enter Code</th>
</tr>
</thead>
</table>

---

**PFIZER CONFIDENTIAL**

Page 89
---

**409 of 564**

Page 209
### Appendix 11. List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AHRQ</td>
<td>Agency Healthcare Research and Quality</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ARISg</td>
<td>Global Adverse Reaction Information System</td>
</tr>
<tr>
<td>AQ</td>
<td>Aggression Questionnaire</td>
</tr>
<tr>
<td>BID</td>
<td>twice daily</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CAR</td>
<td>continuous abstinence rate</td>
</tr>
<tr>
<td>C-CASA</td>
<td>Columbia Classification Algorithm of Suicide Assessment</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Columbia Suicide Severity Rating Scale</td>
</tr>
<tr>
<td>CO</td>
<td>carbon monoxide</td>
</tr>
<tr>
<td>CQR</td>
<td>continuous quit rate</td>
</tr>
<tr>
<td>CGI-I</td>
<td>Clinical Global Impression-Improvement</td>
</tr>
<tr>
<td>CGI-S</td>
<td>Clinical Global Impression- Severity</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
</tr>
<tr>
<td>DSMC</td>
<td>Data Safety Monitoring Committee</td>
</tr>
<tr>
<td>DSM-IV TR</td>
<td>Diagnostic and Statistic Manual of Mental Disorders 4th Edition Text Revision</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ET</td>
<td>early termination</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>intent to treat</td>
</tr>
<tr>
<td>MHP</td>
<td>mental health professional (psychiatrist)</td>
</tr>
<tr>
<td>mm</td>
<td>millimeter</td>
</tr>
<tr>
<td>mmHg</td>
<td>millimeters of mercury</td>
</tr>
<tr>
<td>NAEI</td>
<td>Neuropsychiatric Adverse Event Interview</td>
</tr>
<tr>
<td>NUI</td>
<td>Nicotine Use Inventory</td>
</tr>
<tr>
<td>PDS</td>
<td>Pfizer Data Standards</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PR</td>
<td>pulse rate</td>
</tr>
<tr>
<td>QD</td>
<td>once daily</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SBQ-R</td>
<td>Suicide Behaviors Questionnaire-Revised</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM Disorders</td>
</tr>
<tr>
<td>TQD</td>
<td>target quit day</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
</tbody>
</table>
Appendix 12. CV Required Documents

Deaths and cardiovascular events of interest will be reviewed and adjudicated by an independent events committee. The committee will review all pertinent information for each reported case.

Clinical sites will forward all the available records with the appropriate routing form for adjudication.

Any Hospitalization for loss of consciousness, cardiac or vascular procedures, respiratory diseases (excluding infections and cancer) and generalized edema:

- Admission notes;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Laboratory imaging and ancillary examinations.

Hospitalization for Chest Pain or Angina Pectoris/Unstable angina:

- Admission notes;
- Discharge summary;
- ECG tracing(s) (include eRT ECG);
- Stress test or Thallium scan;
- Angiography report;
- Summary of Event in English (signed by an MD);
- Other (for example, MUGA scan, Holter);
- Cardiac enzymes:
  - CK;
  - CK-MB;
  - LDH;
  - Troponin I;
- Troponin T;

**Hospitalization for Congestive Heart Failure:**

- Admission notes;
- Physician notes/progress reports supporting typical CHF symptoms and signs or other diagnostic test results;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Chest x-ray;
- ECG tracings;
- Ejections fraction by echocardiogram, MUGA scans, etc.;
- Brain natriuretic peptide (BNP) and NT-proBNP results should be submitted, if available;
- Other.

**Coronary Revascularization Procedure (CABG, PTCA, Atherectomy, Transplant, Other)**

- Admission notes;
- Physician notes/progress reports;
- Operative report;
- Catheterization report;
- PTCA operative reports;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Other.

**Non-fatal Myocardial Infarction or Resuscitated Cardiac Arrest**

- Discharge Summary;
• Clinical Notes;
• Summary of Event in English (signed by an MD);
• Cardiac imaging data (if available);
• ECG tracing(s) (include eRT ECG);
• Cardiac enzymes:
  • CK;
  • CK-MB;
  • LDH Troponin I;
  • Troponin I;
  • Other.

**Non-fatal Stroke, TIA**

• Admission and/or physician progress notes, including neurological exam;
• Discharge summary;
• Summary of Event in English (signed by MD);
• Operative Report;
• CT;
• MRI;
• Angiography Report;
• Spinal Fluid Analysis;
• Other.

**First Diagnosis of PVD or Procedure for PVD**

• Physician Notes;
• Summary of Event in English (signed by an MD);
• Diagnostic Tests (angiograms, Dopplers, etc.);
• PVD procedure;
• Percutaneous Revascularization (ie, atherectomy, PTA);
• Amputation;
• Other.

**Serious Cardiac Arrhythmias**

• Physician Notes;
• Summary of Event in English (signed by an MD);
• Diagnostic Tests;
• Admission notes if applicable;
• Discharge summary;
• ECG tracing(s) (include eRT ECG);
• Other (for example, Holter).

**Deaths**

• Physician Notes;
• Summary of Event in English (signed by an MD);
• Admission and/or physician progress notes;
• Diagnostic tests if applicable;
• Discharge summary if applicable;
• Autopsy Report (if performed);
• Other.
Appendix 13. CLINICAL PROTOCOL AMENDMENT 1

Current Amendment: 1

<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Date</th>
<th>Country (ies)</th>
<th>Site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 June 2010</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Previous Amendments:

<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Date</th>
<th>Country (ies)</th>
<th>Site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SUMMARY

Reason(s) for Amendment

The protocol is being amended to incorporate changes requested by the US FDA (Agency), to clarify certain protocol aspects and to correct inconsistencies/typographical errors. The changes requested by FDA were to use a different guidance for suicide risk, clarifying that primary focus of suicide risk assessment is the presence or absence of current significant suicidality. The Agency asked that the following wording was added to the protocol: training and background requirements for administering the SCID; narratives for all moderate events included in the composite primary endpoint; instructions to record all AEs irrespective of the mechanism for ascertainment in the AE CRF; description of AE collection using the NAEI, including guidelines to the investigator in the appendix; instructions in the appendices and text to instruct investigators that CGI-S and CGI-I ratings are in reference to psychiatric diagnoses; revision to the additional inclusion criteria for the neuropsychiatric cohort to specify that both a current condition and a lifetime diagnosis are eligible for inclusion; reference to the pilot study to test the NAEI; and correction on schedule of activities to include C-SSRS assessment at Week 10. Minor corrections for inconsistencies were performed as detailed below.

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

The “change from” section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, text) is used to show the deletion of information from the current text.

The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.
Change From

Change To

1. Section, SCHEDULE OF ACTIVITIES - Study Treatment period and Post Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screen</th>
<th>BL</th>
<th>Wk 1</th>
<th>Wk 2</th>
<th>Wk 3</th>
<th>Wk 4</th>
<th>Wk 5</th>
<th>Wk 6</th>
<th>Wk 7*</th>
<th>Wk 8</th>
<th>Wk 9*</th>
<th>Wk 10</th>
<th>Wk 11*</th>
<th>Wk 12</th>
<th>ET*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History, Demography, Smoking history/ height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs (HR, BP)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCID I and II</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events - Volunteered reporting (NAEI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression Questionnaire</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview (NAEI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBQ-R</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagerström Test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled CO</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense Study Drugs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, Blood Chemistry</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (urine or serum)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Drug Screen (dipstick at site)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Contact Information Card</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### SCHEDULE OF ACTIVITIES - Post - Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Wk 13</th>
<th>Wk 14*</th>
<th>Wk 15*</th>
<th>Wk 16</th>
<th>Wk 17*</th>
<th>Wk 18*</th>
<th>Wk 19*</th>
<th>Wk 20</th>
<th>Wk 21*</th>
<th>Wk 22*</th>
<th>Wk 23*</th>
<th>Wk 24</th>
<th>ET*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events Volunteered reporting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CGI-I</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HADS</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NUI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exhaled CO</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

### Change To

### SCHEDULE OF ACTIVITIES - Study Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screen BL (Day 8)</th>
<th>Wk 2</th>
<th>Wk 3</th>
<th>Wk 4</th>
<th>Wk 5</th>
<th>Wk 6</th>
<th>Wk 7*</th>
<th>Wk 8</th>
<th>Wk 9*</th>
<th>Wk 10</th>
<th>Wk 11*</th>
<th>Wk 12</th>
<th>ET*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent b</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History, Demography, Smoking history/ height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs (HR, BP)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCID I and II</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Volunteered reporting</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression Questionnaire</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview (NAEI)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBQ-R</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagerström Test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled CO</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense Study Drugs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFIZER CONFIDENTIAL
Page 97
417 of 564
Page 217
SCHEDULE OF ACTIVITIES- Post - Treatment Period

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKG</td>
<td>X</td>
</tr>
<tr>
<td>CBC, Blood Chemistry</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy Test(^c) (urine or serum)</td>
<td>X</td>
</tr>
<tr>
<td>Urine Drug Screen(^d) (dipstick at site)</td>
<td>X</td>
</tr>
<tr>
<td>Emergency Contact Information Card</td>
<td>X</td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Wk 13</th>
<th>Wk 14*</th>
<th>Wk 15*</th>
<th>Wk 16</th>
<th>Wk 17*</th>
<th>Wk 18*</th>
<th>Wk 19*</th>
<th>Wk 20</th>
<th>Wk 21*</th>
<th>Wk 22*</th>
<th>Wk 23*</th>
<th>Wk 24</th>
<th>ET(^{12})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Volunteered reporting</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Adverse Event Interview</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUI</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled CO</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications and Non-Drug Treatment</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling (≤10 minutes)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Section 4. SUBJECT SELECTION, 4.1. Inclusion Criteria, 5\(^{th}\) bullet

Change From

- A double barrier method of contraception, eg, condom and/or diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study medication or abstinence.

Change To

- A double barrier method of contraception, eg, condom and diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study medication or abstinence.
3. Section 4. SUBJECT SELECTION, 4.1.1. Additional Inclusion Criteria for Neuropsychiatric Cohort, 2nd paragraph and 2 footnotes

Change From

All subjects will be screened for Axis I and II diagnosis (current and/or past) using DSM IV TR criteria based on clinical assessment and confirmed by SCID (administered by a clinician or trained mental health professional, ie; a PhD level clinical psychologist, or an individual with master level training in related areas [masters level psychologist, social work] who have been trained to use the SCID). Subjects will be included in the psychiatric cohort, if they are considered clinically stable by the Investigator and currently meet criteria, either current or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and have met diagnostic criteria before the initiation of study treatment. If the Investigator is not a psychiatrist or licensed PhD level clinical psychologist, he/she should consult with a mental health professional (MHP) to determine if the subject is stable.

1Clinician is defined as someone licensed to practice medicine according to existing regulations

2Documentation of training will be kept at the clinical site.

Change To

All subjects will be screened for Axis I and II diagnosis (current and/or past) using DSM IV TR criteria based on clinical assessment and confirmed by SCID (administered by a clinician or trained mental health professional, ie; a PhD level clinical psychologist, or an individual with master level training in related areas [masters level psychologist, social work] who have been trained to use the SCID). Subjects will be included in the psychiatric cohort, if they are considered clinically stable by the Investigator and meet criteria, either current or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and have met diagnostic criteria before the initiation of study treatment. If the Investigator is not a psychiatrist or licensed PhD level clinical psychologist, he/she should consult with a mental health professional (MHP) to determine if the subject is stable.

1Clinician is defined as someone licensed to practice medicine according to existing regulations

2Documentation of training will be kept at the clinical site.

4. Section 4. SUBJECT SELECTION, 4.2 Exclusion Criteria, 3rd paragraph, number 3, 4th - 7th bullets

Change From

If the subjects described above (exclusionary co-morbid psychiatric condition) do not meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, they are not eligible for the study. Subjects who meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, and who have a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) may be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent
condition is stable and does not prevent the subject from safely complying with study procedures. In such cases, please consult with the medical monitor.

3. Subjects who are believed to have a suicidal risk at screening, baseline, or after assessment by a qualified mental health professional (Psychiatrist or licensed PhD level clinical psychologist) if a risk assessment interview was required after screening or baseline using the Suicidal Behaviors Questionnaire Revisited (SBQ-R) Appendix 3 and Columbia Suicide Severity Rating Scale (C-SSRS). Appendix 9:

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on items 4, 5 or any suicidal behavioral questions of the C-SSRS. Appendix 9.

- Previous history of suicide behaviors in the past 10 years,

- Any lifetime history of serious or recurrent suicidal behavior,

- SBQ-R total score ≥8.

Change To

If the subjects described above (exclusionary co-morbid psychiatric condition) do not meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, they are not eligible for the study. Subjects who meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, and who have a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) may be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent condition is stable and does not prevent the subject from safely complying with study procedures. In such cases, please consult with the medical monitor.

3. Subjects who are believed to have a suicidal risk at screening, baseline, or after assessment by a qualified mental health professional (Psychiatrist or licensed PhD level clinical psychologist) if a risk assessment interview was required after screening or baseline using the Columbia Suicide Severity Rating Scale (C-SSRS). Appendix 9:

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS. Appendix 9.

- Previous history of suicide behaviors in the past year,

5. Section 6. STUDY PROCEDURES, 6.1. Screening, 4th and 19th bullets

Change From

- Measure and record height and weight;
• Psychiatric evaluation if warranted (See Section 7.1.10 7.1.7).

Change To

• Measure and record height;

• Psychiatric evaluation if warranted (See Section 7.1.10).

6. Section 6. STUDY PROCEDURES, 6.2.1. Baseline Visit (Randomization), 1st and 18th bullets

Change From

• Record sitting blood pressure, and pulse rate and weight;

• Psychiatric evaluation if warranted (See Section 7.1.10 7.1.7).

Change To

• Record sitting blood pressure, pulse rate and weight;

• Psychiatric evaluation if warranted (See Section 7.1.10).

7. Section 6. STUDY PROCEDURES, 6.3.1. Clinic Visits (Weeks 13, 16, 20, 24 and ET24 Visit), 1st bullet

Addition

Record Body Weight (Week 24 and ET24 only);

8. Section 7. ASSESSMENTS, 7.1.1. Adverse Events, 1st, 2nd and 4th paragraphs

Change From

All adverse events (AEs) volunteered, spontaneously observed, or solicited (of all severities) or reported will be recorded in the AE CRF up to and including Week 24.

In addition, actively solicited neuropsychiatric adverse events will be collected by use of the Neuropsychiatric Adverse Event Interview (NAEI) at each clinic visit (starting from baseline) up to and including Week 24. The voluntarily reported AEs will be assessed first at each study visit followed by the NAEI and then the C-SSRS.

Suicide related adverse events will be solicited by completion of the C-SSRS at each clinic visit up to and including Week 24. Any severe neuropsychiatric adverse event(s) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) recorded will require the subject to be referred for a
psychiatric evaluation by a qualified mental health professional MHP (Psychiatrist or licensed PhD level clinical psychologist) (Section 7.1.10 7.1.9) and a narrative will be constructed for each severe event. In the event the investigator meets the requirements of the MHP, he/she may complete this evaluation.

**Change To**

All adverse events (AEs) volunteered, observed, or solicited (of all severities) will be recorded in the AE CRF up to and including Week 24.

Solicited neuropsychiatric adverse events will be collected by use of the Neuropsychiatric Adverse Event Interview (NAEI) at each clinic visit (starting from baseline) up to and including Week 24. The voluntarily reported AEs will be assessed first at each study visit followed by the NAEI and then the C-SSRS.

Suicide related adverse events will be solicited by completion of the C-SSRS at each clinic visit up to and including Week 24. Any severe neuropsychiatric adverse event(s) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) recorded will require the subject to be referred for a psychiatric evaluation by a qualified mental health professional MHP (Psychiatrist or licensed PhD level clinical psychologist) (Section 7.1.10) and a narrative will be constructed for each event. In the event the investigator meets the requirements of the MHP, he/she may complete this evaluation.

**9. Section 7. ASSESSMENTS, 7.1.1.1. Primary Neuropsychiatric Safety Endpoint, 5th and 7th paragraphs**

**Change From**

Items captured from proxy report (ie, PCP, family member) judged to be adverse events by the Investigator;

The primary safety endpoint encompasses events reported (via the AE CRF page) through any of the above three means of assessments. Additionally, the MedDRA version and Preferred Terms to be included in the primary safety endpoint will be described in the Statistical Analysis Plan.

**Change To**

Items captured from proxy report (ie, PCP, family member) judged to be adverse events by the Investigator;

The primary safety endpoint encompasses events reported (via the AE CRF page) through any of the above means of assessments. Additionally, the MedDRA version and Preferred
Terms to be included in the primary safety endpoint will be described in the Statistical Analysis Plan.

10. **Section 7. ASSESSMENTS, 7.1.1.2. Actively Solicited Neuropsychiatric Adverse Events**

**Change From**

The Neuropsychiatric Adverse Event Interview (NAEI) Appendix 6, will actively inquire about the following type of adverse events: aggression, anxiety, agitation, depression, delusions, dissociative states, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, paranoia, panic, and psychosis. If a subject has a positive response to any item on the NAEI, a determination will be made by the investigator as to whether this meets criteria for an adverse event. If it does meet criteria as an adverse event it will be recorded on the adverse event pages of the Case Report Form. **A pilot study is being conducted to test the NAEI in a similar population to the one to be included in this study (patients with and without a history of psychiatric disease enrolled in a smoking cessation program).**

**Change To**

The Neuropsychiatric Adverse Event Interview (NAEI) Appendix 6, will actively inquire about the following type of adverse events: aggression, anxiety, agitation, depression, delusions, dissociative states, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, paranoia, panic, and psychosis. If a subject has a positive response to any item on the NAEI, a determination will be made by the investigator as to whether this meets criteria for an adverse event. If it does meet criteria as an adverse event it will be recorded on the adverse event pages of the Case Report Form. **A pilot study is being conducted to test the NAEI in a similar population to the one to be included in this study (patients with and without a history of psychiatric disease enrolled in a smoking cessation program).**

11. **Section 7. ASSESSMENTS, 7.1.2. Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 9, Appendix 10 and the Suicidal Behaviors Questionnaire (SBQ-R) Appendix 3, 1st-3rd bullets**

**Change From**

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on items 4, 5 or any suicidal behavioral questions of the C-SSRS; Appendix 9;
- Previous history of suicide behaviors in the past 10 years;
- Any lifetime history of serious or recurrent suicidal behavior;
- SBQ-R total score ≥ 8;
Change To

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS; Appendix 9;
- Previous history of suicide behaviors in the past year;


Change From

The CGI-S is a clinician rated instrument measuring the severity of a subject’s psychiatric condition on a 7 point scale at time of assessment, relative to clinician's past experience in patients with same diagnosis. The scores are: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; or 7=extremely ill. The ratings will be applicable even to those without psychiatric diagnoses (e.g., those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). This scale should be administered by the same rater throughout the study whenever possible.

Change To

The CGI-S is a clinician rated instrument measuring the severity of a subject’s psychiatric condition on a 7 point scale at time of assessment, relative to clinician's past experience in patients with same diagnosis. The scores are: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; or 7=extremely ill. The ratings will be applicable even to those without psychiatric diagnoses (e.g., those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). This scale should be administered by the same rater throughout the study whenever possible.

13. Section 7. ASSESSMENTS, 7.1.5. Clinical Global Impression of Improvement (CGI-I) Appendix 8

Change From

The CGI-I is a clinician rated instrument that measures change in subject’s psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale ranging from 1 (very much improved) to 7 (very much worse). The ratings will be applicable even to those without psychiatric diagnoses (e.g., those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No
change” on the CGI-I at follow up visits). This scale should be administered by the same rater throughout the study whenever possible.

Change To

The CGI-I is a clinician rated instrument that measures change in subject’s psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale ranging from 1 (very much improved) to 7 (very much worse). The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). This scale should be administered by the same rater throughout the study whenever possible.


Change From

- Subject answers “yes” on items 4, 5 or on any suicidal behavioral question on C-SSRS during the screening visit or subject answers “yes” on item 4, 5 or on any suicidal behavioral question on C-SSRS during the study;

- Previous history of suicide behaviors in the past 10 years (prior to randomization);

- Any lifetime history of serious or recurrent suicidal behavior (prior to randomization);

- SBQ-R total score ≥8 at screening.

Change To

- Subject answers “yes” on item 5, on C-SSRS during the screening visit or subject answers “yes” on item 4, 5 or on any suicidal behavioral question on C-SSRS during the study;

- Previous history of suicide behaviors in the past year (prior to randomization);

15. Section 7. ASSESSMENTS, 7.1.12. Physical Examination, Vital Signs and Electrocardiogram, 3rd paragraph

Change From

Sitting blood pressure and pulse rate will be measured at the screening and baseline visits and Wk 12 or ET12. Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest
mmHg. All blood pressure measurements are to be taken in the dominant arm with the appropriate size cuff. Pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

**Change To**

Sitting blood pressure and pulse rate will be measured at the screening and baseline visits and Wk 12 or ET_{12}. Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest mmHg. All blood pressure measurements are to be taken in the dominant arm with the appropriate size cuff. Pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

16. **Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.3. Safety Objectives Analysis, 7th paragraph and last 2 bullets**

**Addition**

The safety summaries will also be expanded to specifically include:

- A summary of neuropsychiatric adverse events of interest leading to treatment and/or study discontinuations.
- A summary of neuropsychiatric adverse events of interest resulting in an intervention.

17. **Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.5. Methods and Analysis, last paragraph**

**Addition**

The investigator will record the primary major diagnosis group (the sub-stratification of the psychiatric disorder cohort) in the CRF. Secondary analyses involving this primary major diagnosis group will utilize this classification be completed. Further analysis details will be presented in the SAP.

18. **Section, APPENDICES, Appendix 5. Aggression Questionnaire (AQ), title**

**Change From**

Appendix 5. Aggression Questionnaire (AQ)\(^1\)

**Change To**

Appendix 5. Aggression Questionnaire (AQ)

19. **Section, APPENDICES, Appendix 6. Neuropsychiatric Adverse Events Interview (NAEI), after 1st page**
Addition

General Overview & Background on the NAEI

The NAEI has been designed as a semi-structured interview to systematically assess the presence and severity of specific neuropsychiatric symptoms as part of the adverse event data collection process. The NAEI is used at Baseline to detect symptoms that are present at the time of the subject’s entry into this clinical trial and at follow-up visits to prospectively monitor emergent symptoms. The goal is to facilitate the collection of information relevant to specific neuropsychiatric events of interest in a standardized manner. Standardizing the way in which such information is collected in a clinical trial optimizes reliability and validity across sites and clinicians.

The NAEI is intended to guide the interviewer in determining whether a symptom is present, and then, if it is, clinical significance. In assessing whether a symptom's "clinical significant", it is important to examine the

(1) frequency and duration of the symptom.

(2) severity of the symptom

If the patient responds affirmatively to questions about a specific NAEI symptom, the symptom then must be evaluated by the investigator for clinical presentation and severity and recorded as an adverse event (AE) or serious adverse event (SAE) if warranted. AEs are graded according to their intensity (mild, moderate, or severe) by examining the degree of functional impairment associated with them as per instructions in the protocol. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequela resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. Refer to Protocol Section 8 for more information on both AE and SAE reporting.

The determination whether a symptom is an adverse event and therefore warrants an AE report should always be based on the steps outlined in the figure below:

These administration instructions are intended to help interviewers use the NAEI correctly. Sites are responsible for following these guidelines throughout the course of the study. Sites should keep a copy of these guidelines handy to refer to as needed.

A worksheet for the NAEI interview has been developed and made available to sites to facilitate its use. The worksheet is used for both the baseline and follow-up visits.
The interviewer should take notes on the worksheet to assist with AE reporting if needed and to refer to during future visits.

INTERVIEWER QUALIFICATIONS

The NAEI interview should be conducted by a staff person at the site who has completed training on the NAEI. Only interviewers who have completed the formal training on the NAEI to Pfizer’s standards can administer it for this trial.

If a site needs additional training for a new interviewer, they must contact Pfizer to make arrangements for the necessary training. No interviewer should administer the NAEI without the appropriate training. Refresher training will be required during the study.

Note that where possible, sites are strongly encouraged to have the same individual conduct the volunteered AE collection, the NAEI interview, the C-SSRS, and any other clinical ratings scales included in the protocol.

Sites should make every effort to keep the same interviewer for each subject over the course of the trial.

Time Period to be Rated

At Baseline, symptoms should be assessed for the past two (2) weeks. At follow-up visits, the time period to be rated is since the last clinic visit.

The interviewer should be careful when asking questions to make sure the subject is clear on the time period being rated. It may be helpful to frame questions by frequently reminding the subject of the time frame “In past 2 weeks” (at baseline) or “Since your last visit” (at follow-up) and by probing to make sure the symptoms described did occur during the time period in question (e.g., at baseline asking, “Was that during the past 2 weeks?”).

Materials Needed to Complete the NAEI

The NAEI guidelines should always be available for reference.

In addition, at all visits after the baseline visit, the interviewer should have at hand
- the subject’s AE log worksheet
- previously completed NAEI worksheets

Order of Assessment

The assessment sequence for this trial must be followed carefully. Assessments should be done in the following order:
6. Volunteered AE report – opening question on how the subject has been feeling in general

7. Follow up on previously reported AEs that are still ongoing

8. Clinical rating scales as specified in the protocol

9. NAEI

10. Columbia Suicide Severity Rating Scale

Volunteered AE report: The collection of volunteered AE reports should follow the site’s usual procedures. Generally this is done by asking the subject how s/he has been feeling in general. During the collection of volunteered AE information, the interviewer should be careful to ask sufficient follow-up questions to determine the clinical significance of the reported event and therefore whether an AE report is warranted.

Follow-up of any previously reported AEs: At all visits after the baseline visit, the interviewer then follows up on any previously reported AEs that, according to the AE log worksheet, are still ongoing (i.e., do not have a stop date) to see if resolved. AEs on the AE log worksheet may have been volunteered or solicited at previous visits.

NAEI: The NAEI is designed to guide the interviewer through a series of questions probing for neuropsychiatric symptoms using a semi-structured interview approach (see detailed administration instructions below). In most cases, the interviewer will need to ask all of the NAEI questions. However, some symptoms that are addressed by the NAEI questions may already have been volunteered during the volunteered AE discussion. In such situations, if the interviewer has already gained enough information to fully assess the question, it is not necessary to repeat the respective question(s) during NAEI administration.

BASELINE NAEI

TO BEGIN THE INTERVIEW: The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had during the past two (2) weeks.

The NAEI questions have been grouped into symptom clusters and all questions in each group should be asked before making a determination about a potential adverse event.

The interviewer will have to add their own follow-up questions to the written NAEI questions to obtain necessary information. Follow-up questions should be used as needed for clarification on symptoms and to assess the frequency/duration, severity, and degree of functional impairment related to the symptom. Sample follow-up questions are provided in this document. The interviewer should probe as needed to assess the subject’s experiences and to make an appropriate assessment.
interviewer should be careful to clarify the time period (past 2 weeks) the questions refer to.

As noted before, once a symptom has been identified as present, its clinical significance must be ascertained.

NAEI Item Example:

During the past 2 weeks:

1. Have you been feeling sad, unhappy, worthless, or depressed?

IF YES, SAMPLE FOLLOW-UP QUESTIONS:

- How often have you been bothered by this in the past 2 weeks?
  
  Was it a little bit of the time, some of the time or most of the time?

  Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people in the past 2 weeks?

  IF YES: How hard? Can you give me an example?

FOLLOW-UP VISITS NAEI

The purpose of this assessment is to identify symptoms that have been present since the subject’s last visit and if this represents a change from their last visit. Follow-up questions are provided to help make these ratings.

To begin the follow-up interview: The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had since their last visit.

The same interview flow should be followed as at the baseline visit. In addition, for any symptom that is reported, follow up questions should assess whether this is a change from the last visit.

Follow-up NAEI Item Example:

Since your last clinic visit:

1. Have you been feeling sad, unhappy, worthless, or depressed?

Sample Follow-up Questions:

- How often have you been bothered by this since your last clinic visit?

  Was it a little bit of the time, some of the time or most of the time?
Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people since your last clinic visit?

IF YES: How hard? Can you give me an example?

Has this been a change from the last time you were here?

IF YES: How much of a change?

AFTER COMPLETING THE NAEI AT BASELINE AND FOLLOW-UP VISITS

The interviewer should review the responses to the questions on the NAEI and notes taken during the interview, to determine whether, in his/her clinical judgment, any neuropsychiatric event reported warrants classification as an AE. Both the subject’s answers to the questions and observations made during the interview should serve as the basis for making this determination.

For each solicited adverse event, the interviewer must determine the maximum level of intensity of the symptom as either:

<table>
<thead>
<tr>
<th>MILD</th>
<th>Does not interfere with subject's usual functioning.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODERATE</td>
<td>Interferes to some extent with subject's usual functioning.</td>
</tr>
<tr>
<td>SEVERE</td>
<td>Interferes significantly with subject's usual functioning.</td>
</tr>
</tbody>
</table>

AEs should be added to the subject’s AE log worksheet. This, together with the completed NAEI worksheet should be filed with the subject’s other documents so that they are available for future visits. The site staff should follow Pfizer’s instructions to complete the AE Case Report Form page.

20. Section, APPENDICES, Appendix 7. Global Clinical Impression of Severity (CGI-S), last paragraph

Addition

Note: The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits).
21. Section, APPENDICES, Appendix 8. Global Clinical Impression of Improvement (CGI-I), table and last paragraph

Change From

<table>
<thead>
<tr>
<th>(Check (X) ONE only):</th>
<th>VERY MUCH IMPROVED</th>
<th>NO CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT ASSESSED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MINIMALLY IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH WORSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MINIMALLY IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH WORSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VERY MUCH WORSE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(Check (X) ONE only):</th>
<th>NORMAL, NOT AT ALL ILL</th>
<th>MODERATELY ILL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT ASSESSED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BORDERLINE, MENTALLY ILL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MARKEDLY ILL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MILDLY ILL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEVERELY ILL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMONG THE MOST EXTREMELY ILL PATIENTS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits.

Change To

<table>
<thead>
<tr>
<th>(Check (X) ONE only):</th>
<th>VERY MUCH IMPROVED</th>
<th>NO CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT ASSESSED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MINIMALLY IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH WORSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MINIMALLY IMPROVED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCH WORSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VERY MUCH WORSE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Note: The ratings will be applicable even to those without psychiatric diagnoses (e.g., those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits.

22. Section, APPENDICES, Appendix 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS), (Baseline), 1st page after Disclaimer

Deletion

<table>
<thead>
<tr>
<th>NOT ASSESSED</th>
<th>VERY MUCH IMPROVED</th>
<th>NO CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MUCH IMPROVED</td>
<td>MINIMALLY WORSE</td>
</tr>
<tr>
<td></td>
<td>MINIMALLY IMPROVED</td>
<td>MUCH WORSE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

23. Section, APPENDICES, Appendix 10. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) (Since Last Visit)

Change From


Disclaimer: This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgement.

**SUICIDAL IDEATION**

Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes,” ask questions 3, 4 and 5.

<table>
<thead>
<tr>
<th>Lifetime—Time He/She Felt Most Suicidal Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Wish To Be Dead</td>
</tr>
<tr>
<td>Have you wished you were dead or wished you could go to sleep and not wake up? Yes/No</td>
</tr>
<tr>
<td>Frequency of ideation _____ If yes, describe.</td>
</tr>
<tr>
<td>2. Non-Specific Active Suicidal Thoughts</td>
</tr>
<tr>
<td>Have you actually had any thoughts of killing yourself? Frequency of ideation _____ Yes/No</td>
</tr>
<tr>
<td>If yes, describe.</td>
</tr>
<tr>
<td>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</td>
</tr>
<tr>
<td>Have you been thinking about how you might do this? Frequency of ideation _____ Yes/No</td>
</tr>
<tr>
<td>If yes, describe.</td>
</tr>
<tr>
<td>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</td>
</tr>
</tbody>
</table>
Have you had these thoughts and had some intention of acting on them? Frequency of ideation ______
If yes, describe.
5. Active Suicidal Ideation with Specific Plan and Intent
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan? Frequency of ideation ______
If yes, describe.

INTENSITY OF IDEATION
The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he/she was feeling the most suicidal. Only rate most common if most severe and most common are different.

<table>
<thead>
<tr>
<th>Time He/She Felt Most Suicidal</th>
<th>Most Common</th>
<th>Most Severe</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Ideation Type</th>
<th>Type # (1-5)</th>
<th>Description of Ideation</th>
</tr>
</thead>
</table>

Baseline
Most Common Ideation: ________________________________________________

Most Severe Ideation: ________________________________________________

Frequency
How many times have you had these thoughts?
1. Less than once a week
2. Once a week
3. 2-5 times in week
4. Daily or almost daily
5. Many times each day

Duration
When you have the thoughts how long do they last?
1. Fleeting – few seconds or minutes
2. Less than 1 hour/some of the time
3. 1-4 hours/a lot of time
4. 4-8 hours/most of day
5. More than 8 hours/persistent or continuous

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
1. Easily able to control thoughts
2. Can control thoughts with little difficulty
3. Can control thoughts with some difficulty
4. Can control thoughts with a lot of difficulty
5. Unable to control thoughts
6. Does not attempt to control thoughts

Deterrents
Are there things – anyone or anything (eg family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?
1. Deterrents definitely stopped you from attempting suicide
2. Deterrents probably stopped you
3. Uncertain that deterrents stopped you
4. Deterrents most likely did not stop you
5. Does not apply, wish to die only
Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end pain or stop the way you were feeling (in other words you couldn’t go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
1. Completely to get attention, revenge or a reaction from others
2. Mostly to get attention, revenge or a reaction from others
3. Equally to get attention, revenge or a reaction from others and to end/stop the pain
4. Mostly to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
5. Completely to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).

SUICIDAL BEHAVIOR
(Check all that apply, so long as these are separate events; must ask about all types)

<table>
<thead>
<tr>
<th>Since Last Visit</th>
<th>Lifetime—Time He/She Felt Most Suicidal</th>
</tr>
</thead>
</table>

Actual Attempt:
Have you made a suicide attempt?
Have you done anything to harm yourself?
Have you done anything dangerous where you could have died?
   What did you do?
      Did you _____ as a way to end your life?
      Did you want to die (even a little) when you _____?
      Were you trying to end your life when you _____?
      Or did you think it was possible you could have died from _____?
Or did you do it purely for other reasons / without any intention of killing your self (like to relieve stress, feel better, get sympathy, or to get something else to happen)? (Self-injurious behavior without suicidal intent)
If yes, describe.

Has the subject engaged in Non-Suicidal Self-Injurious Behavior?

Interrupted Attempt:
Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?
If yes, describe.

Aborted Attempt:
Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?
If yes, describe.

Preparatory Acts or Behavior:
Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?
If yes, describe.

Suicidal Behavior:
Suicidal behavior was present during the assessment period?
If yes, describe.
Completed Suicide:

<table>
<thead>
<tr>
<th>ANSWER FOR ACTUAL ATTEMPTS ONLY</th>
<th>Most Recent Attempt Date:</th>
<th>Worst/Most Lethal Attempt Date:</th>
<th>Yes/No Since Last Visitation/First Attempt Date:</th>
</tr>
</thead>
</table>

Actual Lethality/Medical Damage:
0. No physical damage or very minor physical damage (eg, surface scratches).
1. Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains).
2. Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second degree burns; bleeding of major vessel).
3. Moderately severe physical damage; medical hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).
4. Severe physical damage; medical hospitalization with intensive care required (eg, comatose without reflexes; third degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).
5. Death

Potential Lethality: Only Answer if Actual Lethality = 0
0 = Behavior not likely to result in injury
1 = Behavior likely to result in injury but not likely to cause death
2 = Behavior likely to result in death despite available medical care

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. (Oquendo M. A.; Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M. B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 – 130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu.

Change To


PFIZER CONFIDENTIAL
Page 116
436 of 564
Page 236
Disclaimer: This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of Suicidality depends on clinical judgement.

### SUICIDAL IDEATION

<table>
<thead>
<tr>
<th>Question</th>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section.</td>
<td></td>
</tr>
<tr>
<td>If the answer to question 2 is “yes,” ask questions 3, 4 and 5.</td>
<td></td>
</tr>
<tr>
<td><strong>1. Wish To Be Dead</strong></td>
<td>Yes/No</td>
</tr>
<tr>
<td>Have you wished you were dead or wished you could go to sleep and not wake up?</td>
<td></td>
</tr>
<tr>
<td>Frequency of ideation</td>
<td></td>
</tr>
<tr>
<td>If yes, describe.</td>
<td></td>
</tr>
<tr>
<td><strong>2. Non-Specific Active Suicidal Thoughts</strong></td>
<td>Yes/No</td>
</tr>
<tr>
<td>Have you actually had any thoughts of killing yourself? Frequency of ideation</td>
<td></td>
</tr>
<tr>
<td>If yes, describe.</td>
<td></td>
</tr>
<tr>
<td><strong>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</strong></td>
<td>Yes/No</td>
</tr>
<tr>
<td>Have you been thinking about how you might do this? Frequency of ideation</td>
<td></td>
</tr>
<tr>
<td>If yes, describe.</td>
<td></td>
</tr>
<tr>
<td><strong>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</strong></td>
<td>Yes/No</td>
</tr>
<tr>
<td>Have you had these thoughts and had some intention of acting on them? Frequency of ideation</td>
<td></td>
</tr>
<tr>
<td>If yes, describe.</td>
<td></td>
</tr>
<tr>
<td><strong>5. Active Suicidal Ideation with Specific Plan and Intent</strong></td>
<td>Yes/No</td>
</tr>
<tr>
<td>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan? Frequency of ideation</td>
<td></td>
</tr>
<tr>
<td>If yes, describe.</td>
<td></td>
</tr>
</tbody>
</table>

### INTENSITY OF IDEATION

The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he/she was feeling the most suicidal. Only rate most common if most severe and most common are different.

<table>
<thead>
<tr>
<th>Ideation Type</th>
<th>Type # (1-5)</th>
<th>Description of Ideation</th>
<th>Most Common</th>
<th>Most Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Common Ideation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Severe Ideation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Frequency</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>How many times have you had these thoughts?</td>
<td></td>
</tr>
<tr>
<td>1. Less than once a week</td>
<td></td>
</tr>
<tr>
<td>2. Once a week</td>
<td></td>
</tr>
<tr>
<td>3. 2-5 times in week</td>
<td></td>
</tr>
<tr>
<td>4. Daily or almost daily</td>
<td></td>
</tr>
<tr>
<td>5. Many times each day</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Duration</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>When you have the thoughts how long do they last?</td>
<td></td>
</tr>
<tr>
<td>1. Fleeting – few seconds or minutes</td>
<td></td>
</tr>
<tr>
<td>2. Less than 1 hour/some of the time</td>
<td></td>
</tr>
<tr>
<td>3. 1-4 hours/a lot of time</td>
<td></td>
</tr>
<tr>
<td>4. 4-8 hours/most of the day</td>
<td></td>
</tr>
<tr>
<td>5. More than 8 hours/persistent or continuous</td>
<td></td>
</tr>
</tbody>
</table>

| **Controllability** | |
| Could/can you stop thinking about killing yourself or wanting to die if you want | |
to?

1. Easily able to control thoughts
2. Can control thoughts with little difficulty
3. Can control thoughts with some difficulty
4. Can control thoughts with a lot of difficulty
5. Unable to control thoughts
0. Does not attempt to control thoughts

Deterrents
Are there things – anyone or anything (eg family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?

1. Deterrents definitely stopped you from attempting suicide
2. Deterrents probably stopped you
3. Uncertain that deterrents stopped you
4. Deterrents most likely did not stop you
0. Does not apply, wish to die only

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end pain or stop the way you were feeling (in other words you couldn’t go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?

1. Completely to get attention, revenge or a reaction from others
2. Mostly to get attention, revenge or a reaction from others
3. Equally to get attention, revenge or a reaction from others and to end/stop the pain
4. Mostly to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
5. Completely to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).

<table>
<thead>
<tr>
<th>SUICIDAL BEHAVIOR</th>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Attempt:</td>
<td></td>
</tr>
<tr>
<td>Have you made a suicide attempt?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Have you done anything to harm yourself?</td>
<td></td>
</tr>
<tr>
<td>Have you done anything dangerous where you could have died?</td>
<td></td>
</tr>
<tr>
<td>What did you do?</td>
<td>Total # of attempts</td>
</tr>
<tr>
<td>Did you ______ as a way to end your life?</td>
<td></td>
</tr>
<tr>
<td>Did you want to die (even a little) when you _____?</td>
<td></td>
</tr>
<tr>
<td>Were you trying to end your life when you ______?</td>
<td></td>
</tr>
<tr>
<td>Or did you think it was possible you could have died from ______?</td>
<td></td>
</tr>
</tbody>
</table>

Or did you do it purely for other reasons / without any intention of killing your self (like to relieve stress, feel better, get sympathy, or to get something else to happen)?  (Self-injurious behavior without suicidal intent)
If yes, describe |

Has the subject engaged in Non-Suicidal Self-Injurious Behavior? Yes/No

Interrupted Attempt:
Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?
If yes, describe |

Total # of interrupted ___

Aborted Attempt:
Has there been a time when you started to do something to try to end your life but you
Yes/No
stopped yourself before you actually did anything? If yes, describe.  

### Preparatory Acts or Behavior: 
Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?  
If yes, describe.  

### Suicidal Behavior: 
Suicidal behavior was present during the assessment period?  
If yes, describe.  

### Completed Suicide: 
Yes/No  

---

**ANSWER FOR ACTUAL ATTEMPTS ONLY**

<table>
<thead>
<tr>
<th>Actual Lethality/Medical Damage</th>
<th>Most Recent Attempt Date:</th>
<th>Worst/Most Lethal Attempt Date:</th>
<th>Since Last Visit:</th>
</tr>
</thead>
</table>
| 0. No physical damage or very minor physical damage (eg, surface scratches).  
1. Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains).  
2. Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second degree burns; bleeding of major vessel).  
3. Moderately severe physical damage; medical hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).  
4. Severe physical damage; medical hospitalization with intensive care required (eg, comatose without reflexes; third degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).  
5. Death | Enter Code | Enter Code | Enter Code |

### Potential Lethality: Only Answer if Actual Lethality = 0 

<table>
<thead>
<tr>
<th>Potential Lethality</th>
<th>Enter Code</th>
<th>Enter Code</th>
<th>Enter Code</th>
</tr>
</thead>
</table>
| 0 = Behavior not likely to result in injury  
1 = Behavior likely to result in injury but not likely to cause death  
2 = Behavior likely to result in death despite available medical care | Enter Code | Enter Code | Enter Code |

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. (Oquendo M. A.; Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of
research instruments. In M. B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 – 130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu.
A PHASE 4, RANDOMIZED, DOUBLE-BLEIND, ACTIVE AND PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE NEUROPSYCHIATRIC SAFETY AND EFFICACY OF 12 WEEKS VARENICLINE TARTRATE 1 MG BID AND BUPROPION HYDROCHLORIDE 150 MG BID FOR SMOKING CESSATION IN SUBJECTS WITH AND WITHOUT A HISTORY OF PSYCHIATRIC DISORDERS.

Compound: CP-526,555
Compound Name (if applicable): Varenicline Tartrate
US IND Number (if applicable): 58,994
Protocol Number: A3051123
Phase: Phase 4
Version and Date: Amendment 8
Local amendment for Bulgaria, Denmark, Finland, France, Germany, Slovakia and Spain
07 November 2012

European Clinical Trial Database (EudraCT) Number, if applicable: 2010-022914-15

Approval Signature indicates acknowledgement that the protocol meets all necessary requirements as described in this SOP including affirmation that the following requirements have been met:

- Where required, the protocol achieved a satisfactory Protocol Quality Score
- Clinical Operations agreement the protocol is executable
- EUQPPV review is completed for PASS protocols
- Technical and scientific QC has been performed
- Medical review has been performed, as appropriate
- Statistical review has been performed, as appropriate

Print Name: Carla Yunis, MD, MPH
Signature: [Signature]
Date: 07 November 2012

Instructions: Upon completion, file official copy to Trial Master File.

This document contains confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing this document, you agree to hold this information in confidence and not to disclose it to others (except where required by applicable law) or to use it for unauthorized purposes. In the event of an actual or suspected breach of this obligation, Pfizer should be promptly notified.

APPROVED BY PFIZER FOR PUBLIC DISCLOSURE

PFIZER INTERNAL USE ONLY The official version of this form is located in the electronic document management system and accessible via the eSOP portal.
CHANTIX® (varenicline) Tablets

Initial U.S. Approval: 2006

---

**WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS**

See full prescribing information for complete boxed warning.

- Serious neuropsychiatric events have been reported in patients taking CHANTIX. (5.1 and 6.2)
- Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior while taking CHANTIX or shortly after discontinuing CHANTIX. (5.1 and 6.2)
- Weigh the risks of CHANTIX against benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (5.1 and 6.2)

---

**RECENT MAJOR CHANGES**

Dosage and Administration

Usual Dosage for Adults (2.1) 10/2014
Boxed Warning 02/2016

Warnings and Precautions

Neuropsychiatric Symptoms and Suicidality (5.1) 09/2014, 02/2016
Seizures (5.2) 09/2014
Interaction with Alcohol (5.3) 09/2014

---

**INDICATIONS AND USAGE**

CHANTIX is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment. (1 and 2.1)

---

**DOSEAGE AND ADMINISTRATION**

- Begin CHANTIX dosing one week before the date set by the patient to stop smoking. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment. (2.1)
- Starting week: 0.5 mg once daily on days 1-3 and 0.5 mg twice daily on days 4-7. (2.1)
- Continuing weeks: 1 mg twice daily for a total of 12 weeks. (2.1)
- Additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence. (2.1)
- Renal impairment: Reduce the dose in patients with severe renal impairment (estimated creatinine clearance <30 mL/min). (2.2)
- Consider dose reduction for patients who cannot tolerate adverse effects. (2.1)
- Another attempt at treatment is recommended for those who fail to stop smoking or relapse when factors contributing to the failed attempt have been addressed. (2.1)
- Provide patients with appropriate educational materials and counseling to support the quit attempt. (2.1)

---

**DOSEAGE FORMS AND STRENGTHS**

Tablets: 0.5 mg and 1 mg (3)

---

**CONTRAINICATIONS**

History of serious hypersensitivity or skin reactions to CHANTIX. (4)

---

**FULL PRESCRIBING INFORMATION: CONTENTS**

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Usual Dosage for Adults
  2.2 Dosage in Special Populations
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Neuropsychiatric Symptoms and Suicidality
  5.2 Seizures
  5.3 Interaction with Alcohol
  5.4 Accidental Injury
  5.5 Cardiovascular Events
  5.6 Angioedema and Hypersensitivity Reactions
  5.7 Serious Skin Reactions

---

**WARNINGS AND PRECAUTIONS**

- **Serious Neuropsychiatric Symptoms:** Serious neuropsychiatric symptoms have been reported. Observe patients attempting to quit smoking with or without CHANTIX for the occurrence of such symptoms and instruct them to contact a healthcare provider if they experience such symptoms. (5.1)
- **Seizures:** New or worsening seizures have been observed in patients taking CHANTIX. CHANTIX should be used cautiously in patients with a history of seizures or other factors that can lower the seizure threshold. (5.2)
- **Interaction with alcohol:** Increased effects of alcohol have been reported. Instruct patients to reduce the amount of alcohol they consume until they know whether CHANTIX affects them. (5.3)
- **Accidental injury:** Accidental injuries (e.g., traffic accidents) have been reported. Instruct patients to use caution driving or operating machinery until they know how CHANTIX may affect them. (5.4)
- **Cardiovascular events:** A meta-analysis of 15 clinical trials, including a trial in patients with stable cardiovascular disease, demonstrated that while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with CHANTIX. These events occurred primarily in patients with known cardiovascular disease. In both the clinical trial and meta-analysis, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX. Instruct patients to notify their health care providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. (5.5 and 6.1)
- **Angioedema and hypersensitivity reactions:** Such reactions, including angioedema, infrequently life threatening, have been reported. Instruct patients to discontinue CHANTIX and immediately seek medical care if symptoms occur. (5.6 and 6.2)
- **Serious skin reactions:** Rare, potentially life-threatening skin reactions have been reported. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (5.7 and 6.2)
- **Nausea:** Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.8)

---

**ADVERSE REACTIONS**

Most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---

**DRUG INTERACTIONS**

- Other smoking cessation therapies: Safety and efficacy in combination with other smoking cessation therapies has not been established. Coadministration of varenicline and transdermal nicotine resulted in a high rate of discontinuation due to adverse events. (7.1)
- Effect of smoking cessation: Pharmacokinetics or pharmacodynamics of certain drugs may be altered due to smoking cessation with CHANTIX, necessitating dose adjustment. (7.2)

---

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.3)
- Pediatric Use: Safety and effectiveness not established. (8.4)
- Renal Impairment: Dosage adjustment is required for severe renal impairment. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 10/2014, 02/2016
5.8 Nausea

6 ADVERSE REACTIONS
   6.1 Clinical Trials Experience
   6.2 Postmarketing Experience

7 DRUG INTERACTIONS
   7.1 Use With Other Drugs for Smoking Cessation
   7.2 Effect of Smoking Cessation on Other Drugs

8 USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.3 Nursing Mothers
   8.4 Pediatric Use
   8.5 Geriatric Use
   8.6 Renal Impairment

9 DRUG ABUSE AND DEPENDENCE
   9.1 Controlled Substance
   9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action

13 NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
   14.1 Initiation of Abstinence
   14.2 Urg to Smoke
   14.3 Long-Term Abstinence
   14.4 Subjects with Cardiovascular and Chronic Obstructive Pulmonary Disease
   14.5 Subjects with Major Depressive Disorder
   14.6 Subjects with or without a History of Psychiatric Disorder
   14.7 Alternative Instructions for Setting a Quit Date
   14.28 Re-Treatment Study

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
   Medication Guide

*Sections or subsections omitted from the full prescribing information are not listed.
1 INDICATIONS AND USAGE
CHANTIX is indicated for use as an aid to smoking cessation treatment.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage for Adults
Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Provide patients with appropriate educational materials and counseling to support the quit attempt.

The patient should set a date to stop smoking. Begin CHANTIX one week before this date. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment.

CHANTIX should be taken after eating and with a full glass of water.

The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

| Days 1 – 3: | 0.5 mg once daily |
| Days 4 – 7: | 0.5 mg twice daily |
| Day 8 – end of treatment: | 1 mg twice daily |

Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks’ treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence.

Patients who are motivated to quit, and who did not succeed in stopping smoking during prior CHANTIX therapy for reasons other than intolerability due to adverse events or who relapsed after treatment, should be encouraged to make another attempt with CHANTIX once factors contributing to the failed attempt have been identified and addressed.

Consider a temporary or permanent dose reduction in patients who cannot tolerate the adverse effects of CHANTIX.

2.2 Dosage in Special Populations

Patients with Impaired Renal Function. No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), the recommended starting dose of CHANTIX is 0.5 mg once daily. The dose may then be titrated as needed to a maximum dose of 0.5 mg twice a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5)].

Elderly and Patients with Impaired Hepatic Function. No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Use in Specific Populations (8.5)].

3 DOSAGE FORMS AND STRENGTHS
Capsular, biconvex tablets: 0.5 mg (white to off-white, debossed with "PFIZER" on one side and "CHX 0.5" on the other side) and 1 mg (light blue, debossed with "PFIZER" on one side and "CHX 1.0" on the other side).

4 CONTRAINDICATIONS
CHANTIX is contraindicated in patients with a known history of serious hypersensitivity reactions or skin reactions to CHANTIX.

5 WARNINGS AND PRECAUTIONS

5.1 Neuropsychiatric Symptoms and Suicidality
Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX [see Boxed Warning and Adverse Reactions (6.2)]. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been contributed to by the symptomatic nature of psychiatric illness in patients who have stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX.

Adverse events have been reported following pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX. Limited safety data are available from postmarketing smoking cessation studies in two patient groups: 1) patients with major depressive disorder, and 2) patients with stable schizophrenia or schizoaffective disorder [see Adverse Reactions (6.1), Clinical Studies (14.5)].

Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior directed to oneself or others, may have been worsened by concomitant use of alcohol [see Interaction with Alcohol (5.3), Adverse Reactions (6.2)].

Adverse events and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. [see Warnings and Precautions (5.1) and Adverse Reactions (6.2)].

6 ADVERSE REACTIONS

6.1 Clinical Trials

Since the initial signal of neuropsychiatric symptoms and suicidality emerged, additional analyses and studies have been conducted to further evaluate this association.

A causal relationship between these reports and CHANTIX treatment has not been established. Physicians should observe patients attempting to quit smoking with or without CHANTIX for the occurrence of serious neuropsychiatric symptoms and should instruct patients to contact a healthcare provider if they experience such symptoms.

The neuropsychiatric safety of CHANTIX was evaluated in clinical trials, in analyses of combined clinical trials and in observational studies.

Study in Patients with or without a History of Psychiatric Disorder [see Adverse Reactions (6.1), Clinical Trials (14.6)]

CHANTIX was evaluated in a randomized, double-blind, active and placebo-controlled study that included patients with a history of psychiatric disorder (psychiatric cohort, N=4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3984). Subjects aged 18-75

7 CLINICAL STUDIES

In a 12-week, randomized, placebo-controlled study that included patients with a history of psychiatric disorder (psychiatric cohort, N=4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3984). Subjects aged 18-75

8 CLINICAL PHARMACOLOGY

8.1 Pharmacokinetics

The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

| Days 1 – 3: | 0.5 mg once daily |
| Days 4 – 7: | 0.5 mg twice daily |
| Day 8 – end of treatment: | 1 mg twice daily |

Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks’ treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence.

Patients who are motivated to quit, and who did not succeed in stopping smoking during prior CHANTIX therapy for reasons other than intolerability due to adverse events or who relapsed after treatment, should be encouraged to make another attempt with CHANTIX once factors contributing to the failed attempt have been identified and addressed.

Consider a temporary or permanent dose reduction in patients who cannot tolerate the adverse effects of CHANTIX.

8.2 Dosage in Special Populations

Patients with Impaired Renal Function. No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), the recommended starting dose of CHANTIX is 0.5 mg once daily. The dose may then be titrated as needed to a maximum dose of 0.5 mg twice a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5)].

Elderly and Patients with Impaired Hepatic Function. No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Use in Specific Populations (8.5)].

9 CLINICAL STUDIES

9.1 Clinical Trials

In a 12-week, randomized, placebo-controlled study that included patients with a history of psychiatric disorder (psychiatric cohort, N=4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3984). Subjects aged 18-75
years, smoking 10 or more cigarettes per day were randomized 1:1:1:1 to CHANTIX 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment.

The primary safety endpoint was a composite of the following neuropsychiatric (NPS) adverse events: severe events of anxiety, depression, feeling abnormal, or hostility, and moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide.

As shown in Table 1, in the non-psychiatric cohort, the rates of events in the composite endpoint were low across all treatment groups and were similar or lower for each of the active treatments compared to placebo: risk differences (RDs [95% Confidence Interval (CI)]) vs placebo were -1.28% (-2.40, -0.15) for CHANTIX, -0.80% (-1.37, 1.21) for bupropion and -0.21% (-1.54, 1.12) for NRT. The use of CHANTIX, bupropion and NRT in the non-psychiatric cohort was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero). Similarly, the use of CHANTIX was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with bupropion or NRT in the non-psychiatric cohort (-1.19% (-2.30, -0.09) and -1.07 (-2.21, 0.08), respectively).

### Table 1. Number of Patients Reporting the Composite NPS AE Primary Endpoint and Its Components by Treatment Group in Patients without a History of Psychiatric Disorder

<table>
<thead>
<tr>
<th>Component of NPS AE Endpoint</th>
<th>CHANTIX</th>
<th>Bupropion</th>
<th>NRT*</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite NPS AE Endpoint</strong></td>
<td>13 (1.3)</td>
<td>22 (2.2)</td>
<td>25 (2.5)</td>
<td>24 (2.4)</td>
</tr>
<tr>
<td><strong>RD (95% CI) vs Placebo</strong></td>
<td>-1.28 (-2.40, -0.15)</td>
<td>-0.08 (-1.37, 1.21)</td>
<td>-0.21 (-1.54, 1.12)</td>
<td></td>
</tr>
<tr>
<td><strong>Components of NPS AE Endpoint</strong></td>
<td>1.0 (1.0)</td>
<td>0 (0.0)</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>0</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Feeling abnormal</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Hostility</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>10 (1.0)</td>
<td>11 (1.1)</td>
<td>19 (1.9)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Aggression</td>
<td>3 (0.3)</td>
<td>3 (0.3)</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Delusions</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Homicidal ideation</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Panic</td>
<td>0</td>
<td>4 (0.4)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Paranoia</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Suicidal behavior</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Completed suicide</td>
<td>0</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Number of Patients Reporting Suicidal Ideation and/or Behavior on the Columbia-Suicide Severity Rating Scale by Treatment Group in Patients without a History of Psychiatric Disorder

<table>
<thead>
<tr>
<th>RD (95% CI) vs Placebo</th>
<th>CHANTIX</th>
<th>Bupropion</th>
<th>NRT*</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suicidal ideation</strong></td>
<td>7 (0.7)</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td><strong>Suicidal behavior</strong></td>
<td>0</td>
<td>0</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td><strong>Suicide attempt</strong></td>
<td>7 (0.7)</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
<td>6 (0.6)</td>
</tr>
</tbody>
</table>

* NRT = Nicotine replacement therapy patch

The percentage of patients with suicidal ideation and/or behavior based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the CHANTIX and placebo groups during treatment and in the non-treatment follow-up in the non-psychiatric cohort, as shown in Table 2.

There was one completed suicide, which occurred during treatment in a patient treated with placebo in the non-psychiatric cohort.

As shown in Table 3, there were more events reported in patients in the psychiatric cohort in each treatment group compared with the non-psychiatric cohort (Table 1). In the psychiatric cohort, the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo: RDs (95% CI) vs placebo were 1.59% (-0.42, 3.59) for CHANTIX, 1.78% (-0.24, 3.81) for bupropion and 0.37% (-1.53, 2.26) for NRT. The use of CHANTIX, bupropion and NRT in the psychiatric cohort was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs included zero). Similarly, the use of CHANTIX was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with bupropion or NRT in the psychiatric cohort (-0.20% (-2.34, 1.95) and 1.22% (-0.81, 3.25), respectively).

### Table 3. Number of Patients Reporting the Composite NPS AE Primary Endpoint and Its Components by Treatment Group in Patients with a History of Psychiatric Disorder

<table>
<thead>
<tr>
<th>RD (95% CI) vs Placebo</th>
<th>CHANTIX</th>
<th>Bupropion</th>
<th>NRT*</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Completed suicide</strong></td>
<td>1026</td>
<td>1017</td>
<td>1016</td>
<td>1015</td>
</tr>
<tr>
<td><strong>Components of NPS AE Endpoint</strong></td>
<td>67 (6.5)</td>
<td>68 (6.7)</td>
<td>53 (5.2)</td>
<td>50 (4.9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5 (0.5)</td>
<td>4 (0.4)</td>
<td>6 (0.6)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Depression</td>
<td>6 (0.6)</td>
<td>4 (0.4)</td>
<td>7 (0.7)</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>Feeling abnormal</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Hostility</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>25 (2.4)</td>
<td>29 (2.9)</td>
<td>21 (2.1)</td>
<td>22 (2.2)</td>
</tr>
<tr>
<td>Aggression</td>
<td>14 (1.4)</td>
<td>9 (0.9)</td>
<td>7 (0.7)</td>
<td>8 (0.9)</td>
</tr>
<tr>
<td>Delusions</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>2 (0.5)</td>
<td>4 (0.4)</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Homicidal ideation</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td>7 (0.7)</td>
<td>9 (0.9)</td>
<td>3 (0.3)</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>Panic</td>
<td>7 (0.7)</td>
<td>16 (1.6)</td>
<td>13 (1.3)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Paranoia</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
</tr>
</tbody>
</table>

* NRT = Nicotine replacement therapy patch

AE, adverse event; Grade = severe intensity AE; *Grade = moderate and severe intensity AE;
Forty-eight (48) of the 55 patients who reported suicidal ideation or behavior reported a Risk Ratio (RR) of 0.79 (95% Confidence Interval [CI]: 0.46, 1.36), as shown in Table 15. This meta-analysis included one trial (N=127) assessing suicidal ideation and behavior as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included 1907 patients (1130 CHANTIX, 777 placebo) was conducted to compare suicidal ideation and/or behavior (24 CHANTIX, 24 placebo) were observed in the two trials that enrolled patients with a history of schizophrenia, schizoaffective disorder, or another psychiatric disorder.

Table 15. Patients with Suicidal ideation and/or behavior* (n (%)**

<table>
<thead>
<tr>
<th>CHANTIX (N=1130)</th>
<th>Placebo (N=777)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Suicidal ideation and/or behavior*</td>
<td>28 (2.5)</td>
</tr>
<tr>
<td>Patient-years of exposure</td>
<td>325</td>
</tr>
</tbody>
</table>

* Of the events, one patient in each treatment arm reported suicidal ideation or behavior.
** Patients with events up to 30 days after treatment; % are not weighted by study year.

A pooled analysis of 18 double-blind, randomized, placebo-controlled clinical trials, which includes the 5 trials that collected C-SSRS described in Table 15, was conducted to assess the psychiatric safety of CHANTIX. This pooled analysis included 8521 patients (5072 CHANTIX, 3449 placebo), some of whom had psychiatric conditions at baseline. Table 26 describes the most frequently (≥ 1%) reported adverse events related to psychiatric safety. The results showed a similar incidence of common psychiatric events in patients treated with CHANTIX compared to patients treated with placebo.

Table 26. Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Analysis of 18 Clinical Trials

<table>
<thead>
<tr>
<th>CHANTIX (N=5072)</th>
<th>Placebo (N=3449)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety disorders and symptoms</td>
<td>253 (5.0)</td>
</tr>
<tr>
<td>Depressed mood disorders and disturbances</td>
<td>179 (3.5)</td>
</tr>
<tr>
<td>Mood disorders and disturbances NEC*</td>
<td>116 (2.3)</td>
</tr>
</tbody>
</table>

* NEC = Not Elsewhere Classified

Counts (percentages) correspond to the number of patients reporting the event.

Observational Studies

Four observational studies, each including 10,000 to 30,000 users of CHANTIX in the adjusted analyses, compared the risk of selected serious neuropsychiatric events (neuropsychiatric hospitalizations, fatal and non-fatal self-harm) between CHANTIX users and prescription NRT or bupropion users.  All studies were retrospective cohort studies and included patients with and without a psychiatric history.

Two of the studies found no difference in risk of neuropsychiatric hospitalizations between CHANTIX users and nicotine patch users (Hazard Ratio [HR]: 1.14; 95% Confidence Interval [CI]: 0.96–1.34 in the first study, and 0.76; 95% CI: 0.40–1.46 in the second study). However, neither study validated the diagnostic codes used to identify outcomes against medical records. A third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between CHANTIX users and bupropion users (HR: 0.85; 95% CI: 0.55–1.30). Bupropion has also been associated with neuropsychiatric adverse events. A fourth study examined risk of fatal and non-fatal self-harm in users of CHANTIX compared to users of NRT. Although the occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 CHANTIX users and six cases in 81,545 NRT users), this study has important limitations.

Important trends have been captured from the public awareness of reports of neuropsychiatric adverse events in CHANTIX users. CHANTIX users had fewer comorbid conditions that could put them at risk for neuropsychiatric adverse events, suggesting that patients with a history of neuropsychiatric illness were preferentially prescribed NRT, and healthier patients were preferentially prescribed CHANTIX.

Outcomes examined in these studies did not include the full range of neuropsychiatric adverse events that have been reported.

5.2 Seizures

During clinical trials and the post-marketing experience, there have been reports of seizures in patients treated with CHANTIX. Some patients had no history of seizures, whereas others had a history of seizure disorder that was remote or well-controlled. In most cases, the seizure occurred within the first month of therapy. Weigh this potential risk against the potential benefits before prescribing CHANTIX in patients with a history of seizures or other factors that can lower the seizure threshold. Advise patients to discontinue CHANTIX and contact a healthcare provider immediately if they experience a seizure while on treatment [see Adverse Reactions (6.2)].

5.3 Interaction with Alcohol

There have been post-marketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some cases described unusual and sometimes aggressive behavior, and were often accompanied by amnesia for the events. Advise patients to reduce the amount of alcohol they consume.
consume while taking CHANTIX until they know whether CHANTIX affects their tolerance for alcohol [see Adverse Reactions (6.2)].

5.4 Accidental Injury

There have been postmarketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking CHANTIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Advise patients to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

5.5 Cardiovascular Events

In a placebo-controlled clinical trial of CHANTIX administered to patients with stable cardiovascular disease, with approximately 350 patients per treatment arm, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX, but certain nonfatal cardiovascular events occurred more frequently in patients treated with CHANTIX than in patients treated with placebo [see Clinical Trials Experience (6.1)]. Table 47 below shows the incidence of deaths and of selected nonfatal serious cardiovascular events occurring more frequently in the CHANTIX arm compared to the placebo arm. These events were adjudicated by an independent blinded committee. Nonfatal serious cardiovascular events not listed occurred at the same incidence or more commonly in the placebo arm. Patients with more than one cardiovascular event of the same type are counted only once per row. Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina.

Table 47. Mortality and Adjudicated Nonfatal Serious Cardiovascular Events in the Placebo-Controlled CHANTIX Trial in Patients with Stable Cardiovascular Disease

<table>
<thead>
<tr>
<th>Mortality and Cardiovascular Events</th>
<th>CHANTIX (N=350) n (%)</th>
<th>Placebo (N=350) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (Cardiovascular &amp; All-cause up to 52 wks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2 (0.6)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Nonfatal Cardiovascular Events (rate on CHANTIX &gt; Placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 30 days after treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>4 (1.1)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>2 (0.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Beyond 30 days after treatment &amp; up to 52 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>3 (0.8)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Need for coronary revascularization</td>
<td>7 (2.0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Hospitalization for angina pectoris</td>
<td>6 (1.7)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Transient ischemia attack</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>New diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure</td>
<td>5 (1.4)</td>
<td>2 (0.6)</td>
</tr>
</tbody>
</table>

A meta-analysis of 15 clinical trials of ≥12 weeks treatment duration, including 7002 patients (4190 CHANTIX, 2812 placebo), was conducted to systematically assess the cardiovascular safety of CHANTIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis. There were lower rates of all-cause mortality (CHANTIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHANTIX 2 [0.05%]; placebo 2 [0.07%]) in the CHANTIX arms compared with the placebo arms in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred in the trials included in the meta-analysis, as described in Table 48. These events occurred primarily in patients with known cardiovascular disease.

Table 48. Number of MACE cases, Hazard Ratio and Rate Difference in a Meta-Analysis of 15 Clinical Trials Comparing CHANTIX to Placebo*

<table>
<thead>
<tr>
<th></th>
<th>CHANTIX</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=4190</td>
<td>N=2812</td>
<td></td>
</tr>
<tr>
<td>MACE cases, n (%)</td>
<td>13 (0.31%)</td>
<td>6 (0.21%)</td>
</tr>
<tr>
<td>Patient-years of exposure</td>
<td>1316</td>
<td>839</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI)</th>
<th>Rate Difference per 1,000 patient-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.95 (0.79, 4.82)</td>
<td>6.30 (-2.40, 15.10)</td>
</tr>
</tbody>
</table>

*Includes MACE occurring up to 30 days post treatment.

The meta-analysis showed that exposure to CHANTIX resulted in a hazard ratio for MACE of 1.95 (95% confidence interval from 0.79 to 4.82) for patients exposed to 30 days after treatment, which is equivalent to an estimated increase of 6.3 MACE events per 1,000 patient-years of exposure. The meta-analysis showed higher rates of CV endpoints in patients on CHANTIX relative to placebo across different time frames and pre-specified sensitivity analyses, including various study groupings and CV outcomes. Although these findings were not statistically significant they were consistent. Because the number of events was small overall, the power for finding a statistically significant difference in a signal of this magnitude is low.

CHANTIX was not studied in patients with unstable cardiovascular disease or cardiovascular events occurring within two months before screening. Patients should be advised to notify a health care provider of new or worsening symptoms of cardiovascular disease. The risks of CHANTIX should be weighed against the benefits of its use in smokers with cardiovascular disease. Smoking is an independent and major risk factor for cardiovascular disease. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo.

5.6 Angioedema and Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX [see Adverse Reactions (6.2), and Patient Counseling Information (17)]. Clinical signs including swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). There were infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. Instruct patients to discontinue CHANTIX and order medical care if they experience these symptoms.

5.7 Serious Skin Reactions

There have been postmarketing reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients using CHANTIX [see Adverse Reactions (6.2)]. As these skin reactions can be life-threatening, instruct patients to stop taking CHANTIX and contact a healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.

5.8 Nausea

Nausea was the most common adverse reaction reported with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some patients, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. For patients treated to the maximum recommended dose of 1 mg twice daily following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg twice daily following initial titration, the incidence was 16% compared with 11% for placebo. Approximately 3% of patients treated with CHANTIX 1 mg twice daily in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, a dose reduction should be considered.

6 ADVERSE REACTIONS

The following serious adverse reactions were reported in postmarketing experience and are discussed in greater detail in other sections of the labeling:

- Neuropsychiatric symptoms and suicidality [see Boxed Warning and Warnings and Precautions (5.1)]
- Seizures [see Warnings and Precautions (5.2)]
- Interaction with Alcohol [see Warnings and Precautions (5.3)]
- Accidental injury [see Warnings and Precautions (5.4)]
- Cardiovascular Events [see Warnings and Precautions (5.5)]
- Angioedema and hypersensitivity reactions [see Warnings and Precautions (5.6)]
- Serious skin reactions [see Warnings and Precautions (5.7)]

In the placebo-controlled premarketing studies, the most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.

The treatment discontinuation rate due to adverse events in patients dosed with 1 mg twice daily was 12% for CHANTIX, compared to 10% for placebo in
studies of three months’ treatment. In this group, the discontinuation rates that are higher than placebo for the most common adverse events in CHANTIX-treated patients were as follows: nausea (3% vs. 0.5% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo).

Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During the premarketing development of CHANTIX, over 4500 subjects were exposed to CHANTIX, with over 430 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less.

The most common adverse event associated with CHANTIX treatment is nausea, occurring in 30% of patients treated at the recommended dose, compared with 10% in patients taking a comparable placebo regimen [see Warnings and Precautions (3.6)].

Table 39 shows the adverse events for CHANTIX and placebo in the 12-week fixed-dose premarketing studies with titration in the first week [Studies 2 (titrated arm only), 4, and 5]. Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

MedDRA High Level Group Terms (HLGT) reported in ≥ 5% of patients in the CHANTIX 1 mg twice daily dose group, and more commonly than the placebo group, are listed, along with subordinated Preferred Terms (PT) reported in ≥ 1% of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as ‘Insomnia’, ‘initial insomnia’, ‘Middle insomnia’, ‘Early morning awakening’ were grouped, but individual patients reporting two or more grouped events are only counted once.

Table 39: Common Treatment Emergent Adverse Events (%) in the Fixed-Dose Placebo-Controlled Studies (HLGT ≥ 5% of patients in the 1 mg BID CHANTIX Group and more commonly than placebo and PT ≥ 1% in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)

<table>
<thead>
<tr>
<th>SYSTEM ORGAN CLASS</th>
<th>CHANTIX 0.5 mg BID N=129</th>
<th>CHANTIX 1 mg BID N=821</th>
<th>Placebo N=805</th>
</tr>
</thead>
<tbody>
<tr>
<td>GASTROINTESTINAL (GI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Signs and Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Flatulence</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>GI Motility/Defecation Conditions</td>
<td>5</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Salivary Gland Conditions</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>PSYCHIATRIC DISORDERS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>19</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nightmare</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NERVOUS SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>19</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Neurological Disorders</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Numbness</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GENERAL DISORDERS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Disorders NEC</td>
<td>4</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue/Malaise/Anemia</td>
<td>4</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>RESPIRATOR/MEDIAST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Disorders NEC</td>
<td>4</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Rhinorhea</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Upper Respiratory Tract Disorder</td>
<td>7</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>SKIN/SUBCUTANEOUS TISSUE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermal and Dermal Conditions</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>METABOLISM &amp; NUTRITION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite/General Nutrient Disorders</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern and frequency of adverse events during the long-term premarketing trials was similar to those described in Table 39, though several of the most common events were reported by a greater proportion of patients with long-term use (e.g., nausea was reported in 40% of patients treated with CHANTIX 1 mg twice daily in a one-year study, compared to 8% of placebo-treated patients).

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all premarketing clinical trials and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline. Adverse events were categorized using MedDRA, Version 16.0.

The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being actually life-threatening.

Blood and Lymphatic System Disorders: Infrequent anemia, lymphadenopathy, Leukopenia, thrombocytosis, thrombocytopenia.

Cardiac Disorders: Infrequent angina pectoris, myocardial infarction, palpitations, tachycardia. Rare acute coronary syndrome, arrhythmia, atrial fibrillation, bradycardia, cardiac failure, collateral, coronary artery disease, ventricular arrhythmias.

Ear and Labyrinth Disorders: Infrequent tinnitus, vertigo. Rare deafness, Meniere’s disease.

Endocrine Disorders: Infrequent thyroid gland disorders.

Eye Disorders: Infrequent conjunctivitis, eye irritation, eye pain, vision blurred, visual impairment. Rare blindness transient, cataract subcapsular, dry eye, night blindness, ocular vascular disorder, photophobia, retinal breaks.

Gastrointestinal Disorders: Infrequent diarrhea, toothache. Rare dysphagia, esophageal stricture, gastric ulcer, gastrointestinal hemorrhage, mouth ulceration. Rare enterocolitis, esophagitis, gastric ulcer, intestinal obstruction, pancreatitis acute.

General Disorders and Administration Site Conditions: Frequent chest pain, Infrequent chest discomfort, chills, edema, influenza-like illness, pyrexia.

Hepatobiliary Disorders: Rare gall bladder disorders.

Investigations: Infrequent liver function test abnormal, weight increased.

Infrequent electrocardiogram abnormal. Rare muscle enzyme increased, urine analysis abnormal.

Metabolism and Nutrition Disorders: Infrequent diabetes mellitus, hypoglycemia. Rare hyperlipidemia, hypokalemia.

Musculoskeletal and Connective Tissue Disorders: Rare: arthralgia, back pain, myalgia. Infrequent arthritis, muscle cramp, musculoskeletal pain. Rare myositis, osteoporosis.

Nervous System Disorders: Infrequent disturbance in attention, dizziness.

Infrequent amnesia, confusion, migraine, paroxia, syncope, tremor. Rare balance disorder, cerebrovascular accident, dysarthria, mental impairment, multiple sclerosis, VTP norepinephrine, nystagmus, psychomotor hyperactivity, psychomotor skills impaired, restless legs syndrome, sensory disturbance, transient ischemic attack, visual field defect.

Psychiatric Disorders: Infrequent dissociation, lido decreased, mood swings, thinking abnormal. Rare bradypnea, desorientation, euphoric mood.

Respiratory and Urinary Disorders: Infrequent nocturia, pollakiuria, urinary abnormality. Rare nephrothiasis, polyuria, renal failure acute, urethral syndrome, urinary retention.

Reproductive System and Breast Disorders: Infrequent menstrual disorder.
Respiratory, Thoracic and Mediasternal Disorders. *Frequent* respiratory disorders. *In frequent* asthma, epistaxis, rhinitis allergic, upper respiratory tract inflammation. *Rare* pleurisy, pulmonary embolism.

Skin and Subcutaneous Tissue Disorders. *In frequent* acne, dry skin, eczema, erythema, hyperhidrosis, urticaria. *Rare* photosensitivity reaction, psoriasis.

Vascular Disorders. *In frequent* hot flash. *Rare* thrombosis.

CHANTIX has also been studied in postmarketing studies including (1) a trial conducted in patients with chronic obstructive pulmonary disease (COPD), (2) a trial conducted in generally healthy patients (similar to those in the premarketing studies) in which they were allowed to select a quit date between days 8 and 35 of treatment (“alternative quit date instruction trial”), (3) a trial conducted in patients who did not succeed in stopping smoking during prior CHANTIX therapy, or who relapsed after treatment (“re-treatment trial”), (4) a trial conducted in patients with stable cardiovascular disease, (5) a trial conducted in patients with stable schizophrenia or schizoaffective disorder, and, (6) a trial conducted in patients with major depressive disorder and (7) a trial conducted in patients with or without a history of psychotic disorder.

Adverse events in the trial of patients with COPD, in the alternative quit date instruction trial, were quantitatively and qualitatively similar to the observed in premarketing studies. In the re-treatment trial, the profile of common adverse events was similar to that previously reported, but, in addition, varenicline-treated patients also commonly reported diarrhea (6% vs 4% in placebo-treated patients), depressed mood disorders and disturbances (6% vs 1%), and other mood disorders and disturbances (5% vs 2%).

In the trial of patients with stable cardiovascular disease, more types and a greater number of cardiovascular events were reported compared to premarketing studies. Varenicline-treated patients reported treatment emergent and non-treatment emergent cardiovascular events reported with a frequency ≥ 1% in either treatment group in this study were angina pectoris (3.7% and 2.0% for varenicline and placebo, respectively), chest pain (2.5% vs. 2.3%), peripheral edema (2.0% vs. 1.1%), hypertension (1.4% vs. 2.6%), and palpitations (0.6% vs. 1.1%). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment emergent and non-treatment emergent) were adjudicated by a blinded, independent committee. The following treatment emergent adjudicated events occurred with a frequency ≥1% in either treatment group: nonfatal MI (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.6%). Some patients required coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

In the trial of patients with stable schizophrenia or schizoaffective disorder, 128 smokers on antipsychotic medication were randomized 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up. The most common adverse events in patients taking varenicline were nausea (24% vs. 14.0% on placebo), headache (11% vs. 19% on placebo) and vomiting (11% vs. 9% on placebo). Among reported neuropsychiatric adverse events, insomnia was the most frequent event that occurred in either treatment group in ≥5% of subjects at a rate higher in the varenicline group than in placebo (10% vs. 5%). These common and neuropsychiatric adverse events occurred on treatment or within 30 days after the last dose of study drug. There was no consistent worsening of schizophrenia in either treatment group as measured by the Positive and Negative Syndrome Scale. There were no overall changes in extra-pyramidal signs, as measured by the Simpson-Angus Rating Scale. The Columbia-Suicide Severity Rating Scale was administered at baseline and at clinic visits during the treatment and non-treatment follow-up phases. Over half of the patients had a lifetime history of suicidal behavior and/or ideation (62% on varenicline vs. 51% on placebo), but at baseline, no patients had a history of suicidal behavior and/or ideation in either treatment group (2%). Suicidal behavior and/or ideation were reported in 21% of participants treated with varenicline and 18% of those treated with placebo. There were no suicidal events in either treatment group shortly (within one week) after treatment discontinuation (a phenomenon noted in post-marketing reporting). There were no completed suicides. There was one suicide attempt in a varenicline-treated patient. The limited data available from this single smoking cessation study are not sufficient to allow conclusions to be drawn.

In the trial of patients with major depressive disorder, the most common adverse events (≥10%) in subjects taking varenicline were nausea (27% vs. 10% on placebo), headache (17 vs 11%), abnormal dreams (11% vs 8%), insomnia (11% vs 5%) and irritability (11% vs. 8%). Additionally, the following psychiatric AEs were reported in ≥2% of patients in each treatment group (varenicline or placebo, respectively): anxiety (7% vs. 9%), agitation (7% vs. 4%), depressed mood disorders and disturbances (11% vs. 9%), tension (4% vs. 3%), hostility (2% vs. 0.4%) and restlessness (2% vs. 2%). Patients treated with varenicline were more likely than patients treated with placebo to report one or both of these events related to hostility and aggression (3% vs 1%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression during the study in either treatment group. The percentage of subjects with suicidal ideation and/or behavior was similar between the varenicline and placebo groups during treatment (6% and 8%, respectively) and the non-treatment follow-up (6% and 6%, respectively). There was one event of intentional self-injury/possible suicide attempt during treatment (Day 73 in a subject in the placebo group). Suicide could not be ruled out in one subject who died by an overdose of illicit drugs 76 days after last dose of study drug in the varenicline group.

In the trial of patients with or without a history of psychotic disorder, the most common adverse events in subjects treated with varenicline were similar to those reported in premarketing studies. Adverse events reported in ≥10% of subjects treated with varenicline in the entire study population were nausea (25.3% vs 6.8% on placebo) and headache (12.2% vs 9.9% on placebo). Additionally, the following psychiatric adverse events were reported in ≥2% of patients in either treatment group (varenicline vs placebo) by cohort. For the non-psychiatric cohort, these adverse events were abnormal dreams (8% vs. 4%), agitation (3% vs. 3%), anxiety (5% vs. 6%), depressed mood (3% vs. 3%), insomnia (10% vs. 7%), irritability (3% vs. 4%), sleep disorder (3% vs. 2%). For the psychiatric cohort, these adverse events were abnormal dreams (12% vs. 5%), agitation (5% vs. 4%), anxiety (8% vs. 6%), depressed mood (5% vs. 5%), depression (5% vs. 5%), insomnia (9% vs. 7%), irritability (5% vs. 7%), nervousness (2% vs. 3%), sleep disorder (3% vs. 2%).

6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of CHANTIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide in patients attempting to quit smoking while taking CHANTIX [see Warnings and Precautions (5.1)]. Smoking cessation with nicotine withdrawal treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. [Warnings and Precautions (5.1)].

There have been post-marketing reports of new or worsening seizures in patients treated with CHANTIX [see Warnings and Precautions (5.2)]. Some patients requiring cessation with nicotine withdrawal treatment have experienced increased intoxicating effects of alcohol while taking CHANTIX. Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior [see Warnings and Precautions (5.1) and (5.3)].

There have been reports of hypersensitivity reactions, including angioedema [see Warnings and Precautions (5.6)].

There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking CHANTIX [see Warnings and Precautions (5.7)].

There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischemic and hemorrhagic events in patients taking CHANTIX. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out.

7 DRUG INTERACTIONS

Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions [see Clinical Pharmacology (12.3)].

7.1 Use With Other Drugs for Smoking Cessation

Safety and efficacy of CHANTIX in combination with other smoking cessation therapies have not been studied.

Bupropion: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers. The safety of the combination of bupropion and varenicline has not been established.

Nicotine replacement therapy (NRT): Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to
12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone. In this study, eight of twenty-two (36%) patients treated with the combination of varenicline and NRT prematurely discontinued treatment due to adverse events, compared to 1 of 17 (6%) of patients treated with NRT and placebo.

7.2 Effect of Smoking Cessation on Other Drugs
Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C.
There are no adequate and well-controlled studies of CHANTIX use in pregnant women. In animal studies, CHANTIX caused decreased fetal weights, increased auditory startle response, and decreased fertility in offspring. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive and developmental toxicity studies, pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. These exposures were 36 (rats) and 50 (rabbits) times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 1 mg twice daily. While no fetal structural abnormalities occurred in either species, reduced fetal weights occurred in rabbits at the highest dose (exposure 50 times the human exposure at the MRHD based on AUC). Fetal weight reduction did not occur at animal exposures 23 times the human exposure at the MRHD based on AUC.

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. This resulted in exposures up to 36 times the human exposure (based on AUC) at the MRHD of 1 mg twice daily. Decreased fertility and increased auditory startle response occurred in offspring.

8.3 Nursing Mothers
It is not known whether CHANTIX is excreted in human milk. In animal studies varenicline was excreted in milk of lactating animals. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Safety and effectiveness of CHANTIX in pediatric patients have not been established.

8.5 Geriatric Use
A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Dosage and Administration (2.2)].

No dosage adjustment is recommended for elderly patients.

8.6 Renal Impairment
Varenicline is substantially eliminated by renal glomerular filtration along with active tubular secretion. Dose reduction is not required in patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), and for patients with end-stage renal disease undergoing hemodialysis, dosage adjustment is needed. [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
Varenicline is not a controlled substance.

9.3 Dependence

Humans: Fewer than 1 out of 1000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physiologic dependence which is not associated with addiction.

In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers.

Animal Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine; however, in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

10 OVERDOSAGE
In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease [see Clinical Pharmacology (12.3)]; however, there is no experience in dialysis following overdose.

11 DESCRIPTION
CHANTIX tablets contain varenicline (as the tartrate salt), which is a partial agonist selective for α4β2 nicotinic acetylcholine receptor subtypes.

Varenicline, as the tartrate salt, is a powder which is white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyranto[2,3-b][1,3]benzoxazines. (2R,3S)-2,3-dihydroxybutane-1,4-diol (1:1). It is highly soluble in water. Varenicline tartrate has a molecular weight of 361.35 Daltons, and a molecular formula of C19H22N202 • C3H4O2. The chemical structure is:

![Chemical Structure](image)

CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capillary bisconix, white to off-white, film-coated tablet debossed with "Pfizer" on one side and "CHIX 0.5" on the other side and a 1 mg capillary bisconix, light blue film-coated tablet debossed with "Pfizer" on one side and "CHIX 1.0" on the other side. Each 0.5 mg CHANTIX tablet contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base; each 1 mg CHANTIX tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base. The following inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Varenicline binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors. The efficacy of CHANTIX in smoking cessation is believed to be the result of varenicline's activity at α4β2 sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to these receptors.

Electrophysiological studies in vitro and neurochemical studies in vivo have shown that varenicline binds to α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopaminergic system, believed to be the neuronal mechanism underlying reinforcement and reward experienced.
upon smoking. Varenicline is highly selective and binds more potently to α4β2 receptors than to other common nicotinic receptors (>500-fold α3β4, >3500-fold α7, >2,000-fold α1β6), or to non-nicotinic receptors and transporters (>2,000-fold). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 5-HT3 receptor.

12.3 Pharmacokinetics

**Absorption/Distribution** Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was ~98%. Bioavailability of varenicline is unaffected by concomitant food or time-of-day dosing. Plasma protein binding of varenicline is low (<20%) and independent of both age and renal function.

**Metabolism/Elimination** The elimination half-life of varenicline is approximately 24 hours. Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

**Pharmacokinetics in Special Patient Populations** There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

**Renal Impairment** Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤80 mL/min). In subjects with moderate renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80 mL/min). In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage renal disease (ESRD) undergoing a three-hour session of hemodialysis for three days a week, varenicline exposure was increased 2.7-fold following 0.5 mg once daily administration for 12 weeks. The plasma Cmax and AUC of varenicline noted in this setting were similar to those of healthy subjects receiving 1 mg twice daily. [see Dosage and Administration (2.2), and Use in Specific Populations (8.6)]. Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis [see Overdose (10)].

**Geriatric Patients** A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects.

**Pediatric Patients** Because the safety and effectiveness of CHANTIX in pediatric patients have not been established, CHANTIX is not recommended for use in patients under 18 years of age. Single and multiple-dose pharmacokinetics of varenicline have been investigated in pediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight ≥55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg BID was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤35 kg compared to that noted in the adult population.

**Hepatic Impairment** Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment.

**Drug-Drug Interactions** Drug interaction studies were performed with varenicline and digoxin, warfarin, transdermal nicotine, bupropion, cimetidine, and metformin. No clinically meaningful pharmacokinetic drug-drug interactions have been identified.

*In vitro* studies demonstrated that varenicline does not inhibit the following cytochrome P450 enzymes (H20, >6400 ng/mL): 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4. Also, varenicline does not induce the cytochrome P450 enzymes 1A2 and 3A4.

*In vitro* studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (e.g., metformin [see below]) are unlikely to be affected by varenicline.

*In vivo* studies demonstrated the active renal secretion of varenicline is mediated by the human organic cation transporter OCT2. Co-administration with inhibitors of OCT2 (e.g., cimetidine [see below]) may not necessitate a dose adjustment of CHANTIX as the increase in systemic exposure to CHANTIX is not expected to be clinically meaningful. Furthermore, since metabolism of varenicline represents less than 10% of its clearance, drugs known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of CHANTIX [see Clinical Pharmacology (12.3)]. Therefore, a dose adjustment of CHANTIX would not be required.

Metformin: When co-administered to 30 smokers, varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of metformin (500 mg twice daily), which is a substrate of OCT2. Metformin had no effect on varenicline steady-state pharmacokinetics.

Cimetidine: Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) to 12 smokers increased the systemic exposure of varenicline by 29% (90% CI: 21.5%, 36.9%) due to a reduction in varenicline renal clearance.

Digoxin: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers.

Warfarin: Varenicline (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R, S)-warfarin in 24 smokers.

Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics [see Drug Interactions (7.2)].

Use with Other Drugs for Smoking Cessation

Bupropion: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers [see Drug Interactions (7.1)].

Nicotine replacement therapy (NRT): Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of adverse reactions was greater for the combination than for NRT alone [see Drug Interactions (7.1)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis Studies: Four 2-year in vivo mouse and Sprague-Dawley rat studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 3, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 36 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis: Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO-HGPRT assay; and tests for cytogenetic aberrations in vivo in rat bone marrow and in vitro in human lymphocytes.

Impairment of Fertility: There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg twice daily). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg twice daily). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg twice daily).

14 CLINICAL STUDIES

The efficacy of CHANTIX in smoking cessation was demonstrated in six clinical trials in which a total of 3659 chronic cigarette smokers (>10 cigarettes per day) were treated with CHANTIX. In all clinical studies, abstinence from smoking was determined by patient self-report and verified by measurement of exhaled carbon monoxide (CO≤10 ppm) at weekly visits. Among the CHANTIX-treated patients enrolled in these studies, the completion rate was 65%. Except for the dose-ranging study (Study 1) and the maintenance of abstinence study (Study 6), patients were treated for 12 weeks and then followed for 40 weeks post-treatment. Most patients enrolled in these trials were white (79-96%). All studies enrolled almost equal numbers of men and women. The average age of patients in these studies was 43 years. Patients on average had smoked about 21 cigarettes per day for an average of approximately 25 years. Patients set a date to stop smoking (target quit date) with dosing starting 1 week before this date.

Three additional studies were conducted to evaluate the efficacy of CHANTIX in patients with cardiovascular disease, in patients with chronic obstructive pulmonary disease [see Clinical Studies (14.4)], and in patients instructed to select their quit date within days 8 and 35 of treatment [see Clinical Studies (14.5)]. Patients with major depressive disorder [see Clinical Studies (14.5)], patients who had made a previous attempt to quit smoking with CHANTIX, and either did not succeed in quitting or relapsed after treatment [see Clinical Studies (14.5)], and in patients with or without a smoking cessation past smoking history [see Clinical Studies (14.6)] were treated with CHANTIX.
In all studies, patients were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each weekly treatment visit according to Agency for Healthcare Research and Quality guidelines.

14.1 Initiation of Abstinence

**Study 1** This was a six-week dose-ranging study comparing CHANTIX to placebo. This study provided initial evidence that CHANTIX at a total dose of 1 mg per day or 2 mg per day was effective as an aid to smoking cessation.

**Study 2** This study of 627 patients compared CHANTIX 1 mg per day and 2 mg per day with placebo. Patients were treated for 12 weeks (including one week titration) and then followed up for 40 weeks post-treatment. CHANTIX was given in two divided doses daily. Each dose of CHANTIX was given in two different regimens, with and without initial dose titration, to explore the effect of different dosing regimens on tolerability. For the titrated groups, dosage was titrated up over the course of one week, with full dosage achieved starting with the second week of dosing. The titrated and non-titrated groups were pooled for efficacy analysis.

Forty-nine percent of patients receiving CHANTIX 1 mg per day (0.5 mg twice daily) and 53% of patients receiving 2 mg per day (1 mg twice daily) had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% of patients in the placebo group (Figure 1). In addition, 31% of the 1 mg per day group and 31% of the 2 mg per day group were continuously abstinent from one week after TQD through the end of treatment as compared to 8% of the placebo group.

**Study 3** This flexible-dosing study of 312 patients examined the effect of a patient-directed dosing strategy of CHANTIX or placebo. After an initial one-week titration to a dose of 0.5 mg twice daily, patients could adjust their dosage as often as they wished between 0.5 mg once daily to 1 mg twice daily per day. Sixty-nine percent of patients titrated to the maximum allowable dose at any time during the study. For 44% of patients, the modal dose selected was 1 mg twice daily, for slightly over half of the study participants, the modal dose selected was 1 mg/day or less.

Of the patients treated with CHANTIX, 40% had a CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% in the placebo group. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 9% of the placebo group.

**Study 4 and Study 5** These identical double-blind studies compared CHANTIX 2 mg per day, bupropion sustained-release (SR) 150 mg twice daily, and placebo. Patients were treated for 12 weeks and then followed up for 40 weeks post-treatment. The CHANTIX dosage of 1 mg twice daily was achieved using a titration of 0.5 mg once daily for the initial 3 days followed by 0.5 mg twice daily for the next 4 days. The bupropion SR dosage of 150 mg twice daily was achieved using a 3-day titration of 150 mg once daily. Study 4 enrolled 1022 patients and Study 5 enrolled 1023 patients. Patients inappropriate for bupropion treatment or patients who had previously used bupropion were excluded.

In Study 4, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (17%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 12% of the placebo group and 23% of the bupropion SR group.

Similarly in Study 5, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (18%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 11% of the placebo group and 21% of the bupropion SR group.

### Table 11: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval) across different studies

<table>
<thead>
<tr>
<th>Study</th>
<th>CHANTIX 0.5 mg BID</th>
<th>CHANTIX 1 mg BID</th>
<th>CHANTIX Flexible</th>
<th>Bupropion SR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 2</td>
<td>43% (39%, 51%)</td>
<td>51% (44%, 57%)</td>
<td>40% (32%, 48%)</td>
<td>12% (6%, 18%)</td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>44% (38%, 49%)</td>
<td>44% (38%, 49%)</td>
<td>36% (25%, 45%)</td>
<td>12% (7%, 17%)</td>
<td></td>
</tr>
<tr>
<td>Study 5</td>
<td>44% (38%, 49%)</td>
<td>44% (38%, 49%)</td>
<td>36% (25%, 45%)</td>
<td>12% (7%, 17%)</td>
<td></td>
</tr>
</tbody>
</table>

BID = twice daily

### Figure 1: Continuous Abstinence, Weeks 9 through 12

**14.2 Urge to Smoke**

Based on responses to the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal scale "urge to smoke" item, CHANTIX reduced urge to smoke compared to placebo.

### Figure 2: Continuous Abstinence, Weeks 9 through 52

**14.3 Long-Term Abstinence**

Studies 1 through 5 included 40 weeks of post-treatment follow-up. In each study, CHANTIX-treated patients were more likely to maintain abstinence throughout the follow-up period than were patients treated with placebo (Figure 2, Table 11D).
Study 6. This study assessed the effect of an additional 12 weeks of CHANTIX therapy on the likelihood of long-term abstinence. Patients in this study (n=1927) were treated with open-label CHANTIX 1 mg twice daily for 12 weeks. Patients who had stopped smoking for at least a week by Week 12 (n=1210) were then randomized to double-blind treatment with CHANTIX (1 mg twice daily) or placebo for an additional 12 weeks and then followed for 28 weeks post-treatment.

The continuous abstinence rate from Week 13 through Week 24 was higher for patients continuing treatment with CHANTIX (70%) than for patients switching to placebo (50%). Superiority to placebo was also maintained during the 28 weeks post-treatment follow-up (CHANTIX 54% versus placebo 39%).

In Figure 3 below, the X-axis represents the study week for each observation, allowing a comparison of groups at similar times after discontinuation of CHANTIX. PostCHANTIX follow-up begins at Week 13 for the placebo group and Week 25 for the CHANTIX group. The Y-axis represents the percentage of patients who had been abstinent for the last week of CHANTIX treatment and remained abstinent at the given timepoint.

Figure 3: Continuous Abstinence Rate During Nontreatment Follow-Up

14.4 Subjects with Cardiovascular and Chronic Obstructive Pulmonary Disease

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged 35 to 75 years with stable, documented cardiovascular disease (diagnoses other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomized to CHANTIX 1 mg twice daily (n=353) or placebo (n=330) for a treatment of 12 weeks and then followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47%) compared to subjects treated with placebo (14%) and from week 9 through 52 (20%) compared to subjects treated with placebo (7%).

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged ≥ 35 years with mild to moderate COPD and post-bronchodilator FEV1/FVC < 70% and FEV1 ≥ 50% of predicted normal value. Subjects were randomized to CHANTIX 1 mg twice daily (n=253) or placebo (n=237) for a treatment of 12 weeks and then followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (41%) compared to subjects treated with placebo (9%) and from week 9 through 52 (19%) compared to subjects treated with placebo (6%).

Table 812: Continuous Abstinence (95% confidence interval), Studies in Patients with Cardiovascular Disease (CVD) and Chronic Obstructive Pulmonary Disease (COPD)

<table>
<thead>
<tr>
<th>Weeks 9 through 12</th>
<th>Weeks 9 through 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHANTIX 1 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>CHANTIX 1 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>CVD Study</td>
<td></td>
</tr>
<tr>
<td>20% (14%, 29%)</td>
<td>7% (0%, 9%)</td>
</tr>
<tr>
<td>20% (24%, 33%)</td>
<td>19% (12%, 27%)</td>
</tr>
<tr>
<td>COPD Study</td>
<td></td>
</tr>
<tr>
<td>41% (34%, 47%)</td>
<td>19% (6%, 33%)</td>
</tr>
<tr>
<td>41% (16%, 24%)</td>
<td>19% (12%, 27%)</td>
</tr>
<tr>
<td>BID= twice daily</td>
<td></td>
</tr>
</tbody>
</table>

14.5 Subjects with Major Depressive Disorder

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged 18 to 75 years with major depressive disorder without psychotic features (DSM-IV TR). If on medication, subjects were to be on a stable antidepressant regimen for at least two months. If not on medication, subjects were to have experienced a major depressive episode in the past 2 years, which was successfully treated. Subjects were randomized to CHANTIX 1 mg twice daily (n=256) or placebo (n=269) for a treatment of 12 weeks and then followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (36%) compared to subjects treated with placebo (16%) and from week 9 through 52 (20%) compared to subjects treated with placebo (10%).

Table 913: Continuous Abstinence (95% confidence interval), Study in Patients with Major Depressive Disorder (MDD)

<table>
<thead>
<tr>
<th>Weeks 9 through 12</th>
<th>Weeks 9 through 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHANTIX 1 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>CHANTIX 1 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>MDD Study</td>
<td></td>
</tr>
<tr>
<td>90% (80%, 90%)</td>
<td>10% (4%, 25%)</td>
</tr>
<tr>
<td>20% (11%, 29%)</td>
<td>15% (7%, 25%)</td>
</tr>
<tr>
<td>15% (7%, 25%)</td>
<td>10% (4%, 25%)</td>
</tr>
<tr>
<td>BID= twice daily</td>
<td></td>
</tr>
</tbody>
</table>

14.6 Subjects with or without a History of Psychiatric Disorder

CHANTIX was evaluated in a randomized, double-blind, active and placebo-controlled study that included subjects with a history of psychiatric disorder (psychiatric cohort: N=4974) and subjects without a history of psychiatric disorder (non-psychiatric cohort: N=3984). Subjects aged 18-75 years, smoking 10 or more cigarettes per day were randomized 1:1:1 to CHANTIX 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment. [See Warnings and Precautions (5.1)]

In both cohorts, subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo.

Table 14: Continuous Abstinence (95% confidence interval), Study in Patients with or without a History of Psychiatric Disorder

<table>
<thead>
<tr>
<th>Weeks 9 through 12</th>
<th>Weeks 9 through 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Psychiatric</td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
</tr>
<tr>
<td>35% (23%, 48%)</td>
<td>14% (8%, 20%)</td>
</tr>
<tr>
<td>Psychiatric Cohort</td>
<td></td>
</tr>
<tr>
<td>15% (11%, 21%)</td>
<td>8% (4%, 15%)</td>
</tr>
<tr>
<td>BID= twice daily</td>
<td></td>
</tr>
</tbody>
</table>

14.7 Alternative Instructions for Setting a Quit Date

CHANTIX was evaluated in a double-blind, placebo-controlled trial where patients were instructed to select a target quit date between Day 8 and Day 35 of treatment. Subjects were randomized 3:1 to CHANTIX 1 mg twice daily (n=485) or placebo (n=165) for 12 weeks of treatment and followed for another 12 weeks post-treatment. Patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (54%) compared to patients treated with placebo (19%) and from weeks 9 through 24 (35%) compared to subjects treated with placebo (13%).

14.8 Re-Treatment Study

CHANTIX was evaluated in a double-blind, placebo-controlled trial of patients who had made a previous attempt to quit smoking with CHANTIX, and either did not succeed in quitting or relapsed after treatment. Subjects were randomized 1:1 to CHANTIX 1 mg twice daily (n=249) or placebo (n=245) for 12 weeks of treatment and followed for 40 weeks post-treatment. Patients included in this study had taken CHANTIX for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had had smoking for at least four weeks.

Patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (45%) compared to patients treated with placebo (12%) and from weeks 9 through 52 (20%) compared to subjects treated with placebo (5%).

Table 1015: Continuous Abstinence (95% confidence interval), Re-Treatment Study

<table>
<thead>
<tr>
<th>Weeks 9 through 12</th>
<th>Weeks 9 through 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHANTIX 1 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>CHANTIX 1 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>Retreatment Study</td>
<td></td>
</tr>
<tr>
<td>45% (39%, 51%)</td>
<td>26% (19%, 33%)</td>
</tr>
<tr>
<td>12% (5%, 20%)</td>
<td>15% (9%, 21%)</td>
</tr>
<tr>
<td>BID= twice daily</td>
<td></td>
</tr>
</tbody>
</table>
16 HOW SUPPLIED/STORAGE AND HANDLING
CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "Pfizer" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "Pfizer" on one side and "CHX 1.0" on the other side. CHANTIX is supplied in the following package configurations:

<table>
<thead>
<tr>
<th>Packs</th>
<th>Description</th>
<th>NDC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Starting 2 week card: 0.5 mg x 11 tablets and 1 mg x 14 tablets</td>
<td>NDC 0069-0471-01</td>
</tr>
<tr>
<td></td>
<td>Continuing 2 week card: 1 mg x 28 tablets</td>
<td>NDC 0069-0469-11</td>
</tr>
<tr>
<td></td>
<td>Starting 4-week card: 0.5 mg x 11 tablets and 1 mg x 42 tablets</td>
<td>NDC 0069-0471-03</td>
</tr>
<tr>
<td></td>
<td>Continuing 4-week card: 1 mg x 56 tablets</td>
<td>NDC 0069-0469-03</td>
</tr>
<tr>
<td></td>
<td>Starting Month Box: 0.5 mg x 11 tablets and 1 mg x 42 tablets</td>
<td>NDC 0069-0471-02; NDC 0069-0471-03</td>
</tr>
<tr>
<td></td>
<td>Continuing Month Box: 1 mg x 56 tablets</td>
<td>NDC 0069-0469-12; NDC 0069-0469-03</td>
</tr>
<tr>
<td>Bottles</td>
<td>0.5 mg - bottle of 56</td>
<td>NDC 0069-0468-56</td>
</tr>
<tr>
<td></td>
<td>1 mg - bottle of 56</td>
<td>NDC 0069-0469-56</td>
</tr>
</tbody>
</table>

Store at 25 C (77 F); excursions permitted to 15–30 C (59–86 F) (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Medication Guide)

Initiate Treatment and Continue to Attempt to Quit if Lapse
Instruct patients to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date. Alternatively, the patient can begin CHANTIX dosing and then set a date to quit smoking between days 8 and 35 of treatment. Encourage patients to continue to attempt to quit if they have early lapses after quit day [see Dosage and Administration (2.1)]. Encourage patients who are motivated to quit and who did not succeed in stopping smoking during prior CHANTIX therapy for reasons other than intolerability due to adverse events, or who relapsed after treatment to make another attempt with CHANTIX once factors contributing to the failed attempt have been identified and addressed [see Dosage and Administration (2.1), Clinical Studies (14.25)].

How To Take
Advise patients that CHANTIX should be taken after eating, and with a full glass of water [see Dosage and Administration (2.1)].

Starting Week Dosage
Instruct patients on how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening [see Dosage and Administration (2.1)].

Continuing Weeks Dosage
Advise patients that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening [see Dosage and Administration (2.1)].

Dose Adjustment for CHANTIX or Other Drugs
Inform patients that nausea and insomnia are side effects of CHANTIX and are usually transient; however, advise patients that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.
Inform patients that some drugs may require dose adjustment after quitting smoking [see Dosage and Administration (2.1)].

Counseling and Support
Provide patients with educational materials and necessary counseling to support an attempt at quitting smoking [see Dosage and Administration (2.1)].

Neuropsychiatric Symptoms
Inform patients that some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation and suicide when attempting to quit smoking while taking CHANTIX. If patients develop agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to discontinue CHANTIX and report these symptoms to their healthcare provider immediately [see Boxed Warning]. Instruct patients to contact a healthcare professional if they experience such symptoms. [see Warnings and Precautions (5.1), Adverse Reactions (6.2)].

History of Psychiatric Illness
Encourage patients to reveal any history of psychiatric illness prior to initiating treatment.

Nicotine Withdrawal
Inform patients that quitting smoking, with or without CHANTIX, may be associated with nicotine withdrawal symptoms (including depression or agitation) or exacerbation of pre-existing psychiatric illness.

Seizures
Encourage patients to report any history of seizures or other factors that can lower seizure threshold. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately if they experience a seizure while on treatment [see Warnings and Precautions (5.2)].

Interaction with Alcohol
Advise patients to reduce the amount of alcohol they consume while taking CHANTIX until they know whether CHANTIX affects their tolerance for alcohol [see Warnings and Precautions (5.3), Adverse Reactions (6.2)].

Driving or Operating Machinery
Advise patients to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them [see Warnings and Precautions (5.4)].

Cardiovascular Events
Patients should be instructed to notify their health care providers of symptoms of new or worsening cardiovascular events and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. [see Warnings and Precautions (5.5), and Adverse Reactions (6.1)].

Angioedema
Inform patients that there have been reports of angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms [see Warnings and Precautions (5.2), and Adverse Reactions (6.2)].

Serious Skin Reactions
Inform patients that serious skin reactions, such as Stevens-Johnson Syndrome and erythema multiforme, were reported by some patients taking CHANTIX. Advise patients to stop taking CHANTIX at the first sign of rash with mucosal lesions or skin reaction and contact a healthcare provider immediately [see Warnings and Precautions (5.3), and Adverse Reactions (6.2)].

Vivid, Unusual, or Strange Dreams
Inform patients that they may experience vivid, unusual or strange dreams during treatment with CHANTIX.

Pregnancy and Lactation
Patients who are pregnant or breastfeeding or planning to become pregnant should be advised of: the risks of smoking to a pregnant mother and her developing baby, the potential risks of CHANTIX use during pregnancy and breastfeeding, and the benefits of smoking cessation with and without CHANTIX [see Use in Specific Populations (8.1 and 8.3)].
What is the most important information I should know about CHANTIX?

Some people have had serious side effects while using CHANTIX to help them quit smoking, including:

**New or worse mental health problems, such as changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions.** Some people had these symptoms when they began taking CHANTIX, and others developed them after several weeks of treatment, or after stopping CHANTIX.

**Before taking CHANTIX,** tell your doctor if you have ever had depression or other mental health problems. You should also tell your doctor about any symptoms you had during other times you tried to quit smoking, with or without CHANTIX.

**Stop taking CHANTIX and call your doctor right away** if you, your family, or caregiver notice agitation, hostility, depression or changes in your behavior or thinking that are not typical for you, or you develop any of the following symptoms:

- thoughts about suicide or dying, or attempts to commit suicide
- new or worse depression, anxiety, or panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior or mood

When you try to quit smoking, with or without CHANTIX, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

See “What are the possible side effects of CHANTIX?” for more information about other side effects.

What is CHANTIX?

CHANTIX is a prescription medicine to help people stop smoking.

 Quitting smoking can lower your chances of having lung disease, heart disease or getting certain types of cancer that are related to smoking.

It is not known if CHANTIX is safe and effective in children.

It is not known if CHANTIX is safe and effective when used with other stop smoking medicines.

Who should not take CHANTIX?

Do not take CHANTIX if you have had a serious allergic or skin reaction to CHANTIX. Symptoms may include:

- swelling of the face, mouth (tongue, lips, gums), throat or neck
- trouble breathing
- rash, with peeling skin
• blisters in your mouth

What should I tell my doctor before taking CHANTIX?

See “What is the most important information I should know about CHANTIX?”

Before you take CHANTIX, tell your doctor if you:

• use other treatments to quit smoking. Using CHANTIX with a nicotine patch may cause nausea, vomiting, headache, dizziness, upset stomach, and tiredness to happen more often than if you just use a nicotine patch alone.
• have kidney problems or get kidney dialysis. Your doctor may prescribe a lower dose of CHANTIX for you.
• have a history of seizures
• drink alcohol
• have heart or blood vessel problems
• have any other medical conditions
• are pregnant or plan to become pregnant. It is not known if CHANTIX will harm your unborn baby.
• are breastfeeding. It is not known if CHANTIX passes into breast milk. You and your doctor should decide if you will breastfeed or take CHANTIX. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over the counter medicines, vitamins and herbal supplements. Your doctor may need to change the dose of some of your medicines when you stop smoking.

You should not use CHANTIX while using other medicines to quit smoking. Tell your doctor if you use other treatments to quit smoking.

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist when you get a new medicine.

How should I take CHANTIX?

• There are 2 ways that you can use CHANTIX to help you quit smoking. Talk to your doctor about the following 2 ways to use CHANTIX:

  Choose a quit date when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your quit date.

  OR

  Start taking CHANTIX before you choose a quit date. Pick a date to quit smoking that is between days 8 and 35 of treatment.

Starting CHANTIX before your quit date gives CHANTIX time to build up in your body. You can keep smoking during this time. Take CHANTIX exactly as prescribed by your doctor.

• CHANTIX comes as a white tablet (0.5 mg) and a blue tablet (1 mg). You start with the white tablet and then usually go to the blue tablet. See the chart below for dosing instructions for adults.

| Day 1 to Day 3       | White tablet (0.5 mg)       |
|                      | Take 1 tablet each day      |
| Day 4 to Day 7      | White tablet (0.5 mg)       |
|                      | Take 1 in the morning and 1 in the evening |
| Day 8 to end of treatment | Blue tablet (1 mg)       |
|                      | Take 1 in the morning and 1 in the evening |

• Make sure that you try to stop smoking on your quit date. If you slip-up and smoke, try again. Some people need to take CHANTIX for a few weeks for CHANTIX to work best.
Most people will take CHANTIX for up to 12 weeks. If you have completely quit smoking by 12 weeks, your doctor may prescribe CHANTIX for another 12 weeks to help you stay cigarette-free.

Take CHANTIX after eating and with a full glass (8 ounces) of water.

This dosing schedule may not be right for everyone. Talk to your doctor if you are having side effects such as nausea, strange dreams, or sleep problems. Your doctor may want to reduce your dose.

If you miss a dose of CHANTIX, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take your next dose at your regular time.

What should I avoid while taking CHANTIX?

Use caution when driving or operating machinery until you know how CHANTIX affects you. CHANTIX may make you feel sleepy, dizzy, or have trouble concentrating, making it hard to drive or perform other activities safely.

Decrease the amount of alcoholic beverages that you drink during treatment with CHANTIX until you know if CHANTIX affects your ability to tolerate alcohol. Some people have experienced the following when drinking alcohol during treatment with CHANTIX:

- increased drunkenness (intoxication)
- unusual or sometimes aggressive behavior
- no memory of things that have happened

What are the possible side effects of CHANTIX?

Serious side effects of CHANTIX may include:

- See “What is the most important information I should know about CHANTIX?”

- New or worse mental health problems, such as changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions, in people treated with CHANTIX. Call your doctor if you experience any of these symptoms.

  When you try to quit smoking, with or without CHANTIX, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

- Seizures. Some people have had seizures during treatment with CHANTIX. In most cases, the seizures have happened during the first month of treatment with CHANTIX. If you have a seizure during treatment with CHANTIX, stop taking CHANTIX and contact your healthcare provider right away.

- New or worse heart or blood vessel (cardiovascular) problems, mostly in people, who already have cardiovascular problems. Tell your doctor if you have any changes in symptoms during treatment with CHANTIX.

Get emergency medical help right away if you have any of the following symptoms of a heart attack, including:

- chest discomfort (uncomfortable pressure, squeezing, fullness or pain) that lasts more than a few minutes, or that goes away and comes back
- pain or discomfort in one or both arms, back, neck, jaw or stomach
- shortness of breath, sweating, nausea, vomiting, or feeling lightheaded associated with chest discomfort

- Allergic reactions can happen with CHANTIX. Some of these allergic reactions can be life-threatening.

- Serious skin reactions, including rash, swelling, redness, and peeling of the skin. Some of these skin reactions can become life-threatening.
Stop taking CHANTIX and get medical help right away if you have any of the following symptoms:

- swelling of the face, mouth (tongue, lips, and gums), throat or neck
- trouble breathing
- rash with peeling skin
- blisters in your mouth

The most common side effects of CHANTIX include:

- nausea
- sleep problems (trouble sleeping or vivid, unusual, or strange dreams)
- constipation
- gas
- vomiting

Tell your doctor about side effects that bother you or that do not go away.

These are not all the side effects of CHANTIX. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CHANTIX?

- Store CHANTIX at room temperature, between 68°F to 77°F (20°C to 25°C).
- Keep CHANTIX and all medicines out of the reach of children.

General information about CHANTIX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CHANTIX for a condition for which it was not prescribed. Do not give your CHANTIX to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CHANTIX that is written for healthcare professionals.

For more information about CHANTIX and tips on how to quit smoking, go to www.CHANTIX.com or call 1-877-242-6849.

If you are motivated to quit smoking and did not succeed during prior CHANTIX treatment for reasons other than side effects, or if you returned to smoking after treatment, speak with your doctor about whether another course of CHANTIX therapy may be right for you.

What are the ingredients in CHANTIX?

Active ingredient: varenicline tartrate

Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry ® White (for 0.5 mg), Opadry ® Blue (for 1 mg), and Opadry® Clear.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
CHANTIX® (varenicline) Tablets

Initial U.S. Approval: 2006

---

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CHANTIX safely and effectively. See full prescribing information for CHANTIX.

---

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

See full prescribing information for complete boxed warning.

- Serious neuropsychiatric events have been reported in patients taking CHANTIX. (5.1 and 6.2)
- Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (5.7 and 6.2)
- Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (5.7 and 6.2)
- Weigh the risks of CHANTIX against benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (5.1 and 6.2)

---

RECENT MAJOR CHANGES

Dosage and Administration

Usual Dosage for Adults: 1 mg twice daily for 12 weeks. (2.1)

Warnings and Precautions

Neuropsychiatric Symptoms and Suicidality: 09/2014

Seizures: 09/2014

Interaction with Alcohol: 09/2014

---

INDICATIONS AND USAGE

CHANTIX is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment. (1 and 2.1)

---

DOSEAGE AND ADMINISTRATION

- Begin CHANTIX dosing one week before the date set by the patient to stop smoking. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment. (2.1)
- Starting week: 0.5 mg once daily on days 1-3 and 0.5 mg twice daily on days 4-7. (2.1)
- Continuing weeks: 1 mg twice daily for a total of 12 weeks. (2.1)
- An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence. (2.1)
- Consider dose reduction for patients who cannot tolerate adverse effects. (2.1)
- Another attempt at treatment is recommended for those who fail to stop smoking or relapse when factors contributing to the failed attempt have been addressed. (2.1)
- Provide patients with appropriate educational materials and counseling to support the quit attempt. (2.1)

---

DOSEAGE FORMS AND STRENGTHS

Tablets: 0.5 mg and 1 mg (3)

---

CONTRAINDICATIONS

History of serious hypersensitivity or skin reactions to CHANTIX. (4)

---

FULL PRESCRIBING INFORMATION: CONTENTS

---

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

- Seizures: New or worsening seizures have been observed in patients taking CHANTIX. CHANTIX should be used cautiously in patients with a history of seizures or other factors that can lower the seizure threshold. (5.2)
- Interaction with alcohol: Increased effects of alcohol have been reported. Instruct patients to reduce the amount of alcohol they consume until they know whether CHANTIX affects them. (5.3)
- Accidental injury: Accidental injuries (e.g., traffic accidents) have been reported. Instruct patients to use caution driving or operating machinery until they know how CHANTIX may affect them. (5.4)
- Cardiovascular events: A meta-analysis of 15 clinical trials, including a trial in patients with stable cardiovascular disease, demonstrated that while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with CHANTIX. These events occurred primarily in patients with known cardiovascular disease. In both the clinical trial and meta-analysis, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX. Instruct patients to notify their healthcare providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. (5.5 and 6.1)
- Angioedema and hypersensitivity reactions: Such reactions, including angioedema, infrequently life threatening, have been reported. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (5.7 and 6.2)
- Nausea: Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.8)

---

ADVERSE REACTIONS

Most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---

DRUG INTERACTIONS

- Other smoking cessation therapies: Safety and efficacy in combination with other smoking cessation therapies has not been established. Co-administration of varenicline and transdermal nicotine resulted in a high rate of discontinuation due to adverse events. (7.1)
- Effect of smoking cessation: Pharmacokinetics or pharmacodynamics of certain drugs may be altered due to smoking cessation with CHANTIX, necessitating dose adjustment. (7.2)

---

USE IN SPECIFIC POPULATIONS

- Pregnancy: CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration the importance of drug to mother. (8.3)
- Pediatric Use: Safety and effectiveness not established. (8.4)
- Renal Impairment: Dosage adjustment is required for severe renal impairment. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 10/2014
Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 2 weeks’ treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence.

Patients who are motivated to quit, and who did not succeed in stopping smoking during prior CHANTIX therapy for reasons other than intolerability due to adverse events or who relapsed after treatment, should be encouraged to make another attempt with CHANTIX once factors contributing to the failed attempt have been identified and addressed.

Consider a temporary or permanent dose reduction in patients who cannot tolerate the adverse effects of CHANTIX.

### 2.2 Dosage in Special Populations

#### Patients with Impaired Renal Function

No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), the recommended starting dose of CHANTIX is 0.5 mg once daily. The dose may then be titrated as needed to a maximum dose of 0.5 mg twice a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

#### Elderly and Patients with Impaired Hepatic Function

No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Use in Specific Populations (8.5)].

### 3 Dosage Forms and strengths

Capsular, biconvex tablets: 0.5 mg (white to off-white, debossed with "Pfizer" on one side and "CHX 0.5" on the other side) and 1 mg (light blue, debossed with "Pfizer" on one side and "CHX 1.0" on the other side).

### 4 Contraindications

CHANTIX is contraindicated in patients with a known history of serious hypersensitivity reactions or skin reactions to CHANTIX.

### 5 Warnings and Precautions

#### 5.1 Neuropsychiatric Symptoms and Suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX [see Boxed Warning and Adverse Reactions (6.2)]. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking.

Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX.

Advises patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risk of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. [see Warnings and Precautions (5.1) and Adverse Reactions (6.2)].

### 1.1 Initiation of Abstinence

Patients may receive additional advice and counseling to support the quit attempt.

Provide patients with appropriate educational materials and counseling if they are motivated to stop smoking and who are provided additional advice and counseling to support the quit attempt.

### 14.1 Initiation of Abstinence

### 14.2 Urged to Smoke

### 14.3 Long-Term Abstinence

### 14.4 Subjects with Cardiovascular and Chronic Obstructive Pulmonary Disease

### 14.5 Subjects with Major Depressive Disorder

### 14.6 Alternative Instructions for Setting a Quit Date

### 14.7 Re-Treatment Study

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

### Medication Guide

**Preparation:**

CHANTIX is indicated for use as an aid to smoking cessation treatment.

**Dosage and administration:**

CHANTIX should be taken after eating and with a full glass of water.

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

### Medication Guide

**Preparation:**

CHANTIX is indicated for use as an aid to smoking cessation treatment.

**Dosage and administration:**

CHANTIX should be taken after eating and with a full glass of water.

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

### Medication Guide

**Preparation:**

CHANTIX is indicated for use as an aid to smoking cessation treatment.

**Dosage and administration:**

CHANTIX should be taken after eating and with a full glass of water.
CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health outcomes examined and compared the risk of selected serious cardiovascular events (Mortality, Myocardial Infarction, Coronary Revascularization, Stroke, and Hospitalization). Since the initial signal of neuropsychiatric symptoms and suicidality emerged, additional analyses and studies have been conducted to further evaluate this association.

### Analyses of clinical trials

A meta-analysis of 5 randomized, double-blind, placebo-controlled trials, including 1907 patients (1130 CHANTIX, 777 placebo) was conducted to assess suicidal ideation and behavior as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (N=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behavior in patients treated with CHANTIX compared to patients treated with placebo, with a Risk Ratio (RR) of 0.79 (95% Confidence Interval [CI]: 0.46, 1.36), as shown in Table 1. Forty-eight (48) of the 55 patients who reported suicidal ideation or behavior (24 CHANTIX, 24 placebo) were observed in the two trials that enrolled patients with a history of schizophrenia, schizoaffective disorder, or depression. Few events were observed in the other three trials (4 CHANTIX, 3 placebo).

| Table 1. Number of Patients and Risk Ratio for Suicidal Ideation and/or Behavior Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing CHANTIX to Placebo |
|---------------------|---------------------|
| CHANTIX (N=1130)    | Placebo (N=777)     |
| Patients with Suicidal ideation and/or behavior* [n (%)]** | 28 (2.5) | 27 (3.5) |
| Patient-years of exposure | 325 | 217 |
| Risk Ratio * (RR; 95% CI) | 0.79 (0.46, 1.36) |

* Of the events, one patient in each treatment arm reported suicidal behavior
** Patients with events up to 30 days after treatment; % are not weighted by study
# RR of incidence rates per 100 patient years

A pooled analysis of 18 double-blind, randomized, placebo-controlled clinical trials, which includes the 5 trials that collected C-SSRS described in Table 1, was conducted to assess the psychiatric safety of CHANTIX. This pooled analysis included 8521 patients (5072 CHANTIX, 3449 placebo), some of whom had psychiatric conditions at baseline. Table 2 describes the most frequently reported adverse events related to psychiatric safety. The results showed a similar incidence of common psychiatric events in patients treated with CHANTIX compared to patients treated with placebo.

| Table 2. Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Analysis of 18 Clinical Trials |
|---------------------|---------------------|
| CHANTIX (N=5072)    | Placebo (N=3449)    |
| Anxiety disorders and symptoms | 253 (5.0) | 206 (6.0) |
| Depressed mood disorders and disturbances | 179 (3.5) | 108 (3.1) |
| Mood disorders and disturbances NEC* | 116 (2.3) | 53 (1.5) |

* NEC = Not Elsewhere Classified

Counts (percentages) corresponds to the number of patients reporting the event

### 5.5 Cardiovascular Events

In a placebo-controlled clinical trial of CHANTIX administered to patients with stable cardiovascular disease, with approximately 350 patients per treatment arm, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX, but certain nonfatal cardiovascular events occurred more frequently in patients treated with CHANTIX than in patients treated with placebo [see Clinical Trials Experience (6.1)]. Table 3 below shows the incidence of deaths and of selected nonfatal serious cardiovascular events occurring more frequently in the CHANTIX arm compared to the placebo arm. These events were adjudicated by an independent blinded committee. Nonfatal serious cardiovascular events not listed occurred at the same incidence or more commonly in the placebo arm. Patients with more than one cardiovascular event of the same type are counted only once per row. Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina.

| Table 3. Mortality and Adjudicated Nonfatal Serious Cardiovascular Events in the Placebo-Controlled CHANTIX Trial in Patients with Stable Cardiovascular Disease |
|---------------------|---------------------|
| CHANTIX (N=353)    | Placebo (N=350)    |
| Mortality and Cardiovascular Events | n (%) | n (%) |
| Cardiovascular death | 1 (0.3) | 2 (0.6) |
| All-cause mortality | 2 (0.6) | 5 (1.4) |

All studies were retrospective cohort studies and included patients with and without a psychiatric history.

Two of the studies found no difference in risk of neuropsychiatric hospitalizations between CHANTIX users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56–2.34 in the first study, and 0.76; 95% CI: 0.40–1.46 in the second study). However, neither study validated the diagnostic codes used to identify outcomes against medical records. A third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between CHANTIX users and bupropion users (HR 0.85; 95% CI: 0.55-1.30). Bupropion has also been associated with neuropsychiatric adverse events. A fourth study examined risk of fatal and non-fatal self-harm in users of CHANTIX compared to users of NRT. Although the occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 CHANTIX users and six cases in 81,545 NRT users), this study has important limitations. Most importantly, these data were captured following publication of reports of neuropsychiatric adverse events in CHANTIX users. CHANTIX users had fewer comorbid conditions that could put them at risk for neuropsychiatric adverse events, suggesting that patients with a history of neuropsychiatric illness were preferentially prescribed NRT, and healthier patients were preferentially prescribed CHANTIX.

Outcomes examined in these studies did not include the full range of neuropsychiatric adverse events that have been reported.

### 5.2 Seizures

There have been post-marketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some cases described unusual and sometimes aggressive behavior, and were often accompanied by amnesia for the events. Advise patients to reduce the amount of alcohol they consume while taking CHANTIX until they know whether CHANTIX affects their tolerance for alcohol [see Adverse Reactions (6.2)].

### 5.3 Interaction with Alcohol

There have been post-marketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking CHANTIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Advise patients to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

### 5.6 Assessments

Since the initiation of CHANTIX clinical development, additional analyses and studies have been conducted to further evaluate this association.

### Observational Studies

Four observational studies, each including 10,000 to 30,000 users of CHANTIX in the adjusted analyses, compared the risk of selected serious neuropsychiatric events (neuropsychiatric hospitalizations, fatal and non-fatal self-harm), between CHANTIX users and prescription NRT or bupropion users.

Reference ID: 3643541
A meta-analysis of 15 clinical trials of ≥12 weeks treatment duration, including 7002 patients (4190 CHANTIX, 2812 placebo), was conducted to systematically assess the cardiovascular safety of CHANTIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis. There were lower rates of all-cause mortality (CHANTIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHANTIX 2 [0.05%]; placebo 2 [0.07%]) in the CHANTIX arms compared with the placebo arms in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred in the trials included in the meta-analysis, as described in Table 4. These events occurred primarily in patients with known cardiovascular disease.

Table 4. Number of MACE cases, Hazard Ratio and Rate Difference in a Meta-Analysis of 15 Clinical Trials Comparing CHANTIX to Placebo*

<table>
<thead>
<tr>
<th>CHANTIX N=4190</th>
<th>Placebo N=2812</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE cases, n (%)</td>
<td>13 (0.31%)</td>
</tr>
<tr>
<td>Patient-years of exposure</td>
<td>1316</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>1.95 (0.79, 4.82)</td>
</tr>
<tr>
<td>Rate Difference per 1,000 patient-years (95% CI)</td>
<td>6.30 (-2.40, 15.10)</td>
</tr>
</tbody>
</table>

*Includes MACE occurring up to 30 days post treatment.

The meta-analysis showed that exposure to CHANTIX resulted in a hazard ratio for MACE of 1.95 (95% confidence interval from 0.79 to 4.82) for patients up to 30 days after treatment; this is equivalent to an estimated increase of 6.3 MACE events per 1,000 patient-years of exposure. The meta-analysis showed higher rates of CV endpoints in patients on CHANTIX relative to placebo across different time frames and pre-specified sensitivity analyses, including various study groupings and CV outcomes. Although these findings were not statistically significant they were consistent. Because the number of events was small overall, the power for finding a statistically significant difference in a signal of this magnitude is low.

CHANTIX was not studied in patients with unstable cardiovascular disease or cardiovascular events occurring within two months before screening. Patients should be advised to notify a health care provider of new or worsening symptoms of cardiovascular disease. The risks of CHANTIX should be weighed against the benefits of its use in smokers with cardiovascular disease. Smoking is an independent and major risk factor for cardiovascular disease. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo.

5.6 Angioedema and Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX [see Adverse Reactions (6.2), and Patient Counseling Information (17)]. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). There were infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms.

5.7 Serious Skin Reactions

There have been postmarketing reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients using CHANTIX [see Adverse Reactions (6.2)]. As these skin reactions can be life-threatening, instruct patients to stop taking CHANTIX and contact a healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.

5.8 Nausea

Nausea was the most common adverse reaction reported with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some patients, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. For patients treated to the maximum recommended dose of 1 mg twice daily following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg twice daily following initial titration, the incidence was 16% compared with 11% for placebo. Approximately 3% of patients treated with CHANTIX 1 mg twice daily in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, a dose reduction should be considered.

6 ADVERSE REACTIONS

The following serious adverse reactions were reported in postmarketing experience and are discussed in greater detail in other sections of the labeling:

- Neuropsychiatric symptoms and suicidality [see Boxed Warning and Warnings and Precautions (5.1)]
- Seizures [see Warnings and Precautions (5.2)]
- Interaction with Alcohol [see Warnings and Precautions (5.3)]
- Accidental injury [see Warnings and Precautions (5.4)]
- Cardiovascular Events [see Warnings and Precautions (5.5)]
- Angioedema and hypersensitivity reactions [see Warnings and Precautions (5.6)]
- Serious skin reactions [see Warnings and Precautions (5.7)]

In the placebo-controlled premarketing studies, the most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.

The treatment discontinuation rate due to adverse events in patients dosed with 1 mg twice daily was 12% for CHANTIX, compared to 10% for placebo in studies of three months’ treatment. In this group, the discontinuation rates that are higher than placebo for the most common adverse events in CHANTIX-treated patients were as follows: nausea (3% vs. 0.5% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo).

Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During the premarketing development of CHANTIX, over 4500 subjects were exposed to CHANTIX, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less.

The most common adverse event associated with CHANTIX treatment is nausea, occurring in 30% of patients treated at the recommended dose, compared with 10% in patients taking a comparable placebo regimen [see Warnings and Precautions (5.6)].

Table 5 shows the adverse events for CHANTIX and placebo in the 12-week fixed dose premarketing studies with titration in the first week [Studies 2 (titrated arm only), 4, and 5]. Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

MedDRA High Level Group Terms (HLGT) reported in ≥5% of patients in the CHANTIX 1 mg twice daily dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in ≥1% of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as ‘Insomnia’, ‘Initial insomnia’, ‘Middle insomnia’, ‘Early morning awakening’ were grouped, but individual patients reporting two or more grouped events are only counted once.
Table 5: Common Treatment Emergent AEs (%) in the Fixed-Dose Placebo-Controlled Studies (HLG ≤ 5% of patients in the 1 mg BID CHANTIX Group and more commonly than placebo and PT ≥ 1% in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)

<table>
<thead>
<tr>
<th>SYSTEM ORGAN CLASS</th>
<th>CHANTIX 0.5 mg BID (N=129)</th>
<th>CHANTIX 1 mg BID (N=821)</th>
<th>Placebo (N=805)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GASTROINTESTINAL (GI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Signs and Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Flatulence</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>GI Motility/Defecation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Salivary Gland Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>PSYCHIATRIC DISORDERS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Disorder/Disturbances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>19</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>9</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Nightmare</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NERVOUS SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Neurological Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GENERAL DISORDERS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Disorders NEC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Malaise/Asthema</td>
<td>4</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>RESPIRATORY/MEDIAST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Disorders NEC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Upper Respiratory Tract Disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin/Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermal and Dermal Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>METABOLISM &amp; NUTRITION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite/General Nutrient Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased appetite</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Decreased appetite/ Anorexia</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern and frequency of adverse events during the longer-term premarketing trials was similar to that described in Table 5, though several of the most common events were reported by a greater proportion of patients with long-term use (e.g., nausea was reported in 40% of patients treated with CHANTIX 1 mg twice daily in a one-year study, compared to 8% of placebo-treated patients).

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all premarketing clinical trials and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline. Adverse events were categorized using MedDRA, Version 16.0. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

- **Cardiac Disorders**: Infrequent angina pectoris, myocardial infarction, palpitations, tachycardia. Rare: acute coronary syndrome, arrhythmia, atrial fibrillation, bradycardia, cardiac flutter, cor pulmonale, coronary artery disease, ventricular extrasystoles.
- **Ear and Labyrinth Disorders**: Infrequent tinnitus, vertigo. Rare: deafness, Meniere’s disease.
- **Endocrine Disorders**: Infrequent thyroid gland disorders.
- **Eye Disorders**: Infrequent conjunctivitis, eye irritation, eye pain, vision blurred, visual impairment. Rare: blindness transient, cataract subcapsular, dry eye, night blindness, ocular vascular disorder, photophobia, vitreous floaters.
- **Gastrointestinal Disorders**: Infrequent diarrhea, toothache. Infrequent dysphagia, eructation, gastritis, gastrointestinal hemorrhage, mouth ulceration. Rare: enterocolitis, esophagitis, gastric ulcer, intestinal obstruction, pancreatitis acute.
- **General Disorders and Administration Site Conditions**: Infrequent chest pain. Infrequent chest discomfort, chills, edema, influenza-like illness, pyrexia.
- **Hepatobiliary Disorders**: Rare: gall bladder disorder.
- **Investigations**: Infrequent liver function test abnormal, weight increased. Infrequent electrocardiogram abnormal. Rare: muscle enzyme increased, urine analysis abnormal.
- **Metabolism and Nutrition Disorders**: Infrequent diabetes mellitus, hypoglycemia. Rare: hyperlipidemia, hypokalemia.
- **Musculoskeletal and Connective Tissue Disorders**: Rare: arthralgia, back pain, myalgia. Infrequent arthritis, muscle cramp, musculoskeletal pain. Rare: myositis, osteoporosis.
- **Nervous System Disorders**: Infrequent disturbance in attention, dizziness. Infrequent amnesia, convulsion, migraine, paraesthesia, syncope, tremor. Rare: balance disorder, cerebrovascular accident, dysautonomia, mental impairment, multiple sclerosis, VEP nerve paralysis, myasthenia, psychomotor hyperactivity, psychomotor skills impaired, restless leg syndrome, sensory disturbance, transient ischemic attack, visual field defect.
- **Psychiatric Disorders**: Infrequent dissociation, libido decreased, mood swings, thinking abnormal. Rare: bradyphrenia, disincentration, euphonic mood.
- **Respiratory and Urinary Disorders**: Infrequent nocturia, pollakiuria, urine abnormality. Rare: nephrolithiasis, polyuria, renal failure acute, urethral syndrome, urinary retention.
- **Reproductive System and Breast Disorders**: Rare: sexual dysfunction.
- **Respiratory, Thoracic and Mediastinal Disorders**: Infrequent respiratory disorders. Infrequent asthma, epistaxis, rhinitis allergic, upper respiratory tract inflammation. Rare: pleurisy, pulmonary embolism.
- **Skin and Subcutaneous Tissue Disorders**: Infrequent acne, dry skin, eczema, erythema, hyperhidrosis, urticaria. Rare: photosensitivity reaction, psoriasis.
- **Vascular Disorders**: Infrequent hot flash. Rare: thrombosis.

CHANTIX has also been studied in postmarketing trials including (1) a trial conducted in patients with chronic obstructive pulmonary disease (COPD), (2) a trial conducted in generally healthy patients (similar to those in the premarketing studies) in which they were allowed to select a quit date between days 8 and 35 of treatment ("alternative quit date instruction trial"), (3) a trial conducted in patients who did not succeed in stopping smoking during prior CHANTIX therapy, or who relapsed after treatment ("re-treatment trial"), (4) a trial conducted in patients with stable cardiovascular disease, (5) a trial conducted in patients with stable schizophrenia or schizoaffective disorder and (6) a trial conducted in patients with major depressive disorder.

Adverse events in the trial of patients with COPD, in the alternative quit date instruction trial, were quantitatively and qualitatively similar to those observed in premarketing studies. In the re-treatment trial, the profile of common adverse events was similar to that previously reported, but, in addition, varenicline-treated patients also commonly reported diarrhea (6% vs 4% in placebo-treated patients), depressed mood disorders and disturbances (6% vs 1%), and other mood disorders and disturbances (5% vs 2%).

In the trial of patients with stable cardiovascular disease, more types and a greater number of cardiovascular events were reported compared to premarketing studies. Treatment-emergent (on-treatment or 30 days after treatment) cardiovascular events reported with a frequency ≥ 1% in either treatment group in this study were angina pectoris (3.7% and 2.0% for varenicline and placebo, respectively), chest pain (2.3% vs 2.3%), peripheral
edema (2.0% vs. 1.1%), hypertension (1.4% vs. 2.6%), and palpitations (0.6 % vs. 1.1%). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment emergent and non-treatment emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency ≥1% in either treatment group: nonfatal MI (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudication event included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52-week trial.

In the trial of patients with stable schizophrenia or schizoaffective disorder, 128 smokers on antipsychotic medication were randomized 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up. The most common adverse events in patients taking varenicline were nausea (24% vs. 14.0% on placebo), headache (11% vs. 19% on placebo) and vomiting (11% vs. 9% on placebo). Among reported neuropsychiatric adverse events, inmania was the only event that occurred in either treatment group to a rate higher in the varenicline group than in placebo (10% vs. 5%). These common and neuropsychiatric adverse events occurred on treatment or within 30 days after the last dose of study drug. There was no consistent worsening of schizophrenia in either treatment group as measured by the Positive and Negative Syndrome Scale. There were no overall changes in extra-pyramidal signs, as measured by the Simpson-Angus Rating Scale. The Columbia-Suicide Severity Rating Scale was administered at baseline and at clinic visits during the treatment and non-treatment follow-up phases. Over half of the patients had a lifetime history of suicidal behavior and/or ideation (62% on varenicline vs. 51% on placebo), but at baseline, no patients in the varenicline group reported suicidal behavior and/or ideation vs. one patient in the placebo group (2%). Suicidal behavior and/or ideation were reported in 11% of the varenicline-treated and 9% of the placebo-treated patients during the treatment phase. During the post-treatment phase, suicidal behavior and/or ideation were reported in 11% of patients in the varenicline group and 5% of patients in the placebo group. Many of the patients reporting suicidal behavior and ideation in the follow-up phase had not reported such experiences in the treatment phase. However, no new suicidal ideation or behavior emerged in either treatment group shortly (within one week) after treatment discontinuation (a phenomenon noted in post-marketing reporting). There were no completed suicides. There was one suicide attempt in a varenicline-treated patient. The limited data available from this single smoking cessation study are not sufficient to allow conclusions to be drawn.

In the trial of patients with major depressive disorder, the most common adverse events (≥10%) in subjects taking varenicline were nausea (27% vs. 10% on placebo), headache (17 vs 11%), abnormal dreams (11% vs 8%), insomnia (11% vs 5%) and irritability (11% vs. 8%). Additionally, the following psychiatric AEs were reported in ≥2% of patients in either treatment group (varenicline or placebo, respectively): anxiety (7% vs. 9%), agitation (7% vs. 4%), depressed mood disorders and disturbances (11% vs. 9%), tension (4% vs. 3%), hostility (2% vs. 0.4%) and restlessness (2% vs. 2%). Patients treated with varenicline were more likely than patients treated with placebo to report one of the psychiatric AEs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

There have been post-marketing reports of new or worsening seizures in patients treated with CHANTIX [see Warnings and Precautions (5.2)]. There have been post-marketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior [see Warnings and Precautions (5.1) and (5.3)]. There have been reports of hypersensitivity reactions, including angioedema [see Warnings and Precautions (5.6)]. There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking CHANTIX [see Warnings and Precautions (5.7)]. There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischemic and hemorrhagic events in patients taking CHANTIX. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out.

7 DRUG INTERACTIONS

Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions [see Clinical Pharmacology (12.3)].

7.1 Use With Other Drugs for Smoking Cessation

Safety and efficacy of CHANTIX in combination with other smoking cessation therapies have not been studied.

Bupropion: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (24 mg twice daily) in 40 smokers. The safety of the combination of bupropion and varenicline has not been established.

Nicotine replacement therapy (NRT): Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone. In this study, eight of twenty-two (36%) patients treated with the combination of varenicline and NRT prematurely discontinued treatment due to adverse events, compared to 1 of 17 (6%) of patients treated with NRT and placebo.

7.2 Effect of Smoking Cessation on Other Drugs

Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of CHANTIX use in pregnant women. In animal studies, CHANTIX caused decreased fetal weights, physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

There have been post-marketing reports of new or worsening seizures in patients treated with CHANTIX [see Warnings and Precautions (5.2)].

There have been post-marketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior [see Warnings and Precautions (5.1) and (5.3)].

There have been reports of hypersensitivity reactions, including angioedema [see Warnings and Precautions (5.6)].

There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking CHANTIX [see Warnings and Precautions (5.7)].

There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischemic and hemorrhagic events in patients taking CHANTIX. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out.
Safety and effectiveness of CHANTIX in pediatric patients have not been established.

8.5 Geriatric Use

A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-73 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Dosage and Administration (2.2)].

No dosage adjustment is recommended for elderly patients.

8.6 Renal Impairment

Varenicline is substantially eliminated by renal glomerular filtration along with active tubular secretion. Dose reduction is not required in patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), and for patients with end-stage renal disease undergoing hemodialysis, dosage adjustment is needed [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Varenicline is not a controlled substance.

9.3 Dependence

Humans Fewer than 1 out of 100 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction.

In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers.

Animals Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine, however, in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

10 OVERDOSAGE

In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease [see Clinical Pharmacology (12.3)], however, there is no experience in dialysis following overdose.

11 DESCRIPTION

CHANTIX tablets contain varenicline (as the tartrate salt), which is a partial agonist selective for α4β2 nicotinic acetylcholine receptor subtypes.

Varenicline, as the tartrate salt, is a powder which is a white to off-white slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h]benzazepine, (2R,3S)-2,3-dihydroxybutanamide (1:1). It is highly soluble in water. Varenicline tartrate has a molecular weight of 361.35 Daltons, and a molecular formula of C24H29N3O5 • C6H8O7. The chemical structure is:

![Chemical Structure of Varenicline](image)

CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capsule, brown, white to off-white, film-coated tablet debossed with "Pfizer" on one side and "CHX 0.5" on the other side and a 1 mg capsule, brown, light blue film-coated tablet debossed with "Pfizer" on one side and "CHX 1.0" on the other side. Each 0.5 mg CHANTIX tablet contains 0.85 mg of varenicline tartrate equivalent to 0.71 mg of varenicline free base. Each 1 mg CHANTIX tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base. The following inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate, carrageenan, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Varenicline binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors. The efficacy of CHANTIX in smoking cessation is believed to be the result of varenicline’s activity at α4β2 sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to these receptors.

Microscopic/Functional The elimination half-life of varenicline in vivo has shown that varenicline binds to α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to α4β2 receptors than to other common nicotinic receptors (>500-fold α3β4, >3500-fold α3β7, >20,000-fold α1β6), or to non-nicotinic receptors and transporters (>2000-fold). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 3-HT3 receptor.

12.3 Pharmacokinetics

Absorption/Distribution Maximum plasma concentrations of varenicline occur typically within 3–4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was ~90%. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing. Plasma protein binding of varenicline is low (~20%) and independent of both age and renal function.

Pharmacokinetics in Special Patient Populations There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Renal Impairment Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >80 mL/min and <120 mL/min). In subjects with moderate renal impairment (estimated creatinine clearance >50 mL/min and <80 mL/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >90 mL/min). In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage renal disease (ESRD) undergoing a three-hour session of hemodialysis for three days a week, varenicline exposure was increased 2.7-fold following 0.5 mg once daily administration for 12 days. The plasma Cmax and AUC of varenicline noted in this setting were similar to those of healthy subjects receiving 1 mg twice daily. [see Dosage and Administration (2.2), and Use in Specific Populations (8.6)].
Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis [see Overdosage (10)].

Geriatric Patients: A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects.

Pediatric Patients: Because the safety and effectiveness of CHANTIX in pediatric patients have not been established, CHANTIX is not recommended for use in patients under 18 years of age. Single and multiple-dose pharmacokinetics of varenicline have been investigated in pediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight ≤55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg BID was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population.

Hepatic Impairment: Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment.

Drug Interactions: Drug interaction studies were performed with varenicline and digoxin, warfarin, transdermal nicotine, bupropion, cimetidine, and metformin. No clinically meaningful pharmacokinetic drug-drug interactions have been identified.

In vitro studies demonstrated that varenicline does not inhibit the following cytochrome P450 enzymes (IC50 >6400 ng/mL): 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes in vitro, varenicline does not induce the cytochrome P450 enzymes 1A2 and 3A4.

In vivo studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (e.g., metformin [see below]) are unlikely to be affected by varenicline.

In vitro studies demonstrated the active renal secretion of varenicline is mediated by the human organic cation transporter OCT2. Co-administration with inhibitors of OCT2 (e.g., cimetidine [see below]) may not necessitate a dose adjustment of the steady-state pharmacokinetics of CHANTIX, as the increase in systemic exposure of varenicline is not expected to be clinically meaningful. Furthermore, since metabolism of varenicline represents less than 10% of its clearance, drugs known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of CHANTIX [see Clinical Pharmacology (12.3)]; therefore, a dose adjustment of CHANTIX would not be required.

Metformin: When co-administered to 30 smokers, varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of metformin (500 mg twice daily), which is a substrate of OCT2. Metformin had no effect on varenicline steady-state pharmacokinetics.

Cimetidine: Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) to 12 smokers increased the systemic exposure of varenicline by 29% (90% CI: 21.5%, 36.9%) due to a reduction in varenicline renal clearance.

Digoxin: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers.

Warfarin: Varenicline (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R, S)-warfarin in 24 smokers. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics [see Drug Interactions (7.2)].

Use with Other Drugs for Smoking Cessation

Buproprion: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers [see Drug Interactions (7.1)].

Nicotine replacement therapy (NRT): Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of adverse reactions was greater for the combination than for NRT alone [see Drug Interactions (7.1)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline for up to 2 years at oral doses of up to 200 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis: Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations in vivo in rat bone marrow and in vitro in human lymphocytes.

Impairment of Fertility: There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg twice daily). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg twice daily). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg twice daily).

14 CLINICAL STUDIES

The efficacy of CHANTIX in smoking cessation was demonstrated in six clinical trials with a total of 36593 chronic cigarette smokers (≥10 cigarettes per day) were treated with CHANTIX. In all clinical studies, abstinence from smoking was determined by patient self-report and verified by measurement of exhaled carbon monoxide (CO;≥10 ppm) at weekly visits. Among the CHANTIX-treated patients enrolled in these studies, the completion rate was 65%. Except for the dose-ranging study (Study 1) and the maintenance of abstinence study (Study 6), patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. Most patients enrolled in these trials were white (79%-96%). All studies used the same criteria to designate smokers as either treatment failures or treatment successes (≥7 days of smoking abstinence from one week after treatment through the end of treatment).

The average age of patients in these studies was 43 years. Patients on average had smoked about 21 cigarettes per day for an average of approximately 25 years. Patients set a date to stop smoking (target quit date) with dosing starting 1 week before this date.

Three additional studies were conducted in patients with cardiovascular disease, in patients with chronic obstructive pulmonary disease [see Clinical Studies (14.4)], and in patients instructed to select their quit date within days 8 and 35 of treatment [see Clinical Studies (14.5)].

In all studies, patients were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each weekly treatment visit according to Agency for Healthcare Research and Quality guidelines.

14.1 Initiation of Abstinence

Study 1: This was a six-week dose-ranging study comparing CHANTIX to placebo. This study provided initial evidence that CHANTIX at a total dose of 1 mg per day or 2 mg per day was effective as an aid to smoking cessation.

Study 2: This study of 627 patients compared CHANTIX 1 mg per day and 2 mg per day with placebo. Patients were treated for 12 weeks (including one week titration) and then followed for 40 weeks post-treatment. CHANTIX was given in two divided doses daily. Each dose of CHANTIX was given in different regimens, with and without initial dose titration, to explore the effect of different dosing regimens on tolerability. For the titrated groups, dosage was titrated up over the course of one week, with full dosage achieved starting with the second week of dosing. The titrated and nontitrated groups were pooled for efficacy analysis.

Forty-five percent of patients receiving CHANTIX 1 mg per day (0.5 mg twice daily) and 51% of patients receiving 2 mg per day (1 mg twice daily) had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% of patients in the placebo group (Figure 1). In addition, 31% of the 1 mg per day group and 31% of the 2 mg per day group were continuously abstinent from one week after TQD through the end of treatment as compared to 8% of the placebo group.

Study 3: This flexible-dosing study of 312 patients examined the effect of a patient-directed dosing strategy of CHANTIX or placebo. After an initial one-week titration to a dose of 0.5 mg twice daily, patients could adjust their dosage as often as they wished between 0.5 mg once daily to 1 mg twice daily per day. Sixty-nine percent of patients titrated to the maximum allowable dose at any time during the study. For 44% of patients, the modal dose selected was 1 mg twice daily; for slightly over half of the study participants, the modal dose selected was 1 mg/day or less.

Of the patients treated with CHANTIX, 40% had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% in the placebo group. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 9% of the placebo group.

Study 4 and Study 5: These identical double-blind studies compared CHANTIX 2 mg per day, bupropion sustained-release (SR) 150 mg twice daily, and placebo. AUC-based pharmacokinetic analysis and sample size calculations were consistent with those of Study 2 and Study 3. AUC-based pharmacokinetic analysis was consistent with those of Study 2 and Study 3. The trial was designed to achieve similar rates of continuous abstinence as observed in Study 2 and Study 3.
and placebo. Patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. The CHANTIX dosage of 1 mg twice daily was achieved using a titration of 0.5 mg once daily for the initial 3 days followed by 0.5 mg twice daily for the next 4 days. The bupropion SR dosage of 150 mg twice daily was achieved using a 3-day titration of 150 mg once daily. Study 4 enrolled 1022 patients and Study 5 enrolled 1023 patients. Patients inappropriate for bupropion treatment or patients who had previously used bupropion were excluded.

In Study 4, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (17%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 12% of the placebo group and 23% of the bupropion SR group.

Similarly in Study 3, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (18%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 11% of the placebo group and 21% of the bupropion SR group.

**Table 6: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)**

<table>
<thead>
<tr>
<th></th>
<th>CHANTIX 0.5 mg BID</th>
<th>CHANTIX 1 mg BID</th>
<th>CHANTIX Flexible</th>
<th>Bupropion SR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 2</td>
<td>43% (30%, 51%)</td>
<td>51% (44%, 57%)</td>
<td>51% (42%, 59%)</td>
<td>49% (39%, 58%)</td>
<td>12%</td>
</tr>
<tr>
<td>Study 3</td>
<td>40% (32%, 48%)</td>
<td>44% (38%, 49%)</td>
<td>50% (39%, 60%)</td>
<td>47% (37%, 56%)</td>
<td>12%</td>
</tr>
<tr>
<td>Study 4</td>
<td>44% (38%, 50%)</td>
<td>44% (38%, 50%)</td>
<td>40% (30%, 50%)</td>
<td>44% (34%, 54%)</td>
<td>17%</td>
</tr>
<tr>
<td>Study 5</td>
<td>44% (38%, 50%)</td>
<td>44% (38%, 50%)</td>
<td>40% (30%, 50%)</td>
<td>44% (34%, 54%)</td>
<td>17%</td>
</tr>
</tbody>
</table>

**Figure 2: Continuous Abstinence, Weeks 9 through 52**

**Table 7: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval across different studies)**

<table>
<thead>
<tr>
<th></th>
<th>CHANTIX 0.5 mg BID</th>
<th>CHANTIX 1 mg BID</th>
<th>CHANTIX Flexible</th>
<th>Bupropion SR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 2</td>
<td>19% (14%, 24%)</td>
<td>23% (18%, 28%)</td>
<td>4% (1%, 8%)</td>
<td>8% (3%, 12%)</td>
<td>8%</td>
</tr>
<tr>
<td>Study 3</td>
<td>22% (16%, 29%)</td>
<td>16% (12%, 20%)</td>
<td>9% (5%, 13%)</td>
<td>8% (3%, 12%)</td>
<td>8%</td>
</tr>
<tr>
<td>Study 4</td>
<td>31% (17%, 45%)</td>
<td>16% (12%, 20%)</td>
<td>10% (5%, 15%)</td>
<td>10% (5%, 15%)</td>
<td>10%</td>
</tr>
<tr>
<td>Study 5</td>
<td>22% (17%, 29%)</td>
<td>22% (17%, 29%)</td>
<td>10% (5%, 15%)</td>
<td>10% (5%, 15%)</td>
<td>10%</td>
</tr>
</tbody>
</table>

**BID = twice daily**

**Study 6** This study assessed the effect of an additional 12 weeks of CHANTIX therapy on the likelihood of long-term abstinence. Patients in this study (n=1927) were treated with open-label CHANTIX 1 mg twice daily for 12 weeks. Patients who had stopped smoking at least a week by Week 12 (n=1210) were then randomized to double-blind treatment with CHANTIX (1 mg twice daily) or placebo for an additional 12 weeks and then followed for 28 weeks post-treatment.

The continuous abstinence rate from Week 13 through Week 24 was higher for patients continuing treatment with CHANTIX (70%) than for patients switching to placebo (50%). Suppression to placebo was also maintained during 28 weeks post-treatment follow-up (CHANTIX 54% versus placebo 39%).

In Figure 3 below, the x-axis represents the study week for each observation, allowing a comparison of groups at similar times after discontinuation of CHANTIX. Post-CHANTIX follow-up begins at Week 13 for the placebo group and Week 25 for the CHANTIX group. The y-axis represents the percentage of patients who had been abstinent for the last week of CHANTIX treatment and remained abstinent at the given timepoint.

**Figure 3: Continuous Abstinence Rate during Nontreatment Follow-Up**

14.2 Urge to Smoke

Based on responses to the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal scale “urge to smoke” item, CHANTIX reduced urge to smoke compared to placebo.

14.3 Long-Term Abstinence

Studies 1 through 5 included 40 weeks of post-treatment follow-up. In each study, CHANTIX-treated patients were more likely to maintain abstinence throughout the follow-up period than were patients treated with placebo (Figure 2, Table 7).

14.4 Subjects with Cardiovascular and Chronic Obstructive Pulmonary Disease

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged 35 to 75 years with stable, documented cardiovascular disease (diagnoses other than, or in addition to, hypertension...
that had been diagnosed for more than 2 months. Subjects were randomized to CHANTIX 1 mg twice daily (n=353) or placebo (n=350) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47%) compared to subjects treated with placebo (14%) and from week 9 through 52 (20%) compared to subjects treated with placebo (7%). CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged ≥ 5 years with mild-to-moderate COPD with post-bronchodilator FEV1/FVC <70% and FEV1 ≥ 50% of predicted normal value. Subjects were randomized to CHANTIX 1 mg twice daily (n=223) or placebo (n=237) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (41%) compared to subjects treated with placebo (9%) and from week 9 through 52 (19%) compared to subjects treated with placebo (6%).

Table 8: Continuous Abstinence (95% confidence interval), Studies in Patients with Cardiovascular Disease (CVD) and Chronic Obstructive Pulmonary Disease (COPD)

<table>
<thead>
<tr>
<th>Weeks 9 through 12</th>
<th>Weeks 9 through 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHANTIX 1 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>CVD Study</td>
<td>CHANTIX 1 mg BID</td>
</tr>
<tr>
<td>47%</td>
<td>14%</td>
</tr>
<tr>
<td>(42%, 53%)</td>
<td>(11%, 18%)</td>
</tr>
<tr>
<td>COPD Study</td>
<td>CHANTIX 1 mg BID</td>
</tr>
<tr>
<td>42%</td>
<td>9%</td>
</tr>
<tr>
<td>(34%, 47%)</td>
<td>(6%, 13%)</td>
</tr>
</tbody>
</table>

BID = twice daily

14.5 Subjects with Major Depressive Disorder
CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged 18 to 75 years with major depressive disorder without psychotic features (DSM-IV TR). If on medication, subjects were to be on a stable antidepressant regimen for at least two months. If not on medication, subjects were to have experienced a major depressive episode in the past 2 years, which was successfully treated. Subjects were randomized to CHANTIX 1 mg twice daily (n=256) or placebo (n=269) for a treatment of 12 weeks and then followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (36%) compared to subjects treated with placebo (16%) and from week 9 through 52 (20%) compared to subjects treated with placebo (10%).

Table 9: Continuous Abstinence (95% confidence interval), Study in Patients with Major Depressive Disorder (MDD)

<table>
<thead>
<tr>
<th>Weeks 9 through 12</th>
<th>Weeks 9 through 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHANTIX 1 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>MDD Study</td>
<td>CHANTIX 1 mg BID</td>
</tr>
<tr>
<td>36%</td>
<td>16%</td>
</tr>
<tr>
<td>(30%, 42%)</td>
<td>(11%, 26%)</td>
</tr>
</tbody>
</table>

BID = twice daily

14.6 Alternative Instructions for Setting a Quit Date
CHANTIX was evaluated in a double-blind, placebo-controlled trial where patients were instructed to select a target quit date between Day 8 and Day 35 of treatment. Subjects were randomized 3:1 to CHANTIX 1 mg twice daily (n=486) or placebo (n=165) for 12 weeks of treatment and followed for another 12 weeks post-treatment. Patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (54%) compared to patients treated with placebo (19%) and from weeks 9 through 24 (35%) compared to subjects treated with placebo (13%).

14.7 Re-Treatment Study
CHANTIX was evaluated in a double-blind, placebo-controlled trial of patients who had made a previous attempt to quit smoking with CHANTIX, and either did not succeed in quitting or relapsed after treatment. Subjects were randomized 1:1 to CHANTIX 1 mg twice daily (n=249) or placebo (n=245) for 12 weeks of treatment and followed for 40 weeks post-treatment. Patients included in this study had taken CHANTIX for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had been smoking for at least four weeks. Patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (45%) compared to patients treated with placebo (12%) and from weeks 9 through 52 (20%) compared to subjects treated with placebo (3%).

Table 10: Continuous Abstinence (95% confidence interval), Re-Treatment Study

<table>
<thead>
<tr>
<th>Weeks 9 through 12</th>
<th>Weeks 9 through 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHANTIX 1 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>CHANTIX 1 mg BID</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING
CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capscular biconvex, white to off-white, film-coated tablet debossed with "Pzifer" on one side and "CHX 0.5" on the other side and a 1 mg capscular biconvex, light blue film-coated tablet debossed with "Pzifer" on one side and "CHX 1.0" on the other side. CHANTIX is supplied in the following package configurations:

<table>
<thead>
<tr>
<th>Description</th>
<th>NDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packs</td>
<td></td>
</tr>
<tr>
<td>Starting 2 week card: 0.5 mg x 11 tablets and 1 mg x 14 tablets</td>
<td>NDC 0069-0471-01</td>
</tr>
<tr>
<td>Continuing 2 week card: 1 mg x 28 tablets</td>
<td>NDC 0069-0469-11</td>
</tr>
<tr>
<td>Starting 4-week card: 0.5 mg x 11 tablets and 1 mg x 42 tablets</td>
<td>NDC 0069-0471-03</td>
</tr>
<tr>
<td>Continuing 4-week card: 1 mg x 56 tablets</td>
<td>NDC 0069-0469-03</td>
</tr>
<tr>
<td>Starting Month Box: 0.5 mg x 11 tablets and 1 mg x 42 tablets</td>
<td>NDC 0069-0471-02, NDC 0069-0471-03</td>
</tr>
<tr>
<td>Continuing Month Box: 1 mg x 56 tablets</td>
<td>NDC 0069-0469-12, NDC 0069-0469-03</td>
</tr>
<tr>
<td>Bottles</td>
<td></td>
</tr>
<tr>
<td>0.5 mg - bottle of 56</td>
<td>NDC 0069-0468-56</td>
</tr>
<tr>
<td>1 mg - bottle of 56</td>
<td>NDC 0069-0469-56</td>
</tr>
</tbody>
</table>

Store at 25 C (77 F); excursions permitted to 15-30 C (59-86 F) (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Medication Guide)

Initiate Treatment and Continue to Attempt to Quit if Lapse
Instruct patients to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date. Alternatively, the patient can begin CHANTIX dosing and then set a date to quit smoking between days 8 and 35 of treatment. Encourage patients to continue to attempt to quit if they have early lapses after quit day [see Dosage and Administration (2.1)]. Encourage patients who are motivated to quit and who did not succeed in stopping smoking during prior CHANTIX therapy for reasons other than intolerance due to adverse events, or who relapsed after treatment to make another attempt with CHANTIX once factors contributing to the failed attempt have been identified and addressed [see Dosage and Administration (2.1), Clinical Studies (14.7)].

How To Take
Advise patients that CHANTIX should be taken after eating, and with a full glass of water [see Dosage and Administration (2.1)].

Starting Week Dosage
Instruct patients on how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening [see Dosage and Administration (2.1)].

Continuing Weeks Dosage
Advise patients that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening [see Dosage and Administration (2.1)].

Dosage Adjustment for CHANTIX or Other Drugs
Inform patients that nausea and insomnia are side effects of CHANTIX and are usually transient; however, advise patients that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered. Inform patients that some drugs may require dose adjustment after quitting smoking [see Dosage and Administration (2.1)].

Counseling and Support
Provide patients with educational materials and necessary counseling to support an attempt at quitting smoking [see Dosage and Administration (2.1)].

Neuropsychiatric Symptoms
Inform patients that some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia,

Reference ID: 3643541
delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation and suicide when attempting to quit smoking while taking CHANTIX. If patients develop agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to discontinue CHANTIX and report these symptoms to their healthcare provider immediately [see Boxed Warning, Warnings and Precautions (5.1), Adverse Reactions (6.2)].

History of Psychiatric Illness
Encourage patients to reveal any history of psychiatric illness prior to initiating treatment.

Nicotine Withdrawal
Inform patients that quitting smoking, with or without CHANTIX, may be associated with nicotine withdrawal symptoms (including depression or agitation) or exacerbation of pre-existing psychiatric illness.

Seizures
Encourage patients to report any history of seizures or other factors that can lower seizure threshold. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately if they experience a seizure while on treatment [see Warnings and Precautions (5.2)].

Interaction with Alcohol
Advise patients to reduce the amount of alcohol they consume while taking CHANTIX until they know whether CHANTIX affects their tolerance for alcohol [see Warnings and Precautions (5.3), Adverse Reactions (6.2)].

Driving or Operating Machinery
Advise patients to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them [see Warnings and Precautions (5.4)].

Cardiovascular Events
Patients should be instructed to notify their health care providers of symptoms of new or worsening cardiovascular events and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. [see Warnings and Precautions (5.5), and Adverse Reactions (6.1)].

Angioedema
Inform patients that there have been reports of angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms [see Warnings and Precautions (5.2), and Adverse Reactions (6.2)].

Serious Skin Reactions
Inform patients that serious skin reactions, such as Stevens-Johnson Syndrome and erythema multiforme, were reported by some patients taking CHANTIX. Advise patients to stop taking CHANTIX at the first sign of rash with mucosal lesions or skin reaction and contact a healthcare provider immediately [see Warnings and Precautions (5.3), and Adverse Reactions (6.2)].

Vivid, Unusual, or Strange Dreams
Inform patients that they may experience vivid, unusual or strange dreams during treatment with CHANTIX.

Pregnancy and Lactation
Patients who are pregnant or breastfeeding or planning to become pregnant should be advised of: the risks of smoking to a pregnant mother and her developing baby, the potential risks of CHANTIX use during pregnancy and breastfeeding, and the benefits of smoking cessation with and without CHANTIX [see Use in Specific Populations (8.1 and 8.3)].

This product’s label may have been updated. For full prescribing information, please visit www.pfizer.com
• acting aggressive, being angry, or violent
• acting on dangerous impulses
• an extreme increase in activity and talking (mania)
• abnormal thoughts or sensations
• seeing or hearing things that are not there (hallucinations)
• feeling people are against you (paranoia)
• feeling confused
• other unusual changes in behavior or mood

When you try to quit smoking, with or without CHANTIX, you may have symptoms that may be due to nicotine withdrawal, including
urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating,
restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts
when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that
you already have, such as depression.

See “What are the possible side effects of CHANTIX?” for more information about other side effects.

What is CHANTIX?

CHANTIX is a prescription medicine to help people stop smoking.

Quitting smoking can lower your chances of having lung disease, heart disease or getting certain types of cancer that are related to
smoking.

It is not known if CHANTIX is safe and effective in children.

It is not known if CHANTIX is safe and effective when used with other stop smoking medicines.

Who should not take CHANTIX?

Do not take CHANTIX if you have had a serious allergic or skin reaction to CHANTIX. Symptoms may include:

• swelling of the face, mouth (tongue, lips, gums), throat or neck
• trouble breathing
• rash, with peeling skin
• blisters in your mouth

What should I tell my doctor before taking CHANTIX?

See “What is the most important information I should know about CHANTIX?”

Before you take CHANTIX, tell your doctor if you:

• use other treatments to quit smoking. Using CHANTIX with a nicotine patch may cause nausea, vomiting, headache, dizziness, upset stomach, and tiredness to happen more often than if you just use a nicotine patch alone.
• have kidney problems or get kidney dialysis. Your doctor may prescribe a lower dose of CHANTIX for you.
• have a history of seizures
• drink alcohol
• have heart or blood vessel problems
• have any other medical conditions
• are pregnant or plan to become pregnant. It is not known if CHANTIX will harm your unborn baby.
• are breastfeeding. It is not known if CHANTIX passes into breast milk. You and your doctor should decide if you will breastfeed or take CHANTIX. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over the counter medicines, vitamins and herbal supplements. Your doctor may need to change the dose of some of your medicines when you stop smoking.

You should not use CHANTIX while using other medicines to quit smoking. Tell your doctor if you use other treatments to quit smoking.

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist when you get a new medicine.

How should I take CHANTIX?

• There are 2 ways that you can use CHANTIX to help you quit smoking. Talk to your doctor about the following 2 ways to use CHANTIX:

  Choose a quit date when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your quit date.

OR

Start taking CHANTIX before you choose a quit date. Pick a date to quit smoking that is between days 8 and 35 of treatment.

Starting CHANTIX before your quit date gives CHANTIX time to build up in your body. You can keep smoking during this time. Take CHANTIX exactly as prescribed by your doctor.

• CHANTIX comes as a white tablet (0.5 mg) and a blue tablet (1 mg). You start with the white tablet and then usually go to the blue tablet. See the chart below for dosing instructions for adults.

| Day 1 to Day 3 | • White tablet (0.5 mg)  
| | • Take 1 tablet each day |
| Day 4 to Day 7 | • White tablet (0.5 mg)  
| | • Take 1 in the morning and 1 in the evening |
| Day 8 to end of treatment | • Blue tablet (1 mg)  
| | • Take 1 in the morning and 1 in the evening |

• Make sure that you try to stop smoking on your quit date. If you slip-up and smoke, try again. Some people need to take CHANTIX for a few weeks for CHANTIX to work best.

• Most people will take CHANTIX for up to 12 weeks. If you have completely quit smoking by 12 weeks, your doctor may prescribe CHANTIX for another 12 weeks to help you stay cigarette-free.

• Take CHANTIX after eating and with a full glass (8 ounces) of water.

• This dosing schedule may not be right for everyone. Talk to your doctor if you are having side effects such as nausea, strange dreams, or sleep problems. Your doctor may want to reduce your dose.

• If you miss a dose of CHANTIX, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take your next dose at your regular time.

What should I avoid while taking CHANTIX?

• Use caution when driving or operating machinery until you know how CHANTIX affects you. CHANTIX may make you feel sleepy, dizzy, or have trouble concentrating, making it hard to drive or perform other activities safely.

• Decrease the amount of alcoholic beverages that you drink during treatment with CHANTIX until you know if CHANTIX affects your ability to tolerate alcohol. Some people have experienced the following when drinking alcohol during treatment with CHANTIX:

Reference ID: 3643541
What are the possible side effects of CHANTIX?

Serious side effects of CHANTIX may include:

- **Seizures.** Some people have had seizures during treatment with CHANTIX. In most cases, the seizures have happened during the first month of treatment with CHANTIX. If you have a seizure during treatment with CHANTIX, stop taking CHANTIX and contact your healthcare provider right away.

- **New or worse heart or blood vessel (cardiovascular) problems,** mostly in people who already have cardiovascular problems. Tell your doctor if you have any changes in symptoms during treatment with CHANTIX.

Get emergency medical help right away if you have any of the following symptoms of a heart attack, including:

- chest discomfort (uncomfortable pressure, squeezing, fullness or pain) that lasts more than a few minutes, or that goes away and comes back
- pain or discomfort in one or both arms, back, neck, jaw or stomach
- shortness of breath, sweating, nausea, vomiting, or feeling lightheaded associated with chest discomfort

- **Allergic reactions** can happen with CHANTIX. Some of these allergic reactions can be life-threatening.

- **Serious skin reactions,** including rash, swelling, redness, and peeling of the skin. Some of these skin reactions can become life-threatening.

Stop taking CHANTIX and get medical help right away if you have any of the following symptoms:

- swelling of the face, mouth (tongue, lips, and gums), throat or neck
- trouble breathing
- rash with peeling skin
- blisters in your mouth

The most common side effects of CHANTIX include:

- nausea
- sleep problems (trouble sleeping or vivid, unusual, or strange dreams)
- constipation
- gas
- vomiting

Tell your doctor about side effects that bother you or that do not go away.

These are not all the side effects of CHANTIX. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CHANTIX?

- Store CHANTIX at room temperature, between 68°F to 77°F (20°C to 25°C).
- Keep CHANTIX and all medicines out of the reach of children.

General information about CHANTIX
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CHANTIX for a condition for which it was not prescribed. Do not give your CHANTIX to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CHANTIX that is written for healthcare professionals.

For more information about CHANTIX and tips on how to quit smoking, go to www.CHANTIX.com or call 1-877-242-6849.

If you are motivated to quit smoking and did not succeed during prior CHANTIX treatment for reasons other than side effects, or if you returned to smoking after treatment, speak with your doctor about whether another course of CHANTIX therapy may be right for you.

What are the ingredients in CHANTIX?

**Active ingredient:** varenicline tartrate

**Inactive ingredients:** microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry ® White (for 0.5 mg), Opadry ® Blue (for 1 mg), and Opadry® Clear.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by

Pfizer
Pfizer Labs
Division of Pfizer Inc. NY, NY 10017

Revised October 2014

LAB-0328-12.X
FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Usual Dosage
  2.2 Duration of Treatment
  2.3 Individualization of Therapy
  2.4 Maintenance
  2.5 Combination Treatment with ZYBAN and a Nicotine Transdermal System (NTS)
  2.6 Dose Adjustment in Patients with Hepatic Impairment
  2.7 Dose Adjustment in Patients with Renal Impairment
  2.8 Use of ZYBAN with Reversible MAOIs Such as Loxapine or Methylene Blue
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment
  5.2 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
  5.3 Seizure

5.4 Hypertension
5.5 Activation of Mania/Hypomania
5.6 Psychosis and Other Neuropsychiatric Reactions
5.7 Angle-Closure Glaucoma
5.8 Hypersensitivity Reactions
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
  6.2 Postmarketing Experience
7 DRUG INTERACTIONS
  7.1 Potential for Other Drugs to Affect ZYBAN
  7.2 Potential for ZYBAN to Affect Other Drugs
  7.3 Drugs that Lower Seizure Threshold
  7.4 Dopaminergic Drugs (Levodopa and Amantadine)
  7.5 Use with Alcohol
  7.6 MAO Inhibitors
  7.7 Smoking Cessation
  7.8 Drug-Laboratory Test Interactions
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Lactation
  8.3 Nursing Mothers

WARNING: NEUROPSYCHIATRIC REACTIONS; AND SUICIDAL THOUGHTS AND BEHAVIORS

• Seizure risk: The risk is dose-related. Can minimize risk by gradually increasing the dose and limiting daily dose to 300 mg. Discontinue if seizure occurs. (4, 5.3, 7.3)
• Hypertension: ZYBAN can increase blood pressure. Monitor blood pressure before initiating treatment and periodically during treatment, especially if used with nicotine replacement. (5.4)
• Activation of mania/hypomania: Screen patients for bipolar disorder and monitor for these symptoms. (5.5)
• Psychosis and other neuropsychiatric reactions. Instruct patients to contact a healthcare professional if reactions occur. (5.6)
• Angle-closure glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.7)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and ≥1% more than placebo rate) are: insomnia, rhinitis, dry mouth, dizziness, nervous disturbance, anxiety, nausea, constipation, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• CYP2B6 inducers: Dose increase may be necessary if coadministered with CYP2B6 inducers (e.g., ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital and phenytoin) based on clinical response, but should not exceed the maximum recommended dose. (7.1)
• Drugs metabolized by CYP2D6: Bupropion inhibits CYP2D6 and can increase concentrations of: antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecaainide). Consider dose reduction when using with bupropion. (7.2)
• Drugs that lower seizure threshold: Dose ZYBAN with caution. (7.3, 7.3)
• Dopaminergic drugs (levodopa and amantadine): CNS toxicity can occur when used concomitantly with ZYBAN. (7.4)
• MAOIs: Increased risk of hypertensive reactions can occur when used concomitantly with ZYBAN. (7.6)
• Drug-laboratory test interactions: ZYBAN can cause false-positive urine test results for amphetamines. (7.8)

USE IN SPECIFIC POPULATIONS

• Pregnancy: Use only if benefit outweighs potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2016
WARNING: NEUROPSYCHIATRIC REACTIONS; AND SUICIDAL THOUGHTS AND BEHAVIORS

NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR SMOKING CESSATION

Serious neuropsychiatric reactions have occurred in patients taking ZYBAN® for smoking cessation [see Warnings and Precautions (5.1)]. The majority of these reactions occurred during bupropion treatment, but some occurred in the context of discontinuing treatment. In many cases, a causal relationship to bupropion treatment is not certain, because depressed mood may be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking ZYBAN who continued to smoke. The risks of ZYBAN should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared with treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Although ZYBAN is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications WELLBUTRIN®, WELLBUTRIN® SR, and WELLBUTRIN XL®. Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older [see Warnings and Precautions (5.2)].

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

ZYBAN is indicated as an aid to smoking cessation treatment.
2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage

Treatment with ZYBAN should be initiated before the patient’s planned quit day, while the patient is still smoking, because it takes approximately 1 week of treatment to achieve steady-state blood levels of bupropion. The patient should set a “target quit date” within the first 2 weeks of treatment with ZYBAN.

Dosing

To minimize the risk of seizure:

- Begin dosing with one 150-mg tablet per day for 3 days.
- Increase dose to 300 mg per day given as one 150-mg tablet twice each day with an interval of at least 8 hours between each dose.
- Do not exceed 300 mg per day.

ZYBAN should be swallowed whole and not crushed, divided, or chewed, as this may lead to an increased risk of adverse effects including seizures [see Warnings and Precautions (5.3)]. ZYBAN may be taken with or without food [see Clinical Pharmacology (12.3)].

2.2 Duration of Treatment

Treatment with ZYBAN should be continued for 7 to 12 weeks. If the patient has not quit smoking after 7 to 12 weeks, it is unlikely that he or she will quit during that attempt so treatment with ZYBAN should probably be discontinued and the treatment plan reassessed. The goal of therapy with ZYBAN is complete abstinence.

Discuss discontinuing treatment with ZYBAN after 12 weeks if the patient feels ready but consider whether the patient may benefit from ongoing treatment. Patients who successfully quit after 12 weeks of treatment but do not feel ready to discontinue treatment should be considered for ongoing therapy with ZYBAN; longer treatment should be guided by the relative benefits and risks for individual patients.

It is important that patients continue to receive counseling and support throughout treatment with ZYBAN and for a period of time thereafter.

2.3 Individualization of Therapy

Patients are more likely to quit smoking and remain abstinent if they are seen frequently and receive support from their physicians or other healthcare professionals. It is important to ensure that patients read the instructions provided to them and have their questions answered.

Physicians should review the patient’s overall smoking cessation program that includes treatment with ZYBAN. Patients should be advised of the importance of participating in the behavioral...
interventions, counseling, and/or support services to be used in conjunction with ZYBAN [see Medication Guide].

Patients who fail to quit smoking during an attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who are unsuccessful should be evaluated to determine why they failed. A new quit attempt should be encouraged when factors that contributed to failure can be eliminated or reduced, and conditions are more favorable.

2.4 Maintenance

Tobacco dependence is a chronic condition. Some patients may need on-going treatment. Whether to continue treatment with ZYBAN for periods longer than 12 weeks for smoking cessation must be determined for individual patients.

2.5 Combination Treatment with ZYBAN and a Nicotine Transdermal System (NTS)

Combination treatment with ZYBAN and NTS may be prescribed for smoking cessation. The prescriber should review the complete prescribing information for both ZYBAN and NTS before using combination treatment [see Clinical Studies (14)]. Monitoring for treatment-emergent hypertension in patients treated with the combination of ZYBAN and NTS is recommended.

2.6 Dose Adjustment in Patients with Hepatic Impairment

In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum dose should not exceed 150 mg every other day. In patients with mild hepatic impairment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

2.7 Dose Adjustment in Patients with Renal Impairment

Consider reducing the dose and/or frequency of ZYBAN in patients with renal impairment (Glomerular Filtration Rate less than 90 mL per min) [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

2.8 Use of ZYBAN with Reversible MAOIs Such as Linezolid or Methylene Blue

Do not start ZYBAN in a patient who is being treated with a reversible MAOI such as linezolid or intravenous methylene blue. Drug interactions can increase the risk of hypertensive reactions [see Contraindications (4), Drug Interactions (7.6)].

In some cases, a patient already receiving therapy with ZYBAN may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of hypertensive reactions in a particular patient, ZYBAN should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first.
99 Therapy with ZYBAN may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.

100 The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg per kg with ZYBAN is unclear. The clinician should, nevertheless, be aware of the possibility of a drug interaction with such use [see Contraindications (4), Drug Interactions (7.6)].

3 DOSAGE FORMS AND STRENGTHS

106 150 mg – purple, round, biconvex, film-coated, sustained-release tablets printed with “ZYBAN 150”.

4 CONTRAINDICATIONS

• ZYBAN is contraindicated in patients with a seizure disorder.

• ZYBAN is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate-release formulation of bupropion [see Warnings and Precautions (5.3)].

• ZYBAN is contraindicated in patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs [see Warnings and Precautions (5.3), Drug Interactions (7.3)].

• The use of MAOIs (intended to treat psychiatric disorders) concomitantly with ZYBAN or within 14 days of discontinuing treatment with ZYBAN is contraindicated. There is an increased risk of hypertensive reactions when ZYBAN is used concomitantly with MAOIs. The use of ZYBAN within 14 days of discontinuing treatment with an MAOI is also contraindicated. Starting ZYBAN in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated [see Dosage and Administration (2.8), Warnings and Precautions (5.4), Drug Interactions (7.6)].

• ZYBAN is contraindicated in patients with a known hypersensitivity to bupropion or other ingredients of ZYBAN. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported [see Warnings and Precautions (5.8)].

5 WARNINGS AND PRECAUTIONS

5.1 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

Serious neuropsychiatric symptoms have been reported in patients taking ZYBAN for smoking cessation. These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide [see Boxed
Warning, Adverse Reactions (6.2). Observe patients for the occurrence of neuropsychiatric reactions. Instruct patients to contact a healthcare professional if such reactions occur.

In many of these cases, a causal relationship to bupropion treatment is not certain, because depressed mood can be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking ZYBAN who continued to smoke.

The risks of ZYBAN should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared with treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

5.2 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide.

There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) show that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term clinical trials did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24; there was a reduction with antidepressants compared with placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 subjects. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 subjects. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger subjects for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 subjects treated) are provided in Table 1.
Table 1. Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Subjects

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Subjects Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increases Compared with Placebo</td>
</tr>
<tr>
<td>&lt;18</td>
<td>14 additional cases</td>
</tr>
<tr>
<td>18-24</td>
<td>5 additional cases</td>
</tr>
<tr>
<td></td>
<td>Decreases Compared with Placebo</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer case</td>
</tr>
<tr>
<td>≥65</td>
<td>6 fewer cases</td>
</tr>
</tbody>
</table>

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases [see Boxed Warning].

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should
include daily observation by families and caregivers. Prescriptions for ZYBAN should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

5.3 Seizure

ZYBAN can cause seizure. The risk of seizure is dose-related. The dose of ZYBAN should not exceed 300 mg per day [see Dosage and Administration (2.1)]. Discontinue ZYBAN and do not restart treatment if the patient experiences a seizure.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with ZYBAN. ZYBAN is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs [see Contraindications (4), Drug Interactions (7.3)]. The following conditions can also increase the risk of seizure: severe head injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids), metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia), use of illicit drugs (e.g., cocaine), or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

Incidence of Seizure with Bupropion Use

Doses for smoking cessation should not exceed 300 mg per day. The seizure rate associated with doses of sustained-release bupropion in depressed patients up to 300 mg per day is approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1000) at doses up to 400 mg per day.

The risk of seizure can be reduced if the dose of ZYBAN for smoking cessation does not exceed 300 mg per day, given as 150 mg twice daily, and titration rate is gradual.

5.4 Hypertension

Treatment with ZYBAN can result in elevated blood pressure and hypertension. Assess blood pressure before initiating treatment with ZYBAN, and monitor periodically during treatment. The risk of hypertension is increased if ZYBAN is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity [see Contraindications (4)].

Data from a comparative trial of ZYBAN, nicotine transdermal system (NTS), the combination of ZYBAN plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of ZYBAN and NTS. In this trial, 6.1% of subjects treated with the combination of ZYBAN and NTS had
treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of subjects treated with ZYBAN, NTS, and placebo, respectively. The majority of these subjects had evidence of pre-existing hypertension. Three subjects (1.2%) treated with the combination of ZYBAN and NTS and 1 subject (0.4%) treated with NTS had study medication discontinued due to hypertension compared with none of the subjects treated with ZYBAN or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

In a clinical trial of bupropion immediate-release in MDD subjects with stable congestive heart failure (N = 36), bupropion was associated with an exacerbation of pre-existing hypertension in 2 subjects, leading to discontinuation of bupropion treatment. There are no controlled trials assessing the safety of bupropion in patients with a recent history of myocardial infarction or unstable cardiac disease.

5.5 Activation of Mania/Hypomania

Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. There were no reports of activation of psychosis or mania in clinical trials with ZYBAN conducted in nondepressed smokers. Bupropion is not approved for use in treating bipolar depression.

5.6 Psychosis and Other Neuropsychiatric Reactions

Depressed patients treated with bupropion in depression trials have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Instruct patients to contact a healthcare professional if such reactions occur.

In clinical trials with ZYBAN conducted in nondepressed smokers, the incidence of neuropsychiatric side effects was generally comparable to placebo. However, in the postmarketing experience, patients taking ZYBAN to quit smoking have reported similar types of neuropsychiatric symptoms to those reported by patients in the clinical trials of bupropion for depression.

5.7 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including bupropion may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.8 Hypersensitivity Reactions

Anaphylactoid/anaphylactic reactions have occurred during clinical trials with bupropion. Reactions have been characterized by pruritus, urticaria, angioedema, and dyspnea requiring
medical treatment. In addition, there have been rare, spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. Instruct patients to discontinue ZYBAN and consult a healthcare provider if they develop an allergic or anaphylactoid/anaphylactic reaction (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

There are reports of arthralgia, myalgia, fever with rash and other serum sickness-like symptoms suggestive of delayed hypersensitivity.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Neuropsychiatric symptoms and suicide risk in smoking cessation treatment [see Boxed Warning, Warnings and Precautions (5.1)]
- Suicidal thoughts and behaviors in adolescents and young adults [see Boxed Warning, Warnings and Precautions (5.2)]
- Seizure [see Warnings and Precautions (5.3)]
- Hypertension [see Warnings and Precautions (5.4)]
- Activation of mania or hypomania [see Warnings and Precautions (5.5)]
- Psychosis and other neuropsychiatric reactions [see Warnings and Precautions (5.6)]
- Angle-closure glaucoma [see Warnings and Precautions (5.7)]
- Hypersensitivity reactions [see Warnings and Precautions (5.8)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions Leading to Discontinuation of Treatment

Adverse reactions were sufficiently troublesome to cause discontinuation of treatment in 8% of the 706 subjects treated with ZYBAN and 5% of the 313 patients treated with placebo. The more common events leading to discontinuation of treatment with ZYBAN included nervous system disturbances (3.4%), primarily tremors, and skin disorders (2.4%), primarily rashes.

Commonly Observed Adverse Reactions

The most commonly observed adverse reactions consistently associated with the use of ZYBAN were dry mouth and insomnia. The incidence of dry mouth and insomnia may be related to the dose of ZYBAN. The occurrence of these adverse reactions may be minimized by reducing the dose of ZYBAN. In addition, insomnia may be minimized by avoiding bedtime doses.
Adverse reactions reported in the dose-response and comparator trials are presented in Table 2 and Table 3, respectively. Reported adverse reactions were classified using a COSTART-based dictionary.

**Table 2. Adverse Reactions Reported by at Least 1% of Subjects and at a Greater Frequency than Placebo in the Dose-Response Trial**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZYBAN 100 to 300 mg/day (n = 461) %</th>
<th>Placebo (n = 150) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body (General)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flashes</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Tremor</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Thinking abnormality</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Special senses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste perversion</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Adverse Experience (COSTART Term)</td>
<td>ZYBAN 300 mg/day (n = 243)</td>
<td>Nicotine Transdermal System (NTS) 21 mg/day (n = 243)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td><strong>Body</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Neck pain</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Facial edema</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Mouth ulcer</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Thirst</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>40%</td>
<td>28%</td>
</tr>
<tr>
<td>Dream abnormality</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Disturbed concentration</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Tremor</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3939632
<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency 1/100</th>
<th>Frequency 1/100 to 1/1,000</th>
<th>Frequency &gt;1/1,000</th>
<th>Frequency &lt;1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis</td>
<td>12</td>
<td>11</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Increased cough</td>
<td>3</td>
<td>5</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site reaction</td>
<td>11</td>
<td>17</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Urticaria</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste perversion</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
</tr>
</tbody>
</table>

a Subjects randomized to ZYBAN or placebo received placebo patches.

Adverse reactions in a 1-year maintenance trial and a 12-week COPD trial with ZYBAN were quantitatively and qualitatively similar to those observed in the dose-response and comparator trials.

Other Adverse Reactions Observed during the Clinical Development of Bupropion

In addition to the adverse reactions noted above, the following adverse reactions have been reported in clinical trials with the sustained-release formulation of bupropion in depressed subjects and in nondepressed smokers, as well as in clinical trials with the immediate-release formulation of bupropion.

Adverse reaction frequencies represent the proportion of subjects who experienced a treatment-emergent adverse reaction on at least one occasion in placebo-controlled trials for depression (n = 987) or smoking cessation (n = 1,013), or subjects who experienced an adverse reaction requiring discontinuation of treatment in an open-label surveillance trial with bupropion sustained-release tablets (n = 3,100). All treatment-emergent adverse reactions are included except those listed in Tables 2 and 3, those listed in other safety-related sections of the prescribing information, those subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those not reasonably associated with the use of the drug, and those that were not serious and occurred in fewer than 2 subjects.

Adverse reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse reactions are defined as those occurring in at least 1/100 subjects. Infrequent adverse reactions are those occurring in 1/100 to 1/1,000 subjects, while rare events are those occurring in less than 1/1,000 subjects.
Body (General): Frequent were asthenia, fever, and headache. Infrequent were chills, inguinal hernia, and photosensitivity. Rare was malaise.

Cardiovascular: Infrequent were flushing, migraine, postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope.

Digestive: Frequent were dyspepsia and vomiting. Infrequent were abnormal liver function, bruxism, dysphagia, gastric reflux, gingivitis, jaundice, and stomatitis.

Hemic and Lymphatic: Infrequent was ecchymosis.

Metabolic and Nutritional: Infrequent were edema and peripheral edema.

Musculoskeletal: Infrequent were leg cramps and twitching.

Nervous System: Frequent were agitation, depression, and irritability. Infrequent were abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory, depersonalization, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, paresthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania.

Respiratory: Rare was bronchospasm.

Skin: Frequent was sweating.

Special Senses: Frequent was blurred vision or diplopia. Infrequent were accommodation abnormality and dry eye.

Urogenital: Frequent was urinary frequency. Infrequent were impotence, polyuria, and urinary urgency.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZYBAN and are not described elsewhere in the label. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a relationship to drug exposure.

Body (General)

Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness [see Warnings and Precautions (5.8)].

Cardiovascular

Cardiovascular disorder, complete AV block, extrasystoles, hypotension, myocardial infarction, phlebitis, and pulmonary embolism.

Digestive
Colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, increased salivation, intestinal perforation, liver damage, pancreatitis, stomach ulcer, and stool abnormality.

**Endocrine**

Hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

**Hemic and Lymphatic**

Anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

**Metabolic and Nutritional**

Glycosuria.

**Musculoskeletal**

Arthritis and muscle rigidity/fever/rhabdomyolysis, and muscle weakness.

**Nervous System**

Abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, completed suicide, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome (dyskinesia, dystonia, hypokinesia, parkinsonism), hallucinations, increased libido, manic reaction, neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive dyskinesia.

**Respiratory**

Pneumonia.

**Skin**

Alopecia, angioedema, exfoliative dermatitis, hirsutism, and Stevens-Johnson syndrome.

**Special Senses**

Deafness, increased intraocular pressure, and mydriasis.

**Urogenital**

Abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, prostate disorder, salpingitis, urinary incontinence, urinary retention, urinary tract disorder, and vaginitis.
7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect ZYBAN

Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between ZYBAN and drugs that are inhibitors or inducers of CYP2B6.

Inhibitors of CYP2B6

Ticlopidine and Clopidogrel: Concomitant treatment with these drugs can increase bupropion exposure but decrease hydroxybupropion exposure. Based on clinical response, dosage adjustment of ZYBAN may be necessary when coadministered with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) [see Clinical Pharmacology (12.3)].

Inducers of CYP2B6

Ritonavir, Lopinavir, and Efavirenz: Concomitant treatment with these drugs can decrease bupropion and hydroxybupropion exposure. Dosage increase of ZYBAN may be necessary when coadministered with ritonavir, lopinavir, or efavirenz [see Clinical Pharmacology (12.3)] but should not exceed the maximum recommended dose.

Carbamazepine, Phenobarbital, Phenytoin: While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure [see Clinical Pharmacology (12.3)]. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded.

7.2 Potential for ZYBAN to Affect Other Drugs

Drugs Metabolized by CYP2D6

Bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. Therefore, coadministration of ZYBAN with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. Such drugs include certain antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, and sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone and flecainide). When used concomitantly with ZYBAN, it may be necessary to decrease the dose of these CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.

Drugs that require metabolic activation by CYP2D6 to be effective (e.g., tamoxifen) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Patients treated concomitantly with ZYBAN and such drugs may require increased doses of the drug [see Clinical Pharmacology (12.3)].
7.3 Drugs that Lower Seizure Threshold

Use extreme caution when coadministering ZYBAN with other drugs that lower seizure threshold (e.g., other bupropion products, antipsychotics, antidepressants, theophylline, or systemic corticosteroids). Use low initial doses and increase the dose gradually [see Contraindications (4), Warnings and Precautions (5.3)].

7.4 Dopaminergic Drugs (Levodopa and Amantadine)

Bupropion, levodopa, and amantadine have dopamine agonist effects. CNS toxicity has been reported when bupropion was coadministered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Use caution when administering ZYBAN concomitantly with these drugs.

7.5 Use with Alcohol

In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with ZYBAN. The consumption of alcohol during treatment with ZYBAN should be minimized or avoided.

7.6 MAO Inhibitors

Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of MAOIs and bupropion is contraindicated because there is an increased risk of hypertensive reactions if bupropion is used concomitantly with MAOIs. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. At least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with ZYBAN. Conversely, at least 14 days should be allowed after stopping ZYBAN before starting an MAOI intended to treat psychiatric disorders [see Dosage and Administration (2.8), Contraindications (4)].

7.7 Smoking Cessation

Physiological changes resulting from smoking cessation, with or without treatment with ZYBAN, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

7.8 Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. This is due to lack of specificity of some screening tests. False-positive test results may result even following discontinuation of bupropion therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Risk Summary

Data from epidemiological studies of pregnant women exposed to bupropion in the first trimester indicate no increased risk of congenital malformations overall. All pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major malformations, and 15% to 20% for pregnancy loss. No clear evidence of teratogenic activity was found in reproductive developmental studies conducted in rats and rabbits; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at doses approximately 2 times the maximum recommended human dose (MRHD) and greater and decreased fetal weights were seen at doses three times the MRHD and greater. ZYBAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before pharmacological approaches are used.

Human Data

Data from the international bupropion Pregnancy Registry (675 first trimester exposures) and a retrospective cohort study using the United Healthcare database (1,213 first trimester exposures) did not show an increased risk for malformations overall.

No increased risk for cardiovascular malformations overall has been observed after bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester from the international Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first trimester maternal bupropion exposures), which is similar to the background rate of cardiovascular malformations (approximately 1%). Data from the United Healthcare database and a case-control study (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular malformations) from the National Birth Defects Prevention Study (NBDPS) did not show an increased risk for cardiovascular malformations overall after bupropion exposure during the first trimester.

Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted OR = 2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk for LVOTO.
Study findings on bupropion exposure during the first trimester and risk for ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n = 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0) but did not find increased risk for any other cardiovascular malformations studied (including LVOTO as above). The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion exposure and VSD.

For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control studies.

**Animal Data**

In studies conducted in rats and rabbits, bupropion was administered orally during the period of organogenesis at doses of up to 450 and 150 mg per kg per day, respectively (approximately 15 and 10 times the MRHD respectively, on a mg per m² basis). No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg per kg per day, approximately 2 times the MRHD on a mg per m² basis) and greater. Decreased fetal weights were observed at 50 mg per kg and greater.

When rats were administered bupropion at oral doses of up to 300 mg per kg per day (approximately 10 times the MRHD on a mg per m² basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

**8.3 Nursing Mothers**

Bupropion and its metabolites are present in human milk. In a lactation study of 10 women, levels of orally dosed bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL per kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Exercise caution when ZYBAN is administered to a nursing woman.

**8.4 Pediatric Use**

Safety and effectiveness in the pediatric population have not been established [see Boxed Warning, Warnings and Precautions (5.2)].

**8.5 Geriatric Use**

Of the approximately 6,000 subjects who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation trials), 275 were aged ≥65 years and 47 were aged ≥75 years. In addition, several hundred subjects aged ≥65 years participated in clinical trials using the immediate-release formulation of bupropion (depression trials). No overall differences in safety or effectiveness were observed between these subjects and younger
subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be necessary to consider this factor in dose selection; it may be useful to monitor renal function [see Dosage and Administration (2.7), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

8.6 Renal Impairment

Consider a reduced dose and/or dosing frequency of ZYBAN in patients with renal impairment (Glomerular Filtration Rate: less than 90 mL per min). Bupropion and its metabolites are cleared renally and may accumulate in such patients to a greater extent than usual. Monitor closely for adverse reactions that could indicate high bupropion or metabolite exposures [see Dosage and Administration (2.7), Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum dose of ZYBAN is 150 mg every other day. In patients with mild hepatic impairment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing [see Dosage and Administration (2.6), Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Bupropion is not a controlled substance.

9.2 Abuse

Humans

Controlled clinical trials conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed subjects showed some increase in motor activity and agitation/excitement, often typical of central stimulant activity.

In a population of individuals experienced with drugs of abuse, a single oral dose of 400 mg of bupropion produced mild amphetamine-like activity as compared with placebo on the Morphine-Benzodrine Subscale of the Addiction Research Center Inventories (ARCI) and a score greater than placebo but less than 15 mg of the Schedule II stimulant dextroamphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug liking which are often associated with abuse potential.
Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose trials does suggest that the recommended daily dosage of bupropion when administered orally in divided doses is not likely to be significantly reinforcing to amphetamine or CNS stimulant abusers. However, higher doses (which could not be tested because of the risk of seizure) might be modestly attractive to those who abuse CNS stimulant drugs.

ZYBAN is intended for oral use only. The inhalation of crushed tablets or injection of dissolved bupropion has been reported. Seizures and/or cases of death have been reported when bupropion has been administered intranasally or by parenteral injection.

**Animals**

Studies in rodents and primates demonstrated that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavior response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models assessing the positive-reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

The possibility that bupropion may induce dependence should be kept in mind when evaluating the desirability of including the drug in smoking cessation programs of individual patients.

**10 OVERDOSAGE**

**10.1 Human Overdose Experience**

Overdoses of up to 30 grams or more of bupropion have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

**10.2 Overdosage Management**

Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified poison control centers are listed in the Physicians’ Desk Reference (PDR). Call 1-800-222-1222 or refer to [www.poison.org](http://www.poison.org).
There are no known antidotes for bupropion. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Induction of emesis is not recommended.

11 DESCRIPTION

ZYBAN (bupropion hydrochloride) sustained-release tablets are a non-nicotine aid to smoking cessation. ZYBAN is chemically unrelated to nicotine or other agents currently used in the treatment of nicotine addiction. Initially developed and marketed as an antidepressant (WELLBUTRIN [bupropion hydrochloride] tablets and WELLBUTRIN SR [bupropion hydrochloride] sustained-release tablets), ZYBAN is also chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is C\textsubscript{13}H\textsubscript{18}ClNO•HCl. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:

![Structural formula of Bupropion](image)

ZYBAN is supplied for oral administration as 150-mg (purple), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide and is printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism by which ZYBAN enhances the ability of patients to abstain from smoking is not known but is presumed to be related to noradrenergic and/or dopaminergic mechanisms. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine, and does not inhibit the reuptake of serotonin. Bupropion does not inhibit monoamine oxidase.
12.3 Pharmacokinetics

Bupropion is a racemic mixture. The pharmacological activity and pharmacokinetics of the individual enantiomers have not been studied. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

Absorption

The absolute bioavailability of ZYBAN in humans has not been determined because an intravenous formulation for human use is not available. However, it appears likely that only a small proportion of any orally administered dose reaches the systemic circulation intact. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

In humans, following oral administration of ZYBAN, peak plasma concentration (C\text{max}) of bupropion is usually achieved within 3 hours.

ZYBAN can be taken with or without food. Bupropion C\text{max} and AUC were increased by 11% to 35%, and 16% to 19%, respectively, when ZYBAN was administered with food to healthy volunteers in three trials. The food effect is not considered clinically significant.

Distribution

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg per mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion; whereas, the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism

Bupropion is extensively metabolized in humans. Three metabolites are active: hydroxybupropion, which is formed via hydroxylation of the tert-butyl group of bupropion, and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 enzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one-half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion.

This may be of clinical importance, because the plasma concentrations of the metabolites are as high as or higher than those of bupropion.

Following a single-dose administration of ZYBAN in humans, C\text{max} of hydroxybupropion occurs approximately 6 hours post-dose and is approximately 10 times the peak level of the parent drug.
at steady state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours 
and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations 
for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the 
hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (±10) and 
37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, 
respectively.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 
450 mg per day.

**Elimination**

Following oral administration of 200 mg of ^14^C-bupropion in humans, 87% and 10% of the 
radioactive dose were recovered in the urine and feces, respectively. Only 0.5% of the oral dose 
was excreted as unchanged bupropion.

**Population Subgroups**

Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure 
[CHF], age, concomitant medications, etc.) or elimination may be expected to influence the 
degree and extent of accumulation of the active metabolites of bupropion. The elimination of the 
major metabolites of bupropion may be affected by reduced renal or hepatic function because 
they are moderately polar compounds and are likely to undergo further metabolism or 
conjugation in the liver prior to urinary excretion.

**Renal Impairment:** There is limited information on the pharmacokinetics of bupropion in 
patients with renal impairment. An inter-trial comparison between normal subjects and subjects 
with end-stage renal failure demonstrated that the parent drug C_max and AUC values were 
comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion 
metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for subjects with end-stage 
renal failure. A second trial, comparing normal subjects and subjects with moderate-to-severe 
renal impairment (GFR 30.9 ± 10.8 mL per min), showed that after a single 150-mg dose of 
sustained-release bupropion, exposure to bupropion was approximately 2-fold higher in subjects 
with impaired renal function while levels of the hydroxybupropion and 
threo/erythrohydrobupropion (combined) metabolites were similar in the 2 groups. Bupropion is 
extensively metabolized in the liver to active metabolites, which are further metabolized and 
subsequently excreted by the kidneys. The elimination of the major metabolites of bupropion 
may be reduced by impaired renal function. ZYBAN should be used with caution in patients with 
renal impairment and a reduced frequency and/or dose should be considered [see Use in Specific 
Populations (8.6)].

**Hepatic Impairment:** The effect of hepatic impairment on the pharmacokinetics of bupropion 
was characterized in 2 single-dose trials, one in subjects with alcoholic liver disease and one in 
subjects with mild–to-severe cirrhosis. The first trial demonstrated that the half-life of
hydroxybupropion was significantly longer in 8 subjects with alcoholic liver disease than in 8 healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 groups were minimal.

The second trial demonstrated no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 subjects with mild–to-moderate hepatic cirrhosis compared with 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites (t\(_{1/2}\)) in subjects with mild–to-moderate hepatic cirrhosis. In 8 subjects with severe hepatic cirrhosis, significant alterations in the pharmacokinetics of bupropion and its metabolites were seen (Table 4).

Table 4. Pharmacokinetics of Bupropion and Metabolites in Patients with Severe Hepatic Cirrhosis: Ratio Relative to Healthy Matched Controls

<table>
<thead>
<tr>
<th></th>
<th>C_{max}</th>
<th>AUC</th>
<th>t_{1/2}</th>
<th>T_{max}^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>1.69</td>
<td>3.12</td>
<td>1.43</td>
<td>0.5 h</td>
</tr>
<tr>
<td>Hydroxybupropion</td>
<td>0.31</td>
<td>1.28</td>
<td>3.88</td>
<td>19 h</td>
</tr>
<tr>
<td>Threo/erythrohydrobuprop</td>
<td>0.69</td>
<td>2.48</td>
<td>1.96</td>
<td>20 h</td>
</tr>
<tr>
<td>amino alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^a = Difference.

Smokers: The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of ZYBAN, there were no statistically significant differences in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its major metabolites between smokers and nonsmokers.

In a trial comparing the treatment combination of ZYBAN and NTS versus ZYBAN alone, no statistically significant differences were observed between the 2 treatment groups of combination ZYBAN and NTS (n = 197) and ZYBAN alone (n = 193) in the plasma concentrations of bupropion or its active metabolites at Weeks 3 and 6.

Left Ventricular Dysfunction: During a chronic dosing trial with bupropion in 14 depressed subjects with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), there was no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared with healthy volunteers.

Age: The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy trials involving subjects dosed in a range of 300 to 750 mg per day, on a 3-times-daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic trial demonstrated that the
disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another single- and multiple-dose pharmacokinetics trial suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites [see Use in Specific Populations (8.5)].

**Gender:** Pooled analysis of bupropion pharmacokinetic data from 90 healthy male and 90 healthy female volunteers revealed no sex-related differences in the peak plasma concentrations of bupropion. The mean systemic exposure (AUC) was approximately 13% higher in male volunteers compared with female volunteers. The clinical significance of this finding is unknown.

**Drug Interactions**

**Potential for Other Drugs to Affect ZYBAN:** In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between ZYBAN and drugs that are inhibitors or inducers of CYP2B6. In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, fluvoxamine, and nelfinavir inhibit the hydroxylation of bupropion.

**Inhibitors of CYP2B6: Ticlopidine, Clopidogrel:** In a trial in healthy male volunteers, clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily increased exposures (C\text{max} and AUC) of bupropion by 40% and 60% for clopidogrel, and by 38% and 85% for ticlopidine, respectively. The exposures (C\text{max} and AUC) of hydroxybupropion were decreased 50% and 52%, respectively, by clopidogrel, and 78% and 84%, respectively, by ticlopidine. This effect is thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation.

**Prasugrel:** Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel increased bupropion C\text{max} and AUC values by 14% and 18%, respectively, and decreased C\text{max} and AUC values of hydroxybupropion, an active metabolite of bupropion, by 32% and 24%, respectively.

**Cimetidine:** The threo-hydrobupropion metabolite of bupropion does not appear to be produced by cytochrome P450 enzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of bupropion 300 mg with and without cimetidine 800 mg, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C\text{max}, respectively, of the combined moieties of threo-hydrobupropion and erythro-hydrobupropion.

**Citalopram:** Citalopram did not affect the pharmacokinetics of bupropion and its 3 metabolites.

**Inducers of CYP2B6: Ritonavir and Lopinavir:** In a healthy volunteer trial, ritonavir 100 mg twice daily reduced the AUC and C\text{max} of bupropion by 22% and 21%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 23%, the threo-hydrobupropion decreased by 38%, and the erythro-hydrobupropion decreased by 48%.
In a second healthy volunteer trial, ritonavir at a dose of 600 mg twice daily decreased the AUC and the C_max of bupropion by 66% and 62%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by 50%, and the erythrohydrobupropion decreased by 68%.

In another healthy volunteer trial, lopinavir 400 mg/ritonavir 100 mg twice daily decreased bupropion AUC and C_max by 57%. The AUC and C_max of hydroxybupropion were decreased by 50% and 31%, respectively.

Efavirenz: In a trial in healthy volunteers, efavirenz 600 mg once daily for 2 weeks reduced the AUC and C_max of bupropion by approximately 55% and 34%, respectively. The AUC of hydroxybupropion was unchanged, whereas C_max of hydroxybupropion was increased by 50%.

Carbamazepine, Phenobarbital, Phenytoin: While not systematically studied, these drugs may induce the metabolism of bupropion.

Potential for ZYBAN to Affect Other Drugs

Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one trial, following chronic administration of bupropion 100 mg three times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be potential for clinically important alterations of blood levels of co-administered drugs.

Drugs Metabolized by CYP2D6: In vitro, bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. In a clinical trial of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of CYP2D6, bupropion 300 mg per day followed by a single dose of 50 mg desipramine increased the C_max, AUC, and t_1/2 of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Citalopram: Although citalopram is not primarily metabolized by CYP2D6, in one trial bupropion increased the C_max and AUC of citalopram by 30% and 40%, respectively.

Lamotrigine: Multiple oral doses of bupropion had no statistically significant effects on the single-dose pharmacokinetics of lamotrigine in 12 healthy volunteers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime carcinogenicity studies were performed in rats and mice at bupropion doses up to 300 and 150 mg per kg per day, respectively. These doses are approximately 10 and 2 times the MRHD, respectively, on a mg per m² basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg per kg per day (approximately 3 to 10
times the MRHD on a mg per m² basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity assay. Bupropion produced an increase in chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.

A fertility study in rats at doses up to 300 mg per kg per day revealed no evidence of impaired fertility.

14 CLINICAL STUDIES

The efficacy of ZYBAN as an aid to smoking cessation was demonstrated in 3 placebo-controlled, double-blind trials in nondepressed chronic cigarette smokers (n = 1,940, greater than or equal to 15 cigarettes per day). In these trials, ZYBAN was used in conjunction with individual smoking cessation counseling.

The first trial was a dose-response trial conducted at 3 clinical centers. Subjects in this trial were treated for 7 weeks with 1 of 3 doses of ZYBAN (100, 150, or 300 mg per day) or placebo; quitting was defined as total abstinence during the last 4 weeks of treatment (Weeks 4 through 7). Abstinence was determined by subject daily diaries and verified by carbon monoxide levels in expired air.

Results of this dose-response trial with ZYBAN demonstrated a dose-dependent increase in the percentage of subjects able to achieve 4-week abstinence (Weeks 4 through 7). Treatment with ZYBAN at both 150 and 300 mg per day was significantly more effective than placebo in this trial.

Table 5 presents quit rates over time in the multicenter trial by treatment group. The quit rates are the proportions of all subjects initially enrolled (i.e., intent–to-treat analysis) who abstained from Week 4 of the trial through the specified week. Treatment with ZYBAN (150 or 300 mg per day) was more effective than placebo in helping subjects achieve 4-week abstinence. In addition, treatment with ZYBAN (7 weeks at 300 mg per day) was more effective than placebo in helping subjects maintain continuous abstinence through Week 26 (6 months) of the trial.
Table 5. Dose-Response Trial: Quit Rates by Treatment Group

<table>
<thead>
<tr>
<th>Abstinence from Week 4 through Specified Week</th>
<th>Treatment Groups</th>
<th>Placebo (n = 151)</th>
<th>ZYBAN 100 mg/day (n = 153)</th>
<th>ZYBAN 150 mg/day (n = 153)</th>
<th>ZYBAN 300 mg/day (n = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>(95% CI)</td>
<td>%</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Week 7 (4-week quit)</td>
<td></td>
<td>17%</td>
<td>(11-23)</td>
<td>22%</td>
<td>(15-28)</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td>14%</td>
<td>(8-19)</td>
<td>20%</td>
<td>(13-26)</td>
</tr>
<tr>
<td>Week 26</td>
<td></td>
<td>11%</td>
<td>(6-16)</td>
<td>16%</td>
<td>(11-22)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Significantly different from placebo (P ≤ 0.05).

The second trial was a comparator trial conducted at 4 clinical centers. Four treatments were evaluated: ZYBAN 300 mg per day, nicotine transdermal system (NTS) 21 mg per day, combination of ZYBAN 300 mg per day plus NTS 21 mg per day, and placebo. Subjects were treated for 9 weeks. Treatment with ZYBAN was initiated at 150 mg per day while the subject was still smoking and was increased after 3 days to 300 mg per day given as 150 mg twice daily. NTS 21 mg per day was added to treatment with ZYBAN after approximately 1 week when the subject reached the target quit date. During Weeks 8 and 9 of the trial, NTS was tapered to 14 and 7 mg per day, respectively. Quitting, defined as total abstinence during Weeks 4 through 7, was determined by subject daily diaries and verified by expired air carbon monoxide levels. In this trial, subjects treated with any of the 3 treatments achieved greater 4-week abstinence rates than subjects treated with placebo.

Table 6 presents quit rates over time by treatment group for the comparator trial.
Table 6. Comparator Trial: Quit Rates by Treatment Group

<table>
<thead>
<tr>
<th>Abstinence from Week 4 through Specified Week</th>
<th>Placebo (n = 160) % (95% CI)</th>
<th>Nicotine Transdermal System (NTS) 21 mg/day (n = 244) % (95% CI)</th>
<th>ZYBAN 300 mg/day and NTS 21 mg/day (n = 245) % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 7 (4-week quit)</td>
<td>23% (17-30)</td>
<td>36% (30-42)</td>
<td>49% (43-56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>58% (51-64)</td>
</tr>
<tr>
<td>Week 10</td>
<td>20% (14-26)</td>
<td>32% (26-37)</td>
<td>46% (39-52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51% (45-58)</td>
</tr>
</tbody>
</table>

When subjects in this trial were followed out to 1 year, the superiority of ZYBAN and the combination of ZYBAN and NTS over placebo in helping them to achieve abstinence from smoking was maintained. The continuous abstinence rate was 30% (95% CI: 24 to 35) in the subjects treated with ZYBAN and 33% (95% CI: 27 to 39) for subjects treated with the combination at 26 weeks compared with 13% (95% CI: 7 to 18) in the placebo group. At 52 weeks, the continuous abstinence rate was 23% (95% CI: 18 to 28) in the subjects treated with ZYBAN and 28% (95% CI: 23 to 34) for subjects treated with the combination, compared with 8% (95% CI: 3 to 12) in the placebo group. Although the treatment combination of ZYBAN and NTS displayed the highest rates of continuous abstinence throughout the trial, the quit rates for the combination were not significantly higher ($P>0.05$) than for ZYBAN alone.

The comparisons between ZYBAN, NTS, and combination treatment in this trial have not been replicated, and, therefore should not be interpreted as demonstrating the superiority of any of the active treatment arms over any other.

The third trial was a long-term maintenance trial conducted at 5 clinical centers. Subjects in this trial received open-label ZYBAN 300 mg per day for 7 weeks. Subjects who quit smoking while receiving ZYBAN (n = 432) were then randomized to ZYBAN 300 mg per day or placebo for a total trial duration of 1 year. Abstinence from smoking was determined by subject self-report and verified by expired air carbon monoxide levels. This trial demonstrated that at 6 months, continuous abstinence rates were significantly higher for subjects continuing to receive ZYBAN than for those switched to placebo ($P<0.05$; 55% versus 44%).

Quit rates in clinical trials are influenced by the population selected. Quit rates in an unselected population may be lower than the above rates. Quit rates for ZYBAN were similar in subjects with and without prior quit attempts using nicotine replacement therapy.

Treatment with ZYBAN reduced withdrawal symptoms compared with placebo. Reductions on the following withdrawal symptoms were most pronounced: irritability, frustration, or anger;
883 anxiety; difficulty concentrating; restlessness; and depressed mood or negative affect. Depending
884 on the trial and the measure used, treatment with ZYBAN showed evidence of reduction in
885 craving for cigarettes or urge to smoke compared with placebo.

886 Use in Patients with Chronic Obstructive Pulmonary Disease (COPD)
887 ZYBAN was evaluated in a randomized, double-blind, comparator trial of 404 subjects with
888 mild–to-moderate COPD defined as FEV1 greater than or equal to 35%, FEV1/FVC less than or
889 equal to 70%, and a diagnosis of chronic bronchitis, emphysema, and/or small airways disease.
890 Subjects aged 36 to 76 years were randomized to ZYBAN 300 mg per day (n = 204) or placebo
891 (n = 200) and treated for 12 weeks. Treatment with ZYBAN was initiated at 150 mg per day for
892 3 days while the subject was still smoking and increased to 150 mg twice daily for the remaining
893 treatment period. Abstinence from smoking was determined by subject daily diaries and verified
894 by carbon monoxide levels in expired air. Quitters were defined as subjects who were abstinent
895 during the last 4 weeks of treatment. Table 7 shows quit rates in the COPD Trial.

896 Table 7. COPD Trial: Quit Rates by Treatment Group

<table>
<thead>
<tr>
<th>Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 200)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ZYBAN 300 mg/day</td>
</tr>
<tr>
<td>(n = 204)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4-Week Abstinence Period</th>
<th>Placebo % (95% CI)</th>
<th>ZYBAN 300 mg/day % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 9 through 12</td>
<td>12% (8-16)</td>
<td>22%&lt;sup&gt;a&lt;/sup&gt; (17-27)</td>
</tr>
</tbody>
</table>

897<sup>a</sup> Significantly different from placebo (P<0.05).

16 HOW SUPPLIED/STORAGE AND HANDLING
899 ZYBAN sustained-release tablets, 150 mg of bupropion hydrochloride, are purple, round,
900 biconvex, film-coated tablets printed with “ZYBAN 150” in bottles of 60 (NDC 0173-0556-02)
901 tablets and the ZYBAN Advantage Pack® containing 1 bottle of 60 (NDC 0173-0556-01) tablets.
902 Store at room temperature, 20° to 25°C (68° to 77°F); excursions permitted between 15°C and
903 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION
905 Advise the patient to read the FDA-approved patient labeling (Medication Guide).
906 Although ZYBAN is not indicated for treatment of depression, it contains the same active
907 ingredient as the antidepressant medications WELLBUTRIN, WELLBUTRIN SR, and
908 WELLBUTRIN XL. Inform patients, their families, and their caregivers about the benefits and
909 risks associated with treatment with ZYBAN and counsel them in its appropriate use.
A patient Medication Guide about “Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions,” “Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions,” and “What Other Important Information Should I Know About ZYBAN?” is available for ZYBAN. Instruct patients, their families, and their caregivers to read the Medication Guide and assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Advise patients regarding the following issues and to alert their prescriber if these occur while taking ZYBAN.

Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

Inform patients that quitting smoking, with or without ZYBAN, may be associated with nicotine withdrawal symptoms (including depression or agitation), or exacerbation of pre-existing psychiatric illness. Furthermore, some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide when attempting to quit smoking while taking ZYBAN. If patients develop agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to report these symptoms to their healthcare provider immediately.

Suicidal Thoughts and Behaviors

Instruct patients, their families, and/or their caregivers to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Advise families and caregivers of patients to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient’s prescriber or healthcare professional, especially if they are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Severe Allergic Reactions

Educate patients on the symptoms of hypersensitivity and to discontinue ZYBAN if they have a severe allergic reaction to ZYBAN.

Seizure

Instruct patients to discontinue ZYBAN and not restart it if they experience a seizure while on treatment. Advise patients that the excessive use or abrupt discontinuation of alcohol,
benzodiazepines, antiepileptic drugs, or sedatives/hypnotics can increase the risk of seizure. Advise patients to minimize or avoid use of alcohol.

**Angle-Closure Glaucoma**

Patients should be advised that taking ZYBAN can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible (see Warnings and Precautions (5.7)).

**Bupropion-Containing Products**

Educate patients that ZYBAN contains the same active ingredient (bupropion hydrochloride) found in WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL, which are used to treat depression and that ZYBAN should not be used in conjunction with any other medications that contain bupropion (such as WELLBUTRIN, the immediate-release formulation; WELLBUTRIN SR, the sustained-release formulation; WELLBUTRIN XL or FORFIVO XL®, the extended-release formulations; and APLENZIN®, the extended-release formulation of bupropion hydrobromide). In addition, there are a number of generic bupropion HCl products for the immediate-, sustained-, and extended-release formulations.

**Potential for Cognitive and Motor Impairment**

Advise patients that any CNS-active drug like ZYBAN may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Advise patients that until they are reasonably certain that ZYBAN does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery. ZYBAN may lead to decreased alcohol tolerance.

**Concomitant Medications**

Counsel patients to notify their healthcare provider if they are taking or plan to take any prescription or over-the-counter drugs because ZYBAN and other drugs may affect each others’ metabolisms.

**Pregnancy**

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy.

**Precautions for Nursing Mothers**

Advise patients that ZYBAN is present in human milk in small amounts.
Storage Information

Instruct patients to store ZYBAN at room temperature, between 59°F and 86°F (15°C to 30°C) and keep the tablets dry and out of the light.

Administration Information

Instruct patients to swallow ZYBAN tablets whole so that the release rate is not altered. Do not chew, divide, or crush tablets; they are designed to slowly release drug in the body. When patients take more than 150 mg per day, instruct them to take ZYBAN in 2 doses at least 8 hours apart, to minimize the risk of seizures. Instruct patients if they miss a dose, not to take an extra tablet to make up for the missed dose and to take the next tablet at the regular time because of the dose-related risk of seizure. ZYBAN can be taken with or without food. Advise patients that ZYBAN tablets may have an odor.

ZYBAN, WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL are registered trademarks of the GSK group of companies. The other brands listed are trademarks of their respective owners and are not trademarks of the GSK group of companies. The makers of these brands are not affiliated with and do not endorse the GSK group of companies or its products.
MEDICATION GUIDE
ZYBAN® (zi ban)
(bupropion hydrochloride)
Sustained-Release Tablets

Read this Medication Guide carefully before you start taking ZYBAN and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have any questions about ZYBAN, ask your healthcare provider or pharmacist.

IMPORTANT: Be sure to read the three sections of this Medication Guide. The first section is about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with medicines used to quit smoking; the second section is about the risk of suicidal thoughts and actions with antidepressant medicines; and the third section is entitled "What Other Important Information Should I Know About ZYBAN?"

Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with drugs used to quit smoking. Talk to your healthcare provider or your family member’s healthcare provider about:
• all risks and benefits of quit-smoking medicines.
• all treatment choices for quitting smoking.

Some people have had changes in behavior, hostility, agitation, depression, suicidal thoughts or actions while taking ZYBAN to help them quit smoking. These symptoms can develop during treatment with ZYBAN or after stopping treatment with ZYBAN.

If you, your family member, or your caregiver notice agitation, hostility, depression, or changes in thinking or behavior that are not typical for you, or you have any of the following symptoms, stop taking ZYBAN and call your healthcare provider right away:
• thoughts about suicide or dying
• attempts to commit suicide
• new or worse depression
• new or worse anxiety
• panic attacks
• feeling very agitated or restless
• acting aggressive, being angry, or violent
• acting on dangerous impulses

When you try to quit smoking, with or without ZYBAN, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

Before taking ZYBAN, tell your healthcare provider if you have ever had depression or other mental illnesses. You should also tell your healthcare provider about any symptoms you had during other times you tried to quit smoking, with or without ZYBAN.

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Although ZYBAN is not a treatment for depression, it contains bupropion, the same active ingredient as the antidepressant medications WELLBUTRIN®, WELLBUTRIN® SR, and WELLBUTRIN XL®.

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines.

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment.
2. Depression or other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call your healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
Antidepressant medicines can interact with other medicines. Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

It is not known if ZYBAN is safe and effective in children under the age of 18.

What Other Important Information Should I Know About ZYBAN?

Seizures: There is a chance of having a seizure (convulsion, fit) with ZYBAN, especially in people:
- with certain medical problems.
- who take certain medicines.

The chance of having seizures increases with higher doses of ZYBAN. For more information, see the sections “Who should not take ZYBAN?” and “What should I tell my healthcare provider before taking ZYBAN?” Tell your healthcare provider about all of your medical conditions and all the medicines you take. Do not take any other medicines while you are taking ZYBAN unless your healthcare provider has said it is okay to take them.

If you have a seizure while taking ZYBAN, stop taking the tablets and call your healthcare provider right away. Do not take ZYBAN again if you have a seizure.

High blood pressure (hypertension). Some people get high blood pressure that can be severe, while taking ZYBAN. The chance of high blood pressure may be higher if you also use nicotine replacement therapy (such as a nicotine patch) to help you stop smoking (see the section of this Medication Guide called “How should I take ZYBAN?”).

Manic episodes. Some people may have periods of mania while taking ZYBAN, including:
- Greatly increased energy
- Severe trouble sleeping
- Racing thoughts
- Reckless behavior
- Unusually grand ideas
- Excessive happiness or irritability
- Talking more or faster than usual

If you have any of the above symptoms of mania, call your healthcare provider.
• **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while taking ZYBAN, including delusions (believe you are someone else), hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are against you), or feeling confused. If this happens to you, call your healthcare provider.

• **Visual problems.**
  - eye pain
  - changes in vision
  - swelling or redness in or around the eye

Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

• **Severe allergic reactions. Some people can have severe allergic reactions to ZYBAN.** Stop taking ZYBAN and call your healthcare provider right away if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious allergic reaction.

**What is ZYBAN?**

ZYBAN is a prescription medicine to help people quit smoking.

ZYBAN should be used with a patient support program. It is important to participate in the behavioral program, counseling, or other support program your healthcare professional recommends.

Quitting smoking can lower your chances of having lung disease, heart disease, or getting certain types of cancer that are related to smoking.

**Who should not take ZYBAN?**

**Do not take ZYBAN if you:**

- have or had a seizure disorder or epilepsy.
- have or had an eating disorder such as anorexia nervosa or bulimia.
- **are taking any other medicines that contain bupropion, including WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, APLENZIN®, or FORFIVO XL®.** Bupropion is the same active ingredient that is in ZYBAN.
- drink a lot of alcohol and abruptly stop drinking, or take medicines called sedatives (these make you sleepy), benzodiazepines, or anti-seizure medicines, and you stop taking them all of a sudden.
take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.

- **do not take an MAOI within 2 weeks of stopping ZYBAN unless directed to do so by your healthcare provider.**
- **do not start ZYBAN if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your healthcare provider.**
- are allergic to the active ingredient in ZYBAN, bupropion, or to any of the inactive ingredients. See the end of this Medication Guide for a complete list of ingredients in ZYBAN.

**What should I tell my healthcare provider before taking ZYBAN?**

Tell your healthcare provider if you have ever had depression, suicidal thoughts or actions, or other mental health problems. You should also tell your healthcare provider about any symptoms you had during other times you tried to quit smoking, with or without ZYBAN. See “Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions.”

- **Tell your healthcare provider about your other medical conditions, including if you:**
  - have liver problems, especially cirrhosis of the liver.
  - have kidney problems.
  - have, or have had, an eating disorder such as anorexia nervosa or bulimia.
  - have had a head injury.
  - have had a seizure (convulsion, fit).
  - have a tumor in your nervous system (brain or spine).
  - have had a heart attack, heart problems, or high blood pressure.
  - are a diabetic taking insulin or other medicines to control your blood sugar.
  - drink alcohol.
  - abuse prescription medicines or street drugs.
  - are pregnant or plan to become pregnant.
  - are breastfeeding. ZYBAN passes into your milk in small amounts

- **Tell your healthcare provider about all the medicines you take,** including prescription, over-the-counter medicines, vitamins, and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are taking ZYBAN.

**How should I take ZYBAN?**
• Start ZYBAN before you stop smoking to give ZYBAN time to build up in your body. It takes about 1 week for ZYBAN to start working.
• Pick a date to stop smoking that is during the second week you are taking ZYBAN.
• Take ZYBAN exactly as prescribed by your healthcare provider. Do not change your dose or stop taking ZYBAN without talking with your healthcare provider first.
• ZYBAN is usually taken for 7 to 12 weeks. Your healthcare provider may decide to prescribe ZYBAN for longer than 12 weeks to help you stop smoking. Follow your healthcare provider’s instructions.
• **Swallow ZYBAN tablets whole. Do not chew, cut, or crush ZYBAN tablets.** If you do, the medicine will be released into your body too quickly. If this happens you may be more likely to get side effects including seizures. **Tell your healthcare provider if you cannot swallow tablets.**
• ZYBAN tablets may have an odor. This is normal.
• Take your doses of ZYBAN at least 8 hours apart.
• You may take ZYBAN with or without food.
• It is not dangerous to smoke and take ZYBAN at the same time. But, you will lower your chance of breaking your smoking habit if you smoke after the date you set to stop smoking.
• You may use ZYBAN and nicotine patches (a type of nicotine replacement therapy) at the same time, following the precautions below.
  • You should only use ZYBAN and nicotine patches together under the care of your healthcare provider. Using ZYBAN and nicotine patches together may raise your blood pressure, and sometimes this can be severe.
  • Tell your healthcare provider if you plan to use nicotine patches. Your healthcare provider should check your blood pressure regularly if you use nicotine patches with ZYBAN to help you quit smoking.
• If you miss a dose, do not take an extra dose to make up for the dose you missed. Wait and take your next dose at the regular time. **This is very important.** Too much ZYBAN can increase your chance of having a seizure.
• If you take too much ZYBAN, or overdose, call your local emergency room or poison control center right away.

**Do not take any other medicines while taking ZYBAN unless your healthcare provider has told you it is okay.**

**What should I avoid while taking ZYBAN?**
• Limit or avoid using alcohol during treatment with ZYBAN. If you usually drink a lot of alcohol, talk with your healthcare provider before suddenly stopping. If
you suddenly stop drinking alcohol, you may increase your chance of having seizures.

- Do not drive a car or use heavy machinery until you know how ZYBAN affects you. ZYBAN can affect your ability to do these things safely.

**What are possible side effects of ZYBAN?**

ZYBAN can cause serious side effects. See the sections at the beginning of this Medication Guide for information about serious side effects of ZYBAN.

The most common side effects of ZYBAN include:

- trouble sleeping
- stuffy nose
- dry mouth
- dizziness
- feeling anxious
- nausea
- constipation
- joint aches

If you have trouble sleeping, do not take ZYBAN too close to bedtime.

Tell your healthcare provider right away about any side effects that bother you.

These are not all the possible side effects of ZYBAN. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to GlaxoSmithKline at 1-888-825-5249.

**How should I store ZYBAN?**

- Store ZYBAN at room temperature between 59°F and 86°F (15°C to 30°C).
- Keep ZYBAN dry and out of the light.

**Keep ZYBAN and all medicines out of the reach of children.**

**General information about ZYBAN**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZYBAN for a condition for which it was not prescribed.
Do not give ZYBAN to other people, even if they have the same symptoms you have. It may harm them.

If you take a urine drug screening test, ZYBAN may make the test result positive for amphetamines. If you tell the person giving you the drug screening test that you are taking ZYBAN, they can do a more specific drug screening test that should not have this problem.

This Medication Guide summarizes important information about ZYBAN. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZYBAN that is written for health professionals.

For more information about ZYBAN, call 1-888-825-5249.

What are the ingredients in ZYBAN?
Active ingredient: bupropion hydrochloride.

Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide. The tablets are printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

ZYBAN, WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL are registered trademarks of the GSK group of companies.

The other brands listed are trademarks of their respective owners and are not trademarks of the GSK group of companies. The makers of these brands are not affiliated with and do not endorse the GSK group of companies or its products.
Drug Facts

Active ingredient (in each patch)(clear)
Nicotine, 21 mg delivered over 24 hours

Active ingredient (in each patch)(clear)
Nicotine, 14 mg delivered over 24 hours

Active ingredient (in each patch)(clear)
Nicotine, 7 mg delivered over 24 hours

Active ingredient (in each patch)(opaque)
Nicotine, 21 mg delivered over 24 hours

Purpose
Stop smoking aid

Uses
reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings
If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider.
Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Ask a doctor before use if you have

• heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
• high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
• an allergy to adhesive tape or have skin problems because you are more likely to get rashes

Ask a doctor or pharmacist before use if you are

• using a non-nicotine stop smoking drug
• taking a prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

When using this product

• if you have vivid dreams or other sleep disturbances remove this patch at bedtime

Stop use and ask a doctor if

• skin redness caused by the patch does not go away after four days, or if your skin swells, or you get a rash
• irregular heartbeat or palpitations occur
• you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, weakness and rapid heartbeat

Keep out of reach of children and pets.
Used patches have enough nicotine to poison children and pets. If swallowed, get medical help or contact a Poison Control Center right away. Dispose of the used patches by folding sticky ends together. Replace in pouch and discard.

Directions (Clear)
• if you are under 18 years of age, ask a doctor before use
• before using this product, read the enclosed User's Guide for complete directions and other information
• begin using the patch on your quit day
• if you smoke more than 10 cigarettes per day, use according to the following 10-week schedule:

<table>
<thead>
<tr>
<th></th>
<th>STEP 1 (21 mg)</th>
<th>STEP 2 (14 mg)</th>
<th>STEP 3 (7 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-6</td>
<td>Use one 21 mg patch/day</td>
<td>Use one 14 mg patch/day</td>
<td>Use one 7 mg patch/day</td>
</tr>
<tr>
<td>Weeks 7-8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 9-10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• if you smoke 10 or less cigarettes per day, do not use STEP 1 (21 mg). Start with STEP 2 (14 mg) for 6 weeks, then STEP 3 (7 mg) for 2 weeks and then stop.
• steps 2 and 3 allow you to gradually reduce your level of nicotine. Completing the full program will increase your chances of quitting successfully.
• apply one new patch every 24 hours on skin that is dry, clean and hairless. Save pouch for disposing of the patch after use.
• remove backing from patch and immediately press onto skin. Hold for 10 seconds.
• wash hands after applying or removing patch. Throw away the patch by folding sticky ends together. Replace in its pouch and discard. See enclosed User's Guide for safety and handling.
• you may wear the patch for 16 or 24 hours
• if you crave cigarettes when you wake up, wear the patch for 24 hours
• if you have vivid dreams or other sleep disturbances, you may remove the patch at bedtime and apply a new one in the morning
• the used patch should be removed and a new one applied to a different skin site at the same time each day
• do not wear more than one patch at a time
• do not cut patch in half or into smaller pieces
• do not leave patch on for more than 24 hours because it may irritate your skin and loses strength after 24 hours
• it is important to complete treatment. If you feel you need to use the patch for a longer period to keep from smoking, talk to your health care provider.

Directions (Opaque)

• if you are under 18 years of age, ask a doctor before use
• before using this product, read the enclosed User's Guide for complete directions and other information
• stop smoking completely when you begin using the patch
• if you smoke more than 10 cigarettes per day, use according to the following 10-week schedule:

<table>
<thead>
<tr>
<th></th>
<th>STEP 1 (21 mg)</th>
<th>STEP 2 (14 mg)</th>
<th>STEP 3 (7 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-6</td>
<td>Use one 21 mg patch/day</td>
<td>Use one 14 mg patch/day</td>
<td>Use one 7 mg patch/day</td>
</tr>
<tr>
<td>Weeks 7-8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 9-10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• if you smoke 10 or less cigarettes per day, do not use STEP 1 (21 mg). Start with STEP 2 (14 mg) for 6 weeks, then STEP 3 (7 mg) for 2 weeks and then stop.
• steps 2 and 3 allow you to gradually reduce your level of nicotine. Completing the full program will increase your chances of quitting successfully.
• apply one new patch every 24 hours on skin that is dry, clean and hairless. Save pouch for disposing of the patch after use.
• remove backing from patch and immediately press onto skin. Hold for 10 seconds.
• wash hands after applying or removing patch. Throw away the patch by folding sticky ends together. Replace in its pouch and discard. See enclosed User's Guide for safety and handling.
• you may wear the patch for 16 or 24 hours
• if you crave cigarettes when you wake up, wear the patch for 24 hours
• if you have vivid dreams or other sleep disturbances, you may remove the patch at bedtime and apply a new one in the morning
• to avoid possible burns, remove patch before undergoing any MRI (magnetic resonance imaging) procedures
• the used patch should be removed and a new one applied to a different skin site at the same time each day
• do not wear more than one patch at a time
• do not cut patch in half or into smaller pieces
• do not leave patch on for more than 24 hours because it may irritate your skin and loses strength after 24 hours
• it is important to complete treatment. If you feel you need to use the patch for a longer period to keep from smoking, talk to your health care provider.
Other information

- store at 20-25°C (68-77°F)

Inactive ingredients (Clear)
ethylenic vinyl acetate-copolymer, polyisobutylene and high density polyethylene between clear polyester backings

Inactive ingredients (Opaque)
ethylenic vinyl acetate-copolymer, polyisobutylene and high density polyethylene between pigmented and clear polyester backings

Questions or comments?
call toll-free 1-800-834-5895 (English/Spanish) weekdays (9:00 a.m. - 4:30 p.m. ET)

Principal Display Panel
NDC 0135-0194-02
NicoDerm®
CQ®
Nicotine Transdermal System 21 mg Delivered over 24 Hours
STOP SMOKING AID
CLEAR PATCH
EXTENDED RELEASE 24 HOURS
SMARTCONTROL® TECHNOLOGY
NEW DIRECTIONS FOR USE
- Keep Using if You Slip Up and Have a Cigarette
- Use Beyond 10 Weeks if Needed to Quit
STEP 1
IF YOU SMOKE MORE THAN 10 CIGARETTES A DAY, START WITH STEP 1
10 OR LESS CIGARETTES A DAY, START WITH STEP 2
ACTUAL SIZE
14 clear patches (2-week kit)
What is the NicoDerm® CQ® Patch and How is it Used?
NicoDerm®CQ® is a small, nicotine-containing patch. When you put on a NicoDerm®CQ® patch, nicotine passes through the skin and into your body. NicoDerm®CQ® is very thin and uses special material to control how fast nicotine passes through the skin. Unlike the sudden jolts of nicotine delivered by cigarettes, the amount of nicotine you receive remains relatively smooth throughout the 16 or 24 hour period you wear the NicoDerm®CQ® patch. This helps to reduce cravings you may have for nicotine.
READ THE LABEL
- Not for sale to those under 18 years of age.
- Proof of age required.
- Not for sale in vending machines or from any source where proof of age cannot be verified.

NICODERM, NICODERM BURST DESIGN, CQ, COMMITTED QUITTERS, MAN ON STEP Device, SMARTCONTROL are trademarks owned by or licensed to the GSK group of companies.


Page 3 of 14
For more information and for a FREE individualized stop smoking program, please visit www.nicodermcq.com or see inside for more details.

U.S. Patent No. 7,622,136
8,075,911

Read carton and enclosed User's Guide before using this product. Keep this carton and User's Guide. They contain important information

Includes Committed Quitters® Program enrollment offer and User's Guide.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. Complete the full treatment program, applying a new patch every day.
3. Use with a support program as described in the enclosed User's Guide.

For your family's protection, NicoDerm® CQ® patches are supplied in child resistant pouches. Do not use if individual pouch is open or torn.

Manufactured by ALZA Corporation,
Vacaville, CA 95688 for

GlaxoSmithKline

Consumer Healthcare, L.P.
Moon Township, PA 15108

©2014 GSK
102839XB
FDA Briefing Document

Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee

October 16, 2014

Chantix and Serious Neuropsychiatric Adverse Events
DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought varenicline and the risk of serious neuropsychiatric adverse events to this Advisory Committee in order to gain the Committee’s insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
Varenicline and the Risk of Serious Neuropsychiatric Adverse Events

October 16, 2014

Integrated Summary Memorandum

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>2</td>
</tr>
<tr>
<td>Regulatory History</td>
<td>4</td>
</tr>
<tr>
<td>AERS Reviews- 2008</td>
<td>4</td>
</tr>
<tr>
<td>Risk Evaluation and Mitigation Strategy (REMS)/ Postmarketing Requirement (PMR) Clinical Trial</td>
<td>6</td>
</tr>
<tr>
<td>Regulatory Requirements and Guidance Recommendations for the BOXED WARNING Section and Other Relevant Sections of the Labeling</td>
<td>9</td>
</tr>
<tr>
<td>Prescribing Information</td>
<td>9</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>9</td>
</tr>
<tr>
<td>Boxed Warning</td>
<td>9</td>
</tr>
<tr>
<td>Removal of a Boxed Warning</td>
<td>10</td>
</tr>
<tr>
<td>Warnings and Precautions</td>
<td>10</td>
</tr>
<tr>
<td>Contraindications</td>
<td>11</td>
</tr>
<tr>
<td>Usage of Smoking Cessation Prescription Products</td>
<td>12</td>
</tr>
<tr>
<td>Update on Reporting of Neuropsychiatric Adverse Events to FAERS</td>
<td>13</td>
</tr>
<tr>
<td>Division of Epidemiology II Summary of Observational Studies Examining the Relationship Between Varenicline and Neuropsychiatric Adverse Events</td>
<td>14</td>
</tr>
<tr>
<td>Division of Biostatistics VII Summary of Meta-analyses</td>
<td>17</td>
</tr>
<tr>
<td>Discussion/ Interim actions</td>
<td>19</td>
</tr>
</tbody>
</table>
Introduction

Varenicline, a partial α4β2 acetylcholine nicotinic receptor agonist, was approved in May 2006 in the United States “as an aid to smoking cessation treatment.” Varenicline’s approval was based on six placebo- and active-controlled trials of 6 to 12 weeks duration in over 3500 chronic cigarette smokers (average 21 cigarettes per day and average smoking history of 25 years).

Varenicline’s original approved labeling included a listing of the following neuropsychiatric adverse events in the ADVERSE REACTIONS section: insomnia, abnormal dreams, and nightmares. As information about serious neuropsychiatric adverse events emerged in the postmarketing period, the varenicline labeling evolved to incorporate this information:

- **January 2008:** Based on data from spontaneous postmarketing reports of serious neuropsychiatric adverse events, FDA determined that varenicline was associated with serious neuropsychiatric adverse events including suicidal ideation, suicidal behavior, changes in behavior, agitation, depressed mood, and worsening of preexisting psychiatric illness. A new warning was added to the WARNINGS section describing these serious neuropsychiatric adverse events; and recommendations were added for patients, their families, and caregivers to monitor for these serious neuropsychiatric adverse events during varenicline treatment.

- **May 2008:** FDA utilized two postmarketing safety authorities acquired under the FDA Amendments Act of 2007. FDA required Pfizer to implement a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of varenicline as an aid to smoking cessation outweighed its risk of serious neuropsychiatric adverse events. The REMS required a Medication Guide to ensure varenicline-treated patients are aware of the risk of serious neuropsychiatric adverse events. Additionally, FDA issued a postmarketing requirement (PMR) to Pfizer to conduct a randomized controlled trial to assess the risk of serious neuropsychiatric adverse events with varenicline.

- **July 2009:** A BOXED WARNING section was added to the varenicline labeling that described information already included in the WARNINGS section concerning the serious neuropsychiatric adverse events and recommendations to patients and their caregivers to discontinue varenicline if these serious neuropsychiatric adverse events occurred. Furthermore, the WARNINGS section was updated to include additional varenicline-associated serious neuropsychiatric adverse events including hostility, mania, psychosis, hallucinations, and paranoia.

In April 2014, Pfizer submitted a labeling supplement for varenicline (Chantix, NDA 21-928) proposing changes to the varenicline labeling relating to the risk of serious neuropsychiatric adverse events. In the cover letter of this supplement, Pfizer asserts that “…since 2009, more reliable data on the NPS [neuropsychiatric] safety of Chantix have become available, including meta-analyses of placebo-controlled clinical trials and data
from observational studies comparing varenicline to other smoking cessation pharmacotherapies. As presented in this submission, these data do not support an association between treatment with Chantix and serious NPS [neuropsychiatric] events.”

Based on Pfizer-conducted meta-analyses of randomized controlled trials of varenicline and a Pfizer-conducted review of five publications of observational studies of patients treated with varenicline compared to patients treated with nicotine replacement therapy (NRT) or bupropion, Pfizer proposed the following major changes to the varenicline labeling:

- **Highlights of Prescribing Information:**
  - Remove Boxed Warning on Serious Neuropsychiatric Events
  - Under Warnings and Precautions, add a Warning on Serious Neuropsychiatric Events in bolded font
- **BOXED WARNING section of the Full Prescribing Information (FPI):**
  - Remove the box (i.e., remove the single black line) around the Warning on Serious Neuropsychiatric Events and add summaries of information from neuropsychiatric meta-analyses of clinical trial data and observational studies
- **WARNINGS AND PRECAUTIONS section of the FPI**
  - In section 5.1 WARNINGS AND PRECAUTIONS / Neuropsychiatric Symptoms and Suicidality, add information from neuropsychiatric meta-analyses of clinical trial data and observational studies

In the subsequent sections of this briefing document, the following is provided:

- Regulatory history leading to the boxed warning, REMS, and PMR for serious neuropsychiatric adverse events;
- Regulatory requirements and guidance recommendations for BOXED WARNING section and other relevant sections of the labeling;
- Utilization data for varenicline and other smoking cessation treatments;
- Update on neuropsychiatric adverse events reported to FAERS;
- Summary of FDA review of epidemiological studies cited by Pfizer; and
- Summary of FDA review of RCT meta-analyses submitted by Pfizer
Regulatory History

Chantix® (varenicline) is a partial α4β2 acetylcholine nicotinic receptor agonist approved in May 2006 as an aid to smoking cessation. The treatment regimen is 1 mg twice daily for 12 weeks (with an initial one-week titration). A second 12-week course may be taken to increase the chance of maintenance of abstinence.

In May 2007, the European Medicines Agency (EMA- previously, EMEA) informed FDA that they were investigating a signal of suicidality-related adverse events. A chronology of the subsequent regulatory actions and public communications that followed is shown below.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 2006</td>
<td>NDA approval for varenicline in the U.S. (trade name “Chantix”)</td>
</tr>
<tr>
<td>September 2006</td>
<td>Approval in the European Union (trade name “Champix”)</td>
</tr>
<tr>
<td>May 2007</td>
<td>European Medicines Agency informed FDA that they were investigating a signal of suicidal-related events with varenicline and had asked Pfizer to submit a postmarketing suicidal-event analysis.</td>
</tr>
<tr>
<td>Nov 2007</td>
<td>Information added to ADVERSE REACTIONS section of labeling; Early communication of an ongoing safety review</td>
</tr>
<tr>
<td>Jan 2008</td>
<td>Serious neuropsychiatric adverse events information upgraded to the WARNINGS AND PRECAUTIONS section of the labeling</td>
</tr>
<tr>
<td>Feb 2008</td>
<td>Public health advisory issued</td>
</tr>
<tr>
<td>April 2008</td>
<td>Center Director briefing concerning varenicline and serious neuropsychiatric adverse events: discussed the benefits of varenicline to help patients achieve smoking cessation vs. the risk of serious neuropsychiatric adverse events</td>
</tr>
<tr>
<td>May 2008</td>
<td>Added MedGuide-only REMS; issued a postmarketing required study/clinical trial; Updated public health advisory; FAA bans use of varenicline by pilots and air traffic controllers</td>
</tr>
<tr>
<td>July 2009</td>
<td>Added BOXED WARNING section to varenicline and bupropion labeling; Public health advisory issued regarding addition of boxed warning to both varenicline and bupropion</td>
</tr>
<tr>
<td>Oct 2011</td>
<td>Drug Safety Communication issued reporting the results of two FDA-sponsored epidemiology studies that evaluated the risk of serious neuropsychiatric adverse events associated with varenicline</td>
</tr>
</tbody>
</table>

AERS Reviews- 2008

Prior to the addition of the boxed warning for serious neuropsychiatric adverse events, the Division of Adverse Event Analysis II1 completed two reviews of AERS2 cases- one

1 The Division of Adverse Event Analysis II is now called the “Division of Pharmacovigilance II”.
2 The FDA Adverse Events Reporting System was called “Adverse Event Reporting System (AERS)” at the time these reviews were done.
focused on suicidality events (finalized July 2008) and the other focused on neuropsychiatric adverse events not related to suicidality (finalized Dec 2008).

Briefly, the review of suicidality events showed that from initial marketing through November 2007, AERS had 262 cases of suicidal-related events for the smoking cessation drugs (varenicline, n=153; bupropion\(^3\), n=75; transdermal nicotine, n=34). Varenicline had a higher proportion of cases for suicidal ideation (76%) vs. bupropion (61%) or nicotine (47%) and a lower proportion of suicide (attempt and completed) or other self-injurious behavior (24%) than the other drugs (bupropion 39%; transdermal nicotine 53%). Median time to event was 8-14 days.

Varenicline had the largest proportion of reports (24%) in which it was explicitly stated that the suicidal event(s) were a first-time significant behavior change from the past, followed by bupropion (15%) and nicotine (none). Varenicline cases had the most reports that described pre-existing disease worsening (17%) compared to nicotine (12%) and bupropion (8%); depression was the most common pre-existing psychiatric condition that worsened for all three drugs. The overall conclusion was that AERS data suggested a possible association between suicidal events and the use of varenicline and bupropion, given that there were postmarketing cases of positive dechallenge and a few positive rechallenges, a close temporal relationship between the event and drug use, and the occurrence of suicidal events in patients without any psychiatric history.

A recommendation was made to add a BOXED WARNING section to highlight the risk of serious neuropsychiatric adverse events and to request a PMR to determine the incidence of serious neuropsychiatric adverse events with varenicline, especially in patients with preexisting psychiatric disorders. For Zyban (bupropion), which was included as a comparator in this review, there was a similar recommendation to add language to the already existing BOXED WARNING section about the risk of suicidality in those using bupropion for smoking cessation.

A review of AERS cases describing neuropsychiatric adverse events other than suicidality was completed in December 2008. Because of the increased awareness that there was “stimulated” reporting\(^4\) starting in September 2007, this review was conducted from market approval through August 2007. Additionally, because there were few evaluable cases reported with nicotine replacement therapies (NRT) the review focused on only case reports for varenicline and bupropion.

For both varenicline and bupropion, anxiety and depression were the two most commonly reported events. For both drugs, ~20% of the cases reported psychosis/mania or aggression-events. For varenicline, the most common event for the psychosis/mania and aggression groups was hallucination and aggression respectively; for bupropion it was

\(^3\) Bupropion was approved for the treatment of depression as Wellbutrin about a decade before it was approved as Zyban for smoking cessation. In order to limit the review to those exposed to bupropion for the treatment of smoking cessation, included cases had to either reference bupropion by the trade name Zyban, or mention the indication of smoking cessation in the report.

\(^4\) Stimulated reporting is an increase in adverse event reporting that often occurs following any risk communication or media attention to a particular safety issue due to enhanced awareness.
paranoia and hostility respectively. There was a temporal association between the two drugs and all groups of events with a median onset time between three and seven days. Positive dechallenge was reported in 33% and 63% of the varenicline and bupropion cases respectively.

For all event groups, patients with no reported psychiatric history ranged from 17 to 33% for varenicline and 13 to 30% for bupropion. For all event groups, patients with no reported concomitant psychiatric medications ranged from 4% to 13% for varenicline and 0 to 25% for bupropion. There were more cases with varenicline (29-33%) that reported a behavioral change from the patient’s past (i.e., either new experience or disease worsening) than with bupropion (0-9%).

More varenicline patients (27%-53%) had a history of psychiatric disease than bupropion (0%-20%); however, there was a portion of the bupropion population for which unknown medical history was very high (78%). The most commonly reported psychiatric history across the case series was depression and bipolar disorder. Psychiatric medication use ranged from 13% to 73% for varenicline and 21% to 70% for bupropion.

The recommendations included enhancements to the proposed BOXED WARNING section and other parts of labeling to warn of the risk of these other neuropsychiatric adverse events.

Dr. Celia Winchell, Medical Team Leader for Addiction Products, stated in her memo to the file dated 12/12/08, the following rationale for a BOXED WARNING section for varenicline and bupropion, “The need for a boxed warning was discussed extensively at the highest levels of Center management and it was determined that the events met criteria for placement in a boxed warning. Specifically, the events are of a serious nature and have adverse consequences that can be prevented by close monitoring.”

**Risk Evaluation and Mitigation Strategy (REMS)/ Postmarketing Requirement (PMR) Clinical Trial**

As the understanding of the serious neuropsychiatric adverse events with varenicline evolved, it was determined that a REMS was necessary to ensure that the benefits of varenicline outweighed the risks. The May 16, 2008, letter that required the REMS also included issuance of a postmarketing requirement (PMR) for a clinical study or trial to assess the known serious risk of neuropsychiatric adverse events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions. The clinical study or trial was being required because it was determined that neither an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA nor the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA would be sufficient to assess the known serious risk of neuropsychiatric adverse events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions related to the use of varenicline products. A similar REMS and PMR was required of another smoking cessation product, bupropion (Zyban).
After internal deliberation and discussion with Pfizer and GlaxoSmithKline (sponsor of bupropion), further guidance on the PMR was issued in a letter dated June 2, 2009. As seen in the description below, FDA determined that a randomized controlled clinical trial would be required to meet the PMR goals:

A large randomized, double-blind, active- and placebo-controlled trial to compare the risk of clinically significant neuropsychiatric adverse events, including but not limited to suicidality, in individuals using varenicline, bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation over 12 weeks of treatment, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric adverse events compared to individuals without prior history of psychiatric disorders while using varenicline as an aid to smoking cessation. The study should be sufficiently powered to adequately assess clinically significant neuropsychiatric adverse events with each treatment and in both of the two subgroups (i.e., with and without psychiatric disorders).

After a series of discussions internally and with the sponsors, the PMR protocol was found acceptable around July 2010 (see Attachment 1 for the protocol). In recognition of the variable and ill-defined nature of the neuropsychiatric adverse events reported, and the difficulty of capturing such events in traditional MedDRA coding\(^5\), a composite endpoint was developed specifically for the PMR trial and instruments to solicit relevant events were included in the trial procedures. The primary safety endpoint is the occurrence of at least one treatment-emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide.

Two interim analyses were planned for the RCT, the first after half of the patients completed 20 weeks of the trial, and the second when 75% of patients completed the trial to that point. Pfizer’s description of the first interim analysis (submitted October 29, 2013) follows below:

IA1 was designed to assess data on the first 4,000 subjects (50% enrollment) randomized into the study (please refer to Section 2 of the interim analysis plan). The second interim analysis is planned for the first 6,000 subjects randomized (75% enrollment).

The IA1 database snapshot occurred on 5 August 2013 after all IA1 subjects had either completed the Week 20 visit or had discontinued from the study prior to the Week 20 visit. The Week 20 visit was the first scheduled in-clinic visit after the

---

\(^5\) MedDRA (Medical Dictionary for Regulatory Activities) is an international standardized lexicon of medical terms used to code adverse events. MedDRA was developed by the ICH (International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and released in 1999. MedDRA contains about 21,000 different preferred terms (PTs, e.g., nausea, hypotension) for various adverse events. These PTs are vertically grouped into 3 levels. The highest level for a PT is the System Organ Class, of which there are 26 (e.g., Cardiac disorders, Infections and infestations). http://www.meddra.org/sites/default/files/guidance/ file/intguide_17_1_english.pdf
treatment-emergent period (the basis of the primary study endpoint). Of the 4,001 randomized subjects captured in this snapshot, 3,921 also had data confirming at least one dose of study drug. The remaining subjects either did not receive study drug or had missing data for study drug dosing.

The results of this blinded, pooled 50% interim analysis were completed and provided to the unblinded statistician for the IDMC on 12 September 2013. The rate of the primary neuropsychiatric event endpoint was 3.98% (156/3,921). This exceeded the 3.5% threshold specified in the protocol.

As a result, the study will continue enrollment as planned until the results of the second planned interim analysis (IA2) become available. IA2 will be conducted 20 weeks after 6,000 (75%) of the subjects have been randomized.

Pfizer’s description of the second interim analysis (submitted June 10, 2014) follows below:

IA2 was planned to include data from the first 75% (6,000) subjects randomized into the study. The IA2 database snapshot occurred on 24 April 2014 after all IA2 subjects had either completed the Week 20 visit or had discontinued from the study prior to the Week 20 visit. The Week 20 visit was the first scheduled in-clinic visit after the treatment-emergent period (the basis of the primary study endpoint). This snapshot included 6,005 subjects.

The results of this pooled 75% interim analysis were completed and provided to the Independent Data Monitoring Committee (IDMC) on 19 May 2014. In addition to their standard safety review, the IDMC reviewed actual and projected neuropsychiatric adverse event rates for each of the 4 treatment arms in both the neuropsychiatric and the non-neuropsychiatric cohorts and the total population to establish if the planned sample size of 8,000 was sufficient. Their recommendation was to continue the study to the target enrollment of 8,000 as specified in the protocol. The blinded rate of the primary neuropsychiatric adverse event endpoint in the total population was 4.5% (268/6005).

In July 2014, FDA was informed by Pfizer that the RCT completed enrollment, and that the final study report is expected to be submitted in the third quarter of 2015.
Regulatory Requirements and Guidance Recommendations for the BOXED WARNING Section and Other Relevant Sections of the Labeling

A familiarity with the pertinent regulatory requirements and guidance recommendations of the prescribing information is useful for determining 1) If the meta-analyses and observational study data about the risk of serious neuropsychiatric adverse events support removal of the boxed warning in the varenicline labeling; and 2) How the risk information about serious neuropsychiatric adverse events should be communicated in the varenicline labeling.

Prescribing Information
The prescribing information is written for healthcare providers and must:6

- Contain a summary of the essential scientific information needed for the safe and effective use of the drug,
- Be informative and accurate and neither promotional in tone nor false or misleading in any particular, and
- Be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

Adverse Reactions
For the purposes of prescription drug labeling, an adverse reaction (AR) is an undesirable effect reasonably associated with the use of the drug. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.7

Boxed Warning
The BOXED WARNING section of the labeling must be the first section in the FULL PRESCRIBING INFORMATION, must be surrounded by a “box” (i.e., a single black line), and must contain “contraindications or serious warnings, particularly those that may lead to death or serious injury.”8 This section must briefly explain the clinically significant adverse reaction or risk and refer to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS sections. A boxed warning is ordinarily used to highlight for prescribers one of the following situations:9

---

6 See 21 CFR 201.56(a)
7 See 21 CFR 201.57(c)(7)
8 See 21 CFR 201.57(c)(1)
9 See the Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling guidance
• There is an AR so serious\textsuperscript{10} in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling AR) that it is essential that it be considered in assessing the risks and benefits of using a drug;

• There is a serious AR\textsuperscript{7} that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation); or

• FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted [e.g., certain Elements to Assure Safe Use (ETASU) under Risk Evaluation and Mitigation Strategies (REMS)].

A boxed warning can also be used in other situations:\textsuperscript{8}

• To highlight a warning that is especially important to the prescriber.

• For a drug that poses risk-benefit considerations that are unique among drugs in a drug class (e.g., when the drug is the only one in its class to have a particular clinically significant AR or risk and is indicated as a second line therapy because of that clinically significant AR or risk).

Boxed warnings are more likely to be based on observed serious AR, but there are instances when a boxed warning based on an expected AR would be appropriate. For example, an Embryofetal Toxicity boxed warning would be appropriate for a drug based on evidence in humans or animals that drugs in its pharmacologic class pose a serious risk of developmental toxicity during pregnancy, even though no AR was seen with the drug.\textsuperscript{8}

**Removal of a Boxed Warning**

There is no specific regulation or guidance that has established criteria to remove a Boxed Warning. However, if the criteria\textsuperscript{8} for including a boxed warning are no longer met, it is reasonable to remove it.

**Warnings and Precautions**

The WARNINGS AND PRECAUTIONS section should describe serious or clinically significant AR that have occurred with the drug or risks that are expected to occur (e.g., based on the drug class; animal data raise substantial concern about the potential occurrence of the AR in humans). This section “must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.”\textsuperscript{11} The following factors can be used in determining if AR are clinically significant:\textsuperscript{8}

\textsuperscript{10}For the purposes of prescription drug labeling, a serious AR is an AR that results in the following outcomes: Death, life-threatening AR, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. Furthermore, AR may be considered serious if they jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed in this definition. See the *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling* guidance.

\textsuperscript{11}See 21 CFR 201.57(c)(6)
• The relative seriousness of the disease or condition being treated.
  o Non-serious AR caused by drugs intended to treat minor, self-limiting conditions may be considered clinically significant.
  o However, those same AR caused by drugs intended to treat serious or life-threatening conditions (e.g., malignancies) may be considered much less clinically significant and not appropriate for inclusion in this section.
• A high absolute risk or rate of AR occurrence
• An AR that may lead to a potentially serious outcome unless an action is taken (e.g., dosage reduction or discontinuation) to prevent a serious outcome
• An AR that could be prevented or managed with appropriate patient selection, monitoring, or avoidance of concomitant therapy.
• An AR that can significantly affect patient compliance particularly when non-compliance has potentially serious consequences.

Each WARNINGS AND PRECAUTIONS subsection should include a succinct description of a topic and should contain the following (if known):8,11

• A succinct description of the serious or clinically significant AR or risk
• Known risk factors for the AR
• Outcome
• Numerical estimate of the risk or AR rate
• Steps to take to prevent, mitigate, monitor, or manage the AR

**Contraindications**

The CONTRAINDICATIONS section must describe situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal AR) clearly outweighs any possible therapeutic benefit. These situations include the use of the drug in a subpopulation of patients that have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed.12 Contraindications may be based on:8

• Observed AR
• Anticipated AR supported by data (e.g., pharmacology, chemistry, or drug class data; or animal data) and the likelihood and severity of the AR

12 See 21 CFR 201.57(c)(5)
Usage of Smoking Cessation Prescription Products

The overall sales of various smoking cessation products from manufacturer to various distributors, for both prescription (Rx) and over-the-counter (OTC) products, decreased by about 36% from approximately 9.5 million bottles/packages sold in 2009 to 6.1 million bottles/packages sold in 2013. During 2013, prescription products accounted for approximately 52% (3.1 million bottles/packages) and OTC products accounted for approximately 48% (2.9 million bottles/packages) of the total sales of smoking cessation products.\(^{13}\) See Attachment 2 for a full review of the patterns of smoking cessation product usage.

Among prescription smoking cessation products, varenicline accounted for the vast majority of utilization. The number of prescriptions dispensed for varenicline increased from approximately 30 prescriptions dispensed during the 2nd quarter of 2006 (approval in May 2006) to a peak of approximately 2 million prescriptions dispensed in the 4th quarter of 2007 and then eventually decreased to approximately 531,000 prescriptions dispensed in the 1st quarter of 2014.\(^{14}\)

The number of patients receiving dispensed prescriptions for varenicline decreased from approximately 3.9 million patients in 2007 to approximately 1.2 million patients in 2013. Patients aged 45-64 years accounted for majority of the patients receiving a dispensed prescription for varenicline. Females accounted for 53-56% of patients and males accounted for 44-47% of the total patients receiving a dispensed prescription for varenicline during the time period examined. Utilization of Zyban® (brand and generic bupropion), Nicotrol® inhaler and Nicotrol® nasal spray also decreased over time.\(^{15}\)

The overall number of packages of OTC nicotine replacement products sold to consumers through retail settings fluctuated during the time examined with approximately 1.7 million packages sold in the 4th quarter of 2013. Among the OTC nicotine replacement products, the gum formulation accounted for the highest proportion of the total retail sales followed by lozenges and patches.\(^{16}\)

\(^{13}\) IMS Health, IMS National Sales Perspectives\(^\text{TM}\), Data Extracted April 2014
\(^{14}\) IMS Health, National Prescription Audit (NPATM), Data Extracted August 2014
\(^{15}\) IMS Health, Vector One®: Total Patient Tracker, Data Extracted May and August 2014
\(^{16}\) IMS Health, OTC International Market Tracking (OTCIMS), Data Extracted May 2014
Update on Reporting of Neuropsychiatric Adverse Events to FAERS

The Division of Pharmacovigilance II conducted a case-level review of recently (2013-2014) submitted FAERS data for varenicline and serious neuropsychiatric adverse events, as requested by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) in support of the October 16, 2014, Advisory Committee meeting. This case-level review followed an assessment of overall trends in case reporting of serious neuropsychiatric adverse events to FAERS for the years 2008-2013. These assessments provide an update to two prior reviews completed by the Division in 2008 (Attachments 5 and 6).17,18

A total of 105 FAERS cases of varenicline and serious psychiatric events were found during the time period of 1/1/13 to 6/30/14 where a significant behavior change in association with varenicline was stated or implied. These cases consisted of suicidality, psychosis, mania, aggression or other neuropsychiatric adverse events (e.g., depression), and were consistent with the findings of the 2008 reviews, that led to the current Boxed Warning. Characteristics of the events in this review as well as the prior reviews,17,18 include:

- Neuropsychiatric adverse events occurred in patients with and without a history of psychiatric disorders
- Most events occurred while patients were on varenicline; however, some followed discontinuation of varenicline
- There was a relatively short time to event onset (median time of 10 days from starting varenicline to onset of neuropsychiatric symptoms)
- Reports included cases of resolution of neuropsychiatric adverse events following varenicline discontinuation (positive dechallenge), as well as recurrence of neuropsychiatric adverse events when varenicline was restarted (positive rechallenge)

Based upon this updated review, no changes in the varenicline label for serious neuropsychiatric adverse events in the post marketing setting are recommended.

17Pollock M, Mosholder A, Lee J. Governale L. Suicidality associated with varenicline, bupropion, and nicotine transdermal patch. 7/16/08; OSE RCM #2007-2425.
18Pollock M, Mosholder A, Ju J. Psychiatric events (including suicides) associated with varenicline and bupropion. 12/8/08; OSE RCM# 2008-1291.
Division of Epidemiology II Summary of Observational Studies Examining the Relationship Between Varenicline and Neuropsychiatric Adverse Events

The sponsor identified five observational studies of varenicline-associated neuropsychiatric risk (four publications and one unpublished study), including three which examined the association between varenicline and risk of neuropsychiatric medical encounters (i.e., hospitalizations, emergency room visits, and outpatient visits) and two which investigated the association between varenicline and risk of suicide, non-fatal self-harm, and initiation of an antidepressant (as a proxy of incident depression). Please see the Division of Epidemiology II’s (DEPI-II) review of the labeling supplement regarding neuropsychiatric adverse events associated with varenicline (Attachment 7) for a summary of each reviewed study. One of the studies (Thomas et al.) was an expansion of an earlier study (Gunnell et al.).

All the reviewed observational studies were based on population-level data reflecting the real-world smoking cessation product user population. Their inclusion of patients with a history of neuropsychiatric disorders extends the generalizability of the findings, because that population was excluded in most clinical trials conducted to date. The studies also all attempted to control for confounding by employing appropriate design and analytical approaches. Please see Table 1 for a summary of main study findings of the reviewed observational studies.

Table 1 Main study findings of the observational studies on varenicline and risk for neuropsychiatric adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Analyses</th>
<th>Varenicline (N event/Total/IR*)</th>
<th>Reference group</th>
<th>Fully-adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>NRT (N event/total/IR*)</td>
<td>Bupropion (N event/total/IR*)</td>
<td></td>
</tr>
<tr>
<td>Meyer et al. 2013</td>
<td>NPS hospitalization (primary diagnosis) in 30 days</td>
<td>New users, PS-matched</td>
<td>16/10,814/18</td>
<td>14/10,814/16</td>
<td>1.14 (0.56-2.34)</td>
</tr>
<tr>
<td>Meyer et al. 2013</td>
<td>NPS hospitalization (any diagnosis) in 30 days</td>
<td>New users, PS-matched</td>
<td>34/10,710/39</td>
<td>43/10710/49</td>
<td>0.79 (0.50-1.24)</td>
</tr>
<tr>
<td>Meyer et al. 2013</td>
<td>NPS Outpatients visits in 30 days</td>
<td>New users, PS-matched</td>
<td>234/10710/269</td>
<td>327/10710/378</td>
<td>0.71 (0.60-0.84)</td>
</tr>
<tr>
<td>VA study Unpublished</td>
<td>NPS hospitalization (primary diagnosis) in 30 days</td>
<td>New users, PS-matched</td>
<td>16/14,131/16</td>
<td>21/14,131/21</td>
<td>0.76 (0.40-1.46)</td>
</tr>
<tr>
<td>VA study Unpublished</td>
<td>NPS hospitalization (primary diagnosis) in 30 days</td>
<td>Prevalent users, PS-matched</td>
<td>29/12,258/29</td>
<td>94/24,185/47</td>
<td>0.74 (0.49-1.14)</td>
</tr>
</tbody>
</table>

19 Both Thomas et al and Gunnel et al studies were based on the same source data (CPRD) with overlapping time-frames, but Thomas et al included a longer time-frame and linked to two other data sources to enhance outcome ascertainment
As depicted in Table 1, the 95% confidence interval of the outcome risk estimates mostly included 1.0. The only findings that achieved statistical significance are the reduced risk of outpatient neuropsychiatric visits (the VA study) and the reduced risk of initiation of antidepressant therapy (the Thomas et al. study) associated with varenicline (Table 1). However, these two outcome measures are not specific in measuring treatment emergent neuropsychiatric adverse events related to varenicline. Outpatient neuropsychiatric visits may be simply capturing pre-existing psychiatric comorbidities, rather than treatment emergent psychiatric events. Because antidepressants are also used to treat multiple other disorders, including non-psychiatric indications, prescribing of antidepressants cannot be viewed as a specific measure of incident depression.

Although none of the reviewed studies observed a significant increase in the risk of serious neuropsychiatric adverse events (i.e., neuropsychiatric hospitalization or emergency room visit, fatal or non-fatal self-harm) between varenicline and the comparator (bupropion or nicotine replacement therapy), they do not provide reassuring evidence of the absence of risk. Please see DEPI-II’s review, for details of the specific limitations of these studies.

Briefly, the following study limitations have been identified:

- the incompleteness of ascertainment of the examined outcomes;
• the lack of validation of the diagnostic codes used to identify the examined outcomes;
• the use of bupropion (another smoking cessation drug with neuropsychiatric risk) as a comparator;
• the likely presence of “channeling bias” (sicker patients being channeled away from treatment with varenicline);
• the likely presence of residual confounding between varenicline users and nicotine replacement therapy (NRT) users; and
• the limited statistical power.

The observational studies reviewed provided evidence of insufficient quality to either rule in or rule out an increased risk of suicide, non-fatal self-harm, or neuropsychiatric hospitalizations associated with varenicline use. The available observational data also cannot be used to “cap” the varenicline-associated risk for neuropsychiatric outcomes due to the high probability of under-ascertainment of these outcomes in the existing studies. Therefore, the true upper limit of the 95% confidence interval for varenicline-associated neuropsychiatric risk is unknown based on these data. It is our hope that the required post-marketing clinical trial that the sponsor is conducting may allow for more complete risk ascertainment, even though the generalizability of the findings may be limited.
Division of Biostatistics VII Summary of Meta-analyses

A meta-analysis was conducted to evaluate the risk of psychiatric events associated with varenicline relative to placebo in two sets of trials:

- A set of 5 Phase III/IV clinical trials that captured the risk of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS). This set of trials is referred to as the “5-Study Cohort”. It consisted of 1907 randomized subjects: 1130 subjects randomized to varenicline and 777 subjects randomized to placebo.

- A set of 18 Phase II-IV clinical trials, including the trials in the 5-Study Cohort, which captured psychiatric adverse events through MedDRA codes. This set of trials is referred to as the “18-Study Cohort”. It consisted of 8521 randomized subjects: 5072 subjects randomized to varenicline and 3449 subjects randomized to placebo.

To characterize the risk of psychiatric events several endpoints of interest were analyzed.

- Percent of subjects responding “yes” for suicidal ideation (any type) and/or suicidal behavior (any type) based on the C-SSRS.
- Percent of subjects who experienced an adverse event in the Hostility/Aggression MedDRA SMQ.
- Percent of subjects who experienced an adverse event in the MedDRA Psychiatric disorders system organ class (SOC).
- Percent of subjects experiencing an event in the composite endpoint20 specified in ongoing trial A3051123 intended to fulfill the PMR issued in 2008 (PMR endpoint).

Table 2 summarizes the meta-analysis of psychiatric adverse events observed while patients were on randomized treatment or within a window of 30 days after treatment discontinuation. This meta-analysis showed no evidence of increased risk of psychiatric adverse events associated with varenicline relative to placebo.

---

20 PMR endpoint is defined as “at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide.”
Table 2. Summary of Meta-Analysis of Treatment Emergent Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. Trials</th>
<th>Total events</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal Ideation or Behavior</td>
<td>5</td>
<td>55</td>
<td>0.79 (0.46, 1.36)</td>
</tr>
<tr>
<td>Suicide / Self-Injury SMQ</td>
<td>18</td>
<td>25</td>
<td>0.45 (0.19, 1.07)</td>
</tr>
<tr>
<td>Hostility / Aggression SMQ</td>
<td>18</td>
<td>46</td>
<td>1.10 (0.60, 2.03)</td>
</tr>
<tr>
<td>Psychiatric Disorders SOC</td>
<td>18</td>
<td>981</td>
<td>1.03 (0.84, 1.25)</td>
</tr>
<tr>
<td>PMR endpoint</td>
<td>18</td>
<td>245</td>
<td>0.85 (0.64, 1.13)</td>
</tr>
</tbody>
</table>

The meta-analysis has the following limitations:

- All analyses in the 18-Study Cohort were conducted retrospectively. Adverse events of interest were not collected prospectively and, therefore, it is possible that some adverse events may have been underreported in these trials. Specifically, as shown in Section 4.2 of the attached statistical background document, the suicide/self-injury SMQ did not capture some suicide-related adverse events when compared to the C-SSRS instrument. It is possible that the other SMQs in the meta-analysis may have also failed to capture some psychiatric adverse events.

- Forty-eight out of the 55 events in the analysis of suicidal ideation and behavior based on the C-SSRS instrument were observed in two trials that enrolled patients with history of schizophrenia or depression. Only seven events were observed in the other three trials that collected the C-SSRS.

- MedDRA SMQs and SOCs may include adverse events of different severities. It is possible that the SMQs in this meta-analysis may not be adequate to characterize the risk of rare but severe adverse events.

See Attachment 8 for the detailed statistical review.
Discussion/ Interim actions

The original signal for serious neuropsychiatric adverse events came from cases reported to the FDA and described in the medical literature. In this supplement, Pfizer argues that the information garnered from the meta-analyses they conducted and the published observational studies they have reviewed is reassuring and trumps the information culled from the case reports that originally led to the Boxed Warning and Warnings and Precautions statements in varenicline labeling, and that the sum of this new evidence no longer supports the need for a boxed warning for serious neuropsychiatric adverse events.

As summarized above, DB VII and DEPI-II have concerns about the validity of the findings from Pfizer’s meta-analyses and the published observational studies. The limitations of the findings described in each of their reviews and summarized in this document raise questions as to how to best interpret the findings of the meta-analyses and observational studies.

Furthermore, when FDA issued the postmarketing requirement for the randomized controlled trial to evaluate the neuropsychiatric adverse events with varenicline, FDA stated that observational studies would not be adequate to address this safety question. This decision was made because there was a lack of confidence that the kinds of coded data used in observational studies could capture the neuropsychiatric adverse events of interest, and concern about differential selection of patients for treatment with varenicline and the associated bias that could be introduced into comparisons. The required clinical trial includes randomization to treatment, and the neuropsychiatric outcome of interest was custom-crafted as a composite outcome of a series of neuropsychiatric adverse events of a certain severity to specifically capture the kinds of events described in the spontaneous reports.

Based on FDA’s review of the meta-analyses and observational studies submitted by Pfizer, FDA has determined that some information about these data could be included in the varenicline labeling (Attachment 10, Section 5.1) so that prescribers have a full picture of what analyses and studies have been conducted to enhance the understanding of varenicline-associated serious neuropsychiatric adverse events.

However, the determination of whether to remove a boxed warning is a decision for which there is limited precedent. FDA believes that the randomized controlled trial prospectively designed to evaluate the risk of serious neuropsychiatric adverse events with varenicline, whose final study report is expected in a year, should be reviewed and considered as part of such a regulatory action. However, because Pfizer believes the collection of observational and meta-analytic data are alone sufficient, we are bringing this issue to the Committee for discussion.
Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
October 16, 2014

Location: FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committees discussed safety data from observational studies and a meta-analysis of randomized controlled clinical trials that were conducted since the original signal of serious neuropsychiatric adverse events with CHANTIX (varenicline tartrate tablets, NDA 21928, Pfizer, Inc.) emerged. The committees also discussed whether any action needed to be taken with regard to how this risk is described in product labeling.

These summary minutes for the October 16, 2014 joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on November 12, 2014.

I certify that I attended the October 16, 2014 joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/ Kalyani Bhatt, BS, MS
Designated Federal Officer
Psychopharmacologic Drugs Advisory Committee (PDAC)

/s/ Ruth Parker, MD
Acting Committee Chairperson, PDAC
The following is the final report of the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on October 16, 2014. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anesthesia, Analgesia, and Addiction Products and the Office of Surveillance and Epidemiology and posted on the Food and Drug Administration (FDA) website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm394880.htm and http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm380883.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the FDA, Center for Drug Evaluation and Research, met on October 16, 2014, at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided briefing materials from FDA and Pfizer, Inc. The meeting was called to order by Ruth Parker, MD (Acting Chairperson); the conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS, (Designated Federal Officer). There were approximately 115 people in attendance. There were seven Open Public Hearing speakers.

**Issue:** The committees discussed safety data from observational studies and a meta-analysis of randomized controlled clinical trials that were conducted since the original signal of serious neuropsychiatric adverse events with CHANTIX (varenicline tartrate tablets, NDA 21928, Pfizer, Inc.) emerged. The committees also discussed whether any action needed to be taken with regard to how this risk is described in product labeling.

**Attendance:**

**Psychopharmacologic Drugs Advisory Committee Members Present (Voting):** John J. Battisti, PhD, RPh; Thomas A. Grieger, MD; Elizabeth McCarthy, MA, LPC (Consumer Representative); David Pickar, MD

**Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting):** Victor De Gruttola, ScD; Christopher J. Kratochvil, MD

**Psychopharmacologic Drugs Advisory Committee Members (Non-Voting):**

David Michelson, MD (Industry Representative)
Drug Safety and Risk Management Advisory Committee Members (Voting): Brian Erstad, PharmD; Tobias Gerhard, PhD, RPh; Jeanmarie Perrone, MD, FACMT

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Karen M. Hopkins, MD; Marjorie Shaw Phillips, MS, RPh, FASHP; Andy S. Stergachis, PhD, RPh; Til Stürmer, MD, MPH, PhD; Linda Tyler, PharmD, FASHP

Drugs Safety and Risk Management Advisory Committee Members Not Present (Non-Voting): Patrizia Cavazzoni, MD (Industry Representative)

Temporary Members (Voting): Erik Augustson, PhD, MPH; Daniel Budnitz, MD, MPH; Christopher T. Byrd, JD; (Patient Representative); Scott S. Emerson, MD, PhD; Ann M. Malarcher, PhD, MSPH; Stephen R. Marder, MD; Elaine H. Morrato, DrPH; MPH; Ruth M. Parker, MD (Acting Chairperson); Rajiv Rimal, PhD; Christianne L. Roumie, MD, MPH; Andrew J. Saxon, MD

FDA Participants (Non-Voting): Robert Temple MD; John Jenkins, MD; Mary Parks, MD; Celia Winchell, MD; Judith A. Racoosin, MD, MPH; Robert Ball, MD; Solomon Iyasu, MD, MPH; Judy Staffa, PhD, RPh; Chih-Ying (Natasha) Chen, PhD

Designated Federal Officer (Non-Voting): Kalyani Bhatt, BS, MS

Open Public Hearing Speakers: Richard Todd Light, MD, (RxDrugSafety.com); Thomas J. Moore (Institute for Safe Medication Practice); Curt Furberg, PhD (statement read by Thomas J. Moore); Laurén Doamekpor, PhD (Patient, Consumer, and Public Health Coalition); Joe & Teresa Graedon (The People's Pharmacy); Kim Witczak; Diana Zuckerman, PhD (Cancer Prevention and Treatment Fund)

The agenda proceeded as follows:

Call to Order and Introduction of Committee

Conflict of Interest Statement

FDA Introductory Remarks/Regulatory History

FDA Presentation
Regulatory Requirements and Guidance
Recommendations for Warnings and Precautions
and Boxed Warning Sections

INDUSTRY PRESENTATIONS

Background and Overview

Eric Brodsky, MD
Labeling Team Leader
Study Endpoints and Labeling Development
Office of New Drugs (OND), CDER, FDA

Christopher Wohlberg, MD, PhD
Vice President and Safety Surveillance & Risk
Management Group Head, Global Innovative Pharma
Pfizer, Inc.

Current Clinical Trials Data Regarding
Neuropsychiatric Events

Lawrence Samuels, PhD
Senior Director, Medical Affairs
Pfizer, Inc.

INDUSTRY PRESENTATIONS (cont.)

Observational Studies Data Regarding
Neuropsychiatric Events & Public Health
Perspectives

Robert West, PhD
Professor of Health Psychology
Health Behaviour Research Centre
Cancer Research UK Health Behaviour Research Centre
Department of Epidemiology and Public Health
University College London

Clarifying Questions to Industry

BREAK

FDA PRESENTATIONS

Clinical Perspective on Neuropsychiatric Adverse
Events

Celia Winchell, MD
Medical Team Leader, Addiction Products
Division of Anesthesia, Analgesia, and Addiction Products
(DAAAP)
Office of Drug Evaluation II (ODE II)
Office of New Drugs (OND), CDER, FDA

Statistical Review of Meta-analysis

Eugenio Andraca-Carrera, PhD
Reviewer, Division of Biometrics VII
Office of Translational Sciences (OTS)
CDER, FDA

Review of Observational Studies

Natasha Chen, PhD
Reviewer, Division of Epidemiology
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Clarifying Questions to FDA

Open Public Hearing
Questions to the Committee:

1. **DISCUSSION:** Please discuss how you weigh the evidence contributed by the randomized controlled trial (RCT) meta-analyses, observational studies, and spontaneous case reports when evaluating the risk of serious neuropsychiatric adverse events in patients taking varenicline.

   **Committee Discussion:** In general, many of the committee members expressed concerns with the quality of the data presented. The concerns included, but were not limited to, statistical limitations of the trials, misclassification of adverse events, outcome ascertainment in observational studies, and arbitrary cut off points for the outcomes which questioned whether the outcomes were being categorized correctly. Please see the transcript for details of the committee’s discussion.

2. **VOTE:** Based on the data presented on the risk of serious neuropsychiatric adverse events with varenicline, what would you recommend?

   A. Removal of the boxed warning statements regarding risk of serious neuropsychiatric adverse events
   
   B. Modification of the language in the boxed warning
   
   C. Retain the current boxed warning statements and reassess once the ongoing postmarketing randomized controlled trial designed to capture serious neuropsychiatric adverse events is completed

   **DISCUSSION:** Please explain the rationale for your answer, and discuss any additional actions you think the Agency should take regarding the risk of serious neuropsychiatric adverse events with varenicline.

   A: 1           B: 6           C: 11           Abstain: 0

   **Committee Discussion:** The majority of the committee agreed that more data are needed and recommended to retain the current boxed warning statements and reassess once the ongoing post-marketing randomized controlled trial designed to capture serious neuropsychiatric adverse events is complete. Some of the panel members voted to modify labeling by strengthening the language in the boxed warning by including a description of the risk for
sleep disturbances. In addition, some of the committee members expressed concerns that a portion of the Boxed Warning describing the benefits of smoking cessation was promotional, and recommended removal of this content. The member who voted to remove the Boxed Warning stated that the data did not show a definitive safety signal, and that varenicline is no riskier than other drugs with a similar range of neuropsychiatric adverse effects that do not have Boxed Warnings. Please see the transcript for details of the committee’s discussion.

The meeting was adjourned at approximately 4:00 p.m.
Guidance for Industry

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2011
Labeling
Guidance for Industry

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format

Additional copies are available from:

Office of Communications
Division of Drug Information
10001 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov

or

Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2011
Labeling
TABLE OF CONTENTS

I. INTRODUCTION........................................................................................................................................... 2

II. WARNINGS AND PRECAUTIONS SECTION (§ 201.57(c)(6))............................................................. 3
   A. Adverse Reactions That Should Be Included in the WARNINGS AND PRECAUTIONS Section.................................................................................................................................................................................. 3
      1. Serious Adverse Reactions................................................................................................................. 3
      2. Otherwise Clinically Significant Adverse Reactions ....................................................................... 4
      3. Anticipated Adverse Reactions ....................................................................................................... 4
      4. Adverse Reactions Associated with Unapproved Uses .................................................................... 5
   B. Risks or Other Hazards that Should be Included in the WARNINGS AND PRECAUTIONS Section.................................................................................................................................................................................. 5
      1. Laboratory Test Interference........................................................................................................... 5
      2. Drug Interactions.............................................................................................................................. 5
      3. Need for Monitoring to Assess Safety ............................................................................................ 6
   C. Information to Provide in the Description of an Adverse Reaction .................................................... 6
   D. Format.................................................................................................................................................... 7
      1. Individual Subsections ............................................................................................................. 7
      2. Order of Adverse Reactions ....................................................................................................... 7
      3. Cross-Referencing..................................................................................................................... 8
      4. Emphasis in Text...................................................................................................................... 8

III. CONTRAINDICATIONS SECTION (§ 201.57(c)(5)).................................................................................. 8
   A. When to Contraindicate .................................................................................................................. 8
      1. Observed Adverse Reactions........................................................................................................ 8
      2. Anticipated Adverse Reactions .................................................................................................. 8
   B. Information to Provide................................................................................................................ 10
   C. Format............................................................................................................................................... 11
      1. Bulleted list............................................................................................................................... 11
      2. Order of Contraindications ..................................................................................................... 11

IV. BOXED WARNING (§ 201.57(c)(1)) ........................................................................................................ 11
   A. When to Use a Boxed Warning.................................................................................................... 11
   B. Information to Provide................................................................................................................ 12
   C. Format............................................................................................................................................ 12

GLOSSARY.......................................................................................................................................................... 13
Guidance for Industry

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist applicants and reviewers in drafting the WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and BOXED WARNING sections of labeling, as described in the final rule amending the requirements for the content and format of labeling for human prescription drug and biological products (21 CFR 201.56 and 201.57). The recommendations in this guidance are intended to help ensure that the labeling is clear, useful, informative, and, to the extent possible, consistent in content and format.

This guidance provides recommendations on the following:

- How to decide which adverse reactions or other potential safety hazards are significant enough to warrant inclusion in the WARNINGS AND PRECAUTIONS section; what information to include when describing those adverse reactions; and how to organize the WARNINGS AND PRECAUTIONS section

---

1 This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.
2 This guidance applies to drugs, including biological drug products. For the purposes of this guidance, drug product or drug will be used to refer to human prescription drug and biological products that are regulated as drugs.

Note: We update guidances periodically. To make sure you have the most recent version, check the CDER guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
• What situations warrant a contraindication; what information to provide in those situations when the use of the product is contraindicated; and how to organize the CONTRAINDICATIONS section
• When to include a boxed warning; and what information to include in the BOXED WARNING section

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. WARNINGS AND PRECAUTIONS SECTION (§ 201.57(c)(6))

A. Adverse Reactions That Should Be Included in the WARNINGS AND PRECAUTIONS Section

The WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.4

Some factors to consider in assessing whether there is reasonable evidence of a causal relationship include: (1) the frequency of reporting; 2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; (3) evidence of a dose-response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug; (5) the temporal association between drug administration and the event; (6) existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs.

1. Serious Adverse Reactions

An adverse reaction that results in any of the following outcomes should be considered serious and included in the WARNINGS AND PRECAUTIONS section:

• Death
• A life-threatening adverse event
• Inpatient hospitalization or prolongation of existing hospitalization
• A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
• A congenital anomaly or birth defect

4 See the Glossary for definitions of "adverse event" and "adverse reaction."
Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (§§ 312.32(a) and 314.80(a)).

2. Otherwise Clinically Significant Adverse Reactions

Adverse reactions that do not meet the definition of a serious adverse reaction, but are otherwise clinically significant because they have implications for prescribing decisions or patient management, should also be included in the WARNINGS AND PRECAUTIONS section. The following can be factors in determining whether an adverse reaction is otherwise clinically significant:

- Indication

The relative seriousness of the disease or condition treated should be considered. For example, non-serious adverse reactions (e.g., nausea, pruritus, alopecia) caused by drugs intended to treat minor, self-limiting conditions (e.g., allergic rhinitis, cosmetic conditions, transient insomnia) may be considered clinically significant. However, those same adverse reactions caused by drugs intended to treat serious or life-threatening conditions (e.g., cancer) may be considered much less clinically significant and not appropriate for inclusion in this section.

- Incidence

A high absolute risk or rate of occurrence of an adverse reaction can be a factor in deciding whether to include the reaction in this section.

The following types of adverse reactions could be considered otherwise clinically significant:

- An adverse reaction that may lead to a potentially serious outcome unless the dosage or regimen is adjusted, the drug is discontinued, or another drug is administered to prevent the serious outcome
- An adverse reaction that could be prevented or managed with appropriate patient selection, monitoring, or avoidance of concomitant therapy, and prevention or management of the adverse reaction is needed to avoid a potentially serious outcome
- An adverse reaction that can significantly affect patient compliance, particularly when noncompliance has potentially serious consequences

3. Anticipated Adverse Reactions
There are circumstances in which an adverse reaction that has not been observed with a drug can nonetheless be anticipated to occur. The WARNINGS AND PRECAUTIONS section should include serious or otherwise clinically significant adverse reactions (as described in section II.A) that are anticipated to occur with a drug if:

- It appears likely that the adverse reaction will occur with the drug based on what is known about the pharmacology, chemistry, or class of the drug (e.g., a drug with a large QT prolongation effect would be likely to cause Torsades des Pointes arrhythmia even if no cases have yet been seen).

OR

- Animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrating that a drug has teratogenic effects)

Generally, when deemed important for the prescriber, the labeling should acknowledge that the adverse reaction has not been observed with the subject drug, but may be anticipated to occur.

4. Adverse Reactions Associated with Unapproved Uses

FDA may require in the WARNINGS AND PRECAUTIONS section a discussion of an adverse reaction associated with an unapproved use if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard (§ 201.57(c)(6)(i)). The description should include a statement indicating that safety and effectiveness have not been established in that setting and that the use is not approved by FDA.

B. Risks or Other Hazards that Should be Included in the WARNINGS AND PRECAUTIONS Section

1. Laboratory Test Interference

The WARNINGS AND PRECAUTIONS section must briefly note information on any known drug interference with laboratory tests (§ 201.57(c)(6)(iv)). Interference with a laboratory test means that the laboratory test result is inaccurate because the drug interferes with the assay (e.g., a false positive or negative test result is obtained that does not accurately reflect the quantity, presence, or absence of the analyte). It does not refer to a situation in which the test result is accurate, but outside the normal range because of the physiological effects caused by the drug or its metabolites.

Only clinically significant interferences should be included. Interference with a laboratory test would be considered clinically significant if reliance on the erroneous test result would influence clinical decision-making (e.g., false positive hemoccult test).

2. Drug Interactions
The WARNINGS AND PRECAUTIONS section should briefly describe any known or predicted drug interactions with serious or otherwise clinically significant outcomes and cross-reference to any more detailed information elsewhere in the labeling (e.g., DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS, or CLINICAL PHARMACOLOGY sections).

3. Need for Monitoring to Assess Safety

The WARNINGS AND PRECAUTIONS section must identify any laboratory tests that would be helpful or necessary to identify possible adverse reactions (§ 201.57(c)(6)(iii)), or to prevent a serious adverse reaction. Information about the frequency of testing and expected ranges of normal and abnormal values should also be provided if available.

In general, information on monitoring to assess safety appears in WARNINGS AND PRECAUTIONS, and information on monitoring to assess effectiveness appears in DOSAGE AND ADMINISTRATION. In some cases, however, there may not be a clear distinction between monitoring for safety and effectiveness (e.g., cardiac monitoring to assess both safety and effectiveness in patients receiving antiarrhythmic drugs or INR testing to assess both safety and effectiveness in patients receiving warfarin), resulting in some overlap of information in WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION. Sections IIB, IIC, and IID in FDA’s Dosage and Administration Final Guidance (Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format) state that the DOSAGE AND ADMINISTRATION section of the labeling should contain monitoring information to assess both effectiveness and safety, specifically how such monitoring affects dosing of the drug (e.g., titrating the dose, modifying the dose, or discontinuing treatment).

C. Information to Provide in the Description of an Adverse Reaction

There should be a succinct description of each topic selected for inclusion in the WARNINGS AND PRECAUTIONS section. The description should cross-reference any more detailed discussion of the risk elsewhere in labeling (e.g. ADVERSE REACTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, CLINICAL STUDIES). The description should be limited to the following information, and information should be included only if known and important to clinical decision making:

- A succinct description of the adverse reaction and outcome (e.g., when the reaction occurs, whether the reaction abates over time despite continued treatment, time to resolution, significant sequelae).
- A numerical estimate of risk or adverse reaction rate\(^5\)

---

\(^5\) In characterizing overall adverse reaction experience, nonspecific terms that lack a commonly understood or precise meaning should be avoided because use of such terms can be misleading. For example, the terms rare, infrequent, and frequent do not provide meaningful information about the adverse event’s frequency of occurrence.
• Known risk factors for the adverse reaction (e.g., age, gender, race, genetic polymorphism, comorbid conditions, dose, duration of use, coadministered drugs)

• Steps to take to decrease the likelihood, shorten the duration, or minimize the severity of an adverse reaction. These steps could include, for example, necessary evaluation prior to use, titration and other kinds of dose adjustment, monitoring during dose adjustment or prolonged use, avoidance of other drugs or substances, or special care during comorbid events (e.g., dehydration, infection)

• How to treat or otherwise manage an adverse reaction that has occurred

The information and advice provided should be reasonably qualified, where appropriate, to convey whatever uncertainties may exist about judgments and conclusions made (e.g., concerning causality assessments, estimated adverse reaction rates, and value of proposed monitoring).

Ambiguous and uninformative statements (e.g., use with caution) should be avoided. Instead, specific treatment or management strategies should be noted (e.g., consider lower doses or more frequent monitoring). Terminology that generally infers a contraindication (e.g., “Do not use” or “Drug X should not be used”) should not appear in the WARNINGS AND PRECAUTIONS section.

D. Format

1. Individual Subsections

Each adverse reaction, syndrome, or group of reactions with a common pathogenesis (e.g., allergic contact dermatitis, maculopapular drug rash) included in the WARNINGS AND PRECAUTIONS section should have its own numbered subsection. The subsection title should accurately characterize the risk (e.g., 5.1 Thromboembolic Disorders, 5.2 Peripheral Neuropathy). When necessary, information in a subsection can be organized under non-numbered subsections using formatting techniques such as underlining or italicizing for the subheading titles. For example, the text of a subsection entitled “5.1 Thromboembolic Disorders” can include the subheadings “Deep Vein Thrombosis” and “Thrombotic Stroke” (not “5.1.1 Deep Vein Thrombosis” and “5.1.2 Thrombotic Stroke”). Subsection headings that are not useful for signaling the content of the subsection (e.g., General) should be avoided.

2. Order of Adverse Reactions

The order in which adverse reactions are presented in the WARNINGS AND PRECAUTIONS section should reflect the relative clinical significance of the adverse reactions. Factors to consider include the relative seriousness of the adverse reaction, the ability to prevent or mitigate the adverse reaction, and the likelihood of its occurrence.

Footnote 5 continued: If categorizing adverse reactions by frequency, ranges would be helpful in understanding the drug’s safety profile and the ranges should be clearly defined (e.g., occurring at a rate less than 1/100, occurring at a rate of less than 1/500).
3. **Cross-Referencing**

When more detailed information about an adverse reaction is included in another labeling section, the WARNINGS AND PRECAUTIONS section should cross-reference that section (e.g., ADVERSE REACTIONS, DRUG INTERACTIONS, CLINICAL PHARMACOLOGY), rather than repeat the same information. To the extent possible, redundancies should be avoided in labeling, and cross-referencing should be used instead.

4. **Emphasis in Text**

Bolded text or other emphasis can be used to highlight particular adverse reactions or parts of the discussion of particular adverse reactions (e.g., steps to be taken to avoid a problem, subpopulations at particular risk). Emphasis should be used sparingly so that its effect is not diminished. Thus, the entire text of a subsection in WARNINGS AND PRECAUTIONS should not be bolded; rather, bolding should be limited to only one or two sentences. Consider whether information to be emphasized should rise to the level of a Boxed Warning (see Section IV on BOXED WARNING).

**III. CONTRAINDICATIONS SECTION (§ 201.57(c)(5))**

A. **When to Contraindicate**

A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication. If there are no known contraindications for a drug, this section must state “None.”

1. **Observed Adverse Reactions**

For observed adverse reactions, the following would ordinarily be reason to contraindicate a drug:

- The risk of the adverse reaction in the clinical situation to which the contraindication applies, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to any patient.

  **AND**

- The causal relationship between exposure to the drug and the adverse reaction is well established.

2. **Anticipated Adverse Reactions**

Adverse reactions that are anticipated to occur when a drug is used in a specific clinical situation can be the basis for a contraindication.
Anticipated adverse reactions are distinguishable from “theoretical possibilities”. Anticipated adverse reactions are supported by data (e.g., from known pharmacologic effects, class effect, chemical relationships to other drugs known to cause reactions, animal studies) and may be considered for the CONTRAINDICATIONS section. Adverse reactions based wholly on theory (theoretical possibilities) are not supported by data and would not be appropriate to include in the CONTRAINDICATIONS section.

Ordinarily, a drug should be contraindicated on the basis of an anticipated adverse reaction if the risk of the adverse reaction in the clinical situation to which the contraindication will apply, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to any patient:

**AND EITHER**

- Based on what is known about the pharmacology, chemistry, or class of the drug, it appears highly likely that the adverse reaction is caused by the drug.

**OR**

- Animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrating that a drug has teratogenic effects).

The labeling should acknowledge that the adverse reaction has not yet been observed, but is anticipated to occur.

The following illustrate clinical situations for which a contraindication might be appropriate:

- Use in the presence of a comorbid condition or coexistent physiological state (e.g., existing hepatic disease, renal disease, congenital long QT syndrome, hypokalemia, pregnancy or childbearing potential, CYP 2D6 poor metabolizer⁶)

- Use in the presence of a demographic risk factor, such as age, gender or other factors (e.g., contraindication in females of reproductive potential, in children below a certain age)

- Use in a defined subset of patients (e.g., people with mild disease) where the risks of the drug are such that the drug should never be used in that subset of the larger population⁷

---

⁶ Use of a particular drug in a patient with a slow metabolizer status would be contraindicated only in situations where the dose of the drug could not be adequately adjusted.

⁷ The INDICATIONS AND USAGE section must contain information about use of the drug when safety considerations are such that the drug should be reserved for certain patients (e.g., patients with severe disease) or situations (e.g., patients refractory to other drugs) (§ 201.57(c)(2)(i)(B) and (E)). In rare cases, when the risks of the drug clearly outweigh any possible therapeutic benefit and the drug should never be used in a selected patient subset, a contraindication for use of the drug in that subset should also be described in the CONTRAINDICATIONS section.
- Use with coadministered drugs where the combination is dangerous (e.g., MAO inhibitor with a tricyclic antidepressant; a drug known to prolong the QT interval with a drug known to interfere with the metabolism of that drug)

- Use of a drug in patients with known hypersensitivity when severe hypersensitivity reactions have been observed to occur with the drug.

A contraindication in patients with hypersensitivity reactions should be included in labeling only when there are demonstrated cases of hypersensitivity with the product or such reactions may be anticipated based on data from similar drugs (e.g., those in the same pharmacological class or with similar chemical structures, or when cross-sensitivity within a class is a recognized phenomenon). When the risk of using the drug in a patient at risk for such a reaction outweighs the potential benefits (i.e., it would be clinically inappropriate to rechallenge a patient with a history of a hypersensitivity reaction to the drug or a similar drug), a contraindication to use in such patients should be included. Along with the contraindication statement, the labeling should briefly describe the type and nature of the observed (or anticipated) reaction(s), and cross-reference to a more detailed discussion elsewhere in the labeling, as appropriate.

For example:

DRUG-X is contraindicated in patients with a history of a hypersensitivity reaction to [active ingredient]. Reactions have included anaphylaxis and anaphylactoid reactions [see Adverse Reactions (6.2)].

If no such hypersensitivity reactions as noted above have been observed or are unlikely to occur based on the drug's characteristics, no contraindication for hypersensitivity reactions will be included.

Contraindications based on drug interactions with serious outcomes should be described briefly in the CONTRAINDICATIONS section and cross-referenced to more detailed information in the DRUG INTERACTIONS or CLINICAL PHARMACOLOGY sections.

B. Information to Provide

Contraindications should be worded using precise language, e.g., “Drug X is contraindicated in patients with condition Y” (instead of “Drug X should not be used in patients with condition Y”). If a drug has more than one contraindication, use an introductory statement (e.g., "Drug X is contraindicated in:") followed by a bulleted list identifying each contraindication.

For each listed contraindication, provide the following information:

- Brief description of the contraindicated situation or scenario, including any pertinent demographic or identifiable predisposing characteristics

- Description of observed or anticipated consequences of the contraindicated use
C. Format

1. Bulleted list

If a drug has more than one contraindication, FDA recommends that each contraindication be identified in a bulleted list.

2. Order of Contraindications

The order in which contraindications are presented should reflect the relative clinical significance of the listed contraindications. Factors to consider include the severity of the risk and the likelihood of occurrence.

IV. BOXED WARNING (§ 201.57(c)(1))

A. When to Use a Boxed Warning

A boxed warning is ordinarily used to highlight for prescribers one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug

  **OR**

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)

  **OR**

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 “Approval with restrictions to assure safe use” or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) “Risk Evaluation and Mitigation Strategies” Elements to assure safe use).

Infrequently, a boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber (e.g., reduced effectiveness in certain patient populations). Information included in the WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS sections should therefore be evaluated to determine whether it warrants inclusion in a boxed warning.

Boxed warnings are most likely to be based on observed serious adverse reactions, but there are instances when a boxed warning based on an anticipated adverse reaction would be appropriate.
For example, a contraindication to use during pregnancy based on evidence in humans or animals that drugs in a pharmacologic class pose a serious risk of developmental toxicity during pregnancy would usually be in a boxed warning for all drugs in that class, even those in which the adverse reaction has not been observed.

A boxed warning can also be considered for a drug that poses risk–benefit considerations that are unique among drugs in a drug class (e.g., to note when a drug is the only one in its class to have a particular risk and is indicated as second line therapy because of that risk).

B. Information to Provide

A boxed warning provides a brief, concise summary of the information that is critical for a prescriber to consider, including any restriction on distribution or use. There is typically a more detailed discussion of the risk elsewhere in the labeling (e.g., in CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS sections), that must be identified by a cross-reference (§ 201.57(c)(1)).

C. Format

The BOXED WARNING section in the full prescribing information must be formatted in accordance with § 201.57(d). The information in the boxed warning should be in bold print and presented in a bulleted format or some alternative format, such as the use of subheadings, that helps to make the information visually accessible.
GLOSSARY

Adverse Reaction (21 CFR 201.57(c)(7)): For purposes of prescription drug labeling and this guidance, an adverse reaction is an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical bodily function, such as vital signs and electrocardiogram (ECG).

Adverse Event: For the purposes of this guidance, an adverse event refers to any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Reaction: For purposes of this guidance, the term serious adverse reaction refers to any event or reaction that results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.