

## REVIEW AND EVALUATION OF CLINICAL DATA

### Application Information

NDA#: 19-758/S-047  
Sponsor: Novartis  
Due Date: September 1, 2002

### Drug Name:

Generic Name: Clozapine  
Trade Name: Clozaril

### Drug Categorization:

Pharmacological Class: D<sub>4</sub>/5-HT receptor antagonist  
Proposed Indication: Suicidality  
Dosage Forms: 25mg and 100mg tablets  
Route: Oral

### Review Information

Clinical Reviewer: Gregory M. Dubitsky, M.D.  
Completion Date: August 1, 2002

**NDA 19-758/S-047**  
**CLOZARIL FOR SUICIDALITY**  
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## **EXECUTIVE SUMMARY**

### **I. Recommendations**

#### **A. Recommendation on Approvability**

The sponsor is requesting an indication for the use of Clozaril in the treatment of suicidality in patients with schizophrenia and schizoaffective disorder. It is recommended that this indication not be approved.

#### **B. Recommendations for Phase 4 Studies**

At this time, there are no recommendations for Phase 4 studies.

### **II. Summary of Clinical Findings**

#### **A. Brief Overview of the Clinical Program**

Support for the requested indication derives solely from one clinical trial, study ABA 451. This was a multicenter, randomized, open-label comparison of Clozaril and Zyprexa with respect to suicidality risk over a treatment period of 2 years in 980 patients with schizophrenia or schizoaffective disorder. Raters of suicidality outcome measures were to be blinded to the patient's treatment.

#### **B. Efficacy**

On face, study ABA 451 provides evidence to suggest a reduced risk of suicidality over two years among patients treated with Clozaril versus Zyprexa. However, there were a number of irregularities in the conduct and analysis of this study that preclude a definitive interpretation of the study results at this time. These problems are further discussed in section VI.B.12 below.

Moreover, the indication sought by the sponsor, treatment of suicidality, is distinctly different from the indication which may be supported by ABA 451, a reduction in suicide risk with long-term therapy. This issue is discussed in more detail in section VI.C.1 below.

## **C. Safety**

A limited review of the safety data from study ABA 451 revealed a number of clinically significant adverse experiences associated with Clozaril: white blood cell count decreases, bowel obstruction, hyperglycemia, non-vertiginous dizziness, and somnolence.

None of these represented previously unrecognized toxicities which would preclude the approval of this supplement or require amendment of Clozaril labeling.

## **CLINICAL REVIEW**

### **I. Introduction and Background**

#### **A. Role in the Treatment Armamentarium**

Suicide is an important contributor to the shorter life expectancy among patients with schizophrenia compared to the general population. It has been estimated that approximately 10% of patients with schizophrenia commit suicide; this fraction may be even higher in patients with treatment-refractory schizophrenia. Risk factors for suicide in this population appear to be male gender, age under 30 years, depressive symptoms, unemployment, and recent hospital discharge.<sup>1</sup>

Currently, there are no drugs approved for the treatment of suicidal patients with schizophrenia or schizoaffective disorder. If this supplement is approved, Clozaril will be the only agent approved for this indication.

#### **B. Administrative History**

Clozapine is an atypical antipsychotic that has been marketed in the U.S. since 1990 as Clozaril for the treatment of neuroleptic-resistant schizophrenia. Since clozapine had demonstrated the potential to cause agranulocytosis, Clozaril has been distributed under a controlled system to ensure regular monitoring of WBC counts in all patients receiving this drug. All Clozaril-

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<sup>1</sup> American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC, American Psychiatric Association, 1994.

treated patients in this country must be registered in the Clozaril National Registry (CNR).

A few years after the launch of Clozaril in the U.S., data from the FDA Spontaneous Reporting System database suggested an increased all-cause mortality, increased mortality due to acute cardiovascular events, and an increased incidence of pulmonary embolism associated with clozapine.<sup>2</sup> To more formally investigate these safety findings, the innovator company (then Sandoz Pharmaceuticals Corporation) contracted with Epidemiology Resources, Inc. (ERI) to perform a retrospective study of overall and cause-specific mortality in current and former users of Clozaril from CNR data.

One finding that emerged from this study was a markedly reduced risk of death due to suicide (approximately seven-fold) in current compared to past users of Clozaril.<sup>3</sup> Based on this finding as well as a published study by Meltzer and Okayli that purported to show a reduced risk of suicidal behavior during Clozaril treatment compared to pre-Clozaril, Sandoz submitted a supplement (S-028) to describe this finding in Clozaril labeling. They further requested that the Agency consider expanding the indication for Clozaril (i.e., for any schizophrenic patient, regardless of neuroleptic-responsiveness, who exhibits suicidality or hopelessness).<sup>4</sup>

Upon review, we found these findings to be difficult to interpret for various reasons, in particular the fact that the neither study compared randomized samples.<sup>5</sup> Thus, we felt that it would be premature to place this information in labeling at that time.

The sponsor elected to conduct a prospective study to more definitively demonstrate that Clozaril treatment was associated with a reduced risk of suicide. Representatives of Sandoz as well as two consultants to Sandoz (Dr. Herbert Meltzer and Dr. Alexander Walker) met with the Division on 1-13-97 to discuss a proposed protocol for such a study.

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<sup>2</sup> See a clinical review by Dr. James Knudsen dated 2-10-93.

<sup>3</sup> Please see my Review and Evaluation of Clinical Data dated 10-27-95 for a complete description of the ERI study design and findings.

<sup>4</sup> Meltzer HY and Okayli G. Reduction of Suicidality During Clozapine Treatment of Neuroleptic-Resistant Schizophrenia: Impact on Risk-Benefit Assessment. Am J Psychiatry 1995;152:183-190.

<sup>5</sup> See a Memorandum by Dr. Thomas Laughren dated 11-3-95.

Important points conveyed to the sponsor at this meeting included the following:

- there was a concern on the part of the Division that suicidality in patients with schizophrenia may be a pseudospecific phenomenon, i.e., a clinical symptom common to many disorders that is "specific" to schizophrenia in name only as opposed to a distinct clinical entity unique to schizophrenia; if that is the case, a new indication would not be allowed.
- there was a high standard to gain a comparative claim; we would have to be reassured that any between-drug differences were not due to an unfair comparison.
- inclusion of non-treatment resistant patients would be acceptable but results should be presented by subgroup to assess for any interaction with this factor.
- open-label drug administration with a blinded rater of suicidality could be problematic since unblinding of this rater might occur by virtue of medication side effects or hallway conversations.
- labeling of the study results under Indications mandates a higher level of evidence compared to a description of the results under Clinical Trials.
- suicide attempts could be used as a surrogate for completed suicides.
- measures should be taken to minimize the number of patients lost to follow-up.

On 1-16-98, the sponsor (Novartis Pharmaceuticals Corporation at this point) submitted the protocol for a 24-month, prospective, randomized comparison of Clozaril vs. Zyprexa with respect to suicidality in 900 patients with schizophrenia or schizoaffective disorder (study ABA 451). I reviewed this protocol on 1-28-98. Supervisory comments were appended by Dr. Thomas Laughren on 1-29-98, and biometrics comments were provided by Dr. David Hoberman in a 2-10-98 E-Mail. The results from this study form the basis for this sNDA.

Study ABA 451 was initiated on 3-19-98.

A number of protocol amendments to ABA 451 were subsequently submitted by the Novartis. Two important amendments are summarized below:

- Amendment #6 was submitted on 1-2-01. This amendment provided for changes in the primary outcome variable and the primary statistical analysis. The Division met with the sponsor on 5-16-01 to discuss this amendment and reach agreement on its acceptability. This amendment will be discussed in detail in the review of study ABA 451 below.
- Amendment #9, dated on 3-14-00, allowed patients who had dropped out of the study to later re-enter if certain conditions were met. I reviewed this change on 3-24-00 and found it to be unacceptable due to potential confounding of the efficacy analysis. The sponsor was advised to not implement this change in a 5-1-00 letter from the Division.

The last patient in study ABA 451 completed participation on 2-13-01.

A pre-sNDA meeting was held with the sponsor on 9-5-01. The following issues were discussed at this meeting:

- we suggested that the primary analysis should be based on the WLW method with c fixed at 0.5 and the expanded definition for Type 2 Events (see the review of ABA 451 below for details). Other analyses would be considered supplementary.
- we indicated that the sNDA would likely be granted priority status and be taken to the Psychopharmacological Drugs Advisory Committee (PDAC).
- an ISS and ISE would not be needed for this sNDA.
- safety data from only study ABA 451 was required but all relevant information pertaining to suicidality, including published literature, should be submitted.
- after our review of an advance listing of all serious adverse events, we would inform them of which patients warranted submission of a full complement of clinical data (e.g., Case Report Forms).
- we requested a listing of all patients with Type 1 or Type 2 Events, from which we would select a random sample for auditing.
- we stated that if a new indication is granted, it would encompass both refractory and non-refractory patients since both types of patients were studied.

Novartis submitted a draft copy of the study report for ABA 451 on 12-21-01 and requested our feedback. A request for further information was E-Mailed to the sponsor by the

FDA Project Manager, Steve Hardeman, on 1-29-02 and included the following items:

- a in-depth analysis of concomitant psychotropic drug use during the study.
- a listing of the median dose and dose range for each treatment arm by visit.
- primary efficacy analyses for the schizophrenia and schizoaffective disorder subgroups separately.

Novartis submitted this sNDA on 2-28-02.

At a meeting of the review team on 4-4-02, it was decided to file this sNDA with Priority review status.

### **C. Proposed Instructions for Use**

The proposed instructions for use in patients with schizophrenia or schizoaffective disorder with suicidality are essentially identical to those recommended in current labeling for patients with treatment-resistant schizophrenia.

## **II. Clinically Relevant Findings from Other Disciplines and from Consultants**

### **A. Statistical Review and Evaluation**

The Statistical Review and Evaluation is pending completion at this time.

### **B. DSI Clinical Site Inspections**

The following four centers from study ABA 451 were inspected by the Division of Scientific Investigations (DSI): 107, 114, 302, and 956. The report of the DSI site inspections is not yet complete.

## **III. Human Pharmacokinetics and Pharmacodynamics**

No new data regarding human pharmacokinetics or pharmacodynamics have been submitted for review in this supplement.

#### **IV. Description of Clinical Data Sources**

The primary source of clinical data for this supplement is study ABA 451, also known as the International Suicide Prevention Trial or InterSePT. Efficacy data from this trial is discussed in section VI and safety data is discussed in section VII of this review.

##### **A. Study ABA 451**

###### **1. Study Design/Enumeration of Patients**

Study ABA 451 was a prospective, randomized, open-label, 24-month trial in patients with DSM-IV schizophrenia and schizoaffective disorder who were deemed to be at high risk for suicide.

A total of 980 patients were randomized to either Clozaril or Zyprexa in a 1:1 ratio (490 patients per arm).

###### **2. Demographic Characteristics**

The baseline demographic characteristics of the patients in study ABA 451 are displayed in **Appendix IV-1**.

The Clozaril and Zyprexa treatment groups were almost identical in terms of age, gender, and racial composition. Among patients with baseline body weight information, the two groups were very comparable in terms of weight when stratified by gender.

###### **3. Extent of Exposure**

The suggested dosage range for Clozaril in study ABA 451 was 200-900 mg/day and, for Zyprexa, 5-20 mg/day. In the Clozaril group, the overall mean daily dose was 308.7 mg (SD= 555 mg). Among Zyprexa-treated patients, the overall mean daily dose was 17.0 (SD= 25.5 mg).<sup>6</sup>

The overall exposure in terms of treatment duration is summarized in **Appendix IV-2**. In all, 304 Clozaril patients and 312 Zyprexa patients received study drug for at least 631 days. Patient-years of exposure were not provided.

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<sup>6</sup> These figures are based on corrected data submitted to the Agency on 5-17-02.

## **B. Published Literature**

The sponsor performed a literature search of the following databases: Medline (1966-date), Biosis (1993-date), Embase (1974-date), Psycinfo (1887-October 3, 2001), Derwent Drug File (1983-2001), and Sandoz Medical Document (1966-date). These databases were searched using the following string: "(clozapine or Clozaril or Leponex) and (suicide)."

Additionally, an independent internet search using PubMed was conducted utilizing the search terms "clozapine and suicide" and "clozaril and suicide."

Finally, the sponsor located an additional eight papers in the review of the reference lists of identified articles.

Altogether, 70 articles were identified by these searches and were reviewed by the sponsor. Among these, 34 were deemed to be relevant to the effects of Clozaril on suicidality. Of the pertinent articles, 11 described studies, 6 consisted of case reports and observational data, and 17 were review articles of previously published data on suicidality and clozapine.

Case reports cannot provide persuasive evidence of efficacy in suicidality and the review articles contained no data or references not presented in the other papers. Thus, this review will summarize findings of the 11 investigations describing studies of clozapine and suicidality.

## **V. Clinical Review Methods**

### **A. Items Utilized in the Review**

**Appendix V-1** lists the items that were utilized in this review. Also, relevant information from the Division File for IND 8,333 was examined.

Case Report Forms and Narrative Summaries were not submitted for all patients who experienced a serious adverse event (SAE). There were about 1500 adverse experiences classified by the sponsor as "serious" in study ABA 451. Many of these were classified as serious solely by virtue of hospitalization for exacerbation of the primary psychiatric illness. Thus, a listing of all serious adverse events (SAE's) was examined by the undersigned prior to the sNDA submission to identify those

events which warranted submission of a Case Report Form and Narrative Summary. This determination was based on a consideration of the expected clinical seriousness of the events and knowledge of those events already known to be associated with clozapine treatment. The selected adverse events are listed in **Appendix V-2**.

#### **B. Methods Used to Evaluate Data Quality**

The quality of data pertaining to efficacy (suicidality risk) in this supplement was evaluated by examination of randomly selected Case Report Forms. Additionally, a search was conducted for any blinded psychiatrist who had become unblinded during study ABA 451. These two assessments are further described in **section VI.E** below.

The quality of safety data was assessed by an audit of randomly selected Case Report Forms submitted for patients in study ABA 451 who died or experienced other designated serious adverse events. Also, the appropriateness of the coding of reported adverse event terms to MedDRA preferred terminology for patients in study ABA 451 was evaluated by the undersigned. These assessments are further described in **section VII.D** below.

Data quality was also assessed by the Division of Scientific Investigations via on-site inspections of four centers from Study ABA 451 (107, 114, 302, and 956). That inspection report is pending completion at this time.

#### **C. Adherence to Accepted Ethical Standards**

According to the study report (page 19), study ABA 451 was performed in accordance with Good Clinical Practice (GCP) standards.

Additionally, Novartis certifies that it did not and will not use in any capacity the services of any individual debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

#### **D. Evaluation of Financial Disclosure**

Financial disclosure information was requested by the sponsor from principal investigators, blinded raters, and members of the Suicide Monitoring Board (SMB) and Steering Committee (SC).

The following proportions of these individuals responded to the requests by the time this supplement was completed:

- 74% (60/81) of the principal investigators.
- 46% (80/174) of the blinded raters.
- 100% (3/3) of the SMB members.
- 84% (5/6) of the SC representatives.

Novartis states that due diligence is continuing to be exercised to collect financial disclosure information for all principal investigators and blinded raters.

Four principal investigators reported disclosable financial arrangements and interests:

- Vinod Kumar, M.D., of center 115, received consulting fees from the sponsor and began full-time employment with Novartis on 3-26-01. Involvement in study ABA 451 ended on 8-23-00. This center enrolled 4 patients (2 treated with Clozaril and 2 with Zyprexa).
- Alan I. Green, M.D., of center 116, has received support from Novartis as the principal investigator in other ongoing clinical trials as well as grants for other research. This center enrolled 12 patients (6 treated with Clozaril and 6 with Zyprexa).
- George T. Grossberg, M.D., of center 120, has received grants for ongoing research and honorarium from Novartis. This center enrolled 14 patients (7 treated with Clozaril and 7 with Zyprexa).
- Herbert Meltzer, M.D., of center 129, has received research grants from Novartis for a number of projects. This center enrolled 13 patients (7 treated with Clozaril and 6 with Zyprexa).

It is unlikely that these arrangements biased the study results since none of these individuals were raters of suicidality and each of these sites contributed a small fraction of the total patient sample.

## **VI. Integrated Review of Efficacy**

### **A. Overview of Data Relevant to Efficacy**

The demonstration of the efficacy of Clozaril in reducing suicide risk in schizophrenic patients at high risk for suicidality rests on the results of a single, prospective clinical trial, study ABA 451. This study is reviewed in detail below.

As mentioned above, the sponsor's literature search revealed 11 published investigations that produced clinical data relevant to a purported anti-suicide effect of Clozaril. These studies are summarized below. Based on my review of each investigation, they all suffer from significant flaws that render them incapable of providing convincing evidence of an anti-suicide effect.

### **B. Study ABA 451**

#### **1. Investigators/Sites**

In all, 67 centers worldwide enrolled patients in study ABA 451 (31 U.S. centers and 36 foreign centers). The location, number of randomized patients by treatment group, and principal investigator(s) for each of these centers are listed in **Appendix VI-1**.

No principal investigator (PI) was listed as disqualified by the Agency as of 7-16-02.

#### **2. Objectives**

The primary efficacy objective was to demonstrate a decreased risk for suicide among schizophrenic patients treated with Clozaril compared to the risk among patients treated with Zyprexa.

#### **3. Study Population**

A total of 980 patients were randomized to treatment with either Clozaril or Zyprexa in study ABA 451: 396 patients were randomized in the U.S. centers (198 each to Clozaril and Zyprexa) and 584 were randomized in foreign studies (292 each to Clozaril and Zyprexa).

Important inclusion criteria were:

- male or female patients, age 18-65, meeting DSM-IV criteria for schizophrenia or schizoaffective disorder.
- at high risk for suicidality as indicated by one of the following:

- attempted suicide within 3 years of study baseline assessments.
- hospitalized to prevent a suicide attempt within 3 years of baseline assessments.
- moderate to severe suicidal ideation with a depressive component within one week of baseline assessments.
- moderate to severe suicidal ideation with command hallucinations to do self-harm within one week of baseline evaluation.

Although Clozaril is approved only for treatment-resistant schizophrenia in the U.S., patients were enrolled in this trial irrespective of treatment-responsiveness.

Important exclusion criteria were:

- judged to be incompetent to make treatment decisions or refusal to agree to participation.
- no previous exposure to antipsychotic medication.
- extreme psychosis requiring immediate treatment.
- pregnancy or nursing a child.
- highly suicidal patients were not randomized until their condition was stabilized.

Additionally, enrollment of the following patients was discouraged:

- previous inadequate response to adequate doses of Clozaril ( $\geq 600$  mg/day) or Zyprexa ( $\geq 10$  mg/day) for at least 4 weeks.
- good clinical response to either Clozaril or Zyprexa, since they could be randomized to less effective medication.
- requiring complicated regimens of multiple medications.
- history of poor compliance with treatment plans.

## 4. Study Description

### Design

This was a prospective, randomized, open-label, 24-month trial with two active treatment arms, clozapine (Clozaril) and olanzapine (Zyprexa). Eligible patients were randomized in a 1:1 ratio to Clozaril or Zyprexa within each study center. Patients and PI's were not blinded during this study but each site did include blinded raters for efficacy and suicidality assessments.

### Dosing and Concomitant Medications

All study medication was dispensed at the investigational site. The recommended starting dose for Clozaril was 12.5mg bid with a suggested target dose range of 200-900 mg/day. The recommended starting dose for Zyprexa was 5 mg/day with a recommended target dose range of 5-20 mg/day. All patients were titrated to their most effective dose as tolerated. The doses used were to reflect the community norm.

Patients who entered the trial while receiving other antipsychotics were to be cross-titrated. The prior medication was to be weaned as the dose of study medication was titrated to therapeutic levels. Cross-titration was to be completed within 30 days of randomization if possible. Patients who had received depot medication were to be randomized once a full dosing interval had passed.

Randomized patients were allowed to take any medication deemed medically necessary and appropriate by the PI, to include the judicious use of antidepressants to treat worsening suicidal ideation or depression during the trial.

### Assessments

The PI conducted scheduled assessments of suicidality (i.e., completion of the InterSePT Suicidal Thinking and the CGI Severity of Suicidality scales) on a frequent basis.<sup>7</sup> However, information pertaining to a completed suicide, suicide attempt, hospitalization due to imminent suicide risk, or (for inpatients) an increased level of surveillance due to suicidality was collected throughout the 104 week treatment period and recorded in the CRF by the PI. Data relevant to suicides and suicide attempts

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<sup>7</sup> These assessments were conducted at baseline and at the following weeks: 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 60, 68, 80, 92, and 104.

were documented on the Suicide Attempt Form (SAF). Data relevant to hospitalization or increased surveillance due to imminent suicide risk were documented on the Imminent Risk of Suicide Requiring Hospitalization (IRH) form.

Psychiatrists at each site who were blinded to the patient's treatment (Blinded Psychiatrists or BP's) conducted the same assessments of suicidality on a less frequent basis.<sup>8</sup>

Additional efficacy measures (PANSS, CGI for Change in Psychosis, CGI for Severity of Psychosis, Calgary Depression Scale) were performed by blinded raters who could also have acted as the blinded psychiatrists.

#### Dropouts

If a patient discontinued participation in the study for any reason, the PI was to attempt to follow the patient by regular contact with the patient or the patient's family to determine if the patient completed or attempted suicide or was hospitalized for imminent risk of suicide. This follow-up period was to extend to what would have been Week 104 of the patient's treatment. Patients could elect not to be contacted during this period. Patients who consented to this follow-up were considered Retrieved Dropouts (RDO's) and assessments of suicidality by the unblinded PI were done every 12 weeks. Assessments on RDO's included the ISST-PI (InterSePT Scale for Suicidal Thinking-Principal Investigator) and the CGI-SS-PI (Clinical Global Impression of Severity of Suicidality-Principal Investigator); as indicated, the SAF (Suicide Attempt Form) and the IRH (Imminent Risk Requiring Hospitalization) form were also completed. All RDO assessments were completed by unblinded study staff.

Amendment #10 to the study protocol, submitted on 3-14-00, permitted the return of patients who had dropped out due to mild adverse events, loss to follow-up, transportation difficulties, and exacerbation of illness due to noncompliance, among other reasons, to resume study participation on the drug to which they were originally randomized at the study timepoint at which they had dropped out. Such patients had to request to resume study participation and continue to meet all eligibility criteria. Also, the treating physician must have deemed

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<sup>8</sup> Blinded assessments were done at baseline and at the following weeks: 8, 16, 24, 32, 40, 48, 52, 60, 68, 80, 92, and 104.

resumption of study treatment in the best interest of the patient.

Novartis was advised by the Division in a 5-1-00 letter that this amendment was considered likely to confound the assessment of suicidality in this study for several reasons, such as the introduction of a variable (a break in treatment that may include other interim therapy) which could influence the occurrence of suicidality later in the trial. Therefore, the Division recommended that this amendment not be implemented. Despite this advice, it appears that the sponsor implemented this protocol change.

#### Maintenance of Blinding

It was considered possible that any decrease in suicidality observed in Clozaril patients might be due to the frequent contact with healthcare professionals consequent to the mandatory WBC monitoring with Clozaril. WBC monitoring was performed weekly for the first 26 weeks then every 2 weeks thereafter. To balance this potential source of bias between the two groups, Zyprexa patients were also seen on this same schedule for vital sign measurements. Also at these visits, an unblinded healthcare professional assessed the patient's overall psychiatric condition, to include suicidality, and referred the patient to the investigator or other professional for further evaluation and possible intervention when deemed appropriate.

As noted above, patients and PI's were not blinded. To address the possibility of biased assessments of primary outcome occurrences (Type 1 and Type 2 Events), the following measures were instituted.

First, as mentioned above, each site included a psychiatrist who was blinded to the patient's treatment. Ratings on the CGI-SS-BP, to detect a possible Type 2 Event, were performed by the blinded psychiatrist. These individuals affirmed their blinded status or indicated unblinding at each assessment.

Second, the flow of data pertaining to a possible Type 1 event was designed to help assure unbiased detection and confirmation of these events. The relevant personnel and study features are described in detail below.

PI's collected and forwarded all relevant information on any potential Type 1 event to Ingenix Pharmaceutical

Services, Inc., a contract research organization. This included information on all deaths, suicide attempts, psychiatric hospitalizations, discontinuations of study drug, and increased surveillance due to imminent suicide risk. Blinded reviews of the study clinical database were also performed by Ingenix to identify any potential Type 1 events that might have been missed.

Ingenix reviewed the data from the study site and censored any information that was likely to unblind the reader to the patient's treatment, to include signs or symptoms that might unwittingly reveal the patient's treatment. The data were then forwarded to the BP's and to the Suicide Monitoring Board (SMB).

The SMB was a blinded body comprised of three clinicians who are experts in the study of suicide with experience in schizophrenia. The SMB Chairman was Ranga Krishnan, M.D., Duke University Medical Center, Durham, NC; SMB members were Hannele Heila, M.D., National Public Health Institute, Helsinki, Finland, and Isaac Sakinofsky, M.D., University of Toronto, Toronto, Canada.

Under no circumstances was the SMB to be unblinded to the treatment of any study patient. If any member of the SMB became unblinded, the SMB Chairman was to be notified who, in turn, would notify Novartis.

The primary purpose of the SMB was to make determinations regarding the blinded data received from Ingenix as follows:

- for all deaths, to judge whether the death represented a suicide.
- for all self-damaging acts, regardless of intention, to determine if the act represented a serious suicide attempt as opposed to a suicide gesture or non-attempt.
- for all hospitalizations and increases in the level of surveillance for suicide, to ascertain whether these represented interventions to prevent an imminent suicide attempt.
- for all discontinuations from study drug treatment due to increasing suicidality, to determine whether discontinuation occurred because of imminent suicide risk.

The SMB conducted regular teleconferences to discuss blinded data from Ingenix and to reach consensus on each

event. If there was disagreement on a determination, a vote was to be taken and the final determination was defined as that of the majority of the SMB members.

Although blinded data from Ingenix for all potential Type 1 events were also reviewed by the BP's, the determination of the SMB regarding the presence or absence of a Type 1 event was considered primary for purposes of efficacy analysis.

#### Steering Committee

Oversight and guidance for study ABA 451, with the purpose of minimizing risk to study participants and maintaining the scientific integrity of the trial, was provided by the study Steering Committee (SC). Although the SC interacted with a liaison from Novartis (Ravi Anand, M.D.), this committee was considered to be an independent body. The SC was comprised of the Chairman, John Kane, M.D., and members Daniel Casey, M.D., Prof. Frederic Rouillon, Prof. Giovanni Cassano, Prof. Shon Lewis, Prof. Istvan Bitter (resigned November 2000), and Nancy Temkin, Ph.D.

### **5. Efficacy Analysis Plan**

The efficacy analysis plan for this study has been amended from that specified in the original protocol. In the original protocol, two primary variables were specified:

- time from baseline to the first significant suicide attempt or hospitalization due to imminent risk of suicide confirmed by the SMB.<sup>9</sup> This analysis was to be performed using a Cox proportional hazards regression model. Explanatory variables were treatment and the following baseline measures: number of lifetime suicide attempts, active substance/alcohol abuse, pooled country, sex, and age (18-32 years, 33-44 years, and 45 years and older).
- change from baseline in the CGI-SS-BP severity score as rated on a 5-point scale. These data were to be analyzed using an ANCOVA model with the same explanatory variables listed above as well as the baseline CGI-SS-BP severity score.

During the course of study ABA 451, Novartis found that the rate of suicides and suicide attempts was lower than predicted and the rate of loss to follow-up was higher than

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<sup>9</sup> Amendment #1 to the protocol added an increased level of surveillance for suicide risk as a primary outcome.

predicted when the sample size for the trial was computed. Additionally, the sample size calculation did not account for the need to adjust the significance level for multiple comparisons, given that there were two primary efficacy variables. As a result of these factors, Novartis felt that 80% power to detect a intergroup difference would not be achieved and, therefore, it would be more likely that this trial would fail to demonstrate the superiority of Clozaril over Zyprexa in reducing suicidality.

To address this concern, the sponsor convened a group of clinical and statistical experts in August 2000. It was recommended that specific revisions to the primary study objectives and statistical analysis plan be implemented as described below. These changes comprised Amendment #6 to the protocol, which was submitted to the Agency on 1-2-01.

The revised study objective was to demonstrate a decreased risk for suicide among schizophrenic patients treated with Clozaril compared to patients treated with Zyprexa as measured by the time (in days after randomization) to the following two types of events:

Type 1 Event - a significant suicide attempt or completed suicide, hospitalization due to imminent suicide risk, or increased surveillance due to suicide risk, whichever came first and regardless of whether the subject was still on randomized treatment. If none of these events occurred during the entire study period, time was censored on the date of study drug discontinuation or on the last date of retrieved data, whichever was later.<sup>10</sup>

Type 2 Event - 1) worsening of the severity of suicidality as manifested by a score of 6 or 7 (worse or very much worse) on the 7-point change score of the Clinical Global Impression for Severity of Suicidality as rated by a blinded psychiatrist (CGI-SS-BP) or 2) the occurrence of a Type 1 Event, whichever came first and regardless of whether the subject was still on randomized treatment. If neither event occurred throughout the entire study period, time was censored on the date of study drug discontinuation or on the last date of retrieved data, whichever was later.

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<sup>10</sup> Amendment #6 did not specify that time to either type of event or censoring would include time subsequent to premature termination for dropouts.

The revised primary analysis was based on the approach of Wei, Lin, and Weissfeld, known as the WLW method.<sup>11</sup> Using this multiple events analysis technique, the time to the first occurrence of a Type 1 event and time to the first occurrence of a Type 2 event were modeled using a proportional hazards approach to derive treatment effect estimators for each event type, with country pool as strata and treatment group as the only covariate.<sup>12</sup> The WLW method provided a single test for treatment effect based on two time to event endpoints, with the two event types given equal weighting in this case. Then, a two-sided test was performed at the 0.05 level of significance to compare the combined treatment estimators between the two treatment groups.

A number of supplemental analyses were also performed, to include the following:

- the original primary efficacy analyses, as described above.
- analysis of time to Type 1 events using a full Cox proportional hazards regression model adjusted for a number of baseline factors, which permitted assessment of the effect of these factors on time to event.
- analyses for diagnostic subgroups, i.e., patients with schizophrenia versus patients with schizoaffective disorder.
- analyses for geographic subgroups, i.e., North America versus the rest of the world.

## **6. Baseline Patient Characteristics**

At baseline, the Clozaril and Zyprexa treatment groups were comparable in terms of mean PANSS total scores (84.8 vs. 82.6, respectively).

With respect to suicidality, the two treatment arms had almost identical distributions of CGI-Severity of Suicidality scores as rated by the blinded psychiatrists (**Appendix VI-2**). On average, Clozaril patients had a

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<sup>11</sup> Please see the statistical review for further discussion of the WLW methodology.

<sup>12</sup> Countries with small numbers of patients were pooled with other countries to form a "pooled country" factor that was used as a stratum in the statistical analyses. Pooled countries were grouped as follows: U.S. and Canada, S. Africa and the U.K., France and Italy, Argentina and Chile, Croatia and the Czech Republic, and Hungary.

lifetime history of 3.6 suicide attempts compared to 3.2 suicide attempts among Zyprexa patients. About 15% of each group had no history of previous suicide attempts and another 15% of each group had a history of more than 5 suicide attempts. The median number of lifetime hospitalizations to prevent a suicide attempt was 2 in each treatment arm.

Baseline demographic characteristics are displayed in **Appendix IV-1**. The treatment groups were almost identical in terms of age, gender, and racial composition.

Diagnostically, 61% (300/490) of Clozaril and 63% (309/490) of Zyprexa patients were diagnosed with schizophrenia; 39% (190/490) of Clozaril and 37% (181/490) of Zyprexa patients were diagnosed with schizoaffective disorder. About one-fourth of each group was considered treatment-resistant by clinical assessment.

About one-half of each treatment group had a history of alcohol or other substance abuse (48% of Clozaril and 51% of Zyprexa patients). At baseline, 11% of each group had current alcohol or other substance abuse.

The baseline mean total scores for the Calgary Depression Scale (CDS) were very similar between groups: Clozaril= 9.8 (SD=5.9), Zyprexa= 9.9 (SD=5.9). The percentages of patients with each score on the Hopelessness item (item #2) of the CDS were also similar between the two groups at baseline.

## **7. Patient Disposition**

A total of 1,065 patients were screened for study ABA 451. Of these, 980 were randomized to Clozaril (N=490) or Zyprexa (N=490) and comprised the intent-to-treat (ITT) population.

In all, 61% (298/490) of the Clozaril and 62% (303/490) of the Zyprexa patients completed the entire 2 year study. Including retrieved dropouts, 39% (192/490) of the Clozaril and 38% (187/490) of the Zyprexa patients discontinued from the study. These dropouts are enumerated by reason for discontinuation in **Appendix VI-3**. It is notable that 33 Clozaril and 39 Zyprexa patients were lost to follow-up. It is not known if any of these patients were lost due to suicide attempts or completed suicide.

The numbers of patients in the study by visit are displayed in **Appendix VI-4**. At least 70% (344/490) of Clozaril patients were still in-study at the week 40 visit, with 76% (370/490) of the Zyprexa patients still participating at that timepoint.

## **8. Dosing Information**

Ten of the Clozaril patients and 11 of the Zyprexa patients in the ITT population were not dispensed study drug. Also, one of the Clozaril patients and 2 of the Zyprexa patients who were dispensed drug did not take study medication.

Among the 479 Clozaril patients who took study drug, the overall mean daily dose was 308.7 mg (SD= 555 mg). The mean prescribed doses of Clozaril gradually increased from 150 mg/day at week 1 to just under 300 mg/day at week 12; thereafter, mean prescribed doses were in the range of 300 to 334 mg/day, with a maximum of 800 or 900mg/day.

Among the 477 Zyprexa patients who took study drug, the overall mean daily dose was 17.0 mg (SD= 25.5 mg). Mean prescribed doses of Zyprexa gradually increased from 12 mg/day at week 1 to about 17 mg/day after week 10; mean doses remained in the range of 17 to 18 mg/day for the remainder of the trial, with maximum doses of generally 50 mg/day.

Median prescribed doses by visit are presented in **Appendix VI-5**. From week 10 onward, the median doses of Clozaril and Zyprexa were 300 and 20 mg/day, respectively.

## **9. Concomitant Medications**

Patients who entered the study while taking other antipsychotic medication were to be cross-titrated within 30 days of randomization. Also, after randomization, concomitant psychotropic medications were permitted by protocol if deemed necessary and appropriate by the investigator. Psychopharmacologic agents were used by a substantial proportion of patients during the study. For example, among the 479 Clozaril and 477 Zyprexa patients who took study medication, concurrent selective serotonin reuptake inhibitors were used by 39% of Clozaril and 46% of Zyprexa patients. Also, it is notable that 5 patients randomized to Zyprexa received Clozaril concomitantly and

16 patients randomized to Clozaril received Zyprexa concomitantly.

The concomitant use of psychopharmacologic agents during this trial could confound the assessment of an anti-suicide effect. To better appreciate the extent of this potential source of bias, the Division requested that Novartis devise a method to demonstrate that the use of concomitant psychotropic medication is unlikely to have biased the results of study ABA 451. The plan devised by the sponsor and the results of this analysis are described below.<sup>13</sup>

#### Analysis Plan

The sponsor grouped concomitant psychotropic medication used in study ABA 451 into the following groups: antidepressants, antipsychotics, sedatives/anxiolytics, and mood stabilizers. Stimulants and anti-dementia drugs were excluded. Once a medication was assigned to one of the above classes, all uses were included in the analysis (both psychiatric and non-psychiatric indications). However, medication usage based on a PRN schedule was excluded as were antidepressants and mood stabilizers taken for less than 14 days.

To pool the use of medications of different potencies within a class, the dosage of each drug was converted to dosage equivalents within each class based on conversion data and average doses reported in current literature. Antidepressants were converted to fluoxetine equivalents, sedatives/anxiolytics to diazepam equivalents, antipsychotics to haloperidol equivalents, and mood stabilizers to carbamazepine equivalents.

Then, the total AUC (sum of the areas under the converted dosage versus time curves for all drugs within a class) over successive 6 month intervals was calculated for each patient for each concomitant drug class.

Next, the mean dose per patient for each class was calculated by dividing the total AUC by the number of days in-study for that patient during each 6 month interval. For dropouts, no mean dose was computed after the end of the 6 month interval in which the patient dropped out.

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<sup>13</sup> This information was submitted to the NDA on 6-24-02.

Finally, for each drug class and each interval, the average mean dose was determined over all patients. ANCOVA, with terms for treatment, pooled country, and concomitant medication dose at baseline, was performed to compare the least squares mean dosage (LSMD) between treatment groups for each 6 month interval, with statistical significance defined as a p-value  $\leq 0.05$ .

#### Analysis Results

Of all patients who took study drug (N=956), a large proportion took psychopharmacologic drugs concomitantly and were included in the analysis: 84% took antipsychotics, 65% took sedative/anxiolytics, 53% took antidepressants, and 28% took mood stabilizers. **Appendix VI-6** enumerates these patients by treatment group.

Pooling data across all 6 month intervals, the LSMD's for Clozaril were significantly less than for Zyprexa for all four drug classes (**Appendix VI-7**).

A breakdown of the LSMD's by 6 month intervals is provided in **Appendix VI-8** (for antipsychotics), **Appendix VI-9** (antidepressants), **Appendix VI-10** (sedatives/anxiolytics), and **Appendix VI-11** (mood stabilizers). For most comparisons, the LSMD for Clozaril was less than for Zyprexa to a statistically significant degree. For the remainder of the comparisons (i.e., antidepressants during months 13-18 and 19-24 and mood stabilizers during months 19-24), the LSMD's was numerically less for Clozaril than for Zyprexa.

In sum, the sponsor's analysis revealed no evidence to suggest a bias due to concomitant medication usage that favored Clozaril over Zyprexa. These results should be interpreted with a large grain of salt since this analysis is based on an imperfect surrogate measure for the confounding influence of concomitant psychotropic medication on suicidality.

#### **10. Protocol Deviations**

A common protocol deviation was a change in clinical raters during the study. In particular, it was noted that 42% of the Clozaril patients and 44% of Zyprexa patients had a change in the rater for the CGI-SS-BP during their trial participation, which included an assessment by a blinded psychiatrist of the change in suicidality compared to the

patient's condition at baseline. The reliability of this specific rating, which was one of the key outcome variables, may have been compromised by the changes in raters for this scale. The extent to which this was true is very difficult to gauge.

## 11. Study Results

### Psychotic Symptomatology

Both treatment groups experienced improvement in psychotic symptomatology as measured by changes from baseline to end of study (LOCF) in the PANSS total score (-23.6 for Clozaril and -22.4 for Zyprexa; p-value= 0.3591). The PANSS positive and negative subscales and the CGI for severity of psychosis (CGI-SP) provided further evidence of improvement for both Clozaril and Zyprexa patients.

### Enumeration of Patients with Type 1 & Type 2 Events

The numbers and percentages of patients with Type 1 events, as determined by the SMB, and Type 2 events, as determined by the BP's, are displayed in **Table VI-1** below. In the primary analysis, any Type 1 event was taken to imply a Type 2 event; thus, patients with a Type 1 event are a subset of the patients with a Type 2 event. Clearly, the predominant event type was Type 1. For both event types, the proportion of patients with the event was significantly lower in the Clozaril compared to the Zyprexa group.

<b>TABLE VI-1</b>			
<b>NUMBER (%) OF ITT PATIENTS WITH TYPE 1 AND TYPE 2 EVENTS</b>			
<b>Event Type</b>	<b>Clozaril (N=490)</b>	<b>Zyprexa (N=490)</b>	<b>p-value<sup>14</sup></b>
Type 1	102 (20.8%)	141 (28.8%)	0.0049
-Completed Suicide	5 (1.0%)	3 (0.6%)	0.7254
-Suicide Attempt	34 (6.9%)	55 (11.2%)	0.0257
-Hospitalization	82 (16.7%)	107 (21.8%)	0.0518
Type 2	120 (24.5%)	161 (32.9%)	0.0047

### WLW Analysis

The amended primary analysis was a single composite analysis of time to the first occurrence of a Type 1 event and time to the first occurrence to a Type 2 event using WLW methodology, as described above, with equal weighting given to each event type in the model. The analysis was

<sup>14</sup> Based on Fisher's exact test.

based on all randomized patients (490 Clozaril and 490 Zyprexa patients).

The results are summarized in **Appendix VI-12**. The coefficient of combined treatment effect from the primary model was -0.265, with a p-value for the Clozaril/Zyprexa comparison of 0.0309.<sup>15</sup> Examining the WLW treatment effect estimators for Type 1 and Type 2 events separately, there was a significantly lower risk of each event with Clozaril versus Zyprexa: the respective hazard ratios (95% CI) were 0.76 (0.58, 0.98) and 0.78 (0.61, 0.99).<sup>16</sup>

#### Original Primary Analysis

As a supplemental analysis, the sponsor also analyzed the results of this trial utilizing the methods proposed in the original protocol (and Amendment #1). This entailed examination of two variables: 1) the time from baseline to the first significant suicide attempt, hospitalization due to imminent risk of suicide, or an increased level of surveillance for suicide risk (Type 1 event), using a Cox proportional hazards regression model; and 2) change from baseline in the CGI-SS-BP severity of suicidality score as rated on a 5-point scale, analyzed using an ANCOVA model.

The Type 1 event results were similar to those in the amended primary analysis: there was a statistically significant lower risk of a Type 1 event among Clozaril versus Zyprexa patients (regression coefficient for treatment= -0.304, p=0.0211; hazard ratio= 0.74 (95% CI= 0.57, 0.96)). However, results for the change from baseline in the CGI-SS-BP severity score were not statistically significant (regression coefficient= +0.007, p-value= 0.8884).

#### Kaplan-Meier Analysis

A secondary analysis was a Kaplan-Meier survival analysis of the cumulative probabilities of Type 1 events and Type 2 events. Kaplan-Meier survival curves are displayed in **Appendix VI-13** (Type 1 events) and **Appendix VI-14** (Type 2 events). Survival data by visit are displayed in **Appendix VI-15**. The cumulative probabilities of experiencing an event were numerically lower for Clozaril patients than for Zyprexa patients at all visits for each event type.<sup>17</sup> At

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<sup>15</sup> A coefficient <0 indicates that Clozaril was superior to Zyprexa.

<sup>16</sup> A hazard ratio <1 indicates superiority of Clozaril over Zyprexa.

<sup>17</sup> The 95% CI's for the treatment group differences contained zero (implying no difference) up to and including the week 80 visit.

week 104, the cumulative probabilities were significantly lower for Clozaril (Table VI-2 below).

TABLE VI-2 KAPLAN-MEIER ESTIMATES OF THE CUMULATIVE PROBABILITIES OF A TYPE 1 OR TYPE 2 EVENT AT WEEK 104			
Event Type	Clozaril	Zyprexa	p-value <sup>18</sup>
Type 1	0.24	0.32	0.020
Type 2	0.28	0.37	0.027

## 12. Conclusions from Study ABA 451

The results of study ABA 451 appear, on face, to support the hypothesis that Clozaril treatment is associated with a reduced risk of suicidality compared to Zyprexa therapy. However, the validity of this finding is questionable for several reasons:

1) the primary efficacy analysis (WLW methodology) included patients who had dropped out and discontinued study drug but were being followed as retrieved dropouts. In my opinion, to assess the effect of ongoing drug exposure on event occurrence, patients included in the analysis should be receiving drug and patients who drop out of drug treatment should be right-censored at the time of dropout. Otherwise, and particularly in a long-term study like ABA 451, it is very tenuous to ascribe the occurrence or non-occurrence of events to study drug. Censoring dropouts may significantly change the study outcome.

2) Amendment #9 to the study protocol allowed patients who had dropped out of the study to re-enter the trial as full participants at a later date and continue the originally assigned medication on the study day of dropout. This change introduced a variable (a break in treatment that may have included interim interventions) that could have influenced the risk of suicidality after re-entry of these patients, thus confounding the efficacy results. It is not known how many patients actually returned to the study under this amendment.

3) a number of patients (33 Clozaril and 39 Zyprexa patients) were lost to follow-up at some point during this trial. It is not known if any of these patients experienced a suicidality-related event (such as suicide or

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<sup>18</sup> Log rank test.

a serious suicide attempt) that led to study discontinuation. The possibility remains that information about the circumstances of discontinuation in these patients might appreciably change the study results.

4) for a sizeable proportion of patients in each group (42% of Clozaril and 44% of Zyprexa patients), there was a change in the blinded rater who completed the CGI for severity of suicidality (CGI-SS-BP). A key outcome variable was the rating of the change in the patient's suicidality compared to the baseline condition using this scale. The reliability of a new rater in assessing change from the baseline condition is very questionable.

5) a substantial number of patients took concomitant psychiatric medication during this study. While it would be expected to see a large number of such patients taking antipsychotics early in the trial (due to the cross-titration procedure for patients on antipsychotics at study entry), it is noted that 273 Clozaril and 279 Zyprexa patients took concomitant antipsychotics during the last 6 month interval of the study (months 19-24). During this same interval, antidepressants were taken by 169 Clozaril and 201 Zyprexa patients. It is unknown how many of these patients were simply continuing pre-study medication versus the number who were deemed to require the institution of psychotropics for emergent conditions, such as suicidal ideation, during the study. It is acknowledged that the sponsor's analysis of concomitant psychotropic drug use represents a good-faith effort to address this issue and that a complete understanding of the impact of this usage is likely impossible. Nonetheless, the inability to fully quantify this potential confounding influence does not render it ignorable.

6) as is discussed in detail in section VI.E (Assessment of Efficacy Data Quality), an audit of the suicidality data from this trial revealed two potential findings (possible biased SMB determinations and unblinding) that could impact on the reliability of the data from study ABA 451.

The above factors raise a considerable question about the validity of the study findings. At this point in time, the stated findings from study ABA 451 are best considered inconclusive.

## C. Important Clinical Issues Pertinent to Efficacy

### 1. Suicidality Indication

According to the proposed INDICATIONS AND USAGE section of Clozaril labeling, Novartis is seeking approval for the treatment of suicidality in patients with schizophrenia or schizoaffective disorder. Suicidality is defined as actions by a patient committed either with willful intent or as a response to internal compulsions or disordered thinking that put him/herself at high risk for death.

Evidence for this claim is derived from study ABA 451. This trial utilized the following inclusion criteria to identify patients at high risk of suicidality:

- attempted suicide within 3 years of baseline.
- hospitalized to prevent a suicide attempt within 3 years of baseline.
- moderate to severe suicidal ideation with a depressive component within one week of baseline.
- moderate to severe suicidal ideation with command hallucinations to do self-harm within one week of baseline.

To be included in this study, a patient had to meet one of the above criteria. Thus, the study population was likely quite heterogeneous at baseline in terms of imminent suicide risk, ranging from patients with active suicidal ideation and a plan to harm themselves to patients who were hospitalized 3 years before study participation for suicidal ideation which has long since resolved. Clearly, patients were not required to be actively suicidal at the time of study entry. In fact, according to the study report, patients who were "highly suicidal" were not randomized until their condition stabilized.

Critical to the approval of a claim for the treatment of any given condition is the requirement that the effect of the intervention be demonstrated in patients with that condition. Therefore, to the extent that study ABA 451 included patients who were not suicidal at baseline, this trial is not capable of providing evidence of the efficacy of Clozaril in treating suicidality.

Furthermore, the design of ABA 451, which examined the risk of suicidality-related events over a two year period, would not be appropriate to demonstrate efficacy in treating

acute suicidality. A claim for the latter would imply an intervention that reduces the risk of self-harm or death in the short-term (days to a few weeks), not over a period of years.

In summary, an acceptable study for evaluating a treatment for suicidality would enroll actively suicidal patients only and anticipate a response over a relatively brief period of time. ABA 451 is not such a trial.

On the other hand, the results of ABA 451 may be useful in demonstrating a reduced risk of suicidality associated with long term Clozaril versus Zyprexa treatment. The use of Clozaril as a preventive measure in this regard would be a feasible indication for the sponsor to seek. In that case, a critical and difficult clinical issue to be addressed is the identification of patients for whom Clozaril is indicated for the purpose of suicidality prevention. Since it is anticipated that the sponsor will amend this application to seek approval of this use, this issue will be explored further at this point.

The emergence of suicidality is frequently precipitated by external events (e.g., loss of a significant other person or a financial crisis) superimposed on various underlying cofactors (such as substance abuse, depression, or health problems). Unfortunately, due to the unpredictable nature of these precipitants, there is no reliable way of identifying those patients who will become suicidal.

As a conservative practice, any patients with a history of any suicidality might be treated with Clozaril. However, the wisdom of switching large numbers of patients to Clozaril from otherwise effective and well-tolerated antipsychotic therapy or choosing to initiate Clozaril over other drugs that might be better tolerated and perhaps more effective is debatable. Not to be ignored are the cost, inconvenience, and discomfort associated with the white blood cell monitoring required for patients treated with Clozaril.

A better approach would be the use of Clozaril in a more discriminating fashion, such as in patients with a pattern of chronic suicidal behavior or suicidal ideation who are deemed to be at some continuing risk of suicide. It would be difficult to formulate specific criteria for such use for labeling and, ultimately, this decision should depend

on the judgement of the treating physician, who is capable of considering the clinical nuances of the patient's history and presentation and weighing the risks versus potential benefits for the individual patient. But, in this case, it may be more appropriate to simply describe the results of study ABA 451 in labeling and allow prescribers to decide, on a patient-by-patient basis, whether Clozaril is indicated. A potential downside is that some managed healthcare organizations may refuse to subsidize the cost of Clozaril and WBC monitoring for these patients without a formal, labeled indication for such use.

The best solution to this problem is not clear at this time.

## **2. Predictors of Response**

### Covariate Analyses

A covariate analysis was performed on data from study ABA 451 to identify prognostic factors for suicidality using a full Cox proportional hazards regression model for time to a Type 1 event. Covariates included the following: treatment, gender, age group ( $\leq 32$ , 33-44,  $\geq 45$  years), number of lifetime suicide attempts, diagnosis, alcohol or other substance abuse, and a number of baseline ratings, to include the CGI-SS-BP severity score, Calgary Depression Scale score, and the Covi Anxiety Score.

Results are depicted in **Appendix VI-16**. These analyses revealed that treatment, the number of lifetime suicide attempts, and the presence of substance or alcohol abuse were statistically significant prognostic factors for Type 1 events.

Adjusting for risk factors demonstrated a treatment effect favoring Clozaril on SMB-confirmed Type 1 events (hazard ratio= 0.73, p-value= 0.0172). Interestingly, when this analysis is applied to the time to Type 1 events as confirmed by the blinded psychiatrist, Clozaril has a somewhat larger hazard ratio (0.84) and treatment is no longer a statistically significant predictor (p=0.1839).<sup>19</sup>

With respect to the number of lifetime attempts, the hazard ratio was 1.03 (p=0.0001), indicating that an increased

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<sup>19</sup> See Appendix 5.3.1, Table 9.1-5, of the study report.

number of attempts was associated with a very slightly increased risk of a Type 1 event.

Regarding substance or alcohol abuse, the hazard ratio was 1.48 (p=0.0081), indicating an association between alcohol or substance abuse and an increased risk of a Type 1 event.

A similar covariate analysis of time to a Type 2 event revealed analogous findings.

Diagnostic Subgroup Analysis

Although the above analysis did not reveal an significant effect of diagnosis on the time to a Type 1 or Type 2 event, a subgroup analysis was specifically requested by the Division. The numbers and percentages of Clozaril and Zyprexa patients with Type 1 and Type 2 events as well as the Kaplan-Meier cumulative probabilities of events are displayed by diagnostic subgroup (schizophrenia vs. schizoaffective disorder) in **Table VI-3** below. For all treatment group comparisons, Clozaril was numerically superior to Zyprexa in terms of event risk regardless of diagnosis (formal statistical testing was not performed).

<b>TABLE VI-3</b>						
<b>NUMBER (%) OF ITT PATIENTS WITH TYPE 1 AND TYPE 2 EVENTS BY DIAGNOSTIC SUBGROUP<sup>20</sup></b>						
	<b>Clozaril (N=490)</b>			<b>Zyprexa (N=490)</b>		
	<b>n/N</b>	<b>%</b>	<b>KM %</b>	<b>n/N</b>	<b>%</b>	<b>KM %</b>
<b>Schizophrenia</b>						
Type 1	51/300	17.0%	19.5%	82/309	26.5%	29.3%
Type 2	67/300	22.3%	25.9%	98/309	31.7%	35.1%
<b>Schizoaffective Disorder</b>						
Type 1	51/190	26.8%	31.0%	59/181	32.6%	37.2%
Type 2	53/190	27.8%	32.1%	63/181	34.8%	39.5%

The sponsor repeated the WLW analysis for each of the two diagnostic subgroups. The results are presented in **Appendix VI-17**.

For patients with schizophrenia, the results were consistent with those for the entire study population. The combined estimate of treatment effect favored Clozaril over

<sup>20</sup> N= total number of patients in subgroup, n= number of patients with event in subgroup, %= (n/N)×100%, KM %= Kaplan-Meier estimate of the cumulative probability of the event at week 104.

Zyprexa to a statistically significant degree ( $p=0.0298$ ). For Type 1 events, the Clozaril effect was superior ( $p=0.0251$ ) and, for Type 2 events, borderline superior ( $p=0.0516$ ). The hazard ratios (95% CI's) were 0.67 (0.47, 0.95) and 0.73 (0.54, 1.00), respectively.

For patients with schizoaffective disorder, the estimates of treatment effect using the WLW analysis and for Type 1 and Type 2 events separately favored Clozaril but were smaller than in the schizophrenia subgroup; none approached statistical significance. The hazard ratios (95% CI's) for Type 1 and Type 2 events were 0.87 (0.60, 1.27) and 0.85 (0.59, 1.23), respectively.

These data suggest that Clozaril may be less effective in reducing suicide risk in patients with schizoaffective disorder compared to patients with schizophrenia.

#### Geographic Subgroup Analysis

The sponsor repeated the WLW analysis of time to Type 1 and Type 2 events based on geographic subgroups (U.S. and Canada (N. America) vs. the rest of the world). The results are summarized in **Appendix VI-18**. In both subgroups, Clozaril was numerically superior to Zyprexa in the combined estimate of treatment effect as well as for Type 1 and Type 2 events separately. However, statistical superiority was not demonstrated for any comparison in either subgroup. Hazard ratios (95% CI's) were not substantially different between North America and the rest of the world (for Type 1 events, 0.78 (0.56, 1.08) and 0.72 (0.48, 1.08), respectively; for Type 2 events, 0.75 (0.55, 1.04) and 0.81 (0.57, 1.16), respectively).

### **3. Size of Treatment Effect**

In terms of the anti-suicide effect size in study ABA 451, it is useful to consider the cumulative probability of a Type 1 event from the Kaplan-Meier survival analysis.

At week 104, there was a substantial cumulative probability of suicide, attempted suicide, or hospitalization or increased surveillance due to imminent suicide risk in both the Clozaril and Zyprexa treatment groups (0.24 and 0.32, respectively). The 95% CI for the difference between the two groups is (0.02, 0.15). Thus, the point estimate for the difference in cumulative probabilities is not large (0.08) and the true difference may be quite small (0.02).

#### **4. Choice of Dose**

The sponsor is recommending that the dosage of Clozaril for the treatment of schizophrenic and schizoaffective disorder patients at risk for suicide be the same as for patients with treatment-resistant schizophrenia.

Presumably, in study ABA 451, doses were titrated primarily on the basis of tolerability and antipsychotic efficacy, as opposed to antisuicidal efficacy, since most patients did not manifest imminent suicidality most of the time. Based on this assumption, the sponsor's dosing recommendations seem appropriate.

#### **5. Duration of Treatment**

This application seeks an indication for suicidal antipsychotic-naive patients to initiate continuous antipsychotic treatment with Clozaril or for suicidal patients currently treated with another antipsychotic to begin continuous Clozaril therapy either in place of or in addition to their existing treatment.

In this context, the duration of treatment with Clozaril would be dictated by its use as an antipsychotic agent and currently labeled advice would apply.

#### **D. Summary of Pertinent Published Literature**

##### **1. Botsis AJ, et al. Clozapine efficacy on suicidal behavior across two main psychiatric disorders. Eur Neuropsychopharmacol 1997;7:S202.**

This was a prospective study of 10 patients with severe suicidal behavior, 6 diagnosed with schizophrenia and 4 with psychotic depression. These patients had received high doses of typical neuroleptics (and high doses of antidepressants in the depressed patients) for at least 4 weeks, followed by treatment with clozapine (up to 450 mg/day) for 4 weeks. Suicidal behavior and general psychopathology was found to be decreased after 3 weeks of clozapine therapy.

This study was a small, historical control trial. Details of suicidality assessments and findings were not provided.

**2. Ciapparelli A, et al. Clozapine for treatment-refractory schizophrenia, schizoaffective disorder and psychotic bipolar disorder: a 24-month naturalistic study. J Clin Psychiatry 2000;61:329-334.**

This was a prospective study in adult patients with schizophrenia (N=31), schizoaffective disorder (N=26), and psychotic bipolar disorder (N=34). About 25% had suicidal ideation or a history of suicide attempt at baseline. Patients were treated for 24 months with flexible dose clozapine; many patients also received other neuroleptics as well as typical neuroleptics, antidepressants, anticonvulsants, lithium, benzodiazepines, and other medications. An analysis restricted to those with suicidal ideation at baseline revealed a significant reduction in the BPRS-Expanded suicide item at 24 months.

This trial was a historical control trial with efficacy findings confounded by substantial use of concomitant psychotropic medication.

**3. Littrell KH, et al. The experience of hope in adults with schizophrenia. Psychiatric Rehabilitation Journal 1996;19:61-65.**

This was a prospective study of the combined effect of psychosocial treatment and clozapine in 44 adult patients with refractory schizophrenia. The primary study focus was on 14 patients with previous suicide attempts. Patients were assessed after 6 and 12 months of clozapine at a mean dose of 550 mg/day. None of the patients attempted suicide during the 12 month trial period. The authors suggest that combined intervention is associated with decreased suicidality.

This was a historical control trial in a small number of patients with past suicide attempts. Clozapine effects may have been confounded by psychosocial treatment. The methodology for assessing a reduction in suicide potential was not described in detail.

**4. Meltzer HY and Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995;152:183-190.**

This was a retrospective study that included an evaluation of the effect of clozapine on suicidality in 183 patients with neuroleptic-resistant schizophrenia or schizoaffective disorder. Clozapine was begun during an index hospitalization and 88 neuroleptic-resistant patients received clozapine for at least 6 months for a period up to 2 years. Data reflecting suicidal thoughts and suicide attempts prior to clozapine were compared with corresponding measures during clozapine treatment. Results indicated a reduction in suicide attempts from 25% (22/88) pre-clozapine to 3.5% (3/88) after clozapine treatment.

This was a historical control study. Also, although the reduction in the proportion of patients attempting suicide was remarkable, it was not clear that the authors had adequately controlled for the durations of observation during the pre-clozapine and clozapine treatment periods in analyzing the suicidality results, rendering the findings difficult to interpret.

**5. Modaj I, et al. Sudden death in patients receiving clozapine treatment: a preliminary investigation. J Clin Psychopharmacology 2000;20:325-327.**

This retrospective study examined rates of sudden death, suicide, and deaths secondary to known diseases in schizophrenic patients from a mental health center database over a period of 6 years, 8 months. This encompassed 561 patients treated with clozapine and 4918 patients treated with other drugs. Among clozapine patients, 1.07% experienced sudden death compared to 0.28% of non-clozapine patients ( $p < 0.01$ ). A greater proportion of non-clozapine patients died secondary to known diseases (1.75% vs. 0.35%,  $p < 0.05$ ). The fractions of patients who suicided were not significantly different between clozapine and non-clozapine patients (0.36% vs. 0.10%, respectively).

The two treatment groups were not randomized and it does not appear that the authors controlled for duration of exposure or other potentially confounding variables.

**6. Munro J, et al. Active monitoring of 12,760 clozapine recipients in the U.K. and Ireland. Br J Psychiatry 1999;175:576-580.**

Data from 12,760 patients who were registered to receive clozapine in the U.K. and Ireland (Clozaril Patient Monitoring Service or CPMS) were retrospectively analyzed to identify risk factors for agranulocytosis. Of 144 deaths, 13 were noted to be confirmed suicides. Based on a review of the literature, the suicide rate among schizophrenic patients in various cited studies was consistently about 20 times greater than that in the general population. However, the suicide rate in this CPMS cohort was only about 5 times higher than that expected for the U.K. population, suggesting that clozapine may have an anti-suicide effect.

This was an observational study that used literature-reported estimates of suicide risk as a comparator. This trial did not control for the possible effects of regular clinical contact for WBC monitoring on suicide risk. Also, the adequacy of ascertainment of deaths due to suicide is difficult to gauge.

**7. Reid WH, et al. Suicide prevention effects associated with clozapine therapy in schizophrenia and schizoaffective disorder. Psychiatric Services 1998;49:1029-1033.**

This was a retrospective analysis of annual suicide rates among patients who received services from the Texas Department of Mental Health and Mental Retardation. A total of 30,130 patients with schizophrenia and schizoaffective disorder were treated over a two year period (1993-1995). In this population, the average annual suicide rate was 63.1 per 100,000 patients. During a 6 year interval (1991-1996), 1,367 patients received clozapine with only one suicide in this group, yielding an annual rate of 12.74 per 100,000 patients (95% CI 0-53 per 100,000).

This study did not compare randomized groups. Also, it did not control for regular contact associated with WBC monitoring and did not adjust for duration of drug exposure.

**8. Sajatovic M, et al. An assessment of clinical practice of clozapine therapy for veterans. Psychiatric Services 2000;51:669-671.**

This was a retrospective study of 2,996 patients with schizophrenia treated with clozapine in the U.S. Department of Veterans Affairs healthcare system over a 5 year period (1991-1996). Prior to treatment, 42.3% of patients has a history of suicide attempts. Also, 5% attempted suicide and 17.5% had suicidal ideation in the month prior to starting clozapine. During the study observation period, 2 patients (0.1%) died due to suicide.

This study suffers several weaknesses, to include lack of an adequately defined control group, no adjustment for duration of drug exposure, apparent comparison of disparate measures of suicidality (attempts and ideation pre-clozapine versus suicide deaths on clozapine), lack of control for the potential effect of regular patient contact, and possibly inadequate ascertainment of suicide deaths.

**9. Sernyak MJ, et al. Impact of clozapine on completed suicide. Am J Psychiatry 2001;158:931-937.**

This study examined the discharge summaries of 45,917 unique patients with Veterans Affairs (VA) psychiatric hospitalizations of at least one day for the fiscal years 1992 through 1995 in which the primary discharge diagnosis was schizophrenia. From this group, 1,415 patients were identified who started clozapine treatment for the first time during an "index" hospitalization. Then, using a matching process, a two-fold larger (N=2,830) group of control subjects who had not received clozapine during the study period were identified from the remaining discharged patients. Utilizing the National Death Index (NDI), searches were conducted for any study patients who died beginning with the year of discharge and continuing through every subsequent year through the end of 1998. Then, a coding algorithm from the National Center for Health Statistics was used to determine the most probable primary cause of death. The primary clozapine group comprised patients who received clozapine for any length of time. Follow-up time for each individual was calculated as the time between hospital discharge until either the date of death or December 31, 1998. The total follow-up time in each group was used to compute all-cause mortality and

cause-specific mortality rates. The duration of clozapine treatment for each patient was determined using data from the VA's National Clozapine Coordinating Center database. In total, 345 deaths were identified, 250 in the control group and 95 in the clozapine group. Among the deaths that were ruled suicide, 10 occurred in the clozapine group and 23 occurred in the control group. The rate of suicide in the total clozapine group was slightly less than that in the control group but not significantly so (1.50 versus 1.75 per 1,000 person-years;  $p=0.76$ ).

Although this study is more rigorously designed than most previously published studies in this area, it too has flaws. Most importantly, the matching process did not include some factors that might contribute substantially to suicide risk, such as previous suicide attempts and depressive symptomatology. Thus, it is difficult to feel assured that the clozapine and control groups were balanced on important risk factors for suicidality. In addition, it appears that the calculation of follow-up time for clozapine patients may have included time during which the patient did not receive clozapine treatment. If true, this means that the patient exposure time counted under the clozapine group may in fact be inflated and the true rate of suicide in the clozapine group may be considerably higher than computed. This is a potential major confounding factor that does not seem to be addressed in the paper.

**10. Spivak B, et al. Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine. Clin Neuropharmacol 1998;21:245-250.**

This study evaluated the effects of clozapine on multiple variables, including a retrospective analysis of suicidality, in a group of 30 neuroleptic-resistant chronic schizophrenic patients who were treated with clozapine and a control group of 20 chronic schizophrenic patients maintained on a typical antipsychotic for a one year study period. Past suicide attempts were reported in 7/30 clozapine patients and in 11/20 control patients. None of the clozapine patients attempted suicide during the study period compared to 5 patients in the control group; this difference was statistically significant ( $p<0.05$ ).

This is a small study comparing non-randomized groups. There was a numerical difference in the fraction of patients with past suicide attempts between the two groups (7/30 or 23% of clozapine patients versus 11/20 or 55% of the control group), a possible indicator that the control group may have been more prone to suicide attempts. This study also did not control for the possible effects of regular clinical contact associated with WBC monitoring in clozapine patients.

**11. Walker AM, et al. Mortality in current and former users of clozapine. *Epidemiology* 8;1997:671-677.**

This retrospective study of mortality among clozapine-treated patients was based on a cohort of patients in the U.S. Clozaril National Registry (CNR) during the period of April 1, 1991 to December 31, 1993. For each patient, the observation period started with April 1, 1991 or the earliest WBC record in the CNR for patients who began Clozaril after that date. The observation period ended with December 31, 1993, the date on which the patient reached age 101, or the date of death, whichever came first. Then, for each patient, each day during the observation period was classified as current use, recent use (up to and including 3 months after stopping Clozaril), or past use (more than 3 months after stopping Clozaril).

Deaths among this cohort were ascertained using the National Death Index (NDI) and the Social Security Administration Death Master Files using certain matching criteria. Death certificates were then requested from the states and the underlying causes of death were coded in accordance with ICD-9, along with recording of autopsy data. Mortality rates (standardized for age, race, and gender) in current and recent use were compared with rates in past use. The primary analysis focused on patients in the age range 10 to 54 years.

A total of 57,681 patients were eligible for the primary study cohort, representing a total of 85,399 person-years (PY) of observation. There were 396 deaths in this cohort. With respect to deaths due to suicide, the standardized mortality ratios (95% CI), using past use for comparison, were 0.17 (95% CI = 0.10-0.30) for current use and 1.11 (0.62-1.99) for recent use. These data suggest that active clozapine treatment is associated with a reduced risk of suicide.

The finding of a reduced suicide rate during the current use period is difficult to interpret with confidence. These were not randomized samples and it is unknown whether the use periods were balanced for various factors that might contribute to suicide risk. Also, as suggested by the authors, discontinuation of Clozaril due to poor response may select out a subset of patients particularly vulnerable to suicide, shifting these patients to the recent and past use categories. And, as with other studies, the WBC monitoring program may itself produce a bias by reducing the risk of suicidality through regular contact with healthcare staff or by earlier detection of the emergence of suicidality compared to patients in the recent and past use categories.

#### **E. Assessment of Efficacy Data Quality**

A total of 21 CRF's were randomly selected by the undersigned to audit the quality of data pertinent to suicidality from study ABA 451. Of these, 7 were for patients who were identified by the sponsor as not having experienced a Type 1 or Type 2 Event and 14 were identified as having experienced one of these events. The selected samples represent about 1% of the 700 patients not having an event and about 5% of the 280 patients having an event. All 21 patients selected for audit are listed in **Appendix VI-19**.

The primary goal of this audit was to verify that patients were appropriately classified with respect to suicidality based on clinical documentation in the CRF's. For patients with multiple Type 1 Events, this review focused on the first such event. Clinical data from the CRF forms listed in **Appendix VI-20** were examined.

This audit revealed only one finding that was present for 3 of the patients classified as having a Type 1 Event (Zyprexa patient 102-0012, Clozaril patient 127-0007, and Zyprexa patient 201-0004). In each of these 3 cases, the blinded psychiatrist indicated the absence of a Type 1 Event on a particular date whereas the Suicide Monitoring Board (SMB) found that a Type 1 Event had occurred on that date. Curiously, in each case, one of the SMB members initially voted that no event had occurred but subsequently changed to indicate the presence of a Type 1 Event.

To evaluate these discrepancies, I examined clinical documentation provided by the Principal Investigators regarding these events (mainly the "Imminent Risk of Suicide Requiring Hospitalization" and "Suicide Attempt" forms). In each case, I found that the evidence in support of a Type 1 Event was weak. For example, the Principal Investigator indicated a low risk of self-injury for 2 patients who were hospitalized "for imminent risk of suicide." In the third patient, the Principal Investigator clearly indicated that an attention-getting suicide gesture of low risk had occurred although the SMB later determined that this was a suicide attempt. While the accuracy of the SMB determinations is arguable, it is notable that all 3 cases involved a possible error in designating a non-suicidal event as a suicidal-event; I detected no cases where the SMB had made a possible error in the reverse direction.

To better assess this potential source of bias, it is recommended that all SMB documentation (e.g., conference minutes) related to these 3 patients be requested to better assess the determinations made. If that assessment is not reassuring, it is further recommended that relevant CRF forms for all remaining patients for whom there was a discrepancy between the SMB and the blinded psychiatrist be requested from the sponsor and examined. Finally, if that examination reveals a large number of cases with questionable SMB determinations, a reanalysis of the primary efficacy variables excluding these cases is recommended.

An additional audit searched for documentation indicating that the blinded psychiatrist had become unblinded during study ABA 451. Each blinded psychiatrist had the opportunity at each CGI-SS assessment of indicating in the CRF whether they had become unblinded to the patient's treatment. The relevant CRT (CGI002.xpt) was searched for any investigators who indicated unblinding at any visit. This search revealed 6 blinded psychiatrists at 6 different sites who indicated that they had become unblinded to the treatment of the following patients: 110-0001, 117-0001, 119-0002, 122-0006, 131-0005, and 701-0001. The ways in which unblinding occurred were not indicated. The sponsor should be requested to determine, to the extent possible, how these breaches occurred so that the adequacy of blinding in this trial can be more fully evaluated.

In summary, an audit of the suicidality data revealed two potential findings (possible biased SMB determinations and unblinding) that could impact on the reliability of these data. These findings should be further investigated, as recommended above.

#### **F. Conclusions Regarding Efficacy**

The findings of study ABA 451 cannot support the approval of Clozaril for the treatment of suicidality in patients with schizophrenia and schizoaffective disorder, as proposed by the sponsor (see the discussion in section VI.C.1 above).

Nonetheless, this study is capable, by design, of demonstrating a reduced risk of suicidality associated with long-term Clozaril treatment compared to long-term Zyprexa treatment. In this regard, the study results are considered inconclusive at this time given a number of irregularities in the conduct and analysis of this trial, which are discussed in section VI.B.12 above.

The published studies reviewed above suggest, on the whole, that Clozaril may be associated with a reduced risk of suicide compared to other treatments. However, each study suffers flaws which preclude any convincing demonstration of such an effect.

### **VII. Integrated Review of Safety**

#### **A. Methodology of the Safety Review**

Clozaril has been marketed in the U.S. and abroad for several years and the safety profile of Clozaril has been extensively evaluated. Thus, the examination of safety in this review was limited to an assessment of the more serious adverse events observed in study ABA 451, namely: 1) deaths, 2) non-fatal serious adverse events, and 3) adverse events that led to premature termination from the study.

The safety population for study ABA 451 was defined as all randomized patients who took at least one dose of study medication (479 Clozaril-treated patients and 477 Zyprexa-treated patients). The last patient completed this trial on 2-14-01.

For patients who dropped out, the investigator was to maintain regular contact with the patient or family member every 12 weeks up to the time that would have been study week 104 for that patient (i.e., for the remainder of the 2 year observation period).

## **B. Safety Findings**

### **1. Deaths**

A total of 22 patients died during the 2 year observation period or within 30 days of discontinuing study medication: 13 Clozaril patients and 9 Zyprexa patients. Thus, the crude all-cause mortality rate was 2.7% (13/479) for Clozaril and 1.9% (9/477) for Zyprexa. These rates are not significantly different ( $p=0.39$ ; Mantel-Haenszel Chi-Square).

I reviewed the Narrative Summary for each patient who died. **Appendix VII-1** is a line listing of all 22 deaths with the cause of death as determined by my review.

Among the 13 Clozaril patient deaths, 2 occurred more than 30 days after discontinuing treatment and were unlikely to be related to Clozaril treatment (patients 122-0010 and 802-0012). Among the remaining 11 Clozaril deaths, 4 were the result of suicide or complications of a suicide attempt and there was one death each due to pulmonary embolism, overdose, cancer, and cardiac arrest. In 3 cases, the cause of death could not be determined with reasonable certainty.

### **2. All Serious Adverse Events**

The protocol for study ABA 451 defined serious adverse events (SAE's) as those which meet any of the following criteria:

- fatal or life-threatening.
- requires or prolongs hospitalization.
- significantly or permanently disabling or incapacitating.
- cancer, congenital anomaly, or birth defect.
- resulting from an overdose.

All SAE's occurring after signing informed consent until 28 days after stopping study drug were reported.

In the Clozaril group, 48.2% (231/479) of the patients experienced an adverse event classified as serious compared to 49.3% (235/477) of the Zyprexa patients. Appendix 7.2, Listing 10.2-1, of the report for study ABA 451 contains a line listing by patient of all patients who experienced an SAE. An enumeration by treatment group of all SAE's (by MedDRA preferred term) experienced by at least one Clozaril-treated patient is provided in **Appendix VII-2** of this review.

I reviewed the Narrative Summaries for a number of patients with SAE's to obtain further clinical information about the nature and circumstances of the events. The Narrative Summaries reviewed are listed in **Appendix VII-3**. Also, this information was supplemented in many cases by data from the Case Report Tabulations.

Based on a consideration of the above clinical data, I considered the following events reasonably attributable to Clozaril treatment: bowel obstruction, WBC's decreased, hyperglycemia, dizziness, and somnolence. These events will be discussed in **section VII.E** below.

### **3. Dropouts due to Adverse Events**

In the Clozaril treatment group, 8.6% (41/479) of the patients prematurely discontinued treatment due to an adverse event compared to 6.9% (33/477) of the Zyprexa patients. The adverse experiences most commonly leading to dropout in the Clozaril group were WBC's decreased (1.7% of Clozaril and 0.0% of Zyprexa patients) and somnolence (1.0% of Clozaril and 0.2% of Zyprexa patients).

A line listing of all patients who dropped out due to an adverse event may be found in Appendix 7.1, Listing 10.1-2, of the study report for ABA 451. An enumeration of the Clozaril patients who discontinued treatment due to specific adverse events is provided in **Appendix VII-4** of this review.

My examination of the events leading to dropout among the Clozaril-treated patients revealed no clinically important events which I considered attributable to Clozaril beyond those events identified in the above review of SAE's.

### **C. Adequacy of Patient Exposure and Safety Assessments**

Clozaril has been marketed for over a decade for use in patients with schizophrenia. This supplement seeks to add patients with schizoaffective disorder to the target population. There were only 190 patients with schizoaffective disorder randomized to Clozaril in study ABA 451. Although this exposure is small, there is no known reason not to extrapolate the primary safety experience in schizophrenic patients to the schizoaffective disorder population. Thus, this limited exposure should not preclude the approval of this supplement.

The safety assessments in study ABA 451 are considered adequate to detect frequently occurring major toxicities associated with extended Clozaril use in the study population. However, one deficiency was the lack of some routine safety assessments which may have yielded useful long-term data, such as fasting blood glucose levels, cholesterol and triglyceride levels, and ECG's.

### **D. Safety Data Quality and Completeness**

Approximately 5% of the 68 Case Report Forms (CRF's) submitted for patients in study ABA 451 who died or experienced other designated serious adverse events were audited by the undersigned. This audit consisted of an examination of the consistency of adverse event information across the CRF, Narrative Summary, and Case Report Tabulation (CRT) adverse event line listing (AEV001.xpt) for four randomly selected patients (patients 117-0004, 120-0014, 301-0003, and 502-0008). This audit revealed no important discrepancies.

The appropriateness of the coding of reported adverse event terms to MedDRA preferred terminology for patients in study ABA 451 was evaluated by the undersigned. This consisted of an examination of the CRT adverse event line listing, sorted by preferred term and also by reported (verbatim) term. This examination revealed no errors in adverse event coding.

In terms of data completeness, two deficiencies were noted:

- safety findings discovered by non-trial healthcare providers and facilities were often missing.

- follow-up information on abnormalities observed during the trial was often not available, making evaluation of the outcome of these events impossible.

Given the wealth of postmarketing safety data available for Clozaril, these deficiencies should not preclude approval of this supplement.

## **E. Summary of Important Drug-Related Safety Findings**

### **1. WBC Count Decreased**

Eight Clozaril (1.7%) and no Zyprexa patients experienced decreases in white blood cell (WBC) counts that were classified as serious ( $p=0.005$ , MH Chi-Square). Six of these patients dropped out for this reason. None of these patients experienced sepsis, a total WBC count under 1,000/cmm, or an absolute neutrophil count under 500/cmm. The lowest counts were observed in patient 701-0025, who experienced a decrease in total WBC's from 5,900 to 1,700/cmm and in neutrophils from 3,500 to 650/cmm. No follow-up counts were available for this patient.

In terms of the proportions of patients who had a total WBC count  $\leq 2,800$ /cmm at any point during the trial, 1.3% (6/474) of the Clozaril and 0.6% (3/474) of the Zyprexa patients met this criterion ( $p=0.32$ , MH Chi-Square).

No cases of agranulocytosis or aplastic anemia were reported.

Leukopenia is a well-known effect of Clozaril and is the reason Clozaril is available only through a controlled distribution system. Clozaril is considered to be adequately labeled for this adverse event.

### **2. Bowel Obstruction**

In study ABA 451, three Clozaril patients experienced bowel obstructions consistent with paralytic ileus. One of these patients (129-0010) experienced two episodes of obstruction during Clozaril treatment, the last leading to treatment discontinuation. Another patient (301-0019) underwent surgery for a perforated appendix about 2 weeks prior to symptoms of obstruction. Clozaril was stopped, with recovery of bowel function 8 days later. The third patient (302-0010) had a grossly distended transverse colon and

evidence of renal impairment due to dehydration. Clozaril was stopped but he experienced a cardiac arrest of uncertain etiology 2 days later and died. Obstruction in all of these patients resulted in hospitalization and intervention.

Only one Zyprexa-treated patient experienced a bowel obstruction.

Constipation was reported by 25.1% (120/479) of Clozaril patients; 48 of these events were rated as moderate or severe. In the Zyprexa group, 9.6% (46/477) of the patients reported constipation. The difference between the groups was highly statistically significant ( $p < 0.001$ , Mantel-Haenszel Chi-Square).

These events are probably related to the potent anticholinergic effects of Clozaril, which are described in current labeling under PRECAUTIONS/Anticholinergic Toxicity.

### **3. Hyperglycemia**

At least one treatment-emergent adverse event suggesting a problem with glucose regulation was reported in 4.8% (23/479) of the Clozaril and 5.5% (26/477) of the Zyprexa patients in study ABA 451. These events had been coded to one of the following MedDRA preferred terms: hyperglycemia NOS, diabetes mellitus NOS, ketoacidosis, blood glucose increased, glucose tolerance decreased, and glycosuria.

Plasma glucose levels were not routinely assessed during this study. Thus, a more systematic evaluation of glucose dysregulation is not possible.

There have been a number of spontaneous adverse event reports as well as literature reports documenting problems with glucose regulation during treatment with either Clozaril and Zyprexa.<sup>21</sup> The above data are consistent with the possibility that hyperglycemia and diabetes may be causally linked to these agents although such a relationship has not been convincingly demonstrated. Current Clozaril labeling contains a statement under

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<sup>21</sup> For example, see Newcomer JW, et al. Abnormalities in Glucose Regulation During Antipsychotic Treatment of Schizophrenia. Arch Gen Psychiatry. 2002;59:337-345.

PRECAUTIONS/Hyperglycemia that adequately advises prescribers of this possible relationship.

#### **4. Dizziness**

Non-vertiginous dizziness was reported as an adverse event in 26.9% (129/479) of the Clozaril group and 12.4% (59/477) of the Zyprexa group in study ABA 451; this difference is highly significant ( $p < 0.001$ , MH Chi-Square). Events coded to this MedDRA term included dizziness, lightheadedness, and feeling faint. Four Clozaril patients and no Zyprexa patients dropped out due to this adverse experience.

An etiologic explanation for this event is not clear. According to the ADVERSE REACTIONS section of Clozaril labeling, dizziness, to include vertigo, was reported in 19% of Clozaril patients in premarketing clinical trials (N=842). Given that these trials were probably much shorter than study ABA 451, the above finding is considered to be consistent with the figure cited in labeling.

#### **5. Somnolence**

Somnolence was reported as a treatment-emergent adverse experience in 45.9% (220/479) of Clozaril and 24.7% (118/477) of Zyprexa patients in ABA 451. This difference is highly statistically significant ( $p < 0.001$ , MH Chi-Square). This MedDRA preferred term subsumed reported events including drowsiness, sedation, and sleepiness. Five Clozaril patients and one Zyprexa patient dropped out due to this adverse event.

This finding is felt to be consistent with information in the ADVERSE REACTIONS section of Clozaril labeling, which describes drowsiness or sedation in 39% of Clozaril-treated patients in premarketing clinical trials.

#### **F. Safety Conclusions**

This limited review of safety data from study ABA 451 revealed no previously unrecognized toxicities associated with Clozaril which would preclude the approval of this supplement or require amendment of Clozaril labeling.

### **VIII. Dosing, Regimen, and Administration Issues**

The dosing scheme utilized in study ABA 451 is consistent with that currently labeled for the treatment of patients with refractory schizophrenia. If the sponsor elects to pursue approval of a claim for the reduction of suicide risk with long-term therapy, this dosing regimen would be appropriate. However, before approval for this use, it will be critical to decide whether to grant approval as a new indication (as opposed to simply describing the study in labeling under Clinical Trials) and, if so, to delineate in labeling an appropriate target population.

### **IX. Use in Special Populations**

Neither gender nor age group were significant predictors of time to a Type 1 or time to a Type 2 event in covariate analyses using a full Cox proportional hazards regression model. Race was not examined as an explanatory variable in these analyses.

### **X. Review of Proposed Labeling**

Since it is recommended that this supplement not be approved, the sponsor's proposed labeling will not be discussed in this review.

### **XI. Conclusions and Recommendations**

It is recommended that the claim for the use of Clozaril to treat suicidality not be approved. Study ABA 451 was not designed to assess the efficacy of Clozaril in the treatment of suicidality.

If Novartis elects to pursue approval of Clozaril as a long-term measure to reduce the risk of suicidality, it is recommended that the sponsor address the following concerns regarding study ABA 451:

- 1) Apparently a total of 72 study patients were lost to follow-up. Further efforts should be made to ascertain whether the 33 Clozaril and 39 Zyprexa patients who were lost to follow-up committed suicide, attempted suicide, or were hospitalized or placed under increased surveillance due to imminent suicide risk around the time of study discontinuation.

2) The primary efficacy analysis, using the method of Wei, Lin, and Weissfeld, is described as including Type 1 and Type 2 events regardless of whether the patient was taking study medication at the time of the event. This makes attribution of event occurrence or non-occurrence to drug very tenuous in this long-term trial. Additionally, Amendment #9 to the study protocol allowed patients who had dropped out of the study to later return to full study participation. This may have introduced a confounding influence of suicide risk in this trial. Therefore, the primary efficacy analysis should be repeated after right-censoring patients who discontinued study drug, even if those patients later re-entered the study as full participants. Also, this analysis should incorporate any and all new information on the 72 patients who were reported as lost to follow-up (see item 1 above).

3) An audit of suicidality information, including Case Report Forms, on a small sample of study patients revealed three cases in which the SMB determinations are questionable. To permit a more complete understanding of how these determinations were made, all SMB documentation, to include SMB conference minutes, related to the following three patients should be submitted for Agency examination: 102-0012, 127-0007, and 201-0004.

4) It is noted that six Blinded Psychiatrists acknowledged becoming unblinded during the study. These individuals performed CGI-SS-BP ratings on the following study patients: 110-0001, 117-0001, 119-0002, 122-0006, 131-0005, and 701-0001. These instances of unblinding should be investigated to determine how these breaches occurred. The explanations should be provided for our review so that the adequacy of blinding in the trial can be more fully evaluated.

Furthermore, if the sponsor amends this application to pursue the suicidality prevention claim, it may be helpful for the Division to obtain the advice of the Psychopharmacological Drugs Advisory Committee with respect to the following questions:

1) Does study ABA 451 provide adequate evidence to support a claim of reduction in the risk of suicidality? The response should include a consideration of the following:

a) The difference between Clozaril and Zyprexa was not very large. For example, at the end of two years, the cumulative probability of a Type 1 event was 0.24 for Clozaril and 0.32 for Zyprexa, with a 95% confidence interval for the intergroup difference being 0.02 to 0.14.

b) Unlike most claims for psychiatric conditions, this would be based on a single study against a single comparator agent. While published studies do provide evidence suggesting a reduction in suicide risk, none are of such quality that they are capable of providing data that would truly replicate the findings of ABA 451.

c) A large proportion of patients in this trial took concomitant medication that could confound assessment of suicide risk, such as antipsychotics and antidepressants. It would admittedly be virtually impossible to entirely rule out a differential confounding influence that might bias the study results and, to some extent, the sponsor's analysis of such use might be considered reassuring. Nonetheless, there is a need to reasonably judge whether this treatment was so extensive that it significantly degraded the scientific credibility of this trial.

d) For over 40% of the patients in each treatment group, there was a change in the Blinded Psychiatrist who rated the change in the patient's suicidality at each visit relative to the patient's baseline condition. This was a key outcome measure. The reliability of a new rater in assessing change from the baseline condition is questionable.

2) If the answer to the above question is affirmative, what guidance should be provided in labeling to assist prescribers in selecting patients for Clozaril therapy under this claim?

Gregory M. Dubitsky, M.D.  
August 1, 2002

cc: NDA 19-758  
HFD-120/Division File  
HFD-120/GDubitsky  
/TLaughren  
/SHardeman

**SECTION XII:**

**APPENDICES**

**APPENDIX IV-1  
STUDY ABA 451  
BASELINE DEMOGRAPHIC CHARACTERISTICS  
(ALL RANDOMIZED PATIENTS)**

	<b>No. (%) of patients unless otherwise noted</b>	
	<b>Clozaril (n=490)</b>	<b>Zyprexa (n=490)</b>
<b>Age (year)</b>		
Mean (SD)	37.1 (10.3)	37.0 (10.3)
Median	37	36
Range	18-69	18-65
18-32	168 (34.3%)	178 (36.3%)
33-44	216 (44.1%)	204 (41.6%)
≥45	106 (21.6%)	108 (22.0%)
<b>Sex</b>		
Male	301 (61.4%)	301 (61.4%)
Female	189 (38.6%)	189 (38.6%)
<b>Race</b>		
Caucasian	356 (72.7%)	337 (68.8%)
Black	65 (13.3%)	86 (17.6%)
Oriental	6 ( 1.2%)	7 ( 1.4%)
Other	63 (12.9%)	60 (12.2%)
<b>Weight (kg)– Females</b>		
	n=181	n=180
Mean (SD)	74.0 (20.1)	73.2 (18.4)
Median	70	70
Range	40-152	36-133
<b>Weight (kg)– Males</b>		
	n=283	n=289
Mean (SD)	82.8 (18.3)	84.3 (20.9)
Median	80.9	80
Range	45-156	44-166

**APPENDIX IV-2  
STUDY ABA 451  
OVERALL EXPOSURE BY TREATMENT DURATION  
(SAFETY POPULATION)**

<b>Duration of treatment (days)*</b>	<b>No. (%) of patients</b>	
	<b>Clozaril (n=479)</b>	<b>Zyprexa (n=477)</b>
1 – 30	54 (11.3)	26 ( 5.5)
31 – 90	36 ( 7.5)	31 ( 6.5)
91 – 180	25 ( 5.2)	25 ( 5.2)
181 – 270	12 ( 2.5)	22 ( 4.6)
271 – 360	10 ( 2.1)	6 ( 1.3)
361 – 450	17 ( 3.5)	16 ( 3.4)
451 – 540	10 ( 2.1)	22 ( 4.6)
541 – 630	6 ( 1.3)	11 ( 2.3)
≥ 631	304 (63.5)	312 (65.4)
Missing	5 ( 1.0)	6 ( 1.3)

\* Number of days from date of first dose of study medication to date of last known dose of study medication; if either date was missing, the patient was counted in the "missing" category.

<b>APPENDIX V-1 ITEMS REVIEWED</b>	
<b>Submission Date</b>	<b>Item Description</b>
2-28-02	<u>Volume 1</u> Proposed labeling Debarment certification Financial disclosure information <u>Volume 4</u> Published literature reports <u>Electronic Format</u> Study report: ABA 451 Case Report Tabulations: ABA 451 Case Report Forms: ABA 451
3-29-02	Median dose by visit data Diagnostic subgroup efficacy analysis
5-17-02	Correction to ABA 451 Study Report
6-24-02	Analysis of concomitant medication

<b>APPENDIX V-2: SELECTED SERIOUS ADVERSE EVENTS</b>
Myocardial infarction Pericarditis NOS Appendicitis perforated Hematemesis Intestinal obstruction NOS Pancreatitis NOS Neuroleptic malignant syndrome Hepatic disorder NOS Colitis pseudomembranous Accidental overdose (therapeutic agent) Ketoacidosis Tetany Rhabdomyolysis Paraplegia Intra-uterine death Renal failure NOS Pleural effusion Respiratory distress Respiratory failure (exc neonatal) Acute circulatory failure Transient ischemic attack

**APPENDIX VI-1  
STUDY ABA 451**

**STUDY SITES, NUMBER OF PATIENTS ENROLLED, AND PRINCIPAL INVESTIGATORS**

<b>Center Number</b>	<b>Location (country)</b>	<b>Number Enrolled (Clozapine/Zyprexa)</b>	<b>Principal Investigator</b>
101	USA	8/9	H. Edward Logue, M.D.
102	USA	6/7	Pedro Delgado, M.D. Francisco Moreno, M.D.
103	USA	6/5	Dennis Pavlinac, M.D.
104	USA	10/11	Mark H. Rapaport, M.D.
105	USA	14/14	Steven Potkin, M.D.
106	USA	7/8	David A. Sack, M.D.
107	USA	14/14	George M. Simpson, M.D.
108	USA	2/2	Dan L. Zimbroff, M.D.
109	USA	3/2	Ira D. Glick, M.D. Ben H. Flores, M.D.
110	USA	2/1	Doris Gunderson, M.D.
111	USA	4/4	Phillip Seibel, M.D. Adam Lowy, M.D.
112	USA	9/10	Carl Eisdorfer, M.D., Ph.D. Richard Douyon, M.D.
113	USA	3/4	Michael G. Plopper, M.D.
114	USA	16/16	James Chou, M.D. Jean-Pierre Lindenmayer, M.D.
115	USA	2/2	Vinod Kumar, M.D.
116	USA	6/6	Jack Krasuski, M.D. Alan I. Green, M.D.
117	USA	8/6	George Hsu, M.D.

**APPENDIX VI-1  
STUDY ABA 451**

**STUDY SITES, NUMBER OF PATIENTS ENROLLED, AND PRINCIPAL INVESTIGATORS**

<b>Center Number</b>	<b>Location (country)</b>	<b>Number Enrolled (Clozapine/Zyprexa)</b>	<b>Principal Investigator</b>
118	USA	3/2	Oladapo Tomori, M.D.
119	USA	1/1	Richard Balon, M.D.
120	USA	7/7	George T. Grossberg, M.D. Winston W. Shen, M.D. Ricky S. Mofsen, D.O.
122	USA	5/6	Ronald Centric, D.O. Mark W. Viner, M.D. Saide Altinsan, M.D.
123	USA	4/4	Delbert Robinson, M.D.
124	USA	6/7	Jean-Pierre Lindenmayer, M.D.
125	USA	10/11	Naveed Iqbal, M.D.
126	USA	9/8	Jorg J. Pahl, M.D.
127	USA	8/6	Jeffrey-Lee Peters, M.D. Daniel P. Vankammen, M.D., Ph.D.
128	USA	4/6	Richard C. Josiassen, Ph.D.
129	USA	7/6	Herbert Y. Meltzer, M.D.
130	USA	8/8	Mary Ann Knesevich, M.D.
131	USA	4/5	Michael Lesem, M.D. Vaidyanath Iyer, M.D.
132	USA	2/0	Richard Greenberg, M.D.
201	Canada	6/5	Guy Chouinard, M.D., Sc. FRCP, FAPA
203	Canada	4/4	Siemion Altman, M.D., FRCPC
301	UK	9/9	Thomas A. Fahy, M.D.
302	UK	25/24	Prof. Stephen Martin, M.D.

**APPENDIX VI-1  
STUDY ABA 451**

**STUDY SITES, NUMBER OF PATIENTS ENROLLED, AND PRINCIPAL INVESTIGATORS**

<b>Center Number</b>	<b>Location (country)</b>	<b>Number Enrolled (Clozapine/Zyprexa)</b>	<b>Principal Investigator</b>
303	UK	13/12	Sophie Frangou, M.D.
304	UK	7/6	Prof. Ann Mortimer
305	UK	2/4	Anthony Maden, M.D.
401	France	17/16	Prof. Marc Bourgeois
402	France	5/6	Marie-Agathe Zimmermann, M.D.
403	France	11/11	Frederic Khidichian, M.D.
404	France	6/6	Muriel Maurel, M.D.
405	France	4/5	Pierre-Michel Llorca, M.D.
406	France	7/6	Prof. Jean Dalery
501	Italy	2/2	Prof. Alberto Gianneli, M.D.
502	Italy	4/4	Prof. Lilliana Dell'Ossso
505	Italy	4/4	Bernardo Carpiniello, M.D.
506	Italy	3/2	Rosaria Pioli, M.D.
601	Hungary	11/11	Akos Kassai-Farkas, M.D.
602	Hungary	16/16	Eva Morik, M.D.
604	Hungary	16/17	Gyorgy Ostorharics-Horvath, M.D.
605	Hungary	6/6	Laszlo Mod, M.D.
701	Croatia	13/12	Prof. Miro Jakovljevic
702	Croatia	16/18	Prof. Vera Folinegovic-Smale
801	S. Africa	4/4	Prof. Robin A. Emsley
802	S. Africa	7/7	Prof. Carlo Gagiano
803	S. Africa	7/8	Elisabeth Borkowska, M.D. Mohamed Coovadia, M.D.

**APPENDIX VI-1  
STUDY ABA 451**

**STUDY SITES, NUMBER OF PATIENTS ENROLLED, AND PRINCIPAL INVESTIGATORS**

<b>Center Number</b>	<b>Location (country)</b>	<b>Number Enrolled (Clozapine/Zyprexa)</b>	<b>Principal Investigator</b>
901	Czech Republic	5/6	Jaroslav Hronek, M.D. Vanda Benesova, M.D.
902	Czech Republic	7/7	Zdenka Vyhnankova, M.D.
903	Czech Republic	2/4	Ivo Paclt, M.D.
904	Czech Republic	5/5	Libor Chvila, M.D.
951	Argentina	5/4	Pedro Rafael Gargoloff, M.D.
952	Argentina	7/6	Liliana Avigo, M.D.
953	Argentina	5/6	Luis Antonio Bengochea, M.D.
954	Argentina	5/5	Carlos Alberto Morra, M.D.
955	Argentina	9/8	Alberto Bertoldi, M.D.
956	Chile	17/16	Veronica Larach, M.D.

**APPENDIX VI-2:  
STUDY ABA 451  
DISTRIBUTION OF CGI-SS-BP SCORES AT BASELINE**

<b>Baseline CGI-SS-BP Score</b>	<b>Clozaril (N=490) n (n/N%)</b>	<b>Zyprexa (N=490) n (n/N%)</b>
1 (not at all suicidal)	152 (31%)	153 (31%)
2 (mildly suicidal)	131 (27%)	132 (27%)
3 (moderately suicidal)	140 (29%)	141 (29%)
4 (severely suicidal)	58 (12%)	51 (10%)
5 (attempted suicide)	3 (<1%)	4 (<1%)
Missing	6 (1%)	9 (2%)

**APPENDIX VI-3  
STUDY ABA 451  
ENUMERATION OF DROPOUTS BY REASON**

<b>Reason for Discontinuation</b>	<b>Clozaril N=490</b>	<b>Zyprexa N=490</b>
Adverse Events (incl. death)	49	38
Abnormal Laboratory Value/Test Result	3	0
Unsatisfactory Effect on Psychosis	5	9
Unsatisfactory Effect on Suicide Risk	0	6
Protocol Violation	29	20
Withdrawn Consent	50	49
Lost to Follow-Up	33	39
Administrative Reason	23	26
<b>TOTAL DISCONTINUATIONS</b>	<b>192</b>	<b>187</b>

APPENDIX VI-4 STUDY ABA 451 PATIENTS IN-STUDY BY VISIT		
Visit (week)	Clozaril n (% of ITT)	Zyprexa n (% of ITT)
8	411 (84%)	432 (88%)
16	382 (78%)	414 (85%)
24	361 (74%)	399 (81%)
32	356 (73%)	382 (78%)
40	344 (70%)	370 (76%)
48	338 (69%)	364 (74%)
52	337 (69%)	362 (74%)
60	327 (67%)	352 (72%)
68	318 (65%)	344 (70%)
80	308 (63%)	324 (66%)
92	304 (62%)	314 (64%)
104	298 (61%)	303 (62%)

APPENDIX VI-5 STUDY ABA 451 MEDIAN PRESCRIBED DOSES (mg/day) BY VISIT <sup>22</sup>		
Visit (week)	Clozaril	Zyprexa
8	250.0	15.0
16	300.0	20.0
24	300.0	20.0
32	300.0	20.0
40	300.0	20.0
48	300.0	20.0
52	300.0	20.0
60	300.0	20.0
68	300.0	20.0
80	300.0	20.0
92	300.0	20.0
104	300.0	20.0

<sup>22</sup> This information was provided by the sponsor in a 3-29-02 submission.

APPENDIX VI-6 STUDY ABA 451 ENUMERATION OF PATIENTS WITH CONCOMITANT PSYCHOTROPIC MEDICATION USAGE <sup>23</sup>				
Medication Class	Clozaril		Zyprexa	
	All Usage	Analysis Usage	All Usage	Analysis Usage
Antipsychotics	429	410	413	390
Antidepressants	269	241	301	270
Sed/Anxiolytics	341	295	363	325
Mood Stabilizers	147	120	154	144

APPENDIX VI-7 STUDY ABA 451 OVERALL LEAST SQUARES MEAN DOSAGE BY CONCOMITANT MEDICATION CLASS AND TREATMENT GROUP			
Medication Class	Clozaril	Zyprexa	p-value
Antipsychotics	2.1	3.8	0.0002
Antidepressants	16.7	20.7	0.0014
Sed/Anxiolytics	6.3	10.1	<0.0001
Mood Stabilizers	487	621	0.0107

APPENDIX VI-8 STUDY ABA 451 LEAST SQUARES MEAN DOSAGE FOR CONCOMITANT ANTIPSYCHOTIC USAGE BY TREATMENT INTERVAL			
Interval	Clozaril	Zyprexa	p-value
1-6 months	2.7	3.9	0.0060
7-12 months	1.1	3.3	<0.0001
13-18 months	1.1	3.5	<0.0001
19-24 months	1.2	3.4	<0.0001

<sup>23</sup> All Usage enumerates all patients who took at least one dose of concomitant medication in that class. Analysis Usage enumerates patients who took concomitant medication after analysis exclusion criteria were applied.

APPENDIX VI-9 STUDY ABA 451 LEAST SQUARES MEAN DOSAGE FOR CONCOMITANT ANTIDEPRESSANT USAGE BY TREATMENT INTERVAL			
Interval	Clozaril	Zyprexa	p-value
1-6 months	15.9	19.4	0.0005
7-12 months	15.4	20.4	0.0032
13-18 months	16.9	19.7	0.1106
19-24 months	18.1	21.2	0.0914

APPENDIX VI-10 STUDY ABA 451 LEAST SQUARES MEAN DOSAGE FOR CONCOMITANT SEDATIVE/ANXIOLYTIC USAGE BY TREATMENT INTERVAL			
Interval	Clozaril	Zyprexa	p-value
1-6 months	6.8	10.1	0.0001
7-12 months	5.5	9.1	0.0002
13-18 months	5.7	10.4	0.0002
19-24 months	6.3	10.7	0.0027

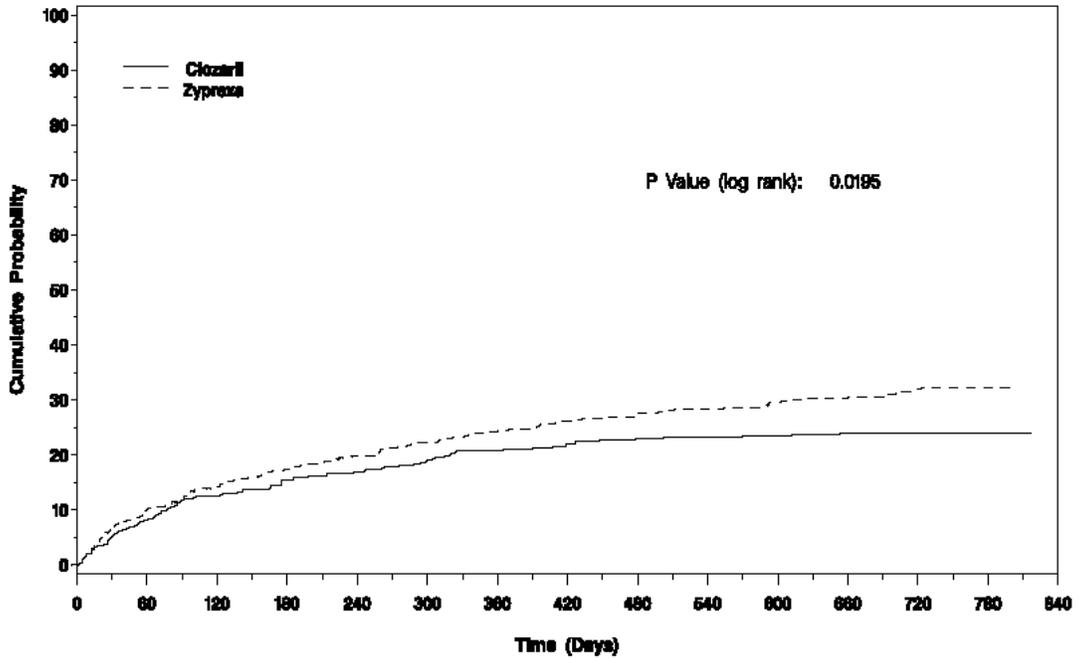
APPENDIX VI-11 STUDY ABA 451 LEAST SQUARES MEAN DOSAGE FOR CONCOMITANT MOOD STABILIZER USAGE BY TREATMENT INTERVAL			
Interval	Clozaril	Zyprexa	p-value
1-6 months	473.2	573.4	0.0166
7-12 months	441.6	638.7	0.0022
13-18 months	455.2	618.3	0.0253
19-24 months	493.1	592.7	0.2157

**APPENDIX VI-12  
STUDY ABA 451  
PRIMARY SUICIDALITY EFFICACY ANALYSIS:  
MULTIPLE EVENTS ANALYSIS OF TIME TO FIRST  
TYPE 1 OR TYPE 2 EVENT (ITT POPULATION)**

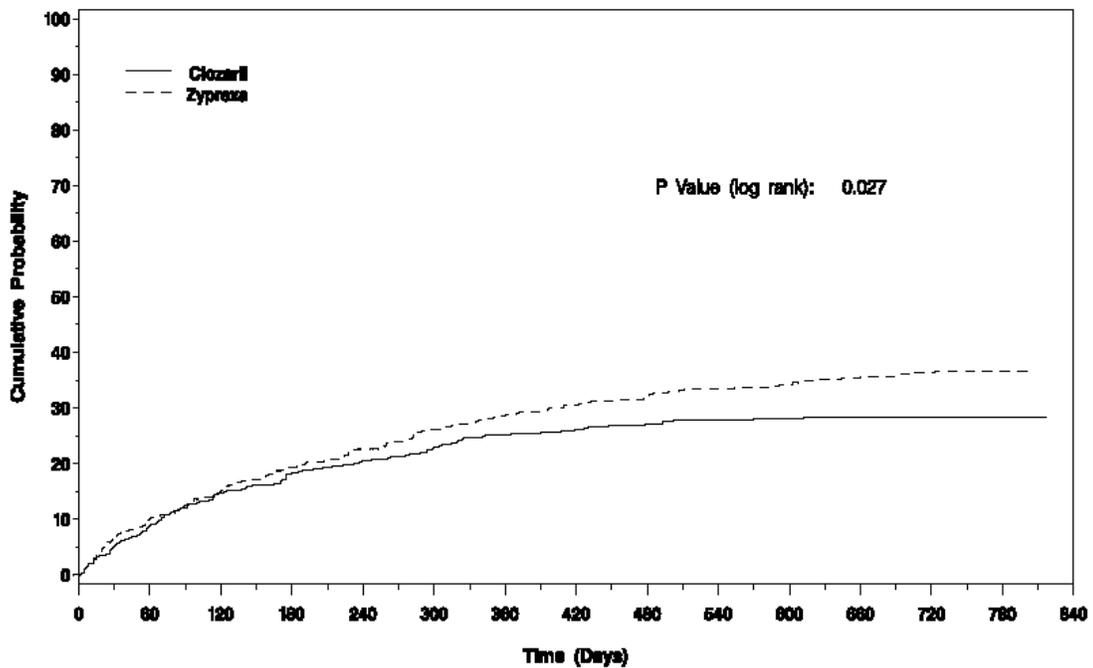
Event Type [1]	Coefficient of Treatment Effect (Beta) [2]	Robust Standard Error of Beta	Weight	P-value[3]	95% C.I. of Beta	Hazard Ratio (exp(Beta)) [2]	95% C.I. of Hazard Ratio
Type 1	-0.280	0.130	0.50	0.0316	(-.54, -.02)	0.76	(0.58, 0.98)
Type 2	-0.250	0.121	0.50	0.0388	(-.49, -.01)	0.78	(0.61, 0.99)
Combined	-0.265	0.123	-	0.0309	(-.51, -.02)	-	-

- [1] Event type 1: Occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance). Only time to the first occurrence (SMB-confirmed) was used in the survival analysis. Event type 2: Occurrence of a significant suicide attempt, hospitalization due to imminent suicide risk (including increased level of surveillance), or worsening of severity of suicidality measured by CGI-SS-BP (change score) of level 6 or 7. Only time to the first occurrence was used in the survival analysis.
- [2] A negative value of beta and a hazard ratio less than 1 indicate that Treatment Group 1 (Clozaril) is better than Treatment Group 2 (Zyprexa).
- [3] P-values were generated using the Normal Approximation Z-test with robust standard error estimates obtained from the WLW survival analysis model, stratified on pooled country and with treatment as the only covariate. Equal weights were applied for each event type.

APPENDIX VI-13  
STUDY ABA 451  
KAPLAN-MEIER SURVIVAL CURVES FOR TYPE 1 EVENTS



APPENDIX VI-14  
STUDY ABA 451  
KAPLAN-MEIER SURVIVAL CURVES FOR TYPE 2 EVENTS



APPENDIX VI-15  
STUDY ABA 451  
KAPLAN-MEIER ESTIMATES OF THE CUMULATIVE PROBABILITY OF A  
TYPE 1 OR TYPE 2 EVENT BY VISIT

	CLOZARIL (n=490)				ZYPREXA (n=490)				95% C.I. of the difference
	n1 <sup>2</sup>	N2 <sup>3</sup>	Cum Prob	95% C.I.	n1 <sup>2</sup>	n2 <sup>3</sup>	Cum Prob	95% C.I.	
<b>Type 1 Event</b>									
Week 0 (Day 0)	490	0	0.00	(0.00, 0.00)	490	0	0.00	(0.00, 0.00)	(0.00, 0.00)
Week 8 (Day 70)	393	43	0.09	(0.09, 0.10)	411	50	0.11	(0.10, 0.11)	(-0.03, 0.05)
Week 24 (Day 182)	346	69	0.16	(0.15, 0.17)	365	81	0.17	(0.16, 0.18)	(-0.03, 0.07)
Week 52 (Day 378)	308	91	0.21	(0.20, 0.22)	312	112	0.25	(0.23, 0.26)	(-0.02, 0.09)
Week 80 (Day 574)	277	100	0.23	(0.22, 0.25)	289	128	0.29	(0.27, 0.30)	(-0.01, 0.11)
Week 104 (Day 742)	36	102	0.24	(0.23, 0.25)	40	141	0.32	(0.31, 0.34)	(0.02, 0.14)
<b>Type 2 Event</b>									
Week 0 (Day 0)	490	0	0.00	(0.00, 0.00)	490	0	0.00	(0.00, 0.00)	(0.00, 0.00)
Week 8 (Day 70)	389	47	0.10	(0.10, 0.11)	410	51	0.11	(0.10, 0.11)	(-0.03, 0.04)
Week 24 (Day 182)	334	81	0.18	(0.17, 0.20)	356	90	0.19	(0.18, 0.21)	(-0.04, 0.06)
Week 52 (Day 378)	290	109	0.25	(0.24, 0.27)	294	132	0.29	(0.28, 0.31)	(-0.02, 0.10)
Week 80 (Day 574)	261	119	0.28	(0.27, 0.30)	251	150	0.34	(0.32, 0.35)	(0.00, 0.12)
Week 104 (Day 742)	34	120	0.28	(0.27, 0.30)	36	161	0.37	(0.35, 0.38)	(0.02, 0.15)

<sup>1</sup> Kaplan-Meier estimates compute the probability of an event (cumulative). Two weeks were added to the visit week when calculating the actual day, e.g., Visit Week 8 = Day (8+2)x7 = Day 70.

<sup>2</sup> n1 represents number of patients at risk.

<sup>3</sup> n2 represents the number of cumulative events.

**APPENDIX VI-16**  
**STUDY ABA 451**  
**COVARIATE ANALYSIS OF TIME TO TYPE 1 EVENT**  
**USING A FULL COX PROPORTIONAL HAZARDS MODEL**

Explanatory Variable <sup>1</sup>	Regression Coefficient (SE) <sup>2</sup>	Hazard Ratio <sup>2</sup>	P- value <sup>3</sup>
Treatment	-0.318 (0.133)	0.73	0.0172
Sex	-0.022 (0.147)	0.98	0.8822
Age Group (33-44)	-0.236 (0.148)	0.79	0.1117
Age Group ( ≥ 45)	-0.205 (0.184)	0.81	0.2643
No. of Lifetime Suicide Attempts	0.024 (0.006)	1.03	0.0001
CGI-SS-BP Severity Score (Q1-Q3)	0.175 (0.239)	1.19	0.4658
CGI-SS-BP Severity Score (≥Q3)	0.475 (0.317)	1.61	0.1344
ISST-BP Total Score[2] (Q1-Q3) <sup>4</sup>	0.100 (0.264)	1.11	0.7042
ISST-BP Total Score (≥Q3) <sup>4</sup>	0.253 (0.323)	1.29	0.4334
CDS (Q1-Q3)	-0.144 (0.223)	0.87	0.5183
CDS (≥Q3)	0.018 (0.296)	1.02	0.9520
Diagnosis	0.101 (0.141)	1.11	0.4749
Substance or Alcohol Abuse	0.395 (0.149)	1.48	0.0081
ESRS Total Score	-0.000 (0.004)	1.00	0.9344
Lindenmayer's PANSS Positive <sup>5</sup>	-0.015 (0.014)	0.99	0.3012
CDS Hopelessness Item	0.059 (0.096)	1.06	0.5393
Covi Anxiety Scale Total Score	0.041 (0.027)	1.04	0.1317

<sup>1</sup>All values of explanatory variables are determined from baseline values. Variable Codes: Treatment (0=Zyprexa, 1=Clozaril); Sex (1=Male, 2=Female); Diagnosis (1=Schizophrenia, 2=Schizoaffective); Substance or Alcohol Abuse (0=No, 1=Yes); CDS hopelessness (0=Absent, 1=Mild, 2=Moderate, 3=Severe).

<sup>2</sup>Refer to detailed statistical analysis plan in Appendix 5.1, §1.1.5.3, for information on calculation of these parameters. Hazard ratios for age group are relative to age group (18-32). Hazard ratios for (Q1-Q3) and (≥Q3) of the CGI-SS-BP, ISST-BP, and CDS scores are relative to (<Q1).

<sup>3</sup>P-values were generated using a full Cox's proportional hazards regression model, stratified on pooled country and with explanatory variables noted above.

<sup>4</sup>ISST is the total score of the 11 ratings (except for item 9) (Lindenmayer, in press).

<sup>5</sup>Lindenmayer et al. 1995

APPENDIX VI-17  
STUDY ABA 451  
MULTIPLE EVENT ANALYSIS OF TIME TO TYPE 1 AND TYPE 2 EVENTS  
BY DIAGNOSTIC SUBGROUP

Subgroup	Event Type [1]	Estimate of Treatment Effect (Beta) [2]	Standard Error of Beta	Weight	P-value [3]	95% C.I. of Beta	Hazard Ratio (exp(Beta)) [2]	95% C.I. of Hazard Ratio
Diagnosis of Schizophrenia	Type 1	-0.402	0.179	0.50	0.0251	(-.75, -.05)	0.67	(0.47, 0.95)
	Type 2	-0.309	0.159	0.50	0.0516	(-.62, 0.00)	0.73	(0.54, 1.00)
	Combined	-0.355	0.164	-	0.0298	(-.68, -.03)	-	-
Diagnosis of Schizoaffective	Type 1	-0.138	0.191	0.50	0.4700	(-.51, 0.24)	0.87	(0.60, 1.27)
	Type 2	-0.160	0.186	0.50	0.3905	(-.53, 0.21)	0.85	(0.59, 1.23)
	Combined	-0.149	0.187	-	0.4256	(-.52, 0.22)	-	-

[1] Event type 1: Occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance). Only time to the first occurrence (SMB-confirmed) was used in the survival analysis. Event type 2: Occurrence of a significant suicide attempt, hospitalization due to imminent suicide risk (including increased level of surveillance), or worsening of severity of suicidality measured by CGI-SS-BP (change score) of level 6 or 7. Only time to the first occurrence was used in the survival analysis.

[2] A negative value of beta and a hazard ratio less than 1 indicate that Treatment Group 1 (Clozaril) is better than Treatment Group 2 (Zyprexa).

[3] P-values were generated using the Normal Approximation Z-test using robust standard error estimates obtained following the WIM method (c=0.5), stratified on pooled country and with treatment as the only covariate.

APPENDIX VI-18  
STUDY ABA 451  
MULTIPLE EVENT ANALYSIS OF TIME TO TYPE 1 AND TYPE 2 EVENTS  
BY GEOGRAPHIC SUBGROUP

Subgroup	Event Type [1]	Estimate of Treatment Effect (Beta) [2]	Standard Error of Beta	Weight	P-value [3]	95% C.I. of Beta	Hazard Ratio (exp(Beta)) [2]	95% C.I. of Hazard Ratio
North America	Type 1	-0.249	0.168	0.50	0.1387	(-.58, 0.08)	0.78	(0.56, 1.08)
	Type 2	-0.282	0.162	0.50	0.0822	(-.60, 0.04)	0.75	(0.55, 1.04)
	Combined	-0.266	0.163	-	0.1031	(-.59, 0.05)	-	-
Rest of the World	Type 1	-0.327	0.207	0.50	0.1135	(-.73, 0.08)	0.72	(0.48, 1.08)
	Type 2	-0.209	0.181	0.50	0.2487	(-.56, 0.15)	0.81	(0.57, 1.16)
	Combined	-0.268	0.187	-	0.1525	(-.64, 0.10)	-	-

[1] Event type 1: Occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance). Only time to the first occurrence (SMB-confirmed) was used in the survival analysis. Event type 2: Occurrence of a significant suicide attempt, hospitalization due to imminent suicide risk (including increased level of surveillance), or worsening of severity of suicidality measured by CGI-SS-8P (change score) of level 6 or 7. Only time to the first occurrence was used in the survival analysis.

[2] A negative value of beta and a hazard ratio less than 1 indicate that Treatment Group 1 (Clozaril) is better than Treatment Group 2 (Zyprexa).

[3] P-values were generated using the Normal Approximation Z-test using robust standard error estimates obtained following the MIW method (c=0.5), stratified on pooled country and with treatment as the only covariate.

<b>APPENDIX VI-19</b>	
<b>CASE REPORT FORMS AUDITED FOR EFFICACY DATA</b>	
<b>(by center-patient)</b>	
<b>Patients without a Type 1 or Type 2 Event</b>	
	112-0020
	114-0033
	201-0011
	601-0020
	604-0021
	902-0004
	956-0032
<b>Patients with a Type 1 or Type 2 Event</b>	
	102-0012
	105-0030
	112-0005
	116-0002
	120-0006
	122-0010
	127-0007
	201-0004
	304-0005
	401-0029
	406-0004
	604-0032
	702-0004
	954-0003

<b>APPENDIX VI-20</b>	
<b>Audit of Efficacy Data</b>	
<b>CRF Forms Examined</b>	
Adverse Events	
Clinical Global Impression for Severity of Suicidality by Blinded Psychiatrist	
Imminent Risk of Suicide Requiring Hospitalization	
Suicide Attempt Form	
Suicide Event Form-Blinded Psychiatrist	
Suicide Event Form-Suicide Monitoring Board	

**APPENDIX VII-1:  
LINE LISTING OF ALL DEATHS (STUDY ABA 451)**

<b>Center/ Subject#</b>	<b>Age</b>	<b>Sex</b>	<b>Last Dose (mg/day)</b>	<b>Days of TX [post-TX]</b>	<b>Cause of Death</b>
<b>CLOZARIL PATIENTS</b>					
101/0016	56	F	300	106	Unknown
114/0003	31	M	400	278	Pulmonary Embolism
117/0004	37	M	50	261	Unknown
122/0010	20	M	400	30[+45]	Suicide
125/0027	37	F	500	393	Unknown
132/0001	33	F	25	64	Overdose (oxycodone)
302/0010	35	M	450	526	Cardiac Arrest
303/0010	35	F	100	703[+?]	Complications 2° Suicide Attempt
401/0001	36	M	200	26	Suicide
401/0022	46	F	325	15[+19]	Cancer
702/0010	38	M	250	79[+1]	Suicide
802/0012	37	M	200	225[+139]	Motor Vehicle Accident
902/0002	42	M	150	417	Suicide
<b>ZYPREXA PATIENTS</b>					
105/0007	40	F	20	770	Overdose (narcotics)
112/0019	47	M	15	15	Overdose (heroin)
117/0005	32	M	20	82	Unknown
301/0002	40	M	15	82[+15]	Suicide
302/0007	48	F	0	0	Myocardial Infarction (prior to TX)
302/0012	58	M	20	482[+6]	Cancer
303/0022	21	M	10	19[+132]	Suicide
953/0007	60	F	10	695	Unknown
953/0011	54	F	20	66	Stroke

**APPENDIX VII-2  
 ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS<sup>24</sup>  
 STUDY ABA 451**

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
<b>CARDIAC DISORDERS</b>		
Angina Pectoris	9 (1.9%)	7 (1.5%)
Arrhythmia NOS	2 (0.4%)	2 (0.4%)
Cardiomegaly NOS	3 (0.6%)	2 (0.4%)
Coronary Artery Disease NOS	3 (0.6%)	0 (0.0%)
Myocardial Infarction	1 (0.2%)	1 (0.2%)
Pericarditis NOS	1 (0.2%)	1 (0.2%)
<b>EAR AND LABYRINTH DISORDERS</b>		
Vertigo NEC	1 (0.2%)	0 (0.0%)
<b>ENDOCRINE DISORDERS</b>		
Hypothyroidism	2 (0.4%)	0 (0.0%)
Thyroid Disorder NOS	1 (0.2%)	0 (0.0%)
<b>EYE DISORDERS</b>		
Conjunctivitis NEC	1 (0.2%)	0 (0.0%)
<b>GASTROINTESTINAL DISORDERS</b>		
Abdominal Distention	19 (4.0%)	12 (2.5%)
Abdominal Pain NOS	1 (0.2%)	0 (0.0%)
Abdominal Pain Upper	5 (1.0%)	4 (0.8%)
Abdominal Pain Upper	1 (0.2%)	0 (0.0%)
Appendicitis Perforated	1 (0.2%)	0 (0.0%)
Colitis Ulcerative	1 (0.2%)	0 (0.0%)

<sup>24</sup> Excludes SAE's reported only in Zyprexa patients. Denominators adjusted for gender, as appropriate.

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 ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS<sup>24</sup>  
 STUDY ABA 451**

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Constipation	2 (0.4%)	0 (0.0%)
Gastric Ulcer Hemorrhage	1 (0.2%)	0 (0.0%)
Gastritis NOS	1 (0.2%)	0 (0.0%)
Gastrointestinal Hemorrhage NOS	2 (0.4%)	1 (0.2%)
Hematemesis	2 (0.4%)	1 (0.2%)
Hiatus Hernia	1 (0.2%)	0 (0.0%)
Incisional Hernia NOS	1 (0.2%)	0 (0.0%)
Inguinal Hernia NOS	1 (0.2%)	0 (0.0%)
Intestinal Obstruction NOS	3 (0.6%)	1 (0.2%)
Irritable Bowel Syndrome	1 (0.2%)	0 (0.0%)
Malabsorption	1 (0.2%)	0 (0.0%)
Nausea	2 (0.4%)	1 (0.2%)
Esophageal Stenosis	1 (0.2%)	0 (0.0%)
Esophagitis NOS	2 (0.4%)	0 (0.0%)
Pancreatitis NOS	1 (0.2%)	2 (0.4%)
Proctitis NOS	1 (0.2%)	0 (0.0%)
Reflux Esophagitis	1 (0.2%)	0 (0.0%)
Vomiting NOS	5 (1.0%)	2 (0.4%)
<b>GENERAL DISORDERS/ADMINISTRATION SITE CONDITIONS</b>	10 (2.1%)	7 (1.5%)
Chest Pain NEC	5 (1.0%)	5 (1.0%)
Fall	1 (0.2%)	0 (0.0%)
Fatigue	2 (0.4%)	1 (0.2%)
Neuroleptic Malignant Syndrome	1 (0.2%)	0 (0.0%)

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 STUDY ABA 451**

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Pyrexia	2 (0.4%)	0 (0.0%)
<b>HEPATOBIILIARY DISORDERS</b>		
	4 (0.8%)	2 (0.4%)
Cholelithiasis	3 (0.6%)	1 (0.2%)
Hepatic Disorder NOS	1 (0.2%)	0 (0.0%)
<b>INFECTIONS AND INFESTATIONS</b>		
	18 (3.8%)	11 (2.3%)
Abscess NOS	1 (0.2%)	0 (0.0%)
Bronchopneumonia NOS	1 (0.2%)	0 (0.0%)
Cellulitis Gangrenous	1 (0.2%)	0 (0.0%)
Colitis Pseudomembranous	1 (0.2%)	0 (0.0%)
Hepatitis Viral NOS	1 (0.2%)	0 (0.0%)
Lung Infection NOS	1 (0.2%)	0 (0.0%)
Meningitis Pneumococcal	1 (0.2%)	0 (0.0%)
Peritoneal Abscess	1 (0.2%)	0 (0.0%)
Pneumonia NOS	7 (1.5%)	4 (0.8%)
Pyelonephritis NOS	1 (0.2%)	1 (0.2%)
Salpingitis NOS	1 (0.5%)	0 (0.0%)
Sepsis NOS	1 (0.2%)	0 (0.0%)
Skin Infection NOS	1 (0.2%)	1 (0.2%)
Upper Respiratory Tract Infection NOS	1 (0.2%)	0 (0.0%)
Viral Infection NOS	1 (0.2%)	0 (0.0%)
Vulvovaginitis Trichomonal	1 (0.5%)	0 (0.0%)
<b>INJURY AND POISONING</b>		
	18 (3.8%)	17 (3.6%)
Accident NOS	2 (0.4%)	1 (0.2%)

APPENDIX VII-2  
 ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS<sup>24</sup>  
 STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Accidental Overdose (therapeutic agent)	4 (0.8%)	2 (0.4%)
Alcohol Intoxication Acute	1 (0.2%)	4 (0.8%)
Ankle Fracture	1 (0.2%)	0 (0.0%)
Burns NOS	1 (0.2%)	0 (0.0%)
Drug Toxicity NOS	1 (0.2%)	1 (0.2%)
Forearm Fracture	1 (0.2%)	0 (0.0%)
Non-accidental Overdose	5 (1.0%)	4 (0.8%)
Overdose NOS	2 (0.4%)	2 (0.4%)
Self Mutilation	1 (0.2%)	1 (0.2%)
Wrist Fracture	1 (0.2%)	0 (0.0%)
<b>INVESTIGATIONS</b>	<b>11 (2.3%)</b>	<b>3 (0.6%)</b>
Blood Test NOS	1 (0.2%)	0 (0.0%)
Hemoglobin Decreased	1 (0.2%)	0 (0.0%)
Platelet Count Decreased	1 (0.2%)	0 (0.0%)
White Blood Cell Decreased	8 (1.7%)	0 (0.0%)
<b>METABOLISM AND NUTRITION DISORDERS</b>	<b>13 (2.7%)</b>	<b>7 (1.5%)</b>
Dehydration	4 (0.8%)	1 (0.2%)
Diabetes Mellitus NOS	4 (0.8%)	6 (1.3%)
Hyperglycemia	3 (0.6%)	0 (0.0%)
Hypokalemia	2 (0.4%)	0 (0.0%)
Ketoacidosis	1 (0.2%)	0 (0.0%)
Polydipsia	1 (0.2%)	0 (0.0%)
Tetany	1 (0.2%)	0 (0.0%)

APPENDIX VII-2  
 ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS<sup>24</sup>  
 STUDY ABA 451

Body System/MedRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
<b>MUSCULOSKELETAL/CONNECTIVE TISSUE/BONE DISORDERS</b>		
Back Pain	5 (1.0%)	3 (0.6%)
Muscle Twitching	2 (0.4%)	2 (0.4%)
Pain in Limb	1 (0.2%)	0 (0.0%)
Pseudoarthrosis	1 (0.2%)	0 (0.0%)
Rhabdomyolysis	1 (0.2%)	0 (0.0%)
Sensation of Heaviness	1 (0.2%)	0 (0.0%)
<b>NEOPLASMS BENIGN AND MALIGNANT</b>		
Basal Cell Carcinoma	4 (0.8%)	4 (0.8%)
Breast Lump NOS	1 (0.2%)	0 (0.0%)
Lymphoma NOS	1 (0.2%)	0 (0.0%)
Uterine Cancer NOS	1 (0.5%)	0 (0.0%)
<b>NERVOUS SYSTEM DISORDERS</b>	26 (5.4%)	15 (3.1%)
Cerebrovascular Accident NOS	1 (0.2%)	1 (0.2%)
Complex Partial Seizures	1 (0.2%)	0 (0.0%)
Convulsions NOS	4 (0.8%)	2 (0.4%)
Disturbance in Attention NEC	1 (0.2%)	0 (0.0%)
Dizziness (excl. vertigo)	3 (0.6%)	0 (0.0%)
Dyskinesia NEC	1 (0.2%)	0 (0.0%)
Dysphonia	1 (0.2%)	0 (0.0%)
Epilepsy NOS	1 (0.2%)	1 (0.2%)
Grand Mal Convulsion	1 (0.2%)	2 (0.4%)
Hypotonia	1 (0.2%)	0 (0.0%)

**APPENDIX VII-2  
 ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS<sup>24</sup>  
 STUDY ABA 451**

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Insomnia NEC	3 (0.6%)	4 (0.8%)
Myoclonic Seizure	1 (0.2%)	0 (0.0%)
Paresthesia NEC	1 (0.2%)	0 (0.0%)
Paraplegia	1 (0.2%)	0 (0.0%)
Sedation	1 (0.2%)	0 (0.0%)
Sleep Apnea Syndrome	1 (0.2%)	0 (0.0%)
Somnolence	3 (0.6%)	0 (0.0%)
Syncope	1 (0.2%)	0 (0.0%)
Tremor NEC	1 (0.2%)	0 (0.0%)
<b>PREGNANCY, PUERPERIUM, AND PERINATAL CONDITIONS</b>	<b>2 (0.4%)</b>	<b>0 (0.0%)</b>
Intrauterine Death	1 (0.5%)	0 (0.0%)
Placenta Previa	1 (0.5%)	0 (0.0%)
Pregnancy NOS	1 (0.5%)	0 (0.0%)
<b>PSYCHIATRIC DISORDERS</b>	<b>185 (38.6%)</b>	<b>206 (43.2%)</b>
Abnormal Behavior NOS	2 (0.4%)	0 (0.0%)
Acute Psychosis	3 (0.6%)	6 (1.3%)
Aggression	5 (1.0%)	7 (1.5%)
Agitation	9 (1.9%)	13 (2.7%)
Agitation Aggravated	3 (0.6%)	2 (0.4%)
Alcoholic Withdrawal Symptoms	1 (0.2%)	1 (0.2%)
Alcoholism	5 (1.0%)	6 (1.3%)
Anhedonia	2 (0.4%)	1 (0.2%)
Anxiety NEC	30 (6.3%)	38 (8.0%)

**APPENDIX VII-2  
 ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS<sup>24</sup>  
 STUDY ABA 451**

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Catatonia	1 (0.2%)	1 (0.2%)
Completed Suicide	5 (1.0%)	3 (0.6%)
Confusion	1 (0.2%)	0 (0.0%)
Confusional State	1 (0.2%)	0 (0.0%)
Delirium	1 (0.2%)	1 (0.2%)
Delusion NOS	14 (2.9%)	16 (3.4%)
Delusion of Grandeur	1 (0.2%)	0 (0.0%)
Depressed Mood	5 (1.0%)	8 (1.7%)
Depression NEC	42 (8.8%)	44 (9.2%)
Drug Addiction	1 (0.2%)	0 (0.0%)
Exacerbation of Anxiety	1 (0.2%)	1 (0.2%)
Hallucination NOS	8 (1.7%)	11 (2.3%)
Hallucination, Auditory	13 (2.7%)	25 (5.2%)
Homicidal Ideation	9 (1.9%)	7 (1.5%)
Intentional Self-Injury	2 (0.4%)	4 (0.8%)
Irritability	1 (0.2%)	4 (0.8%)
Major Depressive Disorder NOS	1 (0.2%)	0 (0.0%)
Mental Disorder NEC	3 (0.6%)	0 (0.0%)
Obsessive Thoughts	1 (0.2%)	1 (0.2%)
Obsessive-Compulsive Disorder	1 (0.2%)	0 (0.0%)
Panic Attack	3 (0.6%)	1 (0.2%)
Paranoia	7 (1.5%)	6 (1.3%)
Psychomotor Retardation	1 (0.2%)	0 (0.0%)

**APPENDIX VII-2  
 ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS<sup>24</sup>  
 STUDY ABA 451**

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Psychotic Disorder NOS	72 (15.0%)	75 (15.7%)
Schizoaffective Disorder	6 (1.3%)	7 (1.5%)
Schizophrenia NOS	11 (2.3%)	15 (3.1%)
Schizophrenia, Disorganized Type	1 (0.2%)	0 (0.0%)
Schizophrenia, Paranoid Type	2 (0.4%)	2 (0.4%)
Self-Induced Vomiting	1 (0.2%)	0 (0.0%)
Self-Injurious Ideation	2 (0.4%)	2 (0.4%)
Sleep Disorder NOS	1 (0.2%)	1 (0.2%)
Stress Symptoms	1 (0.2%)	3 (0.6%)
Suicidal Ideation	77 (16.1%)	109 (22.9%)
Suicide Attempt	32 (6.7%)	56 (11.7%)
Tension	1 (0.2%)	1 (0.2%)
Thinking Abnormal NEC	3 (0.6%)	1 (0.2%)
<b>RENAL AND URINARY DISORDERS</b>		
Calculus Bladder	5 (1.0%)	3 (0.6%)
	1 (0.2%)	0 (0.0%)
Polyuria	1 (0.2%)	0 (0.0%)
Renal Failure NOS	1 (0.2%)	1 (0.2%)
Urinary Incontinence	2 (0.4%)	0 (0.0%)
<b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>		
Amenorrhea NOS	5 (1.0%)	2 (0.4%)
	1 (0.5%)	0 (0.0%)
Orchitis NOS	1 (0.3%)	0 (0.0%)
Ovarian Cyst	1 (0.5%)	1 (0.5%)
Pelvic Pain NOS	1 (0.2%)	0 (0.0%)

**APPENDIX VII-2  
 ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS<sup>24</sup>  
 STUDY ABA 451**

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Vulval Ulceration	1 (0.5%)	0 (0.0%)
<b>RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS</b>	12 (2.5%)	7 (1.5%)
Asthma NOS	1 (0.2%)	3 (0.6%)
Chronic Obstructive Airways Disease	1 (0.2%)	2 (0.4%)
Dyspnea	3 (0.6%)	1 (0.2%)
Hyperventilation	1 (0.2%)	0 (0.0%)
Hypoventilation	1 (0.2%)	0 (0.0%)
Pharyngeal Disorder NOS	1 (0.2%)	0 (0.0%)
Pleural Effusion	1 (0.2%)	0 (0.0%)
Pneumonia Aspiration	1 (0.2%)	0 (0.0%)
Respiratory Distress	1 (0.2%)	0 (0.0%)
Respiratory Failure (excl. neonatal)	2 (0.4%)	1 (0.2%)
<b>SKIN AND CUTANEOUS TISSUE DISORDERS</b>	5 (1.0%)	1 (0.2%)
Dermatitis Medicamentosa	1 (0.2%)	0 (0.0%)
Epidermal Cyst	1 (0.2%)	0 (0.0%)
Hemangioma NOS	1 (0.2%)	0 (0.0%)
Hidradenitis	1 (0.2%)	0 (0.0%)
Rash Papular	1 (0.2%)	0 (0.0%)
<b>SOCIAL CIRCUMSTANCES</b>	12 (2.5%)	18 (3.8%)
Bereavement NOS	1 (0.2%)	0 (0.0%)
Drug Abuse	1 (0.2%)	5 (1.0%)
Social Problem NOS	11 (2.3%)	13 (2.7%)
Treatment Noncompliance	1 (0.2%)	2 (0.4%)

**APPENDIX VII-2  
 ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS<sup>24</sup>  
 STUDY ABA 451**

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
<b>SURGICAL AND MEDICAL PROCEDURES</b>		
Hospitalization NOS	2 (0.4%)	2 (0.4%)
Orthopedic Procedure	1 (0.2%)	1 (0.2%)
<b>VASCULAR DISORDERS</b>		
Acute Circulatory Failure	5 (1.0%)	5 (1.0%)
Deep Venous Thrombosis NOS	1 (0.2%)	0 (0.0%)
Postural Hypotension	1 (0.2%)	0 (0.0%)
Pulmonary Embolism	2 (0.4%)	1 (0.2%)
Transient Ischemic Attack	1 (0.2%)	1 (0.2%)

**APPENDIX VII-3:  
 NARRATIVE SUMMARIES REVIEWED FOR PATIENTS WITH SERIOUS ADVERSE EVENTS  
 (BY CENTER# -PATIENT#)**

109-0016	126-0022	302-0041
117-0004	129-0010	403-0008
120-0003	301-0019	502-0008
120-0014	302-0010	701-0022
126-0017	302-0011	702-0021

**APPENDIX VII-4  
 ENUMERATION OF ADVERSE EVENTS LEADING TO DROPOUT AMONG CLOZARIL-TREATED PATIENTS<sup>25</sup>  
 STUDY ABA 451**

Body System/MedDRA Preferred Term	Number (%) of Pts. with AE Leading to Dropout	
	Clozaril (N=479)	Zyprexa (N=477)
<b>CARDIAC DISORDERS</b>		
Cardiomegaly NOS	3 (0.6%)	0 (0.0%)
Palpitations	1 (0.2%)	0 (0.0%)
Tachycardia NOS	1 (0.2%)	0 (0.0%)
<b>EYE DISORDERS</b>		
Bloodshot Eye	1 (0.2%)	0 (0.0%)
<b>GASTROINTESTINAL DISORDERS</b>		
Abdominal Pain NOS	6 (1.3%)	2 (0.4%)
Aptyalism	1 (0.2%)	0 (0.0%)
Diarrhea NOS	1 (0.2%)	0 (0.0%)
Intestinal Obstruction NOS	3 (0.6%)	0 (0.0%)
Nausea	1 (0.2%)	1 (0.2%)
Salivary Hypersecretion	1 (0.2%)	0 (0.0%)
Vomiting NOS	1 (0.2%)	0 (0.0%)
<b>GENERAL DISORDERS/ADMINISTRATION SITE CONDITIONS</b>		
Pyrexia	1 (0.2%)	0 (0.0%)
<b>INVESTIGATIONS</b>		
Blood Test NOS	11 (2.3%)	8 (1.7%)
Weight Increased	1 (0.2%)	0 (0.0%)
	2 (0.4%)	7 (1.5%)

<sup>25</sup> Excludes AE's leading to dropout only in Zyprexa patients. Denominators adjusted for gender.

**APPENDIX VII-4  
 ENUMERATION OF ADVERSE EVENTS LEADING TO DROPOUT AMONG CLOZARIL-TREATED PATIENTS<sup>25</sup>  
 STUDY ABA 451**

Body System/MedRA Preferred Term	Number (%) of Pts. with AE Leading to Dropout	
	Clozaril (N=479)	Zyprexa (N=477)
White Blood Cell Decreased	8 (1.7%)	0 (0.0%)
<b>METABOLISM AND NUTRITION DISORDERS</b>	2 (0.4%)	2 (0.4%)
Diabetes Mellitus NOS	1 (0.2%)	2 (0.4%)
Hyperglycemia NOS	1 (0.2%)	0 (0.0%)
<b>MUSCULOSKELETAL/CONNECTIVE TISSUE/BONE DISORDERS</b>	2 (0.4%)	1 (0.2%)
Muscle Twitching	1 (0.2%)	0 (0.0%)
Myalgia	1 (0.2%)	0 (0.0%)
Sensation of Heaviness	1 (0.2%)	0 (0.0%)
<b>NEOPLASMS BENIGN AND MALIGNANT</b>	1 (0.2%)	1 (0.2%)
Lymphoma NOS	1 (0.2%)	0 (0.0%)
<b>NERVOUS SYSTEM DISORDERS</b>	11 (2.3%)	2 (0.4%)
Cerebrovascular Accident NOS	1 (0.2%)	0 (0.0%)
Disturbance in Attention NEC	1 (0.2%)	0 (0.0%)
Dizziness (excl. vertigo)	4 (0.8%)	0 (0.0%)
Dysarthria	1 (0.2%)	0 (0.0%)
Memory Impairment	1 (0.2%)	0 (0.0%)
Sedation	1 (0.2%)	0 (0.0%)
Somnolence	5 (1.0%)	1 (0.2%)
Vegetative State Chronic	1 (0.2%)	0 (0.0%)
<b>PREGNANCY, PUERPERIUM, AND PERINATAL CONDITIONS</b>	1 (0.5%)	0 (0.0%)
Pregnancy NOS	1 (0.5%)	0 (0.0%)
<b>PSYCHIATRIC DISORDERS</b>	12 (2.5%)	17 (3.6%)

APPENDIX VII-4  
 ENUMERATION OF ADVERSE EVENTS LEADING TO DROPOUT AMONG CLOZARIL-TREATED PATIENTS<sup>25</sup>  
 STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. with AE Leading to Dropout	
	Clozaril (N=479)	Zyprexa (N=477)
Acute Psychosis	2 (0.4%)	0 (0.0%)
Agitation	1 (0.2%)	0 (0.0%)
Anxiety NEC	2 (0.4%)	0 (0.0%)
Depression NEC	1 (0.2%)	1 (0.2%)
Irritability	1 (0.2%)	0 (0.0%)
Obsessive-Compulsive Disorder	1 (0.2%)	0 (0.0%)
Paranoia	2 (0.4%)	0 (0.0%)
Psychotic Disorder NOS	2 (0.4%)	9 (1.9%)
Suicidal Ideation	1 (0.2%)	4 (0.8%)
Suicide Attempt	1 (0.2%)	3 (0.6%)
<b>RENAL AND URINARY DISORDERS</b>	1 (0.2%)	1 (0.2%)
Urinary Incontinence	1 (0.2%)	0 (0.0%)

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this page is the manifestation of the electronic signature.**  
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/s/

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Greg Dubitsky  
8/1/02 06:06:20 PM  
MEDICAL OFFICER

Thomas Laughren  
8/22/02 09:03:43 AM  
MEDICAL OFFICER

I believe the findings from study ABA 451 are sufficiently positive to justify an approvable action, however, several key questions will need to be satisfactorily addressed before a final action; see memo to file for more detailed comments.--TPL