

CLINICAL REVIEW

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Reviewer Name Glenn B. Mannheim, M.D.
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Established Name PROVIGIL (Modafinil) Tablets
(Proposed) Trade Name SPARLON™
Therapeutic Class Wakefulness-Promoting Agent
Applicant Cephalon

Priority Designation Standard
Formulation Tablets
Dosing Regimen: PROVIGIL: 100 mg, 200 mg
SPARLON™: 85 mg, 170 mg,
255 mg, 340 mg, 425 mg
Indication: Attention Deficit/Hyperactivity
Disorder (ADHD)
Intended Population Children (6-11 Years),
Adolescents (12-17 Years)

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Clinical Review

Glenn B. Mannheim, M.D.

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1 EXECUTIVE SUMMARY

1.1 Background

In 1998, FDA, approved modafinil [Provigil; (NDA 20-717)], a wakefulness-promoting agent to improve wakefulness in adult patients with excessive daytime sleepiness (EDS) associated with narcolepsy. Subsequent approvals occurred (10/2003) for the treatment of EDS associated with Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS), and Shift Work Sleep Disorder (SWSD). Recommended dosing in these disorders was 200 mg once a day, as a single morning dose for patients with narcolepsy and OSAHS, and for SWSD, 1 hour prior to the start of one's work shift. In the various trials leading to approval for these indications, no consistent evidence was demonstrated that doses above 200 mg dose conferred additional benefit, although single doses of 400 mg/day were well tolerated. Provigil (modafinil) tablets come in strengths of 100 and 200 mg, respectively.

The current submission is for modafinil as a new indication in the treatment of attention-deficit/ hyperactivity disorder (ADHD) in children (6-11 Years) and adolescents (12-17 Years). The primary basis for safety and efficacy is three (3) Phase 3 placebo-controlled clinical trials [two (2) variable dose and one (1) fixed dose studies] enrolling over 600 patients between the ages of 6 and 17 years.

In addition, this supplement contains a revised drug product formulation and requests approval of new tablet strengths (85, 170, 255, 340 and 425 mg) specifically developed for the use in this new indication. Approval of a separate brandname¹ (SPARLONTM) for indication and use of modafinil tablets in ADHD is requested by Cephalon (the sponsor) to differentiate this product from the originally approved wakefulness-promoting agent, PROVIGIL[®]. Significant labeling changes are requested (Appendix: List of Proposed Labeling Changes) and labeling was last updated for Provigil (CBE, 12/02/2004) [History of changes since last approved labeling].

¹ The original brandnames submitted, first, ATTENACE, and later, ALTAVIGE were reviewed by the Division of Medication Errors and Technical Support (DMETS) who had objections to these names for reasons identified in this review. The current name which was submitted on 08/23/2005 for consideration is SPARLON.

The studies submitted in support of this sNDA are summarized in the Appendix.

Eight (8) clinical studies involving 933 children and adolescent subjects exposed to modafinil comprise this sNDA. Four (4) of the studies are pharmacokinetic (PK) and, or, pharmacodynamic (PD) studies which involved 302 subjects. These studies are listed below.

C1538d/1024/BA/US (*Study 1024*) was a randomized, open-label crossover study evaluating the bioequivalence of modafinil tablets (five 85-mg tablets versus one 425-mg tablet) in 30 healthy adults.

C1538d/113/BA/US (*Study 113*) was a randomized open-label crossover study comparing the relative bioavailability of 170 mg of modafinil film-coated tablets to 200 mg of Provigil in 24 children (9 years, mean).

C1538d/207/AD/US (*Study 207*) was a phase 2, double-blind, randomized, placebo-controlled, 2-part (5 or 6 weeks per part), crossover study evaluating the dose range, dose frequency, and PK/PD correlation of 5 oral doses of Provigil in 30 children with ADHD (9.5 years, mean), followed by an 8-week open-label extension.

C1538a/213/AD/US (*Study 213*) was a phase 2, 4-week, double-blind, randomized, placebo-controlled, parallel study evaluating the efficacy and safety of Provigil in 248 (9.3 years mean) children with ADHD, followed by an 8-week open-label extension.

Three (3) phase 3, placebo-controlled studies involving 633 subjects (modafinil: 420; placebo: 213) were used to demonstrate primary efficacy and safety. Two (2) are nine (9) week, flexible (up to 425 mg) dose [C1538d/309/AD/US, or, *Study 309* and C1538d/311/AD/US, or, *Study 310*] and one (1), is a seven (7) week (340, or, 425 mg) fixed dose study with a two (2) week withdrawal [C1538d/311/AD/US or, *Study 310*]. The flexible and fixed doses represent 295 and 125 subjects, respectively, who were treated with modafinil.

One (1) study is an on-going, 1-year, open label study C1538d/312/AD/US (*Study 312*) to assess longer term safety and continued efficacy of modafinil. This trial consists of 533 subjects (10.2 years, mean), of which, 372 are from flexible

dose studies (309, 311); 133 subjects from the fixed dose study (310); and 28 subjects from the PK/PD studies (113, 213). At the time of the 4 month submission on 04/19/2005, 48 subject (9 %) have completed the study; 228 subjects (43 %) have been treated for less than 6 months; and 305 (57 %) have been treated for more than 6 months. To date, 279 (52 %) of the subjects have discontinued from the study for various reasons. This 4 month safety update is less than "175 patients treated with modafinil for 12 months" that was agreed upon between the sponsor and FDA in our 07/08/2004 meeting. No individual study report was received for this safety update, however, updated tables for this data was included with an updated, integrated safety set.

Two additional studies in children with ADHD were sponsored by Laboratoire L. Lafon and conducted in France studies *E1044* and *E1047* involving 38 pediatric subjects. Study *E1044* was a pilot, double-blind placebo-controlled trial study of modafinil in ADHD in children; and Study *E1047* was a pilot, open-label study of modafinil in children with ADHD who were responsive to methylphenidate. The sponsor has not included these 2 studies in the integrated safety database for this submission because "validated electronic databases not available". However, clinical study reports are provided.

Study No. C1538a/205/AD/US (*Study 205*) evaluated the use of modafinil for the treatment of ADHD in adults. The sponsor did not submit this study report as part of the current submission as was discussed in our 07/08/2004 meeting. Minutes of that meeting indicate that this study report was previously submitted as part of the safety package to support approved supplement NDA 20-717/S-008. This study was apparently not submitted because it was "negative".

A clinical development program is underway for the use of modafinil in children and adolescents with excessive sleepiness associated with narcolepsy (IND 59, 661). The safety data from those studies are not part of this data set, however, a serious adverse event from that study involving a 6 year old with an episode of a Reye-like illness will be included as it relates to the safe use of modafinil for the proposed ADHD indication

Data from the three pivotal studies 309, 310, and 311 demonstrate the efficacy of modafinil in children and adolescents with ADHD based on the LOCF analysis of the ITT population for the primary efficacy measure, the teacher/phy-

sician-completed ADHD Rating Scale, Fourth Edition (ADHD-RS-IV) (School Version) [$p < 0.001$].

Worrisome safety signals identified in clinical trials include Stevens Johnson Syndrome (and other rashes of unclear significance), a possible Reye's syndrome (and other laboratory, hepatic dysfunction), various psychiatric disorders (e.g. suicidality, depression, agitation, psychosis and phobias), leukopenia/neutropenia; and insomnia (drug: 27 %, placebo; 4 %), anorexia (drug: 16 %, placebo; 3 %), and headaches (drug: 20 %, placebo; 13 %) of modafinil pediatric and adolescent subjects. The presence of a significant amount of insomnia, headaches, or other psychiatric disorders will almost certainly result in off-label and labeled use of many sleep, analgesic and psychiatric medicines which will probably result in increased risk of adverse events (e.g. increased risk of skin, liver, or, psychiatric problems).

Despite, the demonstration of clinical efficacy, the safety profile demonstrates increased and, in this reviewers opinion, unacceptable risks to children and adolescents, resulting in the recommendation that the Agency take a non-approvable action on this submission.

If the outstanding consults bears out the perceived risks, an Agency discussion should be undertaken to discuss the need to halt all clinical development programs currently underway with children (e.g. excessive sleepiness associated with narcolepsy) and to consider the need for recommending a stronger warning for Provigil (modafinil) as it related to the use of this drug in children.

1.2 Recommendation on Regulatory Action

I recommend a "non-approvable" action be taken on modafinil for the added indication of ADHD in children and adolescents and a denial of the request for a partial waiver, requested under CFR Part 314.55(c)(3)(i),f providing efficacy and safety information in the population younger than 6 years.

Basis for Non-Approvable Action(s):

1. A sulfone metabolite accumulates to a greater extent in subjects weighting less than 30 kg and it is uncertain when it reaches steady-state based on the studies performed (approximately 6 weeks ?) so we do not know the absolute

accumulation of the metabolite in this age group. Age range of the 340 mg dose group tested was 5-10 years and the 425 mg dose group was 8-13 years. A disproportionate exposure to the sulfone metabolites of about 6 times occurred in children compared to adolescents and adults.

2. PK/PD and clinical studies have shown that doses of around 340 or 425 mg are needed in order to achieve clinical response (efficacy). Hence, dose reduction will not be useful.
3. Paralleling the disproportionate exposure in children is the observation from controlled clinical trials of very rare adverse events occurring in these younger age groups: Steven Johnson Syndrome (7 years) and other uncertain rashes (1-2/933 vs. 1 per million background) and Reye's-like syndromes (only 36 cases per year since 1987) are only occurring in subjects on modafinil. The mean age of subjects with rash was 8.5 years, did not occur in adolescents and was not observed with the adult experience. The case of Reyes-like syndrome occurred in a 6 year old. The relation to the drug is uncertain, but mean GGT elevations were higher in those receiving increasing exposures as to amount (e.g. 340 and 425 mg/day) and duration of modafinil (14 % on modafinil compared to 1 % on placebo showed increases in GGT over 6 months). Similarly, suicidal ideation and psychosis occurred at a mean age of 8 years (all psychiatric events in placebo; mean age: 10 years) in subjects leaving the trials because of adverse events. Suicidal ideation (6: 12 %; one of which was a possible attempt versus a gesture), agitation (5: 10 %), depression (2: 4 %) psychosis (3: 6 %), another with possible psychosis (1: moderate change in mental status, not specified); and phobias (3: 6 %) were only reported as reasons for discontinuation for subjects on drug.
4. Anorexia (modafinil: 16 %; placebo: 3 %) and insomnia (modafinil: 27 %; placebo: 4 %) are more common than with most stimulants except for Adderall XR. Headache (modafinil: 20 %; placebo: 13 %) seems to be more common in modafinil subjects than others. A table comparing some of the MPH and amphetamine products, which are currently available (e.g. Concerta, Metadate, Ritalin LA, Focalin, Adderall XR), is indicated in Table 1 in the Appendix. The risk of insomnia and headaches will most certainly result in various treatment strategies (e.g. stopping, restarting; using off label and labeled analgesics and sleep medications) perhaps resulting in increased dermatological sensitization, psychiatric, or, other adverse events.

Hence, the risks associated with the use of provigil are greater than the benefits and preclude the safe use of this drug in the intended population for ADHD, a none life-threatening disease and without showing clear, demonstrated advantages over existing stimulants.

1.3 Recommendation on Postmarketing Actions

1.3.1 Risk Management Activity

A Public Advisory Meeting may need to be considered to discuss the issues identified in this review as it relates to continuation of a pediatric development program for modafinil for other indications. Further internal discussion of this issue is recommended.

1.3.2 Required Phase 4 Commitments

- Further work should be undertaken to characterize the clinical significance of the disproportionate sulfone metabolite present in children, if it is ultimately decided by the Agency that the drug is approvable.
- Given the fact that the ADHD subjects who were studied were moderately to severely ill or greater (CGI-S \geq 4) and did not have learning disability (Screening score \geq 80 on the WIAT-II-A), the generalizability of findings from this group of subjects to other children with less severe ADHD (CGI-S < 4) with learning disorders is uncertain, and may need to be considered as a Phase IV commitment.

1.4 Summary of Clinical Findings

1.4.1 Brief Overview of Clinical Program

A table summarizing these trials is included in the Appendix.

Studies 309 and 311 were Phase 3, randomized, double-blind, placebo-controlled, 9-week, flexible-dosage (up to 425 mg/ day), parallel-group studies, conducted to evaluate the efficacy and safety of modafinil (film-coated tablet) in children and

adolescents with ADHD. The primary efficacy measure in these 2 studies was the change from baseline in the teacher/ physician-completed ADHD-RS-IV (School Version) total score at endpoint (week 9 or the last double-blind treatment period visit). Study 309 consisted of 198 subjects (131 modafinil, 67 placebo) and in Study 311 there were 246 subjects (164 modafinil, 82 placebo), totaling 444 subjects (295 modafinil, 149 placebo) for the flexible dose studies.

Study 310 was a Phase 3, randomized, double-blind, placebo-controlled, 9-week, fixed-dosage (340 or 425 mg/ day), parallel-group study conducted to evaluate the efficacy and safety of modafinil (film-coated tablet) in children and adolescents with ADHD. The 9-week period included a 2-week, randomized, double-blinded withdrawal period (weeks 8 and 9). Study 310 consisted of 189 subjects (125 modafinil, 64 placebo).

The total number of subjects in these three (3) double-blind phase III trials was 633 subjects (420 modafinil, 213 placebo).

Study 312 is a one (1) year flexible dose (170-425 mg/day), open label long term extension study (02/28/05 cut-off date) is under way to ascertain continued efficacy and the presence of unusual safety signals. This study involves 533 subjects [M: 391 (73 %); F: 142 (27 %); 10 .2 yrs, mean]. At the time of this 4 month submission, only 48 (9%) of the subjects have completed the study. Two hundred and twenty eight (228: 43 %) have been treated for less than 6 months, while, 305 (57 %) have been treated for more than 6 months. Two hundred and seventy nine (279: 52 %) of the subjects have discontinued from the study.

1.4.2 Efficacy

Data from studies 309, 311 and 310 demonstrate the efficacy in children and adolescents with ADHD.

1.4.3 Safety

Worrisome safety signals identified in clinical trials include Stevens Johnson Syndrome (and other rashes of unclear significance), a possible Reye's syndrome (and other laboratory, hepatic dysfunction), various psychiatric disorders (e.g. suicidality, depression, agitation, psychosis and phobias), leukopenia/neutropenia; and insomnia (drug: 27 %, placebo; 4 %), anorexia (drug: 16 %, placebo; 3 %), and headaches (drug: 20 %,

placebo; 13 %) of modafinil pediatric and adolescent subjects. The presence of a significant amount of insomnia, headaches, or, other psychiatric disorders will almost certainly result in off-label and labeled use of many sleep, analgesic and psychiatric medicines which will probably result in increased risk of adverse events (e.g. increased risk of skin, liver, or, psychiatric problems).

Postmarketing data in children supports this view with the most commonly reported serious ADR's being mania, hallucination, suicide attempt and intentional overdose; and the most commonly reported non-serious ADR's being headache, insomnia, anorexia and drug interaction.

1.4.4 Dosing Regimen and Administration

The clinical pharmacology/biopharmaceutics review states the following, for which the reader is referred for further details.

"Modafinil film-coated tablets should be taken as a single dose, in the morning, with or without food. Dosage should be individualized according to the needs and responses of the patient. In clinical trials, treatment was initiated at 85 mg /day. The daily dosage was increased by 85 mg increments every 2 to 7 days until the optimum or target daily dose was achieved. Doses above 425 mg have not been systematically evaluated.

The following target daily doses are recommended:

- Patients less than 30 kg of body weight: 340 mg
- Patients at least 30 kg of body weight: 425 mg"

1.4.5 Drug-Drug Interactions

The clinical pharmacology/biopharmaceutics review states the following, for which the reader is referred for further details.

"Dosage adjustment should be considered for concomitant medications that are substrates for CYP3A4, such as triazolam and cyclosporine.

Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin (also via CYP2C9) or S-mephenytoin may have prolonged elimination upon co-administration with PROVIGIL and may require dosage reduction and monitoring for toxicity. The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL tablets and for one month after discontinuation of therapy. Alternative or concomitant methods of contraception are

recommended for patients treated with PROVIGIL tablets, and for one month after discontinuation of PROVIGIL."

1.4.6 Special Populations

The reader is referred to the clinical pharmacology/
biopharmaceutics review for a complete discussion of this topic.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

In 1998, FDA, approved modafinil [Provigil; (NDA 20-717)], a wakefulness-promoting agent to improve wakefulness in adult patients with excessive daytime sleepiness (EDS) associated with narcolepsy. Subsequent approvals occurred (10/2003) for the treatment of EDS associated with Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS), and Shift Work Sleep Disorder (SWSD). Recommended dosing in these disorders is 200 mg once a day, as a single morning dose for patients with narcolepsy and OSAHS, and for SWSD, 1 hour prior to the start of one's work shift. In the various trials leading to approval for these indications, no consistent evidence was demonstrated that doses above 200 mg dose conferred additional benefit, although single doses of 400 mg/day were well tolerated. Provigil (modafinil) tablets come in strengths of 100 and 200 mg, respectively.

The current submission is for modafinil as a new indication in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children (6-11 Years) and adolescents (12-17 Years). The primary basis for safety and efficacy is three (3) Phase 3 placebo-controlled clinical trials [two (2) variable dose and one (1) fixed dose studies] enrolling over 600 patients between the ages of 6 and 17 years.

In addition, this supplement contains a revised drug product formulation and requests approval of new tablet strengths (85, 170, 255, 340 and 425 mg) specifically developed for the use in this new indication. Approval of a separate brandname² (SPARLON™) for indication and use of modafinil tablets in ADHD is requested by Cephalon (the sponsor) to differentiate this product from the originally approved wakefulness-promoting agent, PROVIGIL®. Significant labeling changes are requested (Appendix: List of Proposed Labeling Changes) and labeling was last updated for Provigil (CBE, 12/02/2004) [History of changes since last approved labeling].

² The original brandnames submitted, first, ATTENACE, and later, ALTAVIGE were reviewed by the Division of Medication Errors and Technical Support (DMETS) who had objections to these names for reasons identified in this review. The current name which was submitted on 08/23/2005 for consideration is SPARLON.

2.2 Currently Available Treatment for Indications

In 2001, the Clinical Practice Guidelines Subcommittee³ on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement listed many of the following drugs as being available for the treatment of ADHD. This list has been supplemented with current information:

First-Line Treatment

Methylphenidates

Short acting

- Ritalin[®], Methylin[®], Focalin[®]

Intermediate acting

- Ritalin SR[®], Metadate ER[®], Methylin ER[®]

Long acting

- Concerta[®], Metadate CD[®], Ritalin LA[®], Focalin XR[®]

Amphetamines

Intermediate acting

- Adderall[®], Dexedrine spansule[®]

Short acting

- Dexedrine[®], Dextrostat[®]

Long acting

- Adderall XR[®]

Pemoline

- Cylert[®] discontinued by Abbott

Non-Stimulants

- Atomoxetine
– Strattera[®]

Second-Line Treatment: Not FDA Approved

Antidepressants:

Tricyclic antidepressants

- Imipramine, Desipramine

³ Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. 2001. Clinical Practice Guideline: Treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics 108:1033-1044.

Bupropion

- Wellbutrin[®], Wellbutrin SR[®]

2.3 Important Issues with Pharmacologically Related Products

Immediate and sustained oral formulations of methylphenidate, amphetamine have been associated with insomnia, anorexia, weight loss, decreased growth, abdominal pain and hypertension. The Agency is looking at these drugs for potential signals as they relate to sudden death; myocardial infarction; stroke; psychiatric disturbances as suicidality and new onset psychosis; and will be evaluating the need for long-term studies by an upcoming public meeting. A Citizen's Petition is currently before the Agency requesting the removal of Cylert (pemoline) because of an increased risk of unpredictable, serious hepatotoxicity resulting either in death, or, liver transplantation. Atomoxetine (Strattera) has been given a bolded warning because of a risk of serious hepatotoxicity. This drug is also being examined for new onset psychiatric (e.g. risk of suicide) symptoms associated with its routine use.

2.4 Pre- and Post-Submission Regulatory Activity

Presubmission

An end of phase II (EOPII) meeting took place with FDA and Cephalon on 08/23/2003 to discuss the clinical development program for Phase 3. Minutes from the meeting indicate the following:

1. In addition to the two (2) flexible dose titration studies, a 6 week (double blind) study, would be required to establish efficacy in ADHD;
2. The ADHD Rating Scale-School Version would be acceptable as the primary efficacy endpoint;
3. FDA expressed some concern about some 'signals' of low WBC's in some of the patients in Study 213. Cephalon acknowledged that there appeared to be a transient lowering of WBC around 2-3 weeks the clinical significance of which is unknown. FDA recommended good safety monitoring and specifying an algorithm for drug discontinuation and follow-up monitoring if significant neutropenia should occur. Cephalon proposed to increase monitoring to a weekly basis in asymptomatic patients with significant neutropenia and added that the current patients with neutropenic episodes were asymptomatic. In addition, Cephalon

offered to increase monitoring to weekly after 6 months. FDA commented that the data seemed variable, i.e., Pt 24004, Pt 24005 and Pt 24001 need further follow-up.

According to Cephalon's consultant, Dr. Gerson, an ANC of 500 would seem to be a good cut-off since there can be a benign neutropenia with an ANC < 1000. He continued that in children, in general, have lower WBC counts and variability, and that this observed drug associated phenomenon may be metabolically based and transient and may not be clinically significant.

FDA inquired about in vitro bone marrow testing. Cephalon said that no neutropenia was seen in the preclinical adult or juvenile studies. Dr. Gerson added that he thought in vitro bone marrow testing would provide some reassurance but not 100%. FDA remarked that ideally, long-term data with a comparator drug would be useful.

4. Ages 13 - 17 would need to be studied for an adolescent claim for ADHD.
5. What size safety database will be required for an approvable NDA package?

FDA said that between 500 - 600 subjects for one year would be ordinarily required if there are no additional safety issues.

6. In addition, we would like to discuss and reach agreement with the Division on what clinically relevant secondary endpoints could be considered for potential inclusion in labeling at the time of an NDA.

FDA reiterated the division policy on secondary endpoints: the endpoints must be prospectively designated, replicated, prior division agreement should be obtained and the stat plan should protect against a Type 1 error. FDA agreed that a global measure would be acceptable.

7. Additional Points of Discussion:

We informed the sponsor that they will need to conduct a study in juvenile rats to examine drug effects on neurobehavioral and reproductive development. We suggested dosing from about day 10 of age through sexual maturity. Endpoints should include effects on motor activity, learning/memory, and mating/fertility. We suggested that dosing be terminated prior to testing (or that parameters be measured prior to the daily dose) in order to prevent acute drug effects from interfering with assessment of more permanent effects on development. We suggested that the sponsor submit a protocol for our comments. We indicated that this study could be done concurrently with the proposed clinical

trial since previously performed studies in young animals did not reveal serious toxicity.

8. FDA requested PK/PD data from the clinical trial.
9. FDA also recommended monitoring for signs of withdrawal in the clinical trial.

Another meeting took between FDA and Cephalon took place on 07/08/2004 to discuss the content and format of the planned supplemental application to NDA 20-717 for Attention-Deficit Hyperactivity Disorder (ADHD). Selected sections of the minutes of that meeting are noted below:

1. At the time of initial submission, the sNDA will include clinical safety data from approximately 300 children and adolescents with ADHD who have been treated with modafinil for at least 6 months. *The four-month safety update will include data from approximately 175 of these patients treated with modafinil for 12 months, with an additional 90 patients treated for at least 6 months.*

This extent of exposure is consistent with the ICH Guideline for Industry "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions (ICH-E1A)". Does the FDA agree that this would be an acceptable safety data package for filing of this sNDA?

FDA Response: We find this acceptable.

2. FDA stated that we would like to see drug exposure displayed by age and dose. FDA also expressed a preference for exposure by patient-years. Page 27 of the meeting information package was referred to during the discussion. This type of display with additional displays by age appeared acceptable to FDA. It was agreed that age could be captured in groups of 6-12 and 13-17. *FDA asked that Cephalon's narratives for deaths, withdrawals due to AEs, and serious AEs be grouped all together in one place in the submission and state that it is complete.* Cephalon confirmed that would be the case. FDA stated a preference of patient profiles or an algorithm for the reviewer to be able to gather all the relevant data for particular patients (i. e., patients with narratives). It was agreed that Cephalon would provide the reviewer with a sample/ plan ahead of time to address this point. *FDA asked if ECGs in the clinical studies were performed at the estimated tmax of modafinil. Cephalon stated that they were not specifically scheduled in this fashion.* FDA also asked about the adverse event collection during the withdrawal period of our fixed dose study. Cephalon stated that there was adverse event inquiry at 1 and 2 weeks. FDA commented that acute effects, in the first 2 days, are an area of safety interest.

For both points above, FDA acknowledged that Cephalon's trials were completed. Cephalon will take these points into consideration for presentation of data in the sNDA.

3. The completed clinical study report of modafinil tablets for the treatment of ADHD in adults (Study No. C1538a/ 205/AD/US) was previously submitted as part of the safety package to support approved supplement NDA 20- 717/ S- 008. As Cephalon will be seeking approval for the treatment of children and adolescents with ADHD, does the FDA agree that this study does not have to be resubmitted in this sNDA?

FDA Response: Yes. The Division asked why Cephalon did not want to submit this study and Cephalon responded that it was because the study was negative.

4. Cephalon is evaluating the secondary efficacy variables, from the Phase 3 studies, for the purposes of identifying key endpoint(s) for potential inclusion in the labeling. FDA's policy on secondary endpoints was reiterated during the End of Phase 2 meeting: endpoints must be prospectively designed, replicated, prior division agreement should be obtained and the statistical analysis plan should protect against Type 1 error. Can FDA confirm that this is the current policy or advise of any subsequent changes, or provide any additional information to be taken into consideration regarding these specific endpoints?

[We agree with the following response provided by Cephalon in their minutes of July 27, 2004; we have included minor editorial changes.] FDA Response: FDA confirmed that there is no change in their policy. FDA stated that Cephalon's selection of TOVA errors of omission would be "problematic" and they would not permit this as a key secondary efficacy variable for labeling. FDA stated that a critical part of their policy is that the variable looks at something beyond and very different from the primary endpoint domain. FDA's position is that this variable looks at inattention and so does the primary. Cephalon stated that TOVA is more of an objective measure vs. the subjective ADHD Rating Scale. FDA restated that this is still not looking at something very different. Cephalon also raised the point that it is a performance based test. Even though TOVA is performance based evaluation, FDA's position is that it is not adding anything and is still basically measuring the same thing. FDA stated that Cephalon can present a case in the submission, but this is their position.

5. Drug interaction studies: No additional drug interaction studies are requested.

6. Dosing/ administration instructions in the label: Cephalon raised the question of whether or not dosing recommendations could be given by weight; the Agency stated that this would be a matter of review.
7. Cephalon's plans regarding labeling: Cephalon stated that they plan to propose separate labeling and a new tradename. The Division stated that a separate tradename is not acceptable. The Division further stated that at this time the Agency does not permit a separate tradename for the same drug product. The Division agreed that Cephalon could put together an argument and supporting package and send it to FDA for review.

Postsubmission

Cephalon submitted an electronic submission on 12/20/2004 containing efficacy and safety information on the all studies, previously identified, and preliminary safety data on Study 312. A fling review identified potential review issues which were communicated to Cephalon on 03/15/2005 who responded as indicated below (blue font) on 04/13/2005. Clinical issues identified consisted of:

1. Please provide a listing of all serious non-US and US postmarketing serious adverse events. Please include a listing as well as post-marketing reports (serious and non-serious) of leucopenia or neutropenia for Modafinil. The reports should be separated by age (pediatric, adolescents, and adults) and should include an integrated summary and discussion of these experiences.

Cephalon will provide the above requested information in the forthcoming 4-Month Safety Update for this supplemental application.

2. You have not provided an adequate literature search (methodology and results) since only references were listed. Please provide a full review and discussion of the world literature for modafinil targeted to the safety of the present indication of ADHD. Please warrant that this is a complete and detailed review of the world's published literature and identify the cut-off date. The literature review should also include a complete review and discussion of the safety as it applies to any use of modafinil in any indication.

Cephalon will provide the above requested information in the forthcoming 4-Month Safety Update for this supplemental application.

3. Provide the location of the foreign regulatory history in the present submission.

The location of the foreign regulatory history submitted in NDA 20-717/S-019 was provided via electronic mail on March 18, 2005.

4. Provide a table of contents for the ISS.

The electronic bookmarking structure of the Summary of Clinical Safety was reviewed with Dr. Richardae Taylor on March 29, 2005, Based on this review, it was agreed that a separate table of contents for the current document did not need to be provided at this time. It was also agreed that Cephalon would provide a table of contents for the updated Summary of Clinical Safety in the forthcoming 4-Month Safety Update.

The 4-Month Safety Update was received electronically on 04/19/2005 and incorporated additional Study 312 data into the integrated safety summary. No separate study report was received for Study 312. Included with this submission was the following:

1. A listing of all non-U.S. and U.S. serious postmarketing adverse event reports (Appendix D)
2. A listing and discussion (Section 6.2) as well as the reports (Appendix E) of leukopenia and neutropenia for modafinil.
3. Additionally, in response to the request in the March 15, 2005 filing communication, a review of the worldwide published literature is provided in Appendix B.

The review of the worldwide literature was inadequately reviewed in this addendum submission consisting largely of electronic attachments of the articles to a listing.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Postmarketing Drug Risk Assessment (OPDRA):

An October 16, 2000, Office of Postmarketing Drug Risk Assessment (OPDRA) Postmarketing Safety Review/Consult⁴ from Provigil approval date (12/24/1998) to 09/20/2000 looked at neutropenia and leukopenia associated with off-label used of modafinil based on Cephalon Study 206 study showing an

4 Kortepeter C Through Beitz J To Katz R. OPDRA Postmarketing Safety Review/Consult for Neutropenia, Leukopenia, Off-label usage for ADD/ ADHD; 10/16/2000.

unexpected decline in white blood cells (WBC's) and absolute neutrophil counts (ANC's). This review identified two (2) symptomatic cases (fever, chills, flu-like symptoms) of leukopenia (WBC: 1.4, 2.2) in AERS which occurred in adults, 2-3 weeks after the initiation of modafinil. One of these cases was an agranulocytosis. No cases of neutropenia were identified. No cases occurring in pediatric patients (≤ 16 yrs) were identified. The first update of this report was for the period 09/21/2000 to 08/08/2003, and identified one case each of neutropenia/leukopenia and agranulocytosis (previously coded as leukopenia in the previous review). In addition, "there were 20 cases of various infectious processes occurring during modafinil use.

This review like the earlier one stated that there was no objective blood data which might predict patients at risk for developing viral and bacterial infections. The events included the following upper respiratory tract infection (URI)-3, Herpes Zoster, staphylococcus and herpes infection, UTI-3, rash-2 pneumonia-2, cellulites, bone tuberculosis, scabies infestation, viral meningitis, influenza like illness, gastroenteritis, rash and UTI, and erythema multiforme. As similar to the findings noted in the prior documents. "

In response to this sNDA application, a update consult⁵ was done for the period 08/09/2003 to 07/20/2005. It showed one case each of neutropenia (1), febrile neutropenia (1), and pancytopenia (1). None of these cases occurred in pediatric patients. Amongst these three cases there was not enough detail to determine causality.

The Consult notes "that currently there is no pediatric postmarketing issue with modafinil and neutropenia. However, this may be due to limited use of modafinil in pediatric patients. Since a signal for neutropenia was identified in a clinical trial of modafinil treatment for pediatric patients with Attention Deficit Hyperactivity Disorder (ADHD), if modafinil is approved and marketed for pediatric patients with ADHD, appropriate labeling and a possible postmarketing commitment may be needed."

5 Saini S Through Avigan M To Katz R, Second Update AERS report for neutropenia with modafinil; 08/08/2005.

3.2 Division of Medication Errors and Technical Support (DMETS), ODS

A 03/17/2005 consult reviewed the proprietary name, Attenace (NDA#: 20-717/S-019). Upon the initial steps in the proprietary name review process (EPD), the Division of Drug Marketing, Advertising and Communications (DDMAC) did not recommend the use of the proprietary name, Attenace. The consult states:

This drug is indicated for the treatment of attention deficit hyperactivity disorder. When considering the first two syllables of a three syllable name, these five letters (atten) are highly suggestive of "attention," "attend," or "attentive." Definitions for these words include: to be present at; to listen to; close or careful observation; to heed; mental concentration; observant. The drug's therapeutic use is suggested by these first two syllables... Furthermore, definitions for the last syllable, "ACE," suggest "the best," or "first rate." Combining these two suggestive portions create a superiority claim, in that this drug is the best at helping one to be attentive or mentally focused. The name is misleading in the absence of supporting substantial evidence or substantial clinical experience to support this superiority claim."

A 07/20/2005 consult⁶ reviewed the proprietary name, Altavige (NDA#: 20-717/S-019). Upon the initial steps in the proprietary name review process (EPD), the Division of Drug Marketing, Advertising and Communications (DDMAC) did not recommend the use of the proprietary name, Altavige, from a promotional perspective because it's overly fanciful and overstating the efficacy of the product. The consult states:

"We do not recommend approval of the proposed trade name and offer the following comments. The name is misleading because it overstates the efficacy of the drug by suggesting that a patient taking this drug will reach the highest level of vigilance, when such has not been demonstrated by substantial evidence or substantial clinical experience. The first portion of the proposed name, "alta," is Latin, meaning high, lofty or deep. The second portion of the word, "vige", could easily be extracted into vigilance, especially as the consumer base becomes familiar with the indication for this product. Coupling these two images creates the notion of a higher state of

⁶ Wisniewski L. Through Toyer D. To Katz R. ODS Consult 05-0061; Attenace; Altavige: NDA 20-717/S-019; 03/17/2005.

vigilance. This suggestion is particularly concerning given the proposed indication of the product, ADHD. Such product identification is problematic in and of itself, as it could preclude the sponsor from disseminating reminder advertisements or labeling, both of which are prohibited from making any suggestions or representations about the drug being advertised."

An amendment for the replacement brandname (SPARLON) to this application is dated 08/23/2005. A new DMETS consult in response to this is pending.

3.3 Good Clinical Practice Branch/DSI

The Good Clinical Practice Branch I & II (HFD-46), Division of Scientific Investigations, inspected three (3) investigator sites which involved the two (2) flexible dose (309, 311) and one (1) fixed dose (310) Phase 3 studies. No problem was identified at the following clinical site:

Roberta Ball, MD⁷
CNS Research Institute
Philadelphia, PA
Study 311/Patients Enrolled (13)

A clinical inspection summary⁸ indicates that there were no major issues with this site.

Samuel Boellner, MD
Clinical Study Centers
Little Rock, Arkansas
Study 309/ Patients Enrolled (18)

The following site was found not to have adhered to the "applicable statutory requirements and FDA regulations governing the conduct of clinical investigations."

James A. Knutson, M.D.⁹
Eastside Therapeutic Resource
Kirkland, WA
Study 310/Patients Enrolled (21)

7 Khin N. Letter to R. Ball, MD, 07/14/2005.

8 Tavarezpagan J Through Khin N. To Taylor R, Mannheim G, Katz R. Clinical Inspection Summary, NDA 20-717/S-019, Provigil (modafinil; 09/09/2005.

9 Khin N. Letter to J. Knutson, MD, 08/16/2005.

DSI determined that:

- The study was not conducted according to the investigational plan [21 CFR 312.60] based upon:
 - A failure to obtain urine pregnancy tests for several subjects of child bearing potential at specific visits (Subjects: 001: Wk 9; 012: Screening; 014: Screening and week 6/early termination; and 015: Screening and baseline);
 - A failure to obtain hematology tests for several subjects at specified visits (Subjects: 005: Screening, baseline, WK 5; 014: Wks 3, 7)
 - A failure to obtain assent for several subjects (014, 015).

3.4 Office of Clinical Pharmacology and Biopharmaceutics

The review from the Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation I (OCPB/DPE-1) is pending at the writing of this sNDA. Dr. Christine Garnett, the reviewer, and I met on 08/30/2005 to discuss findings from the Clinical Pharmacology Review. She noted that the table below from Study 113, indicated that a sulfone "metabolite accumulates to a greater extent in patients who weigh less than 30 kg. The age range of the 340 mg dose group is 5-10 years and the 425 mg dose group is 8-13 years. Of note, this represents only 2 weeks of daily dosing. Due to the auto induction in CL/F for parent modafinil, steady state is not achieved until 6 weeks (half-life =12 days). Therefore, we do not know the "absolute" accumulation of this metabolite."

Data to be confirmed Pharmacokinetic parameter	Modafinil sulfone			
	340 kg (<30 kg)		425 mg (≥30 kg)	
	Single dose (N=12)	Multiple dose (N=12)	Single dose (N=12)	Multiple dose (N=12)
C _{max} (µg/mL)	1.1±0.31	14.5±7.85	0.6±0.27	4.7±2.90
t _{max} (hr) ³	NA	9.0 [0.0-24.0]	NA	9.0 [1.0-24.0]
t _{1/2} (hr)	NC	NC	NC	NC
AUC ₀₋₂₄ (µg·hr/mL)	21.1±6.02	NA	10.4±4.80	NA
AUC _{0-t} (µg·hr/mL)	NA	314.5±174.54	NA	100.3±61.64

She noted that in her reviews of Studies 206 and 207 (Phase 2 studies), there were several subjects with ANC values less than 1000 mm³. No problems were identified with the pharmacokinetic modeling/simulations of data from Phase 2 studies in children.

3.5 Pharmacology

The review from the Pharmacology is pending at the writing of this sNDA. The significance of the sulfone metabolite accumulation in pediatric subjects was discussed with Dr. Aisar Atrakchi of Pharmacology on 08/31/2005. Her e-mail response of that date is below.

"I have written a memo for the filing meeting held Feb 9 05. The issue of higher levels of the sulfone in pediatric ADHD than in adults and than in repeat dose animals was already known. The sponsor for this reason conducted the following 2 studies where they administered the sulfone directly to rats:

- 10d dose range finder tox/TK in SD rats (#DS-03-043)
- 28d gavage tox/TK with 14d recovery in rats (DS-03-024)

Also there are a number of studies with modafinil in juvenile/neonatal rat and dog where they measured plasma levels and exposure of the sulfone and the acid metabolites.

Based on the 1mo tox/TK with the sulfone, rats were dosed 50, 100, 200mg/kg/d by gavage. The AUC for the sulfone at 200mg/kg/d was 161 and 254ug.hr/ml in males and females respectively, on d1 and the corresponding values on d28 were 120 and 326ug.hr/ml respectively. The AUC in humans based on study 113 (Christine's email to you on Aug 30th) is 315ug.hr/ml following repeat dosing. Therefore, a safety margin of approximately 1 is seen for female rats but <1 in male rats. Based on 13wk oral gavage tox/TK study of modafinil in juvenile rats, TK parameters were measured for mod, mod-acid, and mod-sulfone. AUC for the sulfone at the highest dose of 240mg/kg/d modafinil on d1 was 1131 and 1027ug.hr/ml in males and females respectively, this represent about 4 and 3x the 315ug.hr/ml clinical AUC for the sulfone shown in the table from study 113 (Christine's email to you on Aug 30). The corresponding values on d91 were 49 and 22ug.hr/ml respectively, i.e. exposure decreased with repeated dosing. In 3mo tox/TK with mod in the prejuvenile dog, exposure values for the sulfone at the highest modafinil dose of 75mg/kg/d were 83ug.hr/ml for both males and females on d14 and on d97 they were 48 and 42ug.hr/ml in males and females respectively. Clearly these values are less than the 315ug.hr/ml measured in young patients. Therefore, the rat is the better animal model for safety assessment of the sulfone.

The toxicity profile of the sulfone seems comparable to that of the parent and no new toxicities were observed in the 1mo study. The genetic tox assessment for the sulfone was not done per se because this metabolite is formed by the rat S9 in the studies carried out

with mod and therefore, the genetic potential for the sulfone was assessed indirectly.

Based on the above, I think the safety of the sulfone in children has been assessed. However, I will get back to you soon to confirm this since I really need to review some of these studies in detail."

3.6 Biometrics

The Division of Biometrics I (HFD-710) confirms that the data from the three pivotal studies 309, 310, and 311 demonstrate the efficacy of modafinil in children and adolescents with ADHD.

3.7 CMC (and Product Microbiology, if Applicable)

The reader is referred to the Chemistry Review for this submission.

3.8 Animal Pharmacology/Toxicology

The reader is referred to the Animal Pharmacology/Toxicology Review for this submission and related reviews under IND 59, 661.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Cephalon submitted an electronic submission on 12/20/2004 containing efficacy and safety information on all studies, previously identified, and preliminary safety data on Study 312. A fling review identified potential review issues communicated to Cephalon on 03/15/2005 who responded by e-mail on 03/18 and 3/29/2005, and by letter on 04/13/2005. The 4-Month Safety Update was received electronically on 04/19/2005 and incorporated additional Study 312 data into the integrated safety summary. No separate study report was received for Study 312. Included with this submission was information identified in the filing meeting. The reader should refer to Section 1.7, Pre- and Post-Submission Regulatory Activity for further discussion of these issues.

4.2 Tables of Clinical Studies

Tables 1, entitled, Tables Summarizing Clinical Trials Submitted in Support of sNDA summarizes all the clinical studies submitted for the proposed indication. It is located in the Appendix of this report.

4.3 Review Strategy

The clinical review was divided into two general sections- efficacy and safety review. The review of efficacy focused on the individual pivotal studies. There was no examination of pooled efficacy data. Safety data was examined starting from the integrated summary of safety (ISS). Serious adverse events and adverse dropouts were reviewed for both pivotal studies for the proposed ADHD claim. Data from controlled clinical trials of ADHD were pooled, when appropriate, to explore common and drug related adverse events, treatment related changes in laboratory analytes, changes in vital signs, and other specific searches.

4.4 Data Quality and Integrity

The submission was checked for internal consistency. Various narrative summaries were checked against the table listings to help ensure the accuracy of some of the safety data. The Division of Scientific Investigations (DSI) was consulted and they made sample site visits.

4.5 Compliance with Good Clinical Practices

Trials were conducted in accordance with Good Clinical Practice Guidelines (GCP).

4.6 Financial Disclosures

Cephalon included FDA Form 3455, a Disclosure of Financial Interests and Arrangements of Clinical Investigators for presumably all the investigators for the following clinical trials (309, 310, 311 and 1024). This form states as indicated below.

As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	C1538d/309/AD/US (see attached list)	C1538d/310/AD/US (see attached list)
	C1538d/311/AD/US (see attached list)	C1538/1024/BE/US (see attached list)

A separate Form 3455 and a letter of financial disclosure (11/11/2004) for [redacted] M.D., was included for Site # [redacted], relating to Protocol # [redacted]. Relevant information is pasted below from Form 3455, and the disclosure letter.

<input checked="" type="radio"/> Yes	<input type="radio"/> No	Have you, your spouse or dependent children, the institution with which you are affiliated or any of you combined received payments from Cephalon, Inc. in excess of \$25,000, exclusive of the costs of conducting the clinical studies, such as honoraria, a grant or grants to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation? If yes, the amount and nature of the payment is as follows: <i>honoraria, consultation</i>
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Dr. [redacted] MD, [redacted] Site [redacted] answered yes to question #4 of the financial disclosure form. Dr. [redacted] has received \$448,350 honoraria for consulting and lecturing.

Cephalon was able to reduce bias by thorough study design strategies. These included a multi-center approach (18 sites) with competitive enrollment as well as double blind and placebo controlled study design. Final site enrollment at Dr. [redacted], site [redacted] versus total enrollment was [redacted] (%)

Cephalon certified that it did not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

No signed individual investigator forms were included with this submission.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The reader is referred to the Clinical Pharmacology/Biopharmaceutics Review for a complete discussion.

5.2 Pharmacodynamics

The reader is referred to the Clinical Pharmacology/Biopharmaceutics Review for a complete discussion.

5.3 Exposure-Response Relationships

The reader is referred to the Clinical Pharmacology/Biopharmaceutics Review for a complete discussion.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

These studies were conducted to demonstrate that modafinil is an effective and safe treatment for children and adolescents with ADHD.

6.1.1 Methods

The review of clinical efficacy of provigil for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children between the ages of 6-11 years and adolescents between the ages of 12-17 years focused on three (3) phase III studies involving 420 subjects exposed to modafinil and 213 subjects who received a placebo. These studies consisted of two (2), nine (9) week flexible dosage (up to 425 mg) studies with 9-week double-blind treatment periods; and one seven (7) week fixed dose study (340, 425 mg) followed by a 2-week randomized-withdrawal period. The flexible dose studies were called Study 309 [198 subjects (131 modafinil, 67 placebo)] and Study 311 [246 subjects (164 modafinil, 82 placebo)], respectively. The fixed dose study was called Study 310 [189 subjects (125 modafinil, 64 placebo)].

These studies are indicated in sponsor's Table 1, which is pasted below.

Table 1: Phase 3 Double-Blind, Placebo-Controlled Studies

Study number	Study design	Duration	Number of patients treated			
			Modafinil (mg/day) ^a			Placebo
			≤255	340	425	
C1538d/309/AD/US	Flexible-dosage, parallel-group	9 weeks	31	22	78	67
C1538d/310/AD/US	Fixed-dosage, parallel-group	9 weeks ^b	0	44	81	64
C1538d/311/AD/US	Flexible-dosage, parallel-group	9 weeks	31	36	97	82
Total			62	102	256	213

^a Based on "stable dose" received in studies 309 and 311, and stratification by body weight in study 310.

^b Includes a 2-week withdrawal period.

6.1.2 General Discussion of Endpoints

The primary efficacy variable was the change from baseline to the last post baseline visit on the total score of the teacher/physician-completed ADHD Rating Scale-IV (ADHD-RS-IV) (School Version) for Studies 309, 311 (week 9 or last double blind treatment period visit), and Study 310 (week 7 or the last double-blind treatment period visit). The ADHD-RS-IV (School Version) (Barkley 1990) assesses the frequency of each of 18 individual criteria symptoms of ADHD in the DSM-IV on a 4-point Likert scale (0=never or rarely, 1=sometimes, 2=often, or 3=very often). The ADHD-RS-IV (School Version) was completed by the investigator by interviewing the patient's weekday teacher. At the assessment, the rater asked the teacher to make a determination of symptomatic frequency that best described the child's school behavior (in accordance with DSM-IV guidelines) since the last clinic visit. This assessment was completed at approximately 1300 (± 1 hr) at least 4 days after the patient's last clinic visit and before the upcoming clinic visit. A copy of the ADHD Rating Scale-IV (ADHD-RS-IV) (School Version) is in the Appendix of this report.

The efficacy measures evaluated in the three (3) Phase III placebo-controlled studies are summarized in Table 2, copied from Cephalon's submission¹⁰.

¹⁰ Section 2.7.3 Summary of Clinical Efficacy, Section 1.2.4 Efficacy Measures and Variables, pg. 4.

**Table 2: Efficacy Measures by Double-Blind Study Week
 (Phase 3 Placebo-Controlled Studies)**

Efficacy measure	Baseline	Week 1	Week 2	Week 3	Week 5	Week 7 ^a	Week 9 ^a
Primary efficacy measure							
ADHD-RS-IV (School Version)	All studies ^b	All studies	309 + 311				
Secondary efficacy measures							
ADHD-RS-IV (Home Version)	All studies	All studies	All studies	All studies	All studies	All studies	309 + 311
CGI-C ^c	All studies ^b	All studies	309 + 311				
TOVA	All studies			All studies		All studies	309 + 311
Additional efficacy measures							
SSRS	All studies	–	–	All studies	–	All studies	309 + 311
CPRS:R-S	All studies	–	–	All studies	–	All studies	309 + 311
CHQ	All studies	–	–	–	–	310	309 + 311

^a In study 310, the assessments that were specified at week 7 were performed at week 7 or at the patient's early termination visit. In studies 309 and 311, the assessments that were specified at week 9 were performed at week 9 or at the patient's early termination visit.

^b For patients requiring a washout period, the ADHD-RS-IV (School Version) and the Clinical Global Impression of Severity (CGI-S) were assessed after the washout period. The optional washout period occurred between screening and baseline. For patients not requiring a washout period, the ADHD-RS-IV (School Version) and the CGI-S were assessed at screening.

^c The CGI-S was assessed at the screening/baseline visit, and the Clinical Global Impression of Change (CGI-C) was assessed at all postbaseline visits with respect to changes from the baseline CGI-S assessment.

All studies=The assessment was performed for all 3 placebo-controlled studies (309, 310, and 311 at the specified time point.

ADHD-RS-IV=ADHD Rating Scale, Fourth Edition; CGI-C=Clinical Global Impression of Change; CHQ=Child Health Questionnaire; CPRS:R-S=Conners' Parent Rating Scale, Revised, Short Form; SSRS=Social Skills Rating Scale; TOVA=Test of Variables of Attention.

Reviewer Comment(s):

It is not clear what the mechanics were for each assessment. Did the same physician investigator go to the school each week, or, did the teacher come to the investigator with the child? If the teacher went to the investigator was the teacher paid a stipend for performing this task? No information could be identified by the reviewer about the consistency of the raters from week to week. Did the same teacher do the rating throughout the study? Did the same investigator fill out the form each week?

At the assessment, the rater asked the teacher to make a determination of symptomatic frequency that best described the child's school behavior (in accordance with DSM-IV guidelines) since the last clinic visit. How did the teacher track these behaviors? Were teachers trained according to DSM-IV guidelines, as the sponsor's description might suggest. The sponsor needs to provide more information about the mechanics of using this instrument and any possible variables which may have been introduced into the measurement.

Secondary measures consisted of the ADHD-RS-IV (Home Version), the Clinical Global Impression of Severity (CGI-S), and Change (CGI-C), Test of Variables of Attention (TOVA), Social Skills Rating Scale (SSRS), parent-rated Conners' Parent Rating Scale, Revised, Short Form (CPRS:R-S) and the quality of life Child Health Questionnaire (CHQ).

6.1.3 Study Design

The Phase 3, randomized, placebo-controlled, parallel-group studies 309 and 311 were identically designed flexible-dosage studies with 9-week double-blind treatment periods. Study 310 had a fixed dosage design (340 or 425 mg/ day) with a 7-week double-blind treatment period followed by a 2-week randomized-withdrawal period.

In studies 309 and 311, subjects were randomized to receive either modafinil or placebo tablets (2: 1). The study consisted of a 1 to 4 week screening/washout period, followed by 9 weeks of double blind treatment. Visits included screening, washout, baseline, and weeks 1, 2, 3, 5, 7, and 9 (or early termination). Study drug was titrated individually for each subject on the basis of tolerability and efficacy. At the end of each week of treatment, a patient may have remained at the current dosage or the dosage may have been increased (up to 425 mg/day). If a subject was unable to tolerate the study drug, the dosage may have been decreased (minimum dosage of 170 mg/day). At the completion of the study, subjects were eligible to enroll into a 1 year open-label extension study (C1538d/312/AD/US). In addition, subjects who completed at least 4 weeks of double-blind treatment and did not withdraw due to an adverse event were also eligible to enroll into the open-label extension study.

Study 310 had a 1 to 4 week screening/ washout period, followed by 9 weeks of treatment with the study drug. Patients were randomized at baseline to 1 of 3 treatment groups: modafinil/modafinil; modafinil/placebo; or placebo/ placebo. For the first 7 weeks of treatment, subjects randomized to modafinil weighing less than 30 kg received 340 mg/day of modafinil and subjects weighing at least 30 kg received 425 mg/ day of modafinil. Subjects assigned to placebo received matching placebo on the basis of weight. Study drug was titrated during the first 7 to 9 days of the treatment period. Subjects remained at their

randomized dosage for the remainder of the 7 week, double-blind treatment period. The final 2 weeks (weeks 8 and 9) of the study was the randomized withdrawal period, when modafinil-treated subjects received either modafinil or placebo and placebo-treated subjects continued taking the placebo for a 2-week period according the original randomization. Subjects received either 4 or 5 tablets per day (on the basis of body weight) of 85 mg modafinil or placebo during the withdrawal period. Visits included screening, washout, baseline, and weeks 1, 2, 3, 5, 7, and 9 (or early termination). Subjects who completed at least 4 weeks of double-blind treatment and did not withdraw due to an adverse event were eligible to enroll into a 1 year open-label extension study (Study 312).

The overall study schema for studies 309 and 311 and study 310 is presented in two (2) diagrams submitted by the sponsor which are included in the appendix of this report.

6.1.4 Study Sites, Investigators, Duration of Study

Study 309: This study was conducted over the 6.5-month period from 11/08/2003 to 05/27/2004 by the investigators and at the 18 sites identified in the Appendix.

Study 311: This study was conducted over the 7-month period from 11/11/2003 to 06/11/2004 by the investigators and at the 24 sites identified in the Appendix.

Study 310: This study was conducted over the 6.5-month period from 11/08/2003 to 06/02/2004 by the investigators and at the 17 sites identified in the Appendix.

6.1.5 Study Objectives and Population Studied

Objective(s): The primary objective of these three(3) studies was to evaluate the efficacy of modafinil treatment as compared to placebo, in alleviating the symptoms of ADHD in children and adolescents as assessed by the change from baseline to the last baseline visit [week 9 (Study 309, 311), week 7 (study 310) or early termination] in the total score from the teacher/physician completed ADHD Rating Scale-IV (ADHD-RS-IV) (School Version).

Population: The subjects were to be healthy outpatient children (6-17 years) with an IQ ≥ 80 ¹¹ with moderate to severe^{12,13} DSM-IV diagnosed ADHD¹⁴ without learning disabilities¹⁵ that were attending a full-time school (not home school) and had a teacher willing and able to participate for the duration of the study. Subjects were excluded from the study if they had any psychiatric co-morbidity (psychotic disorder, suicide risk, depression, mood, anxiety disorder, substance abuse, etc.); if they failed to respond to 2 or more adequate courses (dose and duration) of stimulant therapy; had any clinically significant deviation from the normal range(s) in the physical examination findings, ECG results, or clinical laboratory test results (e.g., hematology, serum chemistry, urinalysis) at the screening visit; had an absolute neutrophil count (ANC) was below 1000/mm³; had hypo- or hypertension; had any active, clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematologic, neoplastic, endocrine, neurologic, immunodeficiency, pulmonary, or other major clinically significant disorder/disease; and had a clinically significant illness within 4 weeks of the baseline visit.

Study 309: Of the 200 subjects who were randomized, 128 who received modafinil and 67 who received placebo were analyzed for efficacy. Subject disposition is identified in sponsors Figure 2 included in the Appendix of this report. Demographic and Baseline Characteristics is included in the Appendix. The treatment groups were comparable in demographic and baseline characteristics (mean age: 9.9 years; range: 6-16 years), sex [males > female 2.7:1], most were white (white: 72 %; black 18 %; other: 10 %), and had a mean weight of 40.1 kg (range: 18.6 - 87.1 kg) and a mean height of 141.8 cm (range: 114.3-186.2). Sixty-seven (67: 51 %) of the modafinil and 42 (63 %) 109 of the placebo received prior ADHD medications (Sponsors Table, Summary 15.6). The majority (70%) had the combined subtype of ADHD. CGI-S scores at baseline indicated that approximately 82% of

11 Wechsler Intelligence Scale for Children, Third Edition (WISC-III): two (2) subsets (vocabulary [verbal group] and block design [performance group]) of the WISC-III were used to estimate IQ.

12 Clinical Global Impression Severity of Illness (CGI-S) rating ≥ 4 (moderately-severely ill or greater)

13 Teacher/physician-completed ADHD-RS-IV (School Version) total and/or subscale score of ≥ 1.5 SD above age/gender norm after washout.

14 Diagnostic Interview Schedule for Children, Fourth Edition (DISC-IV)

15 Screening score ≥ 80 on the Wechsler Individual Achievement Test, Second Edition, abbreviated (WIAT-II-A)

subjects were moderately to markedly ill and approximately 17% were severely ill.

Study 311: Of the 248 subjects who were randomized, 164 who received modafinil and 82 who received placebo were analyzed for efficacy. Two subjects randomized to the placebo group did not receive study drug. One additional subject randomized to placebo and 1 subject randomized to modafinil group were not evaluable for efficacy. The treatment groups were comparable in demographic and baseline characteristics (mean age: 10 years; range: 6-17 years), sex [males > female 2.4:1], most were white (white: 77 %; black 10 %; other: 13 %), and had a mean weight of 42.9 kg (range: 18.6 -85.4 kg) and a mean height of 144.2 cm (range: 110.2-195.6). Seventy-six (76: 46 %) of the modafinil and 37 (45 %) of the placebo received prior ADHD medications (Sponsors Table, Summary 15.6). Fifty-nine percent (59 %) had the combined subtype of ADHD, 38 % had the inattentive type, and 3 % had the hyperactive/impulsive type. CGI-S scores at baseline indicated that approximately 85 % of subjects were moderately to markedly ill and approximately 15 % were severely ill.

Study 310: Of the 190 subjects who were randomized, 126 who received modafinil and 64 who received placebo were analyzed for efficacy. Of these, 189 subjects received at least 1 dose of study drug (safety analysis set), 183 had at least 1 post-baseline efficacy assessment (full analysis set), and 120 (63%) subjects completed at least 7 weeks of double-blind treatment. In addition, 120 entered, and 115(61%) completed the randomized withdrawal period. The treatment groups were comparable in demographic and baseline characteristics (mean age: 10.1 years, modafinil; 9.7 years, placebo; range: 6-17 years), sex [males > female; 2.4:1; modafinil: 74 % male, 26 % female; placebo: 66 % male, 34 % female], most were white (white: 80 %; black 11 %; other: 9 %), and had a mean weight of 40.3 kg [(range: 19.6 - 98.4 kg); ≤ 30 kg(36 %), ≥ 30 kg (64 %)] and a mean height of 141.7 cm (range: 112-185). Sixty-six (66: 53 %) of the modafinil and 38 (59 %) of the placebo received prior ADHD medications (Sponsors Table, Summary 15.6). Sixty-seven percent (67 %) had the combined subtype of ADHD, 27 % had the inattentive type, and 5 % had the hyperactive/ impulsive type. CGI-S scores at baseline indicated that approximately 91 % of subjects were moderately to markedly ill and approximately 9 % were severely ill.

Reviewer Comment(s):

Given the fact that the ADHD subjects who were studied were moderately to severely ill or greater (CGI-S \geq 4) and did not have learning disability (Screening score \geq 80 on the WIAT-II-A), the generalizability of findings from this group of subjects to other children with less severe ADHD (CGI-S < 4) with learning disorders is uncertain, and may need to be considered as a Phase IV commitment.

6.1.6 Study Assessments and Analysis Plan

Assessments: Screening assessments were to include a medical and psychiatric history and physical examination, review of inclusion and exclusion criteria, vital signs, recording concomitant medications, clinical laboratories, a 12 lead ECG. Screening diagnostic assessments included: the Diagnostic Interview Schedule for Children, Fourth Edition (DISC-IV); the Wechsler Intelligence Scale for Children, Third Edition (WISC-III); the Wechsler Individual Achievement Test, Second Edition, abbreviated (WIAT-II-A); the Teacher/physician-completed Rating Scale-IV (ADHD-RS-IV) (School Version); and the Clinical Global Impression (CGI).

The primary efficacy measure was the Teacher/physician-completed Rating Scale-IV (ADHD-RS-IV) (School Version). The secondary efficacy measures were the TOVA response time and errors of omissions and commissions [weeks 3, 7, and 9, and last post-baseline visit]; the ; teacher/physician-completed ADHD-RS-IV (School Version) total scores [weeks 1, 2, 3, 5, 7, and 9; subscale scores for inattention and hyperactivity-impulsivity at weeks 1, 2, 3, 5, 7, and 9, and last post-baseline visit- at weeks 3, 7, and 9, and last post-baseline visit]; parent/physician-completed ADHD-RS-IV (Home Version) total and subscale (inattention and hyperactivity-impulsivity) scores [weeks 1, 2, 3, 5, 7, and 9, and last post-baseline visit]; the CGI-C ratings (for improvement of ADHD symptoms) [weeks 1, 2, 3, 5, 7, and 9, and last post-baseline visit]. Additional efficacy variables included the Social Skills Rating Scale (SSRS), the Conners Parent Rating Scale (CPRS: R-S) and the Child Health Questionnaire (CHQ).

Safety monitoring assessment included physical examinations, vital signs, weight, ECG's, clinical laboratories and recording of adverse events.

A copy of the Study Procedures and Assessments for Studies 309, 311 and 310 are included in the Appendix of this report.

Analysis Plan: The primary efficacy variable was the change from baseline to the last double-blind treatment period visit (endpoint) in the total score from the teacher/physician-completed ADHD-RS-IV (School Version). These data were analyzed using an analysis of covariance (ANCOVA) model that includes treatment and center as factors, and the corresponding baseline variable as a covariate.

6.1.7 Disposition of Study Subjects

Diagrams and tables showing Patient Disposition for Studies 309, 311, and 310 are included in the Appendix.

Study Subjects (Study 309): Two hundred (200) subjects were randomized to modafinil (133) or placebo (67). Of these, 198 subjects received at least 1 dose of study drug (131: modafinil; 67: placebo) who were evaluated for safety. One hundred twenty eight (128) subjects on modafinil and 66 subjects on placebo were evaluated for efficacy. One hundred and forty one (141) subjects completed at least 9 weeks of double-blind treatment [modafinil (100); placebo (41)]. Of the 59 subjects who withdrew from the study, 10 subjects (modafinil: 6; placebo: 4) withdrew due to adverse events. The 6 subjects on drug (M: 5; F 1; mean age: 8.3 years) with dose range from 85-425 mg had the following adverse events identified as reasons for discontinuation: insomnia (2), somnolence (1), anorexia (1), emotional lability (1), and headache and fever (1). Review of the vignettes indicated the following additional adverse events present in subjects on drug: rash [with headache and fever (1)]; psychiatric symptoms of emotional lability (2) and agitation (1); and infection (4), dyspepsia (1), abdominal pain (1), tremor (1) and twitching (1). The 4 subjects on placebo (M: 4; mean age: 11.8 years) had the following adverse events identified as reasons for discontinuation: anxiety with tachycardia and insomnia (1), leukopenia (1), nervousness (1) hostility (1). Review of the vignettes indicates the following additional adverse events present in subjects on placebo: difficulty focusing (1). Other events occurring in subjects on drugs included: infection (2), sedation (1); and back pain (1). The most frequent reason for withdrawal was lack of efficacy [modafinil: 15 (11%); placebo: 19 (28%)]. Other reasons for discontinuation included: withdrawn consent [modafinil: 5 (4 %);

placebo: 1 (1 %)], lost to follow-up [modafinil: 5 (4 %); placebo: none)], and other reasons [modafinil: 2 (2 %); placebo: 2 (3 %)].

Study Subjects (Study 311): Two hundred and forty eight (248) subjects were randomized to modafinil (164) or placebo (84). Two subjects randomized to the placebo group did not receive study drug. One additional subject randomized to the placebo group and 1 subject randomized to the modafinil group was not evaluable for efficacy. Of these, 248 subjects received at least 1 dose of study drug (164: modafinil; 82: placebo) who were evaluated for safety. One hundred sixty three (163) subjects on modafinil and 81 subjects on placebo were evaluated for efficacy. One hundred and thirty (130; 52 %) subjects completed 9 weeks of double-blind treatment [modafinil (97); placebo (33)]. Of the 118 subjects (modafinil: 67; placebo: 51) who withdrew from the study, 8 subjects (modafinil: 5; placebo: 3) withdrew due to adverse events. The 5 subjects on drug (M; 3; F 2; mean age: 8.6 years) with dose range from 170-425 mg had the following adverse events identified as reasons for discontinuation, of which two (2) were serious. The serious adverse events were erythema multiforme/Stevens Johnson (1) and peptic ulcer (duodenitis) with spasm (hypertonia). The other coded adverse events were: somnolence (1), dystonia (1) and tachycardia (1). Review of the vignettes indicated the following additional adverse events present in subjects on drug: rash [with fever, vomiting, nausea, dehydration, heart murmur with the peptic ulcer (1)]; possible allergic reaction (1); flushed face [vasodilatation (1)] and palpitations with tachycardia; infection (2) and cough (1). The 3 subjects on placebo (M: 2; F; 1; mean age: 7 years) had the following adverse events identified as reasons for discontinuation: hostility (1), hyperkinesia [hyperactivity (1)], and irritability [nervousness (1)]. Review of the vignettes indicates the following additional adverse events present in subjects on placebo: moodiness [emotional lability] (1); behavioral disturbance [personality disorder (1)]; increased baseline impulsivity (1); and infection (1). The most frequent reason for withdrawal was lack of efficacy [modafinil: 34 (21%); placebo: 37 (44%)]. Other reasons for discontinuation included: withdrawn consent [modafinil: 5 (3 %); placebo: 4 (5 %)], lost to follow-up [modafinil: 6 (4 %); placebo: 1 (1 %)], noncompliance to study medications [modafinil: 1 (< 1 %); placebo: none], noncompliance to study procedures [modafinil: 1 (< 1 %); placebo: 1 (1 %)], and other reasons [modafinil: 16 (10 %); placebo: 5 (6 %)].

Reviewer Comment(s): The study report states that 7 subjects withdrew because of adverse events. However, 8 vignettes (modafinil: 5; placebo: 3) are submitted in the appendix. Detailed information, preferably vignettes should be provided about all subjects who discontinued. Inadequate information is present in Listing 2, Patient Disposition by Treatment Group of Randomized Patients, Study Report, pgs. 1183-1199. Cephalon should provide further information about all subjects categorized as leaving the study because of lack of efficacy.

Study Subjects (Study 310): One hundred and ninety (190) subjects were randomized to modafinil (126) or placebo (64). Of these, 189 subjects received at least 1 dose of study drug (125: modafinil; 64: placebo) who were evaluated for safety. One randomized subject from the 126 subjects did not take any study drug. One hundred twenty (120) subjects on modafinil and 63 on placebo had at least 1 post-baseline efficacy assessment (full analysis set). Of these, 120 subjects (80: modafinil; 40: placebo) completed 7 weeks of double-blind treatment and entered the randomized withdrawal period. (withdrawal analysis set). Of these, 115 subjects (modafinil: 79; placebo: 36) completed the randomized withdrawal period. Of the 70 subjects (37 %; modafinil: 46; placebo: 24) who withdrew from the study during the double-blind treatment period, 13 (10 .4%) subjects, all on modafinil, withdrew because of an adverse event (See Reviewer's Note Below). The 13 subjects on drug (M; 7; F 6; mean age: 9 years) with doses of either 340 mg (n=7) or 425 mg (n=8) had the following adverse events identified as reasons for discontinuation, of which two (2) were serious. The serious adverse events were: asthma attack (momentarily stopping breathing) and a flu syndrome with dehydration. The other coded adverse events were: Emotional lability (2), hallucinations (1), thinking abnormal (1), suicidality (1); nervousness (1); anxiety with tachycardia, dyspnea, abdominal pain and hypertonia (1); abdominal pain with headache and anorexia (1); agitation with insomnia and increased cough (1); insomnia (1); and leukopenia (1). Review of the vignettes indicated the following additional adverse events present in subjects on drug: headaches (4); insomnia (3); dyspepsia (1); neutropenia (1); breathing difficulty with wheezing and red face and possible allergic reaction in subject who stopped breathing (1); fear of eating (1); irritability (1); confusion (1); amblyopia (1); dry mouth (1); and stuttering with incoordination (1). The most frequent reason for withdrawal was lack of efficacy [modafinil: 18 (14%);

placebo: 17 (27%)). Other reasons for discontinuation included: withdrawn consent [modafinil: 7 (6%); placebo: none], protocol violation [modafinil: 1(< 1%); placebo: none], lost to follow-up [modafinil: 1(< 1%); placebo: none], noncompliance to study medications [modafinil: 1(< 1%); placebo: none], noncompliance to study procedures [modafinil: 1(< 1%); placebo: none], and other reasons [modafinil: 6(5 %); placebo: none]. Seventeen (17; 27 %) of subjects in the placebo group in the withdrawal phase withdrew consent. There was one protocol violation in the placebo group during the withdrawal phase [1 (2 %)].

Reviewer Comment(s): The study report states that 11 subjects on modafinil withdrew because of adverse events. However, 12 vignettes (modafinil: 12) are submitted in the appendix of the 310 final study report. In addition, another, serious adverse event (Subject No: 34187) is submitted in the 4 month safety update. Hence, there were 13 (10.4 %) adverse events, of which 2 are serious.

6.1.8 Efficacy Findings

The results of the sponsor's efficacy analysis¹⁶ are presented below. The reading is referred to the Biometrics Consult¹⁷ for further analyses performed. A Table submitted by the sponsor, Table 7: Change from Baseline to Endpoint for the Total Score from the ADHD-RS-IV (School Version)-Full Analysis Set is included in the Appendix of this report. Sponsor's Figure 1 from Section 2.7.3, Summary of Clinical Efficacy (page 45) shows change from baseline to each time point and to endpoint for the total scores from the ADHD Rating Scale-IV (School Version) for the combined patient population of phase 3 placebo-controlled studies(full analysis set)and is pasted below.

Study 309: Statistically significant differences were observed for the ADHD-RS-IV (School Version) total score for the modafinil treatment group compared with the placebo treatment group beginning at week 5 (p=0.0053) and through week 9 (p=0.0006).

Study 311: Statistically significant differences were observed for the ADHD-RS-IV (School Version) total score for the

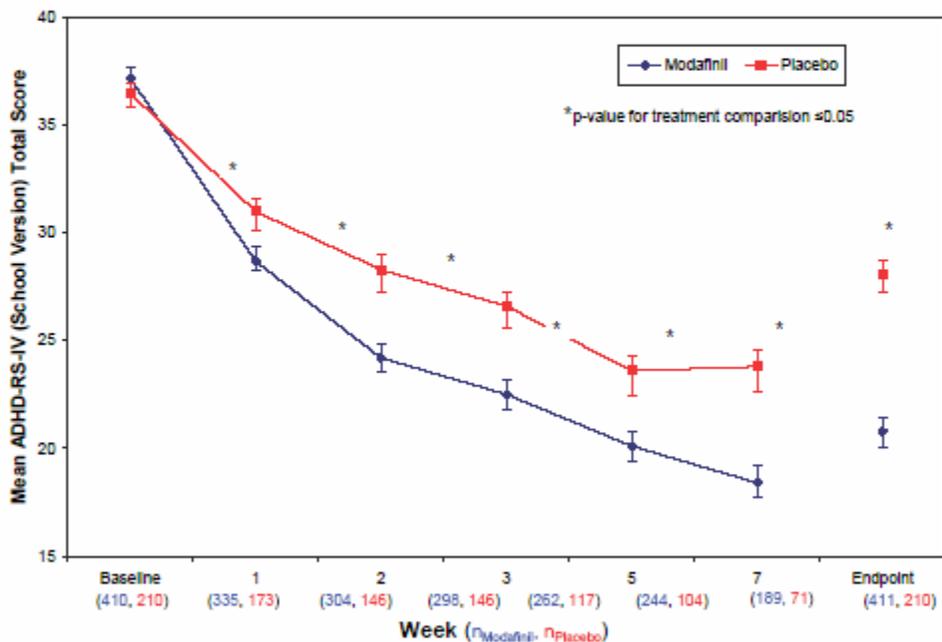
16 2.7.3 Summary of Clinical Efficacy, Section 2, Summary of Results of Individual Studies

17 Division of Biometrics I (HFD-710) Consult for this sNDA

modafinil treatment group compared with the placebo treatment group from week 1 ($p=0.0196$) through week 9 ($p=0.0164$), with the exception of week 5.

Study 310: Statistically significant differences were observed for the ADHD-RS-IV (School Version) total score for the modafinil treatment group compared with the placebo treatment group beginning at week 1 ($p=0.0086$) and through the end of the double-blind treatment period (week 7; $p=0.0003$).

Figure 1: Change From Baseline to Each Time Point and to Endpoint for the Total Scores From the ADHD Rating Scale-IV (School Version) for the Combined Patient Population of Phase 3 Placebo-Controlled Studies (Full Analysis Set)



SOURCE: Summary 5.0.

ADHD=attention-deficit/hyperactivity disorder; ADHD-RS-IV=ADHD Rating Scale, Fourth Edition.

6.1.9 Efficacy Conclusions

Conclusion(s): Data from studies 309, 311 and 310 demonstrate the efficacy in children and adolescents with ADHD.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Two (2) cases of unduplicated sudden death cases in pediatric patients (aged 1-18) with abuse/overdose/suicide deaths excluded were identified from AERS, as part of an internal, division methylphenidate labeling meeting held on 09/09/05. This meeting looked at cases of sudden death associated with off-label use of the ADHD drugs (bupropion and modafinil).

No.	ID	Date of Death	Age	Sex	Indication	Summary
1	US007296	Dec 2000	17	M	“Diurnal Somnolence”	Rare myotonic dystrophy (Steinert’s disease) “characterized by cardiac arrhythmias.” Experienced cardiac arrest during exercise. On modafinil for 11 months, no concomitant meds given.
2	US014951	UNK	UNK	UNK	UNK	Physician report of child or young adult death from cardiac arrhythmia with modafinil use. No other information given. (Received by manufacturer 3/05)

7.1.2 Dropouts and Other Serious\Significant Adverse Events

Serious/significant adverse events resulting in dropouts were identified for skin (erythema multiforme, Steven Johnson Syndrome and other rashes), for liver (possible Reye’s syndrome and possible hepatotoxicity), for psychiatric disorders [suicidality, agitation, depression, psychosis and phobias], and possibly for hematological events (leukopenia, neutropenia possibly with greater susceptibility to infections). Peptic ulcer disease also resulted in dropouts. Overall there were increases and decreases in body weight of $\geq 7\%$ in 32% and 11 % of subjects, respectively.

Steven Johnson Syndrome, Other Rashes, and Other Pediatric Skin Lesions

Review of the discharge summaries for subjects who withdrew from the trial for serious or non-serious reasons, indicated that

twelve (12) subjects (12/101: 12 %) on various doses of modafinil developed rashes, as indicated by the presence of the term. Three (3) of these occurred in the phase three trials (311: 3; 312: 1). No subjects on placebo developed a rash. Five (5) others on modafinil developed hives (2), pruritus, an unspecified allergic reaction, or, a flushed face (?). Other skin lesions present only identified in subjects on modafinil consisted of plantar warts, ringworm, alopecia, tongue blotches, Herpes zoster, red lips, eczema, red lips with a dry mouth, and treatment with Benadryl for an unspecified reason. The types of rashes present consisted of a case of erythema multiforme/Steven Johnson (rash, peeling and blistering over the entire body with involvement of the lips and the urinary tract); one (1) maculopapular rashes characterized as morbilliform, pruritic and, originally thought to be a case of Stevens Johnson; and one (1) had a vesiculobullous rash on the cheeks with severe blisters on the lips. The case of Steven Johnson occurred in Study 311, and the other two (2) cases occurred in Study 207. Descriptions of the rashes were vague for the other eight (8) subjects. In one case the rash developed at day 24, was treated with stopping the drug and with prednisone and Benadryl; and was restarted on 85 mg of modafinil 10 days later, resulting in a recurrence of the rash (positive re-challenge). The mean age for all subjects (M: 20, F: 6) with various skin lesions is 8.5 years (mean). The cases with skin lesions are identified in the table below which was constructed from the vignettes provided by the sponsor. The sponsor's vignette of the case of erythema multiforme/Steven Johnson is pasted below, as are three (3) other suspect cases. The sponsor's complete vignettes are included in the Appendix.

Skin Lesions Identified in the Vignettes of Subjects Leaving the Trials Because of an Adverse Event

Study	Pt No	Age	Sex	Race	Dose	SAE	WAE	Event
207	315	11	F	W	100 mg	X		Turners on somatotropin, DDAVP; fever, abdominal pain, diarrhea X 9days; gen. pruritic maculopapular (morbilliform) rash; ? SJ
	411	10	M	H	100 mg		X	Rash; suicidal ideation, disruptive, aggressive, non-compliant behavior
207 DB	405	7	M	H	200 mg	X		Rash week 1; disruptive behavior week 3-4; abnormal ECG (U waves); suicidal ideation
	18001	6	M	W	300/0 mg		X	Mild HTN, anorexia, severe rash, fever, vomiting, weight decrease (loss)
	8012	9	M	W	200/100 mg		X	Moderate rash
	18004	8	M	W	200/100 mg		X	Fever, vesiculobullous rash on cheeks with severe blisters on lips; insomnia

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	13011	8	M	W	100/200 mg	X	Leukopenia, abdominal pain, nausea, fever, dry hives
	20005	10	M	W	100/200 mg	X	Insomnia, irritability (nervousness), increased labile mood, verbal tic; abdominal pain, nausea, strept throat, fever, rash
	24004	8	F	W	100/200 mg	X	Severe rash, leukopenia
309	19137	10	F	W	255 mg	X	URI, pharyngitis followed by weight loss, indigestion (dyspepsia), rash, headache, fever, tremor, panic attacks (agitation).
	31149	8	F	Brazilian	340 mg	X	Irritability (nervousness), amblyopia, headache, insomnia, dry mouth, confusion, pruritus, conjunctivitis
311	42309	8	M	W	425 mg	X	Fever, vomiting, nausea, rash, dehydration, abdominal pain; diagnosed with duodenal ulcer, duodenitis (peptic ulcer) with spasm (hypertonia); sweating, insomnia, night terror (abnormal dreams), functional heart murmur
	62338	7	M	Asian	340 mg	X	Insomnia, fever, sore throat; rash over entire body, extensive skin peeling; moderate skin blistering; burning on urination; upper and lower lips (Steven Johnson Syndrome); erythema multiforme by history, and SJ by definition
	48361	10	F	W	170 mg	X	Possible allergic reaction; dystonic (dystonia) reaction
	49327	10	F	W	425 mg	X	Palpitations, moderate tachycardia, amblyopia, flushed face (vasodilatation)
	48017	9	M	W	425 mg	X	Knee contusion, plantar warts (benign skin neoplasm); severe pneumonia (i.v. antibiotics) followed later by moderate sinusitis
312	58006	6	M	H	425 mg	X	Abdominal pain, constipation, alopecia, rebound inattention (abnormal thinking), ringworm (fungal dermatitis); followed 3.5 months later by strept throat, emesis, dehydration, ketoacidosis, hypoglycemia
	2007	9	M	B	425 mg	X	Exacerbation of headache; blotches on tongue (tongue disorder), presumptive strep throat; gastroenteritis
	3016	10	M	W	425 mg	X	Varicella (Herpes zoster) week 2, followed at 5.5 months by movement disorder (dystonia)
	29015	7	M	W	340 mg	X	Rash day 24, treated with prednisone + Benadryl; drug stopped X 10 days, restarted at day 34 at 85 mg, with return of rash (positive rechallenge)
	31007	9	M	W	255 mg	X	Dry, reddened lips (dry mouth); insomnia
	34004	7	M	W	340 mg	X	Pharyngitis; insomnia x 3 weeks; dyspepsia; strept throat; hostility; dry mouth; headaches
	34007	12	M	B	425 mg	X	Eczema; pharyngitis at day 164 followed by GGT increase to 3.5 X ULN [77: 3-22]; drug stopped at day 189; GGT decreased to 2.6 ULN [57] at day 196; gamma-glutamyl transpeptidase increased
	49017	6	M	W	340 mg	X	Worsened allergies (allergic reaction) X 26 days; worsening insomnia
	56003	9	W	M	340 mg	X	Fever, generalized body hives (urticaria), swollen eyes (facial edema), vomiting on day 13 resulting in stopping drug; on day 14, ALT elevation to 17.2 times ULN: 517; 0-41) and AST elevation to 10

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57006 7 W M 425 mg X

times ULN ; 409; 0-41), resolving by day 48 to 29 and 28 U/L, respectively.

Increased appetite X 35 days; persisting insomnia; URI (infection), day 22 X 2 weeks; treated with Benadryl on day 23, ? duration and reason; decrease self esteem (personality disorder); emotional lability

No Placebo Cases

SAE=Serious Adverse Event; WAE=Adverse Event Leading to Withdrawal

XXX= Adverse Event Term Identified By Sponsor

XXX Suggestions of Relation to Infection

XXX Psychiatric Worsening

XXX Dermatological

XXX Unusual Cases

Study Number: C1538d/311/AD/US

Patient Number: 062338

Study Drug: Modafinil

Dosage: 340 mg/day (maximum)

Serious Adverse Events: Erythema multiforme, Stevens–Johnson syndrome

This 7-year-old Asian boy with ADHD began treatment with modafinil on 30 March 2004; his dose was titrated to 340 mg/day on study day 15. He had no other abnormal findings in his medical history and was not taking any concomitant medication at entry into the treatment period of the study.

On study day 16, this patient was seen by the investigator and noted to have a sore throat and fever (101.9 degrees Fahrenheit); the patient’s mother reported that he also had a mild rash, which she believed to be insect bites. During the evening of study day 16, the mother reported that “red bumps” developed, which the investigator felt were typical of erythema multiforme. The rash subsequently became extensive and severe, erupting over the patient’s entire body. The patient received 1 dose of amoxicillin trihydrate on study day 17. (NOTE: The MedWatch report states amoxicillin was taken on study day 16.) The results of a Rapid Strep Test on study day 17 were negative for *Streptococcus*. On study day 19, the patient’s pediatrician noted multiple pruritic areas on his stomach and arms. The pediatrician felt it was unlikely the event was related to amoxicillin but changed the treatment to erythromycin. However, the patient never took any of the erythromycin prescribed. The patient subsequently experienced extensive skin peeling with mild to moderate skin blistering. On study day 22, the pediatrician noted the rash had spread to the patient’s face. On study day 23, the patient complained of burning with urination, which was considered the onset of mild Stevens-Johnson syndrome, with 2 areas of mucosal involvement, the urethral meatus and the upper and lower lips. A dermatologist assessed the patient’s rash as erythema multiforme by history and most likely Stevens-Johnson syndrome by definition. On study day 30, the patient had no new lesions and the event was resolved. The patient did not receive study drug from study days 18 through 30 then received 1 dose (last dose) of study drug on study day 31 (mother’s decisions without consulting the investigator). (NOTE: The MedWatch report states the last dose of study drug was on study day 27.) The study drug code was broken at the request of Cephalon Global Product Safety on study day 60.

In the clinical study report database, a serious adverse event of severe erythema multiforma (COSTART: erythema multiforme) and a nonserious adverse event of moderate viral pharyngitis (COSTART: pharyngitis) were noted starting on study day 16. Mild Stevens–Johnson syndrome was also reported as a serious adverse event beginning on study day 23. The patient was withdrawn from the study on day 44 because of the 2 serious adverse events, which were considered possibly related to treatment with study drug. Pharyngitis was considered not related to treatment with study drug. The erythema multiforme was continuing at the time of withdrawal. Stevens–Johnson syndrome resolved on study day 30 with no residual effect, and pharyngitis resolved with no residual effect at an unspecified time. (NOTE: The MedWatch report states that, in the investigator’s opinion, the erythema multiforme was probably secondary to the viral

infection, possibly secondary to modafinil, and remotely possibly related to amoxicillin and that the Stevens-Johnson syndrome was probably related to the viral infection.)

In addition, the patient had an adverse event of mild insomnia on study day 1, which was continuing at the time of his withdrawal from the study. The investigator considered the insomnia probably related to treatment with study drug.

- **Study 207 Double-Blind: Narratives of Serious Adverse Events**

Study Number: C1538a/207/AD/US

Patient Number: 315

Study Drug: PROVIGIL

Dosage: 100 mg/day (Treatment Period 2)

Serious Adverse Event: maculopapular rash (morbilliform rash)

Patient 315 was an 11-year-old Caucasian girl with predominantly Inattentive ADHD, with no other psychiatric comorbidity. The patient appeared thin (weighing 28 kg for her 134.9-cm stature) but was energetic and presented with a medical history significant for Turner's syndrome, a small bladder (nocturnal enuresis), ear infections, and an adverse reaction to insect bites. Patient had been taking somatropin (rDNA origin) injection, intramuscularly; total daily dose unknown) for 7½ years prior to study entry for Turner's syndrome and desmopressin acetate nasal spray (2 sprays per day) for almost 4 months prior to study entry for nocturnal enuresis. Both medications were continued during the study. EMLA cream (5 grams) was also used as a topical anesthetic prior to blood sample collections at the screening, baseline, and week-1 study visits. At the week-1 visit, which occurred on day 4 at the MGH site, the patient reported fever (101 °F), abdominal pain, and diarrhea; these symptoms, although considered by the investigator to be mild in severity, persisted for 9 more days. The patient was not able to attend the week-2 study visit (on day 11) so study drug (the vacation blister pack) was shipped to her home. On day 14, the patient was seen in the emergency room for generalized pruritic urticaria (on face and chest) believed to be contact dermatitis. The patient was treated with diphenhydramine hydrochloride and released. The rash worsened on day 15, and the patient was hospitalized with a provisional diagnosis of Stevens Johnson Syndrome. Study drug treatment was discontinued (day 15) and the blind was broken. The patient received to 200 mg/day of PROVIGIL during week 1, which was administered as 100 mg/day on day 1 and 200 mg/day on days 2 through 7), followed by 100 mg/day of PROVIGIL for days 8 through 15 (study week 2) at study drug discontinuation. The patient was examined by a dermatologist who established that the condition was not Stevens-Johnson Syndrome, but rather a moderate morbilliform rash. Mucosal blisters or erosions were not present. The patient was treated with hydroxyzine embonate, and the rash resolved less than a week later. The investigator assessed that the morbilliform rash was probably related to PROVIGIL treatment.

Study Number: C1538/213/AD/US

Patient Number: 18004

Study Drug: PROVIGIL

Dosage: 200/100 mg

Adverse Events Resulting in Study Withdrawal: fever, rash, rash vesic bull (vesiculobullous rash)

This 8-year-old white boy with ADHD began treatment with PROVIGIL 200/200 mg on 5 April 2002. He took study drug a total of 19 days during the double-blind treatment

period, and his last dose was taken on 23 April 2002. At study entry, this boy had no remarkable medical history and was taking a children's chewable multivitamin.

On 19 April 2002, adverse events of a mild fever and a moderate rash on the cheeks were reported for this child, and severe blisters on his lips (COSTART: rash vesic bull) were reported on 22 April 2002. Study drug was discontinued on 23 April 2002, and the boy was withdrawn from the study. The boy was given cephalexin for the rash and acetaminophen with codeine for the fever and pain related to the rash. On 11 April 2002, an adverse event of mild insomnia was also reported for this child. All of the adverse events resolved with no residual effect, and the investigator considered each event possibly related to treatment with the study drug.

Study Number: C1538/213/AD/US

A brief search of AERS identified four (4) unique cases in the postmarketing experience, in addition to the one (1) case occurring in the clinical trial. These cases are identified in the table below. A ODS consult on this issue is pending. A brief search performed by them identified seven (7) unique cases.

AERS DataMart Cases

Report No.	Age	Sex	Diagnosis/ Comment	Other Meds/ Time of Onset Post Provigil Tx	Med Hx	Suspected Causation by Reviewer
4376619	7	M	EM/SJ (from Cephalon trial database and in AERS). Mouth and body rash with bx for EM	No/ Symptoms two week post treatment	ADHD	Probable
4193236	27	F	SJ/ mouth and vaginal lesions)	No/No time given	SAS	Possible to Probable
4677929	54	M	SJ—Bx consistent with SJ/EM	Yes (Multiple-with definite other suspected drugs, e.g. phenytoin)/ No Time given	Admitted for SAH - event occurred during	No- to many drug confounders

3882684	28	F	SJ/EM - clinically (skin and mouth)-bx results note EM only	Yes/No time given	admission. Fatigue, SLE	Possible to Probable
4449260	68	F	EM(this was the final diagnosis/SJ- note rash over body, sore throat and ulcers	Yes/ Two weeks after treatment	Narcolepsy	Possible to Probable

Reviewer Comment(s):

The background rate of Steven Johnson is around 1 per million. Drug-induced Steven Johnson Syndrome is usually so rare that drugs that are associated with Steven Johnson Syndrome usually do not show cases in clinical trials. This experience with modafinil in children and adolescents indicates a rate of 1 (possibly 3) of Steven Johnson Syndrome out of a total of 933 subjects exposed to modafinil, of which 626 subjects were from all the phase III studies (309, 311, 310, and 312). This is unusually high. Drug-induced Steven Johnson Syndrome is usually so rare that drugs that are associated with Steven Johnson Syndrome usually do not show cases in clinical trials. This events (s) and the other cases of rash are occurring only in subjects on modafinil, and only in children (6-11 years; mean age: 8.5 years) and are not occurring in either adolescents (12-17 years), and not serious skin rashes were present in the adult trials in SWSD and OSAHS. In addition, many other rashes are occurring only in children on modafinil. These findings would be consistent with the striking observation concerning the pediatric pharmacokinetic data showing that the sulfone exposure as measured by AUC is three times that of the parent for young kids, but only 1/2 that of the parent for adults. If so, then kids would be getting 6 times the exposure to the sulfone.

Possible Reye's Syndrome and Other Cases Involving the Liver

Review of the discharge summaries for subjects who withdrew from the trial for serious or non-serious reasons, identified five (5) subjects (5/101: 5 %) having abnormal liver function tests, of these, in only three (3) were the liver adverse event term listed as the basis for leaving the trial. These cases are identified in the table below which were put together from the

vignettes submitted by the sponsor. The values identified in four (4) of the vignettes were clinically significant showing ALT's which were 17.2 times, the upper limit of normal (ULN) and AST's up to 10 times ULN. Review of Sponsor's Listing 4.1.3 (Clinical Significant Abnormal Values for Selected Chemistry Laboratory Parameters for All Studies of Randomized Patients) and Listing 4.1.1 (Clinical Significant Abnormal Values for Selected Chemistry Laboratory Parameters for Phase 3 Double-Blind Studies, Randomized Patients) identified subjects who had liver function tests that were 3 times the ULN. Listing 4.1.3 identifies 4 subjects with SGOT elevations (128-453 U/L; 0-42 U/L: Normal; one subject with 10.7 times ULN), 10 with SGPT elevations (65-517 U/L; 5-20 U/L: Normal; one subject with 26 times ULN), 5 with GGT elevations (62-282 U/L; 3-22 U/L: Normal; one subject with 13 times ULN) and 5 with total bilirubin elevations (2-3.2 mg/dl; 0.1-1.2 mg/dl: Normal; one subject with 13 times ULN). None of the subjects identified in these vignettes could be found by this reviewer in the above referenced listings which have been attached in the Appendix of this report. All subjects in Listing 4.1.3 were on modafinil and none were on placebo. Listing 4.1.1 identifies two (2) subjects on placebo, not identified in Listing 4.1.3, who had isolated SGPT elevations (131 and 160 U/L; one subject with 8 times ULN).

In addition one subject in Cephalon's on-going clinical trial for the use of modafinil to improve wakefulness in children with excessive daytime sleepiness (EDS) associated with narcolepsy (I 59, 661) developed a Reye-like syndrome, as indicated by a recent 15 day report which was submitted to the agency. The case describes a 6 year old male who developed increased ammonia, decreased phosphorous, delirium, confusional state, somnolence and convulsions in study C1538/3027/NA/MN requiring intubation and monitoring in an ICU setting. The child was treated with doses of 100-400 mg/day. Concomitant medications identified in MedWatch were Allegra X 1 week prior to the event and Flonase X 2 weeks prior to the event (dose unspecified). A copy of the IND safety report submitted by the sponsor is pasted below.

The sponsor states: "In the Phase 3 double-blind studies, mean changes from baseline to endpoint showed a mean increase from baseline (6.3 U/L) in the modafinil group compared to a mean decrease (-0.1 U/L) in the placebo group. There was also a mean increase in alkaline phosphatase in the modafinil group (16.8 U/L) which was approximately twice that observed in the placebo group (7.6 U/L). The effects of modafinil on alkaline

phosphatase and GGT appeared to be more pronounced in the higher dosage groups (340 and 425 mg/day) than among subjects receiving ≤255 mg/day. Similar results were observed for subjects receiving modafinil in all studies combined (Table 22, Appendix".¹⁸ The sponsor states that "in previous clinical studies of modafinil in adults, mean values for GGT and alkaline phosphatase and mean changes from baseline were shown to increase with increasing exposure to modafinil...Similar to the findings in adults, progressive mean increases in GGT were observed over time during treatment with modafinil for up to 6 months¹⁹" (Table 23, Appendix). Shifts in GGT from normal at baseline to high at endpoint were observed by the sponsor for 59 (14%) subjects in the modafinil treatment group compared to 3 (1%) subjects in the placebo group. The sponsor further states that in both groups of studies, the mean increases in alkaline phosphatase and GGT were not accompanied by increases in AST, ALT, or total bilirubin. Across all studies, only 5 (<1%) subjects who received modafinil had GGT values that met the criterion for clinically significant abnormality.

18 2.7.4 Summary of Clinical Safety, Clinical Laboratory Evaluations, Serum Chemistry, Changes from Baseline, pg. 34.

19 2.7.4 Summary of Clinical Safety, Clinical Laboratory Evaluations, Serum Chemistry, Changes from Baseline, pg. 39.

Liver Cases Identified in the Vignettes of Subjects Leaving the Trials Because of an Adverse Event

Study	Pt No	Age	Sex	Race	Dose	SAE	WAE	Event
	2004	14	M	B	340 mg		X	Headache, nausea; <u>leukopenia (2 events)</u> , neutropenia; increased SGOT, AST, SGPT; decreased monocytes; increased lymphocytes; <u>myalgia; cough, hot feeling (feverish)</u> , fatigue (asthenia)
	6007	9	M	W	425 mg		X	Insomnia x 5.5 months; ALT (SGPT) 2 X ULN [64: 5-30], GGT increase [25: 3-22] day 58; decreased by day 80 [ALT: 39, GGT: 23], then ALT 8.7 times ULN [262] and GGT 4.3 times ULN [95] by day 213; stopped at day 217; ALT [41] and GGT [19] decline by day 255; <u>SGPT increased, gamma-glutamyl transpeptidase increased</u>
	34007	12	M	B	425 mg		X	<u>Eczema</u> ; pharyngitis at day 164 followed by GGT increase to 3.5 X ULN [77: 3-22]; drug stopped at day 189; GGT decreased to 2.6 ULN [57] at day 196; <u>gamma-glutamyl transpeptidase increased</u>
	56003	9	W	M	340 mg		X	<u>Fever, generalized body hives (urticaria), swollen eyes (facial edema), vomiting on day 13 resulting in stopping drug</u> ; on day 14, ALT elevation to 17.2 times ULN: 517; 0-41) and AST elevation to 10 times ULN ; 409; 0-41), resolving by day 48 to 29 and 28 U/L, respectively.
	59010	7	W	F	340 mg		X	Cough on day 12; hyperglycemia (146) on day 28; liver function tests continued to worsen reaching 1.8 times ULN for ALT [56: 5-30] and 1.5 times ULN [34: 3-22] for GGT by month 4, and 1.3 times ULN for AST by month 3 [52: 0-41] resulting in stopping study drug by day 147; abdominal pain by day 31; URI (infection) on day 38; <u>liver function tests abnormal</u>
IND 59, 661 (080) C1538/3027/NA/ MN/US014983		6	?	M	400 mg	X		Increased ammonia, decreased phosphorous, delirium, confusional state, somnolence and convulsions requiring intubation and monitoring in an ICU setting; <u>? Reye's</u> , acute hepatic encephalopathy

None of the 7 vignettes for the placebos had Liver Symptoms

SAE=Serious Adverse Event; WAE=Adverse Event Leading to Withdrawal

XXX= Adverse Event Term Identified By Sponsor

XXX Suggestions of Relation to Infection

XXX Psychiatric Worsening

XXX Dermatological

XXX Unusual Cases

**IND Safety Report: US014983: Brief Description of Current Case:
Delirium, Seizures, Increased Serum Ammonia, Decreased Serum
Phosphate, Confusion**

28-, 30-31-Mar-05: Patient 7004 [] is a 6-year-old Caucasian male with a history of excessive sleepiness associated with narcolepsy. This patient was enrolled in the protocol C1538/3027/NA/MN, "A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Provigil (Modafinil) Treatment (100, 200 and 400 mg/day) in Children and Adolescents with Excessive Sleepiness Associated with Narcolepsy." On 11-Mar-05, the patient was randomized to Provigil and received the first dose of study medication, at a dose of 400mg daily.

On 22-Mar-05, eleven days after the first dose of study medication, the patient developed nausea and emesis with a probable fever. He was treated with Emetrol (fructose, dextrose, and phosphoric acid). On 23-Mar-05, the patient was diagnosed with probable pharyngitis by his pediatrician and was treated with amoxicillin. The following day, the results of throat cultures were negative. On 26-Mar-05, the patient was admitted to the hospital for somnolence, and the study medication was discontinued. The results of initial diagnostic testing including serum chemistries, liver function, toxicology, and a computed tomography (CT) of the head were negative. He was transferred to an intensive care unit in another facility due to progressive delirium and hallucinations. On 27-Mar-05, the patient developed seizures and was sedated and intubated. Further testing revealed an elevated serum ammonia level and a decreased serum phosphate level. An analysis of the patient's cerebral spinal fluid was negative, as well as, a neurology consult. The investigator indicated that the etiology appeared to be metabolic. On 30-Mar-05, the patient was extubated but remained somnolent. The patient remains hospitalized at the time of this report. In the investigator's opinion, the life threatening events of delirium, seizures, nausea, and emesis were possibly related to the study medication, and the event of pharyngitis was unlikely related to the study medication.

30-Mar-05; 01-, 04-06-Apr-05: On 11-Mar-05, the patient received the first dose of Provigil at a dose of 100mg daily, not 400mg daily as initially reported. The dose was titrated over the following seven days to a total daily dose of 400mg daily. On 22-Mar-04, the administration of Emetrol was discontinued. Further evaluation revealed the patient's serum ammonia was elevated to 145. His serum phosphate was "very low" and "was difficult to return to normal." On 27-Mar-05, the nausea, emesis, and pharyngitis resolved. On 28-Mar-05, the seizures resolved. On 29-Mar-05, the delirium resolved. On 31-Mar-05, the patient was alert and tolerating breakfast. On 01-Apr-04, he was transferred out of intensive care to a pediatric floor. On 03-Apr-05, he was discharged home.

20-May-05: The patient number was incorrectly reported as 7004. The correct patient number is 704. The investigator no longer considers the events of nausea, emesis and

pharyngitis as serious adverse events. Pharyngitis was likely due to an acute viral illness the patient experienced prior to the onset of the serious adverse events. On [] the patient experienced somnolence, increased serum ammonia, decreased serum phosphate, and confusion and was admitted to the hospital. The event of somnolence remains ongoing. In the investigator's opinion, the life threatening events of somnolence, increased serum ammonia, decreased serum phosphate, confusion, delirium and seizures were possibly related to the study medication.

For a detailed case description see attached Form FDA3500A (US014983*).

Review of This Case and Similar IND Safety Reports

This is the first report of increased serum ammonia, decreased serum phosphate and confusion received by Cephalon with a possible causal relationship to study medication under this IND (59,522). There have been no other reports of increased serum ammonia, decreased serum phosphate and confusion occurring under any other Cephalon sponsored clinical study of modafinil. The event of somnolence is referenced in the Investigator Brochure.

For the review of this case and similar IND Safety Reports please see the initial report submitted 08-Apr-05 (Serial No. 070).

Conclusions and Recommendations

The conclusion of Cephalon Clinical Research and Clinical Safety is that no apparent association between the study medication and increased serum ammonia, decreased serum phosphate and confusion was present and that no alterations to protocol conduct are deemed necessary.

* Refers to Clintrace case ID numbers in Cephalon's Product Safety database

Reviewers Comments

The combination of increased serum ammonia, disturbances of consciousness, confusion and seizures may be seen with Reye Syndrome and, or, acute hepatic encephalopathy (coma) and with several other disorders. Insufficient ancillary and clinical data is provided with this vignette to make a definitive diagnosis. A review of the labeling for Allegra (fexofenadine hydrochloride) and Flonase (fluticasone propionate) does not support relatedness of these agents to this subject's adverse experience.

This case is alarming. An article by Belay²⁰ published in the NEJM in 1999, reviewed Reye's syndrome in the US from 1981-1997. The article notes that "After a peak of 555 cases in children reported in 1980, there have been no more than 36 cases per year since 1987." This sharp decline was based on showing an association between the uses of aspirin during varicella or influenza-like and the risk of getting the illness. This encephalopathy is associated with fatty degeneration of the liver and occurs usually after influenza or varicella. Inborn metabolic errors may mimic this but these usually are evident by 3 years of age. In the review reported by Belay, "antecedent illnesses were reported in 93 percent of the children, and detectable blood salicylate levels in 82 percent. The overall case fatality rate was 31 percent. The case fatality rate was highest in children under five years of age (relative risk, 1.8; 95 percent confidence interval, 1.5 to 2.1) and in those with a serum ammonia level above 45 µg per deciliter (26 µmol per liter) (relative risk, 3.4; 95 percent confidence interval, 1.9 to 6.2)."

Insufficient information is present to know if this is a case of Reye's, or, if modafinil is even causative. What is known about the relation of modafinil to liver function raises serious concerns. These are: 1) mean increases in GGT occurring only in subjects taking modafinil; 2) mean GGT elevations are higher in those receiving increasing exposures (e.g. 340 and 425 mg/day) of modafinil; 3) 14 % on modafinil compared to 1 % on placebo showed increases in GGT over 6 months; and 4) the outliers identified above seem to suggest that some subjects may have experienced reversible hepatic injury. Dr. John Senior is presently reviewing this case and the issue of potential liver toxicity associated with modafinil. Further information is needed on the case of possible Reye's (hospital records, discharge summary, all laboratory and other diagnostic tests), as well as on the other cases identified in the vignette table. The sponsor should provide a vignette for all cases of LFT elevations, and if possible, copies of all ancillary studies done on any of these subjects. The sponsor should reconcile the Listings with the vignettes and make sure that that vignettes

20 Belay ED, ET. Al. Reye's syndrome in the United States from 1981 through 1997. N Engl J Med 1999 May 6; 340(18):1377-82.

with subjects meeting the sponsors criteria for significance should be entered to those listings²¹.

Suicidality, Psychosis and Other Psychiatric Adverse Events

Review of the discharge summaries for subjects who withdrew from the trial for serious or non-serious reasons, identified sixty (60) subjects (52/101; 51 % on drug; 8/8: 100 % on placebo. However the type and frequency of psychiatric events differed between the two (2) groups. Some subjects had more than one psychiatric event. Suicidal ideation²² (6: 12 %; one of which was a possible attempt versus a gesture), agitation (5: 10 %) depression (2: 4 %) psychosis²³ (3: 6 %), another with possible psychosis (1: moderate change in mental status, not specified); and phobias (3: 6 %). Irritability (nervousness) [10: 19 % (drug); 3: 37 % (placebo)], emotional lability (moodiness) [9: 17 % (drug); 2: 25 % (placebo)], anxiety [4: 8 % (drug); 1: 12.5 % (placebo)], hostility (increased anger) [4: 8 % (drug); 2: 25 % (placebo)] occurred more frequently in subjects on placebo, however, the number of the events in the placebo group was too small to make any meaningful comparisons. Mean age of subjects with suicidal ideation and psychosis was 8 years, and mean age of subjects in the placebo group with psychiatric events was 10 years. The table below summarizes the vignettes of subjects who left the trials because of psychiatric adverse events.

Reviewer Comment(s):

The most striking thing in this limited look is that certain psychiatric disorders (suicidality, depression, agitation, psychosis and phobias) are only occurring in subjects on drug. The reason for this is uncertain, given the younger age of

21 A Safety Update on this case was sent to the Agency on 09/20/2005 . It indicates that "The parents reported using Tylenol (acetaminophen) to treat the fever. There was no report of aspirin use as symptomatic treatment prior to hospitalization. In addition, there were no reported community outbreaks of varicella or influenza coincident with this event" (Note: 09/07/2005).

22 Subjects with suicidal ideation: No. 411 in Study 206, No. 207 in Study 405, No. 411 in Study 207, No. 11002 in Study 213, No. 40178 in Study 309 and No. 14016 in Study 311. Subject No. 14016 in Study 311 put a rope around neck and might have been a gesture.

23 Subjects with psychosis: Subject no. 410 in Study 206 (formication), No. 11002 in Study 213 (command auditory hallucinations with suicidal ideation), No. 40629 in Study in Study 309 (mild hallucinations, NOS) and No. 37688 (moderate change in mental status, thinking).

8 years of subjects with suicidal ideation and psychosis one might wonder if there is any relation of these adverse events to the higher sulfone exposure in young children.

The most commonly reported psychiatric event in $\geq 5\%$ of all subjects in all modafinil or placebo groups in phase III double blind controlled trials was insomnia (modafinil: 115/420: 27 %; placebo: 8/213: 4 %) and nervousness (modafinil: 19/420: 5 %; placebo: 9/213: 4 %). The most frequently occurring psychiatric adverse in subjects on modafinil in all studies (Appendix: Table 15) is insomnia (277: 30 %), nervousness (61:7 %), emotional lability (46: 5 %) and somnolence 42 (5 %). Given the significant sleep disruption (insomnia), one must wonder, what, if any relationship it may have to the onset of psychiatric symptoms [Appendix: Table 13: Number of Patients With the Most Frequently Occurring Adverse Events ($\geq 5\%$ of Patients in the All Modafinil or Placebo Treatment Groups) by Body System and Adverse Event Type Phase 3 Double-Blind, Placebo-Controlled Studies].

Several psychiatric adverse events were not listed as the reason for discontinuation, and were incorrectly coded. Subject 1105 in Study 1105 was discontinued because of somnolence, but review of the adverse event indicates that the subject probably had irritability (nervousness) resulting in the off-label use of risperidone which in turn resulted in a seizure [based on prolonged non-responsiveness, presence of a Todd's paralysis (facial palsy) and incontinence]. Subject 410 in Study 206 had disorderly, aggressive behavior and experienced formication (bugs crawling over the skin) and by definition could not have had paresthesia (abnormal sensation of skin with no physical cause). Subject 14016 in Study 311 had bizarre behavior; putting rope around his neck was listed as discontinuing because of a personality disorder. Subject 411 in Study 206 was listed as discontinuing because of a rash, but the vignette indicates suicidal ideation. The sponsor needs to make sure that the coding is accurate for this submission.

Psychiatric Events* Identified in the Vignettes of Subjects Leaving the Trials Because of an Adverse Event

Study	Pt No	Age	Sex	Race	Dose	SAE	WAE	Event
113	1105	6	M	W	340 mg	X		Probable Todd's paralysis (incontinence, non-responsive, facial); irritable (nervousness), headache, somnolence
206	103	12	F	W	400 mg		X	Sinus headache, nausea, decreased appetite,

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	19012	9	M	W	340 mg	X	Exercised induced asthma, irritability (nervousness); followed by abdominal pain, vomiting, nausea, dehydration, metabolic acidosis; two stomach ulcers (gastric), positive for <i>Helicobacter pylori</i> ; weight loss
312	58006	6	M	H	425 mg	X	Abdominal pain, constipation, alopecia, rebound inattention (abnormal thinking), ringworm (fungal dermatitis); followed 3.5 months later by strept throat, emesis, dehydration, ketoacidosis, hypoglycemia
	11008	7	M	W	425 mg	X	Chin laceration (accidental injury), abdominal pain; sadness (depression), obsessive rumination, negative thoughts (abnormal thinking)
	17011	7	M	W	255 mg	X	Mood lability X 2 mths, fatigue (asthenia) X 1.5 mths; abdominal pain, nausea, vomiting; agitation
	18015	7	F	W	170 mg	X	Insomnia X 2 mths; increased irritability (nervousness), agitation
	27014	8	M	W	340 mg	X	Insomnia x 2 weeks; anxiety
	52008	7	M	H	425 mg	X	Increase in appetite (day 36) with hypercholesterolemia; viral syndrome (headache, abdominal pain, vomiting) on day 122; worsening ADHD with increased hyperactivity (hyperkinesia and impulsivity (personality disorder), and insomnia on day 156.
	54019	14	M	W	425 mg	X	Insomnia, malodorous urine (urine abnormality), anorexia (day 2); moderate depression (day 21) which resolved by day 38 with stopping drug.
	55002	7	M	W	340 mg	X	Oppositional defiant disorder (personality disorder)
	57001	8	W	M	425 mg	X	Constipation; insomnia x 1.5 mths, increasing in severity by 5 mths; weight loss (8.8 lbs) X 5 mths; anxiety (psychosocial stressors)
	57006	7	W	M	425 mg	X	Increased appetite X 35 days; persisting insomnia; URI (infection), day 22 X 2 weeks; treated with Benadryl on day 23, ? duration and reason; decrease self esteem (personality disorder); emotional lability
	57009	7	W	M	255 mg	X	Irritability (nervousness) and increased emotional sensitivity (emotional lability), day 8; middle of night insomnia
E1044	A-11	9	?	M	100-200 mg	X	Inflammation of vocal cords; persistent insomnia; agitation, excitation; lack of efficacy
	D-03	12	?	M	100 mg	X	Fits of anger, anxiety
E1047	08	7	?	M	300 mg	X	Worsening of attention deficit disorder and concentration
	13	12	?	M	200 mg	X	Headaches, asthenia, worsening of school performance, behavior disorder
	48210	8	F	W	Placebo	X	Pharyngitis, nausea, irritability (nervousness), moodiness (emotional lability)
	51138	7	M	W	Placebo	X	Anger (hostility), behavioral disturbance (personality disorder)
	59198	6	M	H	Placebo	X	Hyperactivity (hyperkinesia), increased baseline impulsivity
	48210	8	F	W	Placebo	X	Pharyngitis, nausea, irritability (nervousness), moodiness (emotional lability)
	1114	8	M	B	Placebo	X	Cough, sore throat, moderate anxiety, tachycardia, severe insomnia
	2259	14	M	B	Placebo	X	Fever, sore throat, leukopenia, neutropenia, monocytosis; sedation, lethargy (somnia), difficulty focusing (abnormal thinking), muscle pain-soreness (legs, back)

2282	13	M	W	Placebo	Increased irritability (nervousness)
10176	12	M	W	Placebo	Rage (hostility)

*Cases of insomnia, somnolence, asthenia, tics, anorexia, and changes in weight were excluded from this analysis.

SAE=Serious Adverse Event; WAE=Adverse Event Leading to Withdrawal

XXX= Adverse Event Term Identified By Sponsor

XXX Suggestions of Relation to Infection

XXX Psychiatric Worsening

XXX Dermatological

XXX Unusual Cases

Hematological Events: Leukopenia, Neutropenia

The reader is referred to Section 1.21.5 Laboratory Findings, Hematology, and the Reviewer's Comments.

Peptic Ulcer Disease

Two subjects on modafinil (No. 42309 and 19012) developed peptic ulcer disease, one of which was positive for Helicobacter pylori. In addition one (No. 42309) had fever, nausea and rash.

Reviewer's Comments:

This reviewer is uncertain what the normal background rate is for these two adverse events in the pediatric population. However, it appears most unusual. Safety and gastrointestinal consults will need to address this.

Changes in Body Weight over Time

Overall there were increases and decreases in body weight of $\geq 7\%$ in 32% and 11 % of subjects, respectively. The reader is referred to Section 1.21.5 Laboratory Findings, Vital Signs Including Body Weight, Clinically Significant Abnormalities in Vital Signs, Body Weight, and Reviewer's Comments.

7.1.3 Common Adverse Events

Subject disposition for all phase 3 double blind controlled studies is summarized in sponsor's Table 6 below.

**Table 6: Disposition of Patients
 Phase 3 Double-Blind, Placebo-Controlled Studies
 (All Randomized Patients)**

Patient disposition	Number (%) of patients				
	Modafinil				Placebo (N=215)
	≤255 mg/day (N=64)	340 mg/day (N=102)	425 mg/day (N=257)	All modafinil (N=423)	
Randomized, not treated	2 (3)	0	1 (<1)	3 (<1)	2 (<1)
Safety analysis set	62 (97)	102 (100)	256 (>99)	420 (>99)	213 (>99)
Completed study	36 (56)	65 (64)	176 (68)	277 (65)	114 (53)
Discontinued study	28 (44)	37 (36)	81 (32)	146 (35)	101 (47)
Adverse event	7 (11)	7 (7)	7 (3)	21 (5)	7 (3)
Lack of efficacy	4 (6)	15 (15)	48 (19)	67 (16)	73 (34)
Consent withdrawn	6 (9)	3 (3)	8 (3)	17 (4)	11 (5)
Protocol violation	0	1 (<1)	0	1 (<1)	1 (<1)
Lost to follow-up	6 (9)	4 (4)	2 (<1)	12 (3)	1 (<1)
Noncompliance to study drug	0	2 (2)	0	2 (<1)	0
Noncompliance to study procedures	1 (2)	0	1 (<1)	2 (<1)	1 (<1)
Other	4 (6)	5 (5)	15 (6)	24 (6)	7 (3)

SOURCE: Summary 1.0.1.

"In the Phase 3 double-blind, placebo-controlled studies, the mean duration of modafinil treatment (based on stable dose of modafinil administered) was 50.1 days, for a total of 58.4 patient-years (Sponsor Table 8, below). The majority (86%) of patients received more than 1 month of treatment. Including dose titration, the mean average daily dose of modafinil was 333.5 mg for all modafinil-treated patients combined."

**Table 8: Extent of Exposure to the Study Drug
 Phase 3 Double-Blind, Placebo-Controlled Studies**

Exposure to treatment	Modafinil					Placebo (N=213)
	≤255 mg/day (N=62)	340 mg/day (N=102)	425 mg/day (N=256)	All modafinil (N=420)		
Duration of treatment (days)						
Mean	45.5	47.8	52.1	50.1	47.6	
SD	24.38	16.46	13.79	16.57	16.50	
Median	62.0	49.0	52.0	51.5	49.0	
Min, max	2.0, 71.0	3.0, 77.0	7.0, 77.0	2.0, 77.0	3.0, 108.0	
Weeks/months treated, n (%)						
≤2 weeks	11 (18)	6 (6)	7 (3)	24 (6)	11 (5)	
>2 weeks and ≤1 month	8 (13)	12 (12)	14 (5)	34 (8)	23 (11)	
>1 month and ≤3 months	43 (69)	84 (82)	235 (92)	362 (86)	178 (84)	
>3 months and ≤6 months	0	0	0	0	1 (<1) ^b	
Number of patient-years ^a	7.83	13.55	37.04	58.42	28.18	
Average daily dose						
Mean	206.73	314.06	371.89	333.46	0.0	
SD	57.76	73.96	73.56	92.02	0.0	
Median	215.53	308.72	361.59	337.30	0.0	
Min, max	65.9, 304.6	29.1, 511.7	163.9, 571.5	29.1, 571.5	0.0, 0.0	

SOURCE: Summary 2.1.1.

^a Patient-years = (mean treatment duration x number of patients)/365.25 days.

^b 1 patient in the placebo treatment group in study 311 received study drug for 108 days, which was outside the 3-month visit window.

Min=minimum; max=maximum; SD=standard deviation.

The sponsor states:

"In the Phase 3 double-blind, placebo- controlled studies (studies 309, 310, and 311), 78% of subjects on modafinil and 63% on placebo reported at least 1 adverse event during double-blind treatment (Table 12). Treatment-related events were 55% for subjects on modafinil and 29% for subjects on placebo. For all Phase 3 studies (including the open- label extension study 312), 87% of subjects on modafinil reported at least 1 adverse event, and 65% reported at least 1 treatment-related adverse event. For all studies combined (e.g., Phases 1, 2, and 3), 85% of subjects on modafinil reported at least 1 adverse event, and 63% reported at least 1 treatment- related adverse event.

In the Phase 3 double-blind, placebo-controlled studies, serious adverse events were reported for less than 1% of subjects in the modafinil treatment group and none of the patients in the placebo treatment group (Table 12), and adverse events leading to discontinuation from study were reported for 5% of patients in the modafinil treatment group and 3% of patients in the placebo treatment group.

For all studies combined (i.e., Phases 1, 2, and 3), serious adverse events were reported for 2% of modafinil- treated

patients, and withdrawal due to adverse events was reported for 9% of modafinil- treated patients."

Table 12: Overview of Adverse Events

Category	Number (%) of patients			
	Phase 3 double-blind studies		All Phase 3 studies	All studies
	Modafinil (N=420)	Placebo (N=213)	Modafinil (N=626)	Modafinil (N=933)
Any adverse event	328 (78)	135 (63)	545 (87)	794 (85)
Treatment-related adverse events	229 (55)	62 (29)	407 (65)	587 (63)
Serious adverse events	4 (<1)	0	12 (2)	17 (2)
Withdrawals due to adverse events	23 (5)	7 (3)	59 (9)	82 (9)
Deaths	0	0	0	0

SOURCE: Summaries 4.1.1, 4.1.2, 4.1.3, 4.3.1, 4.3.2, 4.3.3, 4.5.1, 4.5.2, 4.5.3, 4.6.1, 4.6.2, and 4.6.3.

Incidence of Common Adverse Events²⁴:

The sponsor states:

"In the Phase 3 double-blind, placebo-controlled studies, 78% on modafinil and 63% on placebo reported at least 1 adverse event during double-blind treatment (Table 13). The overall incidence of adverse events was similar for the 3 modafinil dosage groups: 79%, 82%, and

24 2.7.4 Summary of Clinical Safety, 4-Month Safety Update; 2.1.1 Common Adverse Events; pgs. 27-31.

76%, respectively, for the ≤ 255 mg/day, 340 mg/day, and 425 mg/day dosage groups. The most common adverse events among patients who received modafinil were insomnia, headache, anorexia (reported as decreased appetite by investigators and coded to anorexia under COSTART), infection, and abdominal pain. Adverse events with an incidence of $\geq 5\%$ in either treatment group that occurred more frequently with modafinil treatment than with placebo treatment included headache, abdominal pain, fever, anorexia, insomnia, and nervousness. In particular, insomnia was reported by 27% of patients in the modafinil treatment group compared to 4% of patients in the placebo treatment group, headache was reported by 20% of modafinil-treated patients compared to 13% of placebo-treated patients, and anorexia was reported by 16% of modafinil-treated patients compared to 3% of placebo-treated patients. In addition, weight loss was reported for 16 (4%) patients in the modafinil treatment group and 1 (<1%) patient in the placebo group (see Summary 4.1.1). There were no clear dose-related trends with respect to the frequency of specific adverse events."

Table 13: Number of Patients With the Most Frequently Occurring Adverse Events ($\geq 5\%$ of Patients in the All Modafinil or Placebo Treatment Groups) by Body System and Adverse Event Type Phase 3 Double-Blind, Placebo-Controlled Studies

Body system Adverse event	Number (%) of patients				
	Modafinil			All modafinil (N=420)	Placebo (N=213)
	≤ 255 mg/day (N=62)	340 mg/day (N=102)	425 mg/day (N=256)		
No. of patients with any AE	49 (79)	84 (82)	195 (76)	328 (78)	135 (63)
Body as a whole					
Headache	13 (21)	23 (23)	46 (18)	82 (20)	27 (13)
Infection	7 (11)	9 (9)	30 (12)	46 (11)	28 (13)
Abdominal pain	6 (10)	9 (9)	25 (10)	40 (10)	17 (8)
Fever	6 (10)	6 (6)	9 (4)	21 (5)	7 (3)
Digestive					
Anorexia	12 (19)	22 (22)	33 (13)	67 (16)	6 (3)
Vomiting	2 (3)	9 (9)	10 (4)	21 (5)	13 (6)
Nervous					
Insomnia	21 (34)	37 (36)	57 (22)	115 (27)	8 (4)
Nervousness	6 (10)	9 (9)	4 (2)	19 (5)	9 (4)
Respiratory					
Cough increased	5 (8)	7 (7)	20 (8)	32 (8)	16 (8)
Rhinitis	4 (6)	7 (7)	20 (8)	31 (7)	21 (10)
Pharyngitis	5 (8)	6 (6)	19 (7)	30 (7)	15 (7)

SOURCE: Summary 4.1.1.
 AE=adverse event.

"The most common adverse events (reported by $\geq 5\%$ of patients in either the modafinil or placebo treatment groups) occurred with similar frequency across the individual Phase 3 double-blind studies (Table 14)."

Table 14: Number of Patients With the Most Frequently Occurring Adverse Events (≥5% of Patients in Either Treatment Group) by Study Phase 3 Double-Blind, Placebo-Controlled Studies

Body system Adverse event	Number (%) of patients					
	Study C1538d/309/AD/US		Study C1538d/310/AD/US		Study C1538d/311/AD/US	
	Modafinil (N=131)	Placebo (N=67)	Modafinil (N=125)	Placebo (N=64)	Modafinil (N=164)	Placebo (N=82)
No. of patients with at least 1 AE	103 (79)	43 (64)	92 (74)	32 (50)	133 (81)	60 (73)
Body as a whole						
Headache	29 (22)	6 (9)	21 (17)	9 (14)	32 (20)	12 (15)
Infection	14 (11)	6 (9)	13 (10)	10 (16)	19 (12)	12 (15)
Abdominal pain	16 (12)	3 (4)	12 (10)	5 (8)	12 (7)	9 (11)
Fever	6 (5)	3 (4)	7 (6)	2 (3)	8 (5)	2 (2)
Digestive						
Anorexia	23 (18)	2 (3)	18 (14)	1 (2)	26 (16)	3 (4)
Vomiting	8 (6)	4 (6)	3 (2)	2 (3)	10 (6)	7 (9)
Nervous						
Insomnia	37 (28)	5 (7)	30 (24)	0	48 (29)	3 (4)
Nervousness	7 (5)	3 (4)	5 (4)	1 (2)	7 (4)	5 (6)
Respiratory						
Cough increased	12 (9)	6 (9)	7 (6)	3 (5)	13 (8)	7 (9)
Rhinitis	10 (8)	7 (10)	5 (4)	5 (8)	16 (10)	9 (11)
Pharyngitis	11 (8)	9 (13)	5 (4)	1 (2)	14 (9)	5 (6)

SOURCE: Clinical study reports, studies 309, 310, and 311.
 AE=adverse event.

7.1.4 Laboratory Findings

Chemistry²⁵: The only notable differences between the modafinil and placebo treatment groups were observed for *uric acid*, *alkaline phosphatase*, and *GGT*. For *uric acid*, a mean decrease from baseline (- 19.4 μ mol/ L) was observed in the modafinil group compared to a mean increase (3.1 μ mol/ L) in the placebo group. For *alkaline phosphatase*, mean increases from baseline were observed in both treatment groups; however, the increase in the modafinil group (16.8 U/ L) was approximately twice that observed in the placebo group (7.6 U/ L). For *GGT*, a mean increase from baseline (6.3 U/ L) was observed in the modafinil group compared to a mean decrease (- 0.1 U/ L) in the placebo group. *The effects of modafinil on alkaline phosphatase and GGT appeared to be more pronounced in the higher dosage groups (340 and 425 mg/ day) than among patients receiving ≤ 255 mg/ day.* Similar results were observed for patients receiving modafinil in all studies combined (Portion of Table 22 in Appendix). In both groups of studies, *the mean increases in alkaline phosphatase and GGT were not accompanied by increases in AST, ALT, or total bilirubin.*

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In previous clinical studies of modafinil in adults, mean values for GGT and alkaline phosphatase and mean changes from baseline were shown to increase with increasing exposure to modafinil. Therefore, changes in these parameters in the Phase 3 pediatric ADHD studies including the open-label extension study were examined by time interval (Table 23, Appendix). Similar to the findings in adults, progressive mean increases in GGT were observed over time during treatment with modafinil for up to 6 months. Mean increases in alkaline phosphatase appeared to peak within the first month of modafinil treatment.

Shifts in GGT from normal at baseline to high at endpoint were observed for 59 (14%) subjects in the modafinil treatment group compared to 3 (%) subjects in the placebo group in the Phase 3 double-blind studies.

The sponsor further states that "Across all studies, only 6 (<1%) patients who received modafinil had GGT values that met the criterion for clinically significant abnormality."

**Table 25: Clinically Significant Serum Chemistry Values by Treatment Group
 Phase 3 Double-Blind, Placebo-Controlled Studies, and
 All Studies Combined**

Serum chemistry variable	Criteria	Number (%) of patients		
		Phase 3 double-blind, placebo-controlled studies		All studies combined
		Modafinil (N=420)	Placebo (N=213)	Modafinil (N=933)
Uric acid	M: $\geq 625 \mu\text{mol/L}$ F: $\geq 506 \mu\text{mol/L}$	0	0	1 (<1)
AST	$\geq 3 \times \text{ULN}$	0	0	4 (<1)
ALT	$\geq 3 \times \text{ULN}$	3 (<1)	1 (<1)	8 (<1)
Alkaline phosphatase	$\geq 2 \times \text{ULN}$	0	0	5 (<1)
GGT	$\geq 3 \times \text{ULN}$	1 (<1)	0	6 (<1)
Total bilirubin	$\geq 34.2 \mu\text{mol/L}$	0	0	1 (<1)

SOURCE: Summaries 5.5.1 and 5.5.3.

M=male; F=female; ULN=upper limit of normal range; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transpeptidase.

Reviewer Comment(s):

As stated in Section 1.21.2, Drop-Outs and Other Serious\ Significant Adverse Events\Possible Reye's Syndrome and Other Cases Involving the Liver, several additional cases were identified which apparently are not part of Sponsor's Listing 4.1.3 (Clinical Significant Abnormal Values for Selected Chemistry Laboratory Parameters) and Listing 4.1.1(Clinical

Significant Abnormal Values for Selected Chemistry Laboratory Parameters for Phase 3 Double-Blind Studies). The pertinent section is again noted below.

"Review of the discharge summaries for subjects who withdrew from the trial for serious or non-serious reasons, identified five (5) subjects (5/101: 5 %) having abnormal liver function tests, of these, in only three (3) were the liver adverse event term listed as the basis for leaving the trial.

These cases are identified in the table below which were put together from the vignettes submitted by the sponsor. The values identified in four (4) of the vignettes were clinically significant showing ALT's which were 17.2 times, the upper limit of normal (ULN) and AST's up to 10 times ULN. Review of Sponsor's Listing 4.1.3 (Clinical Significant Abnormal Values for Selected Chemistry Laboratory Parameters for All Studies of Randomized Patients) and Listing 4.1.1 (Clinical Significant Abnormal Values for Selected Chemistry Laboratory Parameters for Phase 3 Double-Blind Studies, Randomized Patients) identified subjects who had liver function tests that were 3 times the ULN. Listing 4.1.3 identifies 4 subjects with SGOT elevations (128-453 U/L; 0-42 U/L: Normal; one subject with 10.7 times ULN), 10 with SGPT elevations (65-517 U/L; 5-20 U/L: Normal; one subject with 26 times ULN), 5 with GGT elevations (62-282 U/L; 3-22 U/L: Normal; one subject with 13 times ULN) and 5 with total bilirubin elevations (2-3.2 mg/dl; 0.1-1.2 mg/dl: Normal; one subject with 13 times ULN). None of the subjects identified in these vignettes could be found by this reviewer in the above referenced listings which have been attached in the Appendix of this report. All subjects in Listing 4.1.3 were on modafinil and none were on placebo. Listing 4.1.1 identifies two (2) subjects on placebo, not identified in Listing 4.1.3, who had isolated SGPT elevations (131 and 160 U/L; one subject with 8 times ULN)."

The sponsor should provide a vignette for all cases of LFT elevations, and if possible, copies of all ancillary studies done on any of these subjects. The sponsor should reconcile the Listings with the vignettes and make sure that that vignettes with subjects meeting the sponsors criteria for significance should be entered to those listings. Dr. John Senior is presently reviewing this case and the issue of potential liver toxicity associated with modafinil.

Hematology²⁶: In initial studies conducted with modafinil in children and adolescents with ADHD, transient decreases were seen in WBC counts and ANC. A similar trend was not seen in

26 2.7.4 Summary of Clinical Safety, 4-Month Safety Update; 3.2 Hematology: pgs. 47-53.

studies with adult patients. In the Phase 3 double- blind, placebo-controlled studies, the mean change from baseline to endpoint in WBC count was $- 0.9 \times 10^9/ L$ for the modafinil treatment group and $- 0.1 \times 10^9/ L$ for the placebo treatment group. The mean change in ANCs was $- 0.4 \times 10^9/ L$ for the modafinil treatment group and $- 0.1 \times 10^9/ L$ for the placebo treatment group. For all studies combined (all modafinil), mean changes from baseline to endpoint in WBC count and ANCs were $- 0.8 \times 10^9/ L$ and $- 0.4 \times 10^9/ L$, respectively. The sponsor states that despite the decreases observed, the mean values for WBC count and ANCs remained well within the normal range. There were no other trends in mean changes from baseline to endpoint in hematology parameters (Sponsors Table 26 in the Appendix).

Changes in WBC counts and ANCs in all Phase 3 studies (including the open- label extension study) are shown by time interval in Table 27. Mean decreases in WBC count appeared to plateau at 1 to 3 months of modafinil treatment. Progressive mean decreases in ANCs were observed through 6 months of treatment.

Table 27: Mean Changes From Baseline in White Blood Cell Count and Absolute Neutrophil Count by Time Interval in All Phase 3 Studies

Timepoint	All modafinil (N=626)					
	White blood cell count ($\times 10^9/L$)			Absolute neutrophil count ($\times 10^9/L$)		
	n	Mean (SD)	Min, max	n	Mean (SD)	Min, max
Baseline	619	7.4 (2.05)	3.2, 18.6	619	4.0 (1.60)	1.4, 12.2
Mean change from baseline to:						
≤2 weeks	548	-0.5 (2.09)	-8.0, 13.5	548	-0.2 (1.85)	-7.5, 12.2
≤1 month	610	-0.8 (2.06)	-7.9, 13.5	610	-0.4 (1.77)	-7.5, 11.5
≤3 months	613	-1.0 (2.04)	-10.3, 7.2	613	-0.5 (1.72)	-8.5, 6.8
≤6 months	613	-1.1 (1.94)	-11.7, 7.1	613	-0.6 (1.63)	-9.1, 6.6
≤9 months	613	-1.0 (1.97)	-10.6, 7.1	613	-0.5 (1.64)	-7.3, 6.6
≤12 months	613	-0.9 (2.05)	-12.2, 8.1	613	-0.4 (1.73)	-9.0, 8.0

SOURCE: Summaries 9.1.2 and 9.2.2.

Min=minimum; max=maximum; SD=standard deviation.

The sponsor states that in the Phase 3 double-blind studies, there were no marked differences between the modafinil and placebo treatment groups in the incidence of clinically significantly abnormal hematology values (Table 29). In particular, clinically significant low ANC values ($\leq 1 \times 10^9/ L$) were seen for 7 (2%) patients in the modafinil treatment group and for 5 (2%) patients in the placebo treatment group, while clinically significant low WBC values ($\leq 3 \times 10^9/ L$) were seen for 8 (2%) modafinil- treated patients and 3 (1%) placebo-

treated subjects. In all studies combined, clinically significant low ANC values were seen for 31 (3%) patients and clinically significant low WBC values were seen for 40 (4%) of the subjects.

**Table 29: Clinically Significant Hematology Values by Treatment Group
 Phase 3 Double-Blind, Placebo-Controlled Studies, and
 All Studies Combined**

Hematology Variable	Criteria	Number (%) of patients		
		Phase 3 double-blind studies		All studies combined
		Modafinil (N=420)	Placebo (N=213)	Modafinil (N=933)
White blood cell count	$\leq 3.0 \times 10^9/L$	8 (2)	3 (1)	40 (4)
	$\geq 20 \times 10^9/L$	0	1 (<1)	1 (<1)
Hemoglobin	M: ≤ 115 g/L; F: ≤ 95 g/L	0	0	2 (<1)
ANC	$\leq 1.0 \times 10^9/L$	7 (2)	5 (2)	31 (3)
Eosinophils	$\geq 10.0\%$	27 (6)	10 (5)	101 (10)
Platelets	$\leq 75 \times 10^9/L$	2 (<1)	1 (<1)	4 (<1)
	$\geq 700 \times 10^9/L$	0	0	2 (<1)

SOURCE: Summaries 5.6.1 and 5.6.3.
 M=male; F=female; ANC=absolute neutrophil count.

Reviewer Comment(s):

The clinical significance of the decreases in white blood cells (WBC's) and neutrophils (ANC) are uncertain and of unclear significance. Chapter 27 (Hematological Disorders) in the Current Pediatric Diagnosis & Treatment²⁷ defines neutropenia as "an absolute neutrophil (granulocyte) count of less than 1500/uL in childhood or below 1000/uL between ages 1 week and 2 years." This value is higher than the value defining clinical significance used by the sponsor of Absolute neutrophil counts (ANC) of $\leq 1 \times 10^9$. This should be corrected. The same article states that:

"The most common causes of neutropenia are viral infection or drugs resulting in decreased production in the marrow or increased destruction or both. Severe bacterial infections may be associated with neutropenia.

A. SYMPTOMS AND SIGNS

Acute severe bacterial or fungal infection is the most significant complication of neutropenia. Although the risk is increased when the absolute neutrophil count is less than 500/uL, the actual susceptibility is variable and depends on the cause of neutropenia, marrow reserves, and other factors. The most common types of infection include septicemia, cellulitis, skin abscesses, pneumonia, and perirectal abscesses. Sinusitis,

27 Current Pediatric Diagnosis & Treatment-17th Ed. (2005): Chapter 27. Hematologic Disorders, Section on Disorders of Leukocytes- Ambruso DR, Hays T, Lane PA and Nuss R.

aphthous ulcers, gingivitis, and periodontal disease also cause significant problems for these patients. In addition to local signs and symptoms, patients may have chills, fever, and malaise.

B. LABORATORY FINDINGS

In the evaluation of neutropenia (eg, persistent, intermittent, cyclic), careful attention should be paid to the duration and pattern of neutropenia, the types of infections and their frequency, and phenotypic abnormalities on physical examination. A careful family history and blood counts from the parents are useful. If an acquired cause, such as viral infection or drug, is not obvious and no other primary disease is present, white blood cell counts, white cell differential, and platelet and reticulocytes counts should be completed once or twice weekly for 4- 6 weeks to determine the possibility of cyclic neutropenia."

The common occurrence of infections in this age group makes it hard to determine relatedness to changes in WBC and ANC, especially if it is cyclical. The sponsor needs to identify any subjects who had infections during their treatment and correlate changes in these laboratory parameters with the presence or absence of infection and infection type. Many vignettes for subjects who left the study indicate infections, but in certain cases there is no laboratory or ancillary data in the vignette to determine clinical significance and, or, relatedness. For example, two (2) subjects, both on drugs in Study 311 have peptic ulcer disease (No. 42309 and 19012), one of which is positive for *Helicobacter pylori*. In addition one (No. 42309) had fever, nausea and rash. Similarly, twelve (12) subjects on various doses of modafinil developed rashes (Section 1.21.2 Dropouts and Other Serious\Significant Adverse Events), one of which was an erythema multiforme\Stevens Johnson and one subject in a related study of modafinil developed a Reye's like illness. Subject 12001 was reported to have paresthesias progressing from the upper to the lower extremities over 2 days in the context of nausea, headache, anorexia and abdominal pain. This could be nothing or this could be seen with a Gullian Barre like illness, polyneuritis, or encephalitis. Hence, it is essential to know the relatedness to these cases with vital signs, hematological and chemistry parameters.

7.1.5 Vital Signs

Vital Signs Including Body Weight²⁸: The sponsor states that "In the Phase 3 double-blind, placebo-controlled studies, there were no differences between the modafinil and placebo treatment groups with respect to changes in vital signs, including pulse, sitting systolic and diastolic blood pressure, and body temperature.

Patients in the modafinil treatment group had a mean decrease (0.7 kg) in body weight from baseline to endpoint, while patients in the placebo treatment group had a mean increase (1.0 kg) in body weight. For all studies combined, a mean increase (1.0 kg) was seen in body weight from baseline to endpoint. Values at baseline and endpoint and the corresponding changes from baseline for vital sign measurements including body weight are summarized by treatment group in Summaries 6.1.1 (Phase 3 double-blind studies), 6.1.2 (all Phase 3 studies), and 6.1.3 (all studies combined)." These listings have not been included in the Appendix of this report. The reader is referred to pages 761-767 of the above referenced report for the listings. Sponsors Table 31 entitled Vital Signs and Changes from Baseline to Endpoint by Treatment Group is included in the Appendix. Summary Table 6.1 indicates mean endpoint changes for the following:

Pulse: 4.5 bpm (< 255 mg), 2.1 bpm (340 mg), 4.5 bpm (< 255 mg), 0.5 bpm (425 mg), 1.5 bpm (all modafinil) compared to 1.1 bpm (placebo).

Sitting Systolic BP (mmHg): -1.6 (< 255 mg), -1.9 (340 mg), -0.8 (425 mg), -1.2 (all modafinil) compared to -0.9 (placebo).

Sitting Diastolic BP (mmHg): -0.6 (< 255 mg), 0.8 (340 mg), -1.1(425 mg), -0.6 (all modafinil) compared to -0.3 (placebo).

Height (cm): 0.7 (< 255 mg), 1.2 (340 mg), 0.8(425 mg), 0.9 (all modafinil) compared to 0.9 (placebo).

Weight (kg): -0.3 (< 255 mg), -0.5 (340 mg), -0.8(425 mg), -0.7 (all modafinil) compared to 1.0 placebo)

Body Temperature [C]: 0 (< 255 mg), 0.2(340 mg), 0(425 mg), 0.1 (all modafinil) compared to -0 placebo) (?)

28 2.7.4 Summary of Clinical Safety, 4-Month Safety Update; 4. Vital Signs, Physical Findings, and Other Observations Related to Safety, pgs. 54-60.

Clinically Significant Abnormalities in Vital Signs, Body

Weight: In the Phase 3 double-blind studies, *clinically significant decreases* ($\geq 7\%$) in body weight were observed in 36 (9%) subjects on modafinil and 3 (1%) subjects on placebo (Table 32, below). For all studies combined (all modafinil), *clinically significant increases* in body weights were observed in 199 (21%) subjects and decreases in body weight were observed in 103 (11%) subjects.

Table 32: Clinically Significant Abnormal Vital Signs Measurements by Treatment Group in the Phase 3 Double-Blind, Placebo-Controlled Studies, and All Studies Combined

Variable	Criteria	Number (%) of patients		
		Phase 3 double-blind, placebo-controlled studies		All studies
		Modafinil (N=420)	Placebo (N=213)	Modafinil (N=933)
Pulse	≥ 120 bpm and increase ≥ 15 bpm	6 (1)	2 (<1)	28 (3)
	≤ 50 bpm and decrease ≥ 15 bpm	1 (<1)	0	2 (<1)
Sitting systolic BP	≥ 130 mm HG and increase ≥ 20 mm Hg	9 (2)	1 (<1)	29 (3)
	≤ 80 mm HG and decrease ≥ 20 mm Hg	5 (1)	2 (<1)	18 (2)
Sitting diastolic BP	≥ 85 mm HG and increase ≥ 15 mm Hg	5 (1)	1 (<1)	29 (3)
	≤ 50 mm HG and decrease ≥ 15 mm Hg	19 (5)	9 (4)	86 (9)
Weight	Increase $\geq 7\%$	9 (2)	29 (14)	199 (21)
	Decrease $\geq 7\%$	36 (9)	3 (1)	103 (11)
Temperature	≥ 38.3 and increase $\geq 1.1^\circ\text{C}$	2 (<1)	1 (<1)	8 (<1)

SOURCE: Summaries 6.2.1 and 6.2.3.

bpm=beats per minute; BP=blood pressure.

Following up to 12 months of treatment with modafinil in the open-label extension study (study 312), *clinically significant increases in body weight were observed in 32% of subjects*, and *clinically significant decreases in body weight were observed in 11% of subjects*. There were mean decreases from baseline in body weight at week 2, month 1, month 2, and month 3 of open-label treatment. Thereafter, mean increases in body weight were observed through month 12, and the mean change from baseline to the last visit included in this safety update was a mean increase of 1.6 kg. (Sponsors Figure 1 in Appendix, Mean Changes from Baseline in Body Weight during Double Blind and Open Label Periods)

The trend for overall increases in body weight with continued exposure to modafinil was observed even among modafinil-treated subjects who had clinically significant changes from baseline (increases or decreases) in body weight during the open-label study.

Reviewer Comment(s):

The increases in body weight of $\geq 7\%$ and decreases of body weight observed in 32% and 11% of subjects is concerning. The sponsor needs to provide the completed year long, open label data set and correlate changes in weight with changes in cholesterol and other vital signs. The long term significance is unclear. One might just catch up and stabilize after an initial weight loss, but, similarly one might continue to gain weight which might predispose some of these children who use this drug over years to metabolic syndrome and potentially have an impact on longevity.

The summary did not contain an overview of vital signs testing in the development program.

7.1.5.1.1 Marked outliers and dropouts for vital sign abnormalities

No discussion could be identified in 2.7.4 Summary of Clinical Safety, 4-Month Safety Update which constituted the sponsor's integrated summary of safety.

7.1.6 Electrocardiograms (ECGs)²⁹

No overview discussion was present of ECG testing in the development program, including brief review of preclinical results. It is unclear from the information whether the ECG's were interpreted by a pediatric cardiologist. Differences between findings between SE-008 which suggested a mild trend in intervals pediatric populations.

The sponsor states that in "the Phase 3 double-blind, placebo-controlled studies, there were no clinically meaningful differences between the modafinil treatment group and the placebo treatment group with respect to ECG interval durations and changes from baseline to endpoint (Sponsors Table 33 in Appendix). The distribution of maximum changes from baseline and maximum values on treatment in corrected QT interval were similar for modafinil-treated patients and placebo-

²⁹ 2.7.4 Summary of Clinical Safety, 4-Month Safety Update; 4.2 Electrocardiography Results, pgs. 58-60.

treated patients in the Phase 3 double-blind studies regardless of the correction formula used (i.e., Bazett, Fridericia, or Neuro Pharm) (Sponsors Table 34 in Appendix). On the basis of QTc interval Fridericia, there were no modafinil-treated patients with increases from baseline of more than 60 msec and no individual maximum values greater than 450 msec."

Newly Diagnosed Electrocardiogram Abnormalities: The sponsor states that in "the Phase 3 double-blind, placebo- controlled studies, newly diagnosed abnormal ECG findings during the study were reported for 26 (7%) patients in the modafinil treatment group and 10 (5%) patients in the placebo treatment group (Table 35, below). Overall, there is no difference in the percent of patients with newly diagnosed ECG abnormalities between the Phase 3 double- blind studies and all studies. Of the 45 (out of 533; 8 %) patients with newly diagnosed ECG abnormalities in study 312, only 4 of the abnormalities (reported for 1 patient each) were considered clinically significant by the investigator and reported as adverse events (tachycardia, ECG abnormality, bradycardia, and first degree AV block)."

Table 35: Number (%) of Patients With Newly Diagnosed Electrocardiogram Abnormalities by Treatment Group in the Phase 3 Double-Blind, Placebo-Controlled Studies and All Studies Combined

Variable, n (%)	Phase 3 double-blind, placebo controlled studies		All studies
	Modafinil (N=420)	Placebo (N=213)	Modafinil (N=933)
Patients with postbaseline ECGs	399 (100)	202 (100)	867 (100)
Newly diagnosed abnormalities	26 (7)	10 (5)	95 (11)

SOURCE: Summaries 7.2.1 and 7.2.3.

ECG=Electrocardiogram

Reviewer Comment(s): Despite the fact that no group differences are detectable the sponsor should provide a listing of all subjects for each group, including the subject identification number, date of ECG, relation to dosing, ECG finding, so that a meaningful comparison can be made. Similarly, for the 45 subjects with newly diagnosed ECG abnormalities in study 312, the sponsor should provide the same, and the basis for the investigator's determination of clinical significance. Clinical and vital sign correlations should be made. All ECG's should have been or should be reviewed by a pediatric cardiologist.

7.1.6.1.1 Analyses focused on outliers or shifts from normal to abnormal

No such discussion could be identified in 2.7.4 Summary of Clinical Safety, 4-Month Safety Update which constituted the sponsor's integrated summary of safety.

7.1.6.1.2 Marked outliers and dropouts for ECG abnormalities

Group, but not individual differences, could be identified in 2.7.4 Summary of Clinical Safety, 4-Month Safety Update which constituted the sponsor's integrated summary of safety.

7.1.7 Adverse Events by Subgroups³⁰

The sponsor presented adverse events occurring in $\geq 5\%$ of subjects within a subgroup in the Phase 3 double-blind, placebo-controlled studies.

Gender: *"For the subgroups by gender, the overall incidence of adverse events was higher for girls receiving modafinil (83%) than for boys receiving modafinil (76%). In particular, the incidences of headache, anorexia, and insomnia among modafinil-treated girls (23%, 21%, and 31%, respectively) were higher than those observed for modafinil-treated boys (18%, 14%, and 26%, respectively). Among girls, the difference between the modafinil and placebo treatment groups in the incidence of some adverse events, including headache, abdominal pain, fever, pain, anorexia, and rash, was more marked than among boys. However, some of these differences may be due to the smaller sample size for girls (Sponsor's Table 36 Appendix)."*

Race: *"There were no marked differences in overall incidence of adverse events between white patients who received modafinil (79%) and patients of other races who received modafinil (77%), or for the incidence of specific adverse events (Sponsor's Table 37 Appendix)."*

Age: *"For the subgroups by age (Sponsor's Table 38 Appendix), the overall incidence of adverse events was similar for modafinil-treated patients <12 years of age (80%) and those ≥ 12 years of age (75%). Among modafinil-treated patients, the incidence of headache was higher for patients ≥ 12 years of age (25%) than for those <12 years of age (17%), while the incidences of anorexia and insomnia were higher among the younger patients receiving modafinil (18% and 31%, respectively) than among older patients (11% and 20%, respectively)."*

³⁰ 2.7.4 Summary of Clinical Safety, 4-Month Safety Update; 5. Safety in Special Groups and Situations, pgs. 61-66.

Weight: "The overall incidence of adverse events was similar for modafinil-treated patients weighing < 30 kg (80%) and those weighing ≥ 30 kg (77%) (Sponsor's Table 39 Appendix). *The incidence of headache was higher for modafinil-treated patients weighing ≥ 30 kg (21%) than for those weighing < 30 kg (16%), while the incidences of anorexia and insomnia were lower for patients weighing ≥ 30 kg (15% and 24%, respectively) than for those weighing < 30 kg (19% and 34%, respectively).*"

7.1.7.1.1 Analyses focused on measures of central tendency

No such analyses could be located in the Safety Report.

7.1.8 Special Safety Studies

No such studies could be located in the Safety Report except measuring for withdrawal (see below, 7.1.9).

7.1.9 Withdrawal Phenomena and/or Abuse Potential³¹

The sponsor states:

"The effects of withdrawal of modafinil treatment were examined in study 310 using the Subject's Treatment Emergent Symptom Scale (STESS) scores. After 7 weeks of double-blind treatment in this study, patients entered a 2-week (weeks 8 and 9) randomized withdrawal period, during which modafinil-treated patients received either modafinil or placebo and placebo-treated patients continued taking placebo according to the original randomization scheme.

Comparable reductions in STESS scores were observed for all 3 treatment groups during the 2-week withdrawal period, indicating that abruptly withdrawing from modafinil treatment did not have an effect on physical and emotional health (Sponsor's Table 41 in Appendix)."

Drug Abuse: "Modafinil (PROVIGIL) is listed in Schedule IV of the Controlled Substances Act."

7.1.10 Human Reproduction and Pregnancy Data

The sponsor states³²:

31 2.7.4 Summary of Clinical Safety, 4-Month Safety Update; 5.6 Drug Abuse; 5.7 Withdrawal and Rebound; pgs. 68-69.

32 Summary of Clinical Safety, 4-Month Safety Update; 5.4 Use in Pregnancy and Lactation; pg. 68.

"Pregnant or lactating females and females of child-bearing potential were excluded from the pediatric ADHD studies. The use of modafinil during pregnancy has not been studied and there were no pregnancies reported during these studies."

In the post-marketing experience the sponsor reports³³ that 90 (3 %) of 2578 ADR were for pediatric patients though 17 years and 506 (20 %) were for patients for who there were insufficient data to determine age. Included among these cases were 5 infant reports, of which 4 were congenital anomalies and 1 was a premature birth. They report a worldwide postmarketing usage from 98/30/94-02/28/05 at more than 185 million treatment days. In addition, there were 4 cases of abortions, 2 premature labors and 1 pre-eclampsia. Portions of tables submitted by the sponsor are included in the Appendix of this report.

Reviewer Comment(s):

Labeling should reflect this information about post-marketing events.

7.1.11 Assessment of Effect on Growth³⁴

The sponsor states:

"In order to evaluate possible effects of modafinil on normal development in children receiving treatment, height and weight Z scores and percentile scores (adjusted for age and sex) were determined *in the open-label extension study (study 312)*. Changes from baseline to endpoint in height and weight Z- scores (all modafinil) were - 0.0 and - 0.2, respectively. Changes from baseline to endpoint in height and weight percentile scores were - 0.3 and - 5.4, respectively. These results suggest a small decrease in body weight among patients receiving modafinil relative to the normal pediatric population. Actual values and changes from baseline to endpoint in height and weight Z- scores and height and weight percentile scores in study 312 are presented in Summaries 9.9 and 9.10, respectively."

Reviewer Comment (s):

Z scores and percentile scores should be calculated, when available, from baseline at study entry into Studies 309, 311

33 Summary of Clinical Safety, 4-Month Safety Update; 6 Postmarketing Data; pgs. 70, 173-174, 199-200.

34 2.7.4 Summary of Clinical Safety , 4-Month Safety Update 5.1.2 Effect on Normal Development in Children; pgs. 67; 832, 834.

and 310 and last available endpoint in Study 312. Since, 279 (52 %) of the subjects have already discontinued from study 312 for various reasons at the 4 month submission, and since, 48 subject (9 %) have completed the study at the same time period, these measurements have limited value. Normative data used should be defined.

7.1.12 Overdose Experience³⁵

The sponsor states:

"A total of 151 dosages of modafinil at 1000 mg/ day (5 times the current adult maximum recommended daily dose of 200 mg) or more have been recorded for 32 individuals. Two patients participating in foreign studies in depression took doses of 4500 and 4000 mg of modafinil intentionally. In both cases, the adverse events observed were limited, expected, and not life threatening, and the patients recovered fully by the following day. In neither of these cases nor in other instances of dosages of more than 1000 mg/ day, including up to 21 consecutive days of administration of modafinil at 1200 mg/ day, were any unexpected effects of specific organ toxicities observed. Other observed high dose effects include anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time.

In the Phase 3 ADHD studies, 38 patients received > 425 mg of modafinil (doses of 510 to 850 mg/ day of modafinil), either intentionally or unintentionally. The average age of these patients was 10.7 years, the average weight was 46.6 kg, the average duration at the higher dose was 44 days, and like the remainder of the study population, were predominantly white males. Of the 15 adverse events that were reported during the period of time at the higher dose, almost all of them were cold/ flu symptom- related. Only 1 patient reported insomnia as a result of an accidental overdose (i.e., 850 mg)."

7.1.13 Postmarketing Experience³⁶

Cephalon's "rough estimates" of postmarketing exposure to modafinil (based on worldwide sales data) from the period of 09/30/94-02/18/05 is 185 million patient- treatment days and an average daily dose of 242 mg in the US and 267 mg in Ex US

35 2.7.4 Summary of Clinical Safety, 4-Month Safety Update; 5.5. Overdose, pg. 68.

36 2.7.4 Summary of Clinical Safety , 4-Month Safety Update 6.1; Postmarketing Data; pgs. 70-75.

territories. Previous exposure was based upon an average daily dose of 300 mg and 250 mg respectively. This distinction is not clear.

The sponsor states:

"Of 2578 ADR case reports received, 1982 (77%) were for adults, 90 (3%) were for pediatric patients through 17 years of age, and 506 (20%) were for patients for whom there were insufficient data to determine age. These 2578 reports included a total of 5308 ADRs. Of the 2578 reports, 239 were serious and included a total of 500 serious ADRs. There were 5 case reports with age reported as zero (0). These are fetal exposure reports (mother taking modafinil during pregnancy) and are included in the category "through 17 years of age" as noted above. Of these 5 infant reports, 4 were congenital anomalies and 1 was a premature birth (Sponsor's Table Included in Appendix).

Of the 1982 case reports received for adults, 189 (10%) reports included serious ADRs. For adults, the most commonly reported serious ADRs (at least 8 reports) were drug interaction (14), psychotic disorder (10) and myocardial infarction (8). The body systems (SOCs) associated with the greatest number of serious ADRs were the psychiatric (18%), nervous (16%), general (10%), cardiac (7%), and investigations (7%). The SOCs associated with the greatest number of non-serious ADRs were the nervous (19%), psychiatric (17%), general (14%), gastrointestinal (13%), and investigations (7%). The most commonly reported non-serious ADRs (at least 25 reports) are displayed in Table 42" (Sponsor's Table Included in Appendix).

"A total of 10 reports of leukopenia or neutropenia associated with modafinil use were identified in all postmarketing reports and are summarized in Table 43" (Sponsor's Table Included in Appendix). The sponsor states that of "of the 7 ADR reports included in this analysis, none involved a pediatric or adolescent patient. The mean age of the 7 patients was 43 years (range=29-51 years)."

"Of the 90 case reports received for pediatric patients through 17 years of age, 15 (17%) included serious ADRs. These 90 case reports included a total of 183 ADRs of which 36 (20%) were serious. For this population, the most commonly reported serious ADRs (at least 2 reports) were mania, hallucination, suicide attempt, premature baby, and intentional overdose (2 each). The most commonly reported non-serious ADRs (at least 4 reports) were headache and insomnia (8 each), anorexia (5), drug interaction and irritability (4 each). The SOCs associated with the greatest number of serious ADRs were the psychiatric (31%), congenital and familial (19%), pregnancy and injury (11% each), and vascular (6%). The SOCs associated with the greatest number of nonserious ADRs were the psychiatric (20%), nervous (15%), gastrointestinal (14%), general (13%) and skin (9%)."

Cephalon states that they identified 3 events that warrant inclusion in the current modafinil labeling. "These are agranulocytosis (2 spontaneous reports with apparently different mechanisms) and symptoms of mania and/or psychosis. Inclusion in the labeling was based on clinical importance of the events and is not an indication of drug-relatedness."

Reviewer Comment(s):

It is unclear to this reviewer what the status of the safety reporting was worldwide from 1994-1998, since Provigil was not approved in the United States until 1998. Sales estimates may not mean drug use. Total exposure in the pediatric age groups is not separated from the worldwide exposures. Hence, the number of ADR's may be underreported and the use may be over-estimated, inadvertently minimizing any possible signal.

For this population, *the most commonly reported serious ADRs (at least 2 reports) were mania, hallucination, suicide attempt, premature baby, and intentional overdose (2 each).* The most commonly reported non-serious ADRs (at least 4 reports) were headache and insomnia (8 each), anorexia (5), drug interaction and irritability (4 each). The SOCs associated with the greatest number of serious ADRs were the psychiatric (31%), congenital and familial (19%), pregnancy and injury (11% each), and vascular (6%). *The SOCs associated with the greatest number of nonserious ADRs were the psychiatric (20%), nervous (15%), gastrointestinal (14%), general (13%) and skin (9%).*

In the pediatric population, the most commonly reported serious ADR's were *mania, hallucination, suicide attempt, premature baby, and intentional overdose. This signal was present in the controlled trials in adverse events leading to discontinuation. In those trials, suicidal ideation (6: 12 %; one of which was a possible attempt versus a gesture), agitation (5: 10 %) depression (2: 4 %) psychosis (3: 6 %), another with possible psychosis (1: moderate change in mental status, not specified); and phobias (3: 6 %) were seen. In the controlled trials suicide ideation and psychosis occurred at a younger mean age (8 years) than those on placebo (10 years).*

"In the ADR's, headache, insomnia, anorexia and *drug interaction* were the most commonly reported non-serious ADR's in children. The SOCs associated with the greatest number of nonserious ADRs were the *psychiatric (20%), nervous (15%), gastrointestinal (14%), general (13%) and skin (9%).*" In the controlled trials

anorexia (modafinil: 16 %; placebo: 3 %), insomnia (modafinil: 27 %; placebo: 4 %) and headache (modafinil: 20 %; placebo: 13 %) were common. Review of the discharge summaries for subjects who withdrew from the controlled trial for serious or non-serious reasons, indicated that twelve (12) subjects (12/101: 12 %) on various doses of modafinil developed rashes. One was a definite case of erythema multiforme/Stevens Johnson Syndrome, and 1-2 other cases were suggestive. Hence, problems involving the skin were present more frequently in the ADR and the trial data.

A concern raised by this reviewer in earlier comments was that the presence of a significant amount of insomnia, headaches, or, other psychiatric disorders will almost certainly result in off-label and labeled use of many sleep, analgesic and psychiatric medicines which will probably result in increased risk of adverse events (e.g. increased risk of skin, liver, or, psychiatric problems). The presence of increased drug interaction in the ADR experience only leads credo to this view.

It is interesting that increased *gastrointestinal* (14%) were present in the ADR's given that 2 *peptic ulcers* were identified in the controlled trials. A gastrointestinal consult should be considered to address this issue.

Further review of the postmarketing reports of leukopenia and neutropenia should be undertaken after the corrections identified in Reviewer Comment(s), Section 7.1.4 Laboratory Findings/Hematology of this report are completed.

7.1.14 Adequacy of Overall Clinical Experience

A complete year-long data set for Study 312 is needed to help adequately characterize the safety profile of modafinil in children and adolescents.

7.1.15 Adequacy of Special Animal and/or In Vitro Testing

The reader is referred to Pharmacology's Review as to the adequacy of the testing submitted in support of this submission.

7.1.16 Adequacy of Routine Clinical Testing

No information is provided about the relation between ECG and dosing and clinical and vital sign correlations to ECG changes (if any) to make meaningful comparisons. Relationships between adverse event data, vital signs and laboratory data is not provided preventing meaningful correlations.

7.1.17 Adequacy of Metabolic, Clearance, and Interaction Workup

The reader is referred to Pharmacology's Review as to the adequacy of this information.

Reviewer Comment(s):

Given the high amount of the adverse events of insomnia and headaches, a determination needs to be made as to the adequacy of testing for possible drugs which may be used and the potential interactions which may result.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In the proposed packing labeling, under Dosage and Administration, Cephalon proposes the following:

“DOSAGE and ADMINISTRATION

Initial Treatment

ATTENACE should be taken as a single dose, in the morning, with or without food. Dosage should be individualized according to the needs and responses of the patient. In clinical trials, treatment was initiated at 85 mg /day. The daily dosage was increased by 85 mg increments every 2 to 7 days until the optimum or target daily dose was achieved. Doses above 425 mg have not been systematically evaluated. (See **CLINICAL TRIALS**).

The following target daily doses of ATTENACE are recommended:

Patients less than 30 kg of body weight: 340 mg

Patients at least 30 kg of body weight: 425 mg

Maintenance/Extended Treatment

There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with ATTENACE. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use ATTENACE for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Dosage adjustment should be considered for concomitant medications that are substrates for CYP3A4, such as triazolam and cyclosporine (See **PRECAUTIONS, Drug Interactions**).

Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin (also via CYP2C9) or S-mephenytoin may have prolonged elimination upon coadministration with ATTENACE and may require dosage reduction and monitoring for toxicity.

In patients with severe hepatic impairment, the dose of ATTENACE should be reduced to one-half of that recommended for patients with normal hepatic function (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).”

The reader is referred to the Clinical Pharmacology/
Biopharmaceutics Review for further discussion of this issue.

8.2 Drug-Drug Interactions

The sponsor states³⁷:

“No drug interaction studies have been conducted with modafinil in the pediatric ADHD patient population. The following information relating to potential drug interactions is presented in the current prescribing information for modafinil (PROVIGIL) use in adults:

Drug-Drug Interactions: Because modafinil and modafinil sulfone are reversible inhibitors of the drug-metabolizing enzyme CYP2C19, co-

37 2.7.4 Summary of Clinical Safety, 4-Month Safety Update; 5.3 Drug Interactions, pgs. 67-68.

administration of modafinil with drugs such as diazepam, phenytoin and propranolol, which are largely eliminated via that pathway, may increase the circulating levels of those compounds. In addition, in individuals deficient in the enzyme CYP2D6 (ie, 7- 10% of the Caucasian population; similar or lower in other populations), the levels of CYP2D6 substrates such as tricyclic antidepressants and selective serotonin reuptake inhibitors, which have ancillary routes of elimination through CYP2C19, may be increased by co- administration of modafinil. Dose adjustments may be necessary for patients being treated with these and similar medications.

Coadministration of modafinil with other central nervous system active drugs such as methylphenidate and dextroamphetamine did not significantly alter the pharmacokinetics of either drug. Chronic administration of modafinil 400 mg was found to decrease the systemic exposure to two CYP3A4 substrates, ethinyl estradiol and triazolam, after oral administration suggesting that CYP3A4 had been induced. Chronic administration of modafinil can increase the elimination of substrates of CYP3A4. Dose adjustments may be necessary for patients being treated with these and similar medications.

An apparent concentration- related suppression of CYP2C9 activity was observed in human hepatocytes after exposure to modafinil in vitro suggesting that there is a potential for a metabolic interaction between modafinil and the substrates of this enzyme (e.g., S-warfarin, phenytoin). However, in an interaction study in healthy volunteers, chronic modafinil treatment did not show a significant effect on the pharmacokinetics of warfarin when compared to placebo."

8.3 Special Populations

In the proposed packing labeling, under Special Populations, Cephalon proposes the following:

"Special Populations

The effect of gender, age, and weight on modafinil pharmacokinetics in children and adolescents with ADHD were examined using a population pharmacokinetic approach.

Gender Effect: The pharmacokinetics of modafinil are not affected by gender.

Age Effect: The estimated $t_{1/2}$ for the youngest patients (aged 6 to 7 years) studied is approximately 7 hours, and the $t_{1/2}$ for the oldest patients (aged 16 to 17 years) is approximately 10 hours. The general trend in the data indicates that there is a shift that begins between 9 and 11 years of age towards an increase in $t_{1/2}$.

Weight Effect:

In children and adolescents, body weight has a significant effect on both clearance and volume of distribution of modafinil. Volume of distribution increases linearly with weight. Clearance also increases with increasing weight up to approximately 30 kg, after which clearance remains relatively constant with increasing weight.

Based on these data, a modafinil dose of 340 mg in children and adolescents weighing less than 30 kg and 425 mg in children and adolescents weighing 30 kg or more consistently results in similar systemic exposures, indicating that the use of weight as a surrogate for dose selection is appropriate (See **DOSAGE and ADMINISTRATION**).

Race Effect: Modafinil pharmacokinetics are similar between Caucasian and African American populations. However, there were a limited number of patients in other race groups in the clinical trials which makes it difficult to fully elucidate any potential effect in these subgroups (approximately 90% of patients were Caucasian and African American).

Renal Impairment: In adults, severe chronic renal failure (creatinine clearance up to 20 mL/min) did not significantly affect the pharmacokinetics of modafinil administered at 200 mg, but exposure to modafinil acid was increased 9-fold (See **PRECAUTIONS**). No renal impairment studies have been conducted in children or adolescents.

Hepatic Impairment: Because modafinil is exclusively metabolized in the liver, hepatic impairment is expected to have an impact on the pharmacokinetic profile of the compound. Adult patients with cirrhosis have a decreased ability to metabolize modafinil, compared with healthy subjects. The oral clearance of modafinil was decreased by approximately 60%, and the steady-state concentration doubled, compared with values in healthy subjects. These results indicate that the dosage of modafinil should be reduced in patients with severe hepatic impairment (See **PRECAUTIONS and DOSAGE AND ADMINISTRATION**). No hepatic impairment studies have been specifically conducted in children or adolescents.

Pharmacodynamics

Clinical trial data indicate that administration of 340 mg of modafinil in children and adolescents with body weights less than 30 kg and 425 mg of modafinil in children and adolescents with body weights greater than or equal to 30 kg, achieve a sustained systemic exposure (approximately 150 µg/mL) which correlates with a clinically significant effect. A less than optimal response is observed with inadequate systemic exposures. Over time, there were no observed trends towards a change in exposure or clinical effect.”

8.4 Advisory Committee Meeting

An Advisory Committee Meeting should be held to discuss the safety issues and its impact on whether modafinil should be approved for any indication in pediatrics, and, if so, under what circumstances, and what should be the correct labeling.

8.5 Literature Review

Among the issues identified in the filing meeting for this sNDA and which was submitted to Cephalon on 03/15/2005 was the adequacy of the literature review provided. This was based on Cephalon providing only a sheet entitled literature references which was electronically connected to the articles on the list (Sec. 5.4: Literature References). We stated:

“You have not provided an adequate literature search (methodology and results) since only references were listed. Please provide a full review and discussion of the world literature for modafinil targeted to the safety of the present indication of ADHD. Please warrant that this is a complete and detailed review of the world’s published literature and identify the cut-off date. The literature review should also include a complete review and discussion of the safety as it applies to any use of modafinil in any indication.”

Appendix B of the Summary of Clinical Safety 4 Month Safety³⁸ Update Report submitted by Cephalon on 04/19/2005 states the following:

1. That “a worldwide modafinil literature review, covering the period 1 January 1998 through 30 June 2002, was previously submitted in the approved efficacy supplement S-008 to NDA 20-717 (sNDA 20-717/S008, submitted 20 December 2002). A total of 139

³⁸ Summary of Clinical Safety 4 Month Safety, Appendix B, Literature Review (Data on Humans), pgs. 88-91.

international publications, including 131 on adults and 8 on children, were reviewed and provided in the abovementioned submission. The majority of these publications were relative to disorders of sleep and wakefulness... The publications on children included approximately 62 subjects who were exposed to modafinil at dosages ranging from 50 to 400 mg/day for up to 17 months. No deaths or serious adverse events were reported in children."

2. That "safety information from the worldwide literature on modafinil published between 1 January 2002 and 1 April 2005 was searched and that these publications are listed at the end of this section" (electronically connected to the article). The sponsor states that:

"The safety profile of modafinil reported in the literature relative to the disorder of ADHD evaluated in this application is similar to that previously reported for modafinil."

The sponsor further states "that all publications (regardless of publication date) on modafinil in Medline were searched for leukopenia and/or neutropenia. No publications were found relating to modafinil and leukopenia and/or neutropenia".

The sponsor concluded that "the literature reviews discussed above, represent a complete review of the worldwide published literature through 1 April 2005. No additional safety information beyond that which is presented in other sections of this application, or in the PROVIGIL product labeling, was revealed. The literature supports the conclusion that modafinil is well tolerated in healthy subjects and the patient populations studied".

Reviewer Comment(s):

It is unclear which articles the sponsor is referring. A discussion of the individual articles would have been helpful.

9 OVERALL ASSESSMENT

9.1 Conclusions

- Modafinil was shown to be clinically effective in the treatment of ADHD in children and adolescents based on the (ADHD-RS-IV) (School Version) [$p < 0.001$].

- A sulfone metabolite accumulates to a greater extent in subjects weighting less than 30 kg and it is uncertain when it reaches steady-state based on the studies performed (approximately 6 weeks ?) so we do not know the absolute accumulation of the metabolite in this age group. Age range of the 340 mg dose group tested was 5-10 years and the 425 mg dose group was 8-13 years. A disproportionate exposure to the sulfone metabolites of about 6 times occurred in children compared to adolescents and adults.
- PK/PD and clinical studies have shown that doses of around 340 or 425 mg are needed in order to achieve clinical response (efficacy). Hence, dose reduction will not be useful.
- Paralleling the disproportionate exposure in children is the observation from controlled clinical trials of very rare adverse events occurring in these younger age groups: Steven Johnson Syndrome (7 years) and other uncertain rashes (1-2/933 vs. 1 per million background) and Reye's-like syndromes (only 36 cases per year since 1987) are only occurring in subjects on modafinil. The mean age of subjects with rash was 8.5 years, did not occur in adolescents and was not observed with the adult experience. The case of Reyes-like syndrome occurred in a 6 year old. The relation to the drug is uncertain, but mean GGT elevations were higher in those receiving increasing exposures as to amount (e.g. 340 and 425 mg/day) and duration of modafinil (14 % on modafinil compared to 1 % on placebo showed increases in GGT over 6 months). Similarly, suicidal ideation and psychosis occurred at a mean age of 8 years (all psychiatric events in placebo; mean age: 10 years) in subjects leaving the trials because of adverse events. Suicidal ideation (6: 12 %; one of which was a possible attempt versus a gesture), agitation (5: 10 %), depression (2: 4 %) psychosis (3: 6 %), another with possible psychosis (1: moderate change in mental status, not specified); and phobias (3: 6 %) were only reported as reasons for discontinuation for subjects on drug.
- Anorexia (modafinil: 16 %; placebo: 3 %) and insomnia (modafinil: 27 %; placebo: 4 %) are more common than with most stimulants except for Adderall XR. Headache (modafinil: 20 %; placebo: 13 %) seems to be more common in modafinil subjects than others. A table comparing some of the MPH and amphetamine products, which are currently available (e.g. Concerta, Metadate, Ritalin LA, Focalin, Adderall XR), is indicated in

Table 1 in the Appendix. The risk of insomnia and headaches will most certainly result in various treatment strategies (e.g. stopping, restarting; using off label and labeled analgesics and sleep medications) perhaps resulting in increased dermatological sensitization, psychiatric, or, other adverse events.

- The post-marketing ADR's confirmed potential risks in this population (Section 7.1.13 Postmarketing Experience).

9.2 Recommendation on Regulatory Action

A non-approvable action is recommended.

The risks associated with the use of provigil are greater than the benefits and preclude the safe use of this drug in the intended population for ADHD, a non life-threatening disease and without showing clear, demonstrated advantages over existing stimulants.

If outstanding consults bears out the perceived risks, an Agency discussion should be undertaken to discuss the need to halt all clinical development programs currently underway with children (e.g. excessive sleepiness associated with narcolepsy) and to consider the need for recommending a stronger warning for Provigil (modafinil) as it related to the use of this drug in children.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

A Public Advisory Meeting may need to be considered to discuss the issues identified in this review as it relates to continuation of a pediatric development program for modafinil for other indications. Further internal discussion of this issue is recommended.

9.3.2 Required Phase 4 Commitments

- Further work should be undertaken to characterize the clinical significance of the disproportionate sulfone metabolite present in children, if it is ultimately decided by the Agency that the drug is approvable.

- Given the fact that the ADHD subjects who were studied were moderately to severely ill or greater (CGI-S \geq 4) and did not have learning disability (Screening score \geq 80 on the WIAT-II-A), the generalizability of findings from this group of subjects to other children with less severe ADHD (CGI-S < 4)with learning disorders is uncertain, and may need to be considered as a Phase IV commitment.

9.4 Labeling Review

If a decision is ultimately made by the Agency that modafinil will be approved for this indication, an addendum filing to this sNDA will be made.

9.5 Comments to Applicant

- At the 07/28/2004 meeting between FDA and Cephalon, Cephalon stated that the four-month safety update will include data from approximately 175 of these patients treated with modafinil for 12 months. This was not the case. Re-submit when the study is completed.
- Provide safety information about Adult ADHD (Study 205) so that safety comparison can be made between age groups.
- The acceptability of the proposed tradename (SPARLON) are under review.
- The ADHD subjects who were studied were moderately to severely ill or greater (CGI-S \geq 4) and did not have learning disability (Screening score \geq 80 on the WIAT-II-A). Discuss the generalizability of findings from this group of subjects to other children with less severe ADHD (CGI-S < 4)with learning disorders.
- The complete year-long data set for Study 312 is needed to help adequately characterize the safety profile of modafinil in children and adolescents.
- Given the disproportionate amount of the adverse events of insomnia and headaches, what management recommendations would you propose for consumers who develop these adverse events? What drug interactions do you anticipate? Provide vital signs

for all subjects who developed headaches. Provide the vital signs correlating with symptoms. Describe the headache type, prior history of headaches, duration of symptoms, and your experience as to the clinical management.

- Given the occurrence of a documented case of erythema multiforme/Stevens Johnson in your pediatric clinical program provide a complete clinical description of all types of rashes in your clinical program. Risks should be determined and compared between children, adolescents, placebo and the adult experience(s).
- Provide hospital records, discharge summary, all laboratory and other diagnostic tests for all subjects who were hospitalized in your pediatric and adolescent program. If you cannot obtain this information, demonstrate to the Agency that you have made due-diligence.

Inconsistencies were identified which should be resolved.

- The study report states that 11 subjects on modafinil withdrew because of adverse events. However, 12 vignettes (modafinil: 12) are submitted in the appendix of the 310 final study report. In addition, another, serious adverse event (Subject No: 34187) is submitted in the 4 month safety update. Hence, there were 13 (10.4 %) adverse events, of which 2 were serious.
- Reconciling number of rashes reported in the vignettes with number of rashes listed.
- Review of the vignettes for subjects who withdrew from the trial for serious or non-serious reasons, identified five (5) subjects (5/101: 5 %) having abnormal liver function tests, of these, in only three (3) were the liver adverse event term listed as the basis for leaving the trial. *The values identified in four (4) of the vignettes were clinically significant showing ALT's which were 17.2 times, the upper limit of normal (ULN) and AST's up to 10 times ULN.* Review of Sponsor's Listing 4.1.3 (Clinical Significant Abnormal Values for Selected Chemistry Laboratory Parameters for All Studies of Randomized Patients) and Listing 4.1.1 (Clinical Significant Abnormal Values for Selected Chemistry Laboratory Parameters for Phase 3 Double-Blind Studies, Randomized Patients) identified subjects who had liver function tests that were 3

times the ULN. Listing 4.1.3 identifies 4 subjects with SGOT elevations (128-453 U/L; 0-42 U/L: Normal; one subject with 10.7 times ULN), 10 with SGPT elevations (65-517 U/L; 5-20 U/L: Normal; one subject with 26 times ULN), 5 with GGT elevations (62-282 U/L; 3-22 U/L: Normal; one subject with 13 times ULN) and 5 with total bilirubin elevations (2-3.2 mg/dl; 0.1-1.2 mg/dl: Normal; one subject with 13 times ULN). None of the subjects identified in these vignettes could be found by this reviewer in the above referenced listings. All subjects in Listing 4.1.3 were on modafinil and none were on placebo. Listing 4.1.1 identifies two (2) subjects on placebo, not identified in Listing 4.1.3, who had isolated SGPT elevations (131 and 160 U/L; one subject with 8 times ULN). Explain and reconcile. The subjects were 2004, 6007, 34007, 56003 and 50910.

- Several psychiatric adverse events were not listed as the reason for discontinuation, and were incorrectly coded. Subject 1105 in Study 1105 was discontinued because of somnolence, but review of the adverse event indicates that the subject probably had irritability (nervousness) resulting in the off-label use of risperidone which in turn resulted in a seizure [based on prolonged non-responsiveness, presence of a Todd's paralysis (facial palsy) and incontinence]. Subject 410 in Study 206 had disorderly, aggressive behavior and experienced formication (bugs crawling over the skin) and by definition could not have had paresthesia (abnormal sensation of skin with no physical cause). Subject 14016 in Study 311 had bizarre behavior; putting rope around his neck was listed as discontinuing because of a personality disorder. Subject 411 in Study 206 was listed as discontinuing because of a rash, but the vignette indicates suicidal ideation. Make sure that the coding is accurate.

The following additional information should be provided.

- Further information is needed on the case of hyper-ammonemia [IND 59, 661 (080): C1538/3027/NA/MN/US014983]. The sponsor should show due diligence to obtain the hospital records, discharge summary, all laboratory and other diagnostic tests, as well as for 2004, 6007, 34007, 56003 and 50910.
- Provide vignettes for all cases of LFT elevations, and if possible, copies of all ancillary studies done on any of these subjects. The sponsor should reconcile the Listings with the

vignettes and make sure that that vignettes with subjects meeting the sponsors criteria for significance should be entered to those listings.

- Two subjects on modafinil (No. 42309 and 19012) developed peptic ulcer disease, one of which was positive for *Helicobacter pylori*. In addition one (No. 42309) had fever, nausea and rash. Describe the frequency of these adverse events in relation to background incidence. Is this more than is expected? A complete discussion is recommended.
- The clinical significance of the decreases in white blood cells (WBC's) and neutrophils (ANC) are uncertain and of unclear significance. Chapter (Hematological Disorders) in the Current Pediatric Diagnosis & Treatment³⁹ defines neutropenia as "an absolute neutrophil (granulocyte) count of less than 1500/uL in childhood or below 1000/uL between ages 1 week you used [(ANC) of $\leq 1 \times 10^9$]. Correct this.

The common occurrence of infections in this age group makes it hard to determine relatedness to changes in WBC and ANC, especially if it is cyclical. Identify any subjects who had infections during treatment and correlate changes in laboratory parameters with the presence or absence of infection and infection type.

Many vignettes for subjects who left the study indicate infections, but in certain cases there is no laboratory or ancillary data in the vignette to determine clinical significance and, or, relatedness. For example, two (2) subjects, both on drugs in Study 311 have peptic ulcer disease (No. 42309 and 19012), one of which is positive for *Helicobacter pylori*. In addition one (No. 42309) had fever, nausea and rash. Similarly, twelve (12) subjects on various doses of modafinil developed rashes (Section 1.21.2 Dropouts and Other Serious\Signicant Adverse Events), one of which was an erythema multiforme\Stevens Johnson and one subject in a related study of modafinil developed a Reye's like illness. Subject 12001 was reported to have paresthesias progressing from the upper to the lower extremities over 2 days in the context of nausea, headache, anorexia and abdominal pain. This

³⁹ Current Pediatric Diagnosis & Treatment-17th Ed. (2005): Chapter 27. Hematologic Disorders, Section on Disorders of Leukocytes- Ambruso DR, Hays T, Lane PA and Nuss R.

could be nothing or this could be seen with a Gullian Barre like illness, polyneuritis, or encephalitis. Hence, it is essential to know the relatedness to these cases with vital signs, hematological and chemistry parameters.

- Increases in body weight of $\geq 7\%$ and decreases of body weight observed in 32% and 11 % of subjects is concerning. Provide the completed year long, open label data set and correlate changes in weight with changes in cholesterol and other vital signs. Discuss potential long term significance. One might just catch up and stabilize after an initial weight loss, but, similarly one might continue to gain weight which might predispose some of these children who use this drug over years to metabolic syndrome and potentially have an impact on longevity.
- No overview of vital signs testing in the development program could be provided in the safety summary (ISS). Please identify, and if it is not present provide.
- No discussion could be identified in the safety summary (ISS) of marked outliers and dropouts for vital sign abnormalities. If none, state so. Otherwise, please provide.
- Provide information on ECG data in relation to dosing. Describe how and who interpreted the ECG's? Were all ECG's reviewed by a pediatric cardiologist? Of the, 45 subjects with newly diagnosed ECG abnormalities in study 312, identify these abnormalities and provide the basis for the investigator's determination of clinical significance. Clinical and vital sign correlations should be made. All ECG's should have been or should be reviewed by a pediatric cardiologist, if previously not done.
- Regarding Effects on Growth, Z scores and percentile scores should be calculated, when available, from baseline at study entry into Studies 309, 311 and 310 and last available endpoint in Study 312. Since, 279 (52 %) of the subjects have already discontinued from study 312 for various reasons at the 4 month submission, and since, 48 subject (9 %) have completed the study at the same time period, these measurements have limited value. Normative data used should be defined.

- Please discuss the disproportionate exposure of children to the sulfone metabolite and correlate this with all adverse event data by children and adolescents.

10 APPENDICES

10.1 Approximate Incidence Rates for Anorexia and Insomnia Reported with ADHD Stimulants (Methylphenidates, Amphetamines)

SPARLON™ (Modafinil)	Anorexia	Modafinil (n =426) 16 %	Placebo (n =213) 3 %
	Insomnia	27 %	4 %
	Headaches	20 %	13 %
Adderall XR⁴⁰	Anorexia	Adderall XR (n =374) 22 %	Placebo (n=210) 2%
	Insomnia	17%	2%
	Headaches	≤ 1 %	≤ 1 %
Ritalin ® LA⁴¹	Anorexia	Ritalin ® LA(n =65) 2 (3.1)	Placebo (n =71) (0.0)
	Insomnia	2 (3.1)	(0.0)
	Headaches	≤ 2 %	≤ 2 %
Metadate ® CD⁴²	Anorexia	METADATE ® CD (n=188) 9%	Placebo (n=190) 2%
	Insomnia	5%	2%
	Headaches	12 %	8 %
Focalin⁴³	Anorexia	Focalin (n=79) 6 %	Placebo (n=82) 1 %
	Insomnia	≤ 5 %	≤ 5 %
	Headaches	≤ 5 %	≤ 5 %
Concerta™⁴⁴	Anorexia	CONCERTA™ (n=106) 4%	Placebo (n=99) 0%
	Insomnia	4%	1%
	Headaches	14 %	10 %

40 Adverse Events (Double-Blind Trials): Adverse Events Reported by More Than 1% of Pediatric Patients Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 584 Patient Clinical Study

41 Treatment-emergent adverse events with an incidence > 2% among Ritalin LA-treated subjects, during the two-week double-blind phase of the clinical study

42 Incidence of Treatment-Emergent Events in a Pool of 3-4 Week Clinical Trials of METADATE CD

43 Adverse Events Occurring at an Incidence of 5% or More Among Focalin-Treated Patients

44 Incidence of Treatment-Emergent Events in a 4-Week Placebo-Controlled Clinical Trial of CONCERTA™

10.2 Tables Summarizing Clinical Trials Submitted in Support of sNDA

Table 1: Tabular Listing of All Clinical Studies Included in This Submission

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen ^a Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Comparative Bioavailability and Bioequivalence Studies							
C1538/1024/BE/US A Randomized, Open-Label Crossover Study to Evaluate the Bioequivalence of Modafinil Tablets (Five 85-mg Tablets Versus One 425-mg Tablet) in Healthy Subjects Phase 1	1 center Swearingen USA	Completed 16Aug04- 28Aug04	Healthy adults Pharmacokinetics: C _{max} AUC _{0-∞} AUC _{0-t} t _{max} λ _z t _{1/2} CL/F V/F Safety: AEs laboratory tests serum chemistry hematology urinalysis vital signs ECG physical examination	Modafinil: d1 and d9 5 x 85-mg tablets and 1 x 425-mg tablet in randomized sequence 2 single doses	Modafinil film- coated tablets: 85-mg tablet (03033B5a) 425-mg tablet (04178B5a)	N=30 31.6 (18-45) 15/15 (50/50) 6/24 (20/80) 71.5 (56.2-90.3)	NA

^a Modafinil was administered orally in all studies.
 Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen* Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Comparative Bioavailability and Bioequivalence Studies (Continued)							
C1538d/113/BA/US A Randomized Open-Label Study to Compare the Relative Bioavailability of 170 mg of Modafinil Film-Coated Tablets to 200 mg of PROVIGIL™ and to Assess the Pharmacokinetic and Safety Profile of Multiple Doses of the Modafinil Film-Coated Tablets Administered at Doses of 340 and 425 mg to Children and Adolescents With Attention-Deficit/Hyperactivity Disorder Phase 1	1 center Boellner USA	Completed 11Jul03- 10Aug03	Pediatric ADHD Pharmacokinetics: C _{max} AUC _{0-12, 0-24, 0-48} AUC _{0-∞} t _{max} λ _z t _{1/2} CL/F V/F Efficacy: ADHD-RS-IV (Home Version) Safety: AEs laboratory tests serum chemistry hematology urinalysis vital signs ECGs physical examination concomitant medications	Modafinil: d1 and d8 2 x 85-mg film-coated tablets and 2 x 100-mg PROVIGIL tablets in randomized sequence 2 single doses Modafinil: once daily (AM) d9 to d22 <30 kg: up to 340 mg/d (n=12) ≥30 kg: up to 425 mg/d (n=12) (dose titrated over first 7 days) 2 wks	Modafinil 85-mg film-coated tablet (03033B5a) PROVIGIL (modafinil) 100-mg tablet (02047B5a)	N=24 9.0 (6-13) 17/7 (71/29) 13/11 (54/46) 32.9 (18.6-58.1)	NA

* Modafinil was administered orally in all studies.
 Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen ^a Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Patient Pharmacokinetic (PK) and Initial Tolerability Study							
C1538a/206/PK/US A 4-Week Open-Label Pharmacokinetic and Tolerability Study of PROVIGIL™ (Modafinil) in Children With Attention- Deficit/Hyperactivity Disorder (ADHD) Followed by an Optional 8-Week Extension of PROVIGIL Treatment Phase 2	3 centers Gaultieri Labellarte McCarthy USA	Completed 20Apr00– 26Aug00	Pediatric ADHD Efficacy: ADHD RS-IV (School Version) ADHD RS-IV (Home Version) CGI-C math test (Permanent Product Score) Pharmacokinetics: modafinil, modafinil metabolite(s), plasma levels after single (100-mg) and multiple (100-, 200-, 300-, and 400-mg) doses Safety: laboratory tests chemistry hematology urinalysis vital signs ECG physical examination AEs	Modafinil: once daily (AM) d1 to d8 100 mg/d d9 to d15 200 mg/d d16 to d22 300 mg/d d23 to d29 400 mg/d (dose increased depending on tolerability) up to 8 additional wks at maximum tolerated dose	PROVIGIL (modafinil) 100-mg tablet (1538-FL16-1 906101 99019B5 99017B5)	N=20 9.4 (6–12) 11/9 (55/45) 18/2 (90/10) 35.4 (19.0–58.9)	NA

^a Modafinil was administered orally in all studies.
 Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen ^a Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Patient Pharmacodynamic (PD) and PK/PD Study							
C1538a/207/AD/US A Phase 2, Double-Blind, Randomized, Placebo-Controlled, 2-Part (5 or 6 Weeks per Part), Crossover Study to Evaluate the Dose Range, Dose Frequency, and Pharmacokinetic/Pharmacodynamic Correlation of 5 Oral Doses of PROVIGIL™ (Modafinil) in Children with Attention Deficit/Hyperactivity Disorder Followed by an 8-Week Open-Label Extension Phase 2	3 centers Wigal Spencer Greenhill USA	Double-blind phase (Part A): Completed 5Jul00–6Sep00 (Part B not done)	Pediatric ADHD Efficacy: ADHD RS-IV (Home Version) CGL-C SKAMP Math Test for Permanent Product Score Pharmacology: modafinil, modafinil metabolite(s), plasma levels after single (100-mg) and multiple (100-, 200-, 300-, and 400-mg) doses Safety: laboratory tests chemistry hematology urinalysis vital signs ECG physical examination AEs	Modafinil: once daily (AM) 1 wk each 100 mg/d 200 mg/d 300 or 400 mg/d (based on body weight) placebo: once daily (AM) 1 wk ADDERALL® (Shire Pharmaceuticals, plc): po, 10 mg once or twice daily (wk 5)	PROVIGIL (modafinil) 100-mg tablets (00010B5a) placebo tablets (00012B5a)	N=48 9.2 (5–13) 38/10 (79/21) 24/24 (50/50) 34.4 (18.2–90.2)	NA

^a Modafinil was administered orally in all studies. Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen* Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Efficacy and Safety Studies: Controlled Clinical Studies							
C1538a/213/AD/US A 4-Week, Double-Blind, Randomized, Placebo-Controlled, Parallel Study to Evaluate the Efficacy and Safety of PROVIGIL™ (Modafinil) in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder, Followed by an 8-Week Open-Label Extension Phase 2	28 centers Apter Boellner Chandler Connor Couch Hartman McCarthy DePriest Lopez McCarty Lee Pahl Plizska Hedrick Rugino Keating Smith Wigal Biederman Helfing (2 centers) Repass Northam Cecil Ingenito Levine McConville Wynn USA	Double-blind phase: Completed 19Feb02– 31May02	Pediatric ADHD Efficacy: ADHD RS-IV (School Version) ADHD RS-IV (Home Version) CGI-C CADS-P CSWS GSI TOVA Safety: ANCs WBC count laboratory tests chemistry hematology urinalysis vital signs ECG physical examination AEs	Modafinil: twice daily (AM/PM) 100 mg/200 mg (n=48) 200 mg/100 mg (n=49) 300 mg/0 mg (n=50) 200 mg/200 mg (n=50) placebo: twice daily (n=51) 4 wks	PROVIGIL (modafinil) 100-mg tablets (01009B5a) placebo tablets (01008B5a, 01041B5a)	N=248 (197 modafinil, 51 placebo) 9.3 (6–14) 185/63 (75/25) 202/46 (81/18) 36.8 (18.2–89.4)	NA

* Modafinil was administered orally in all studies.
 Abbreviations on last page.

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Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen* Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Efficacy and Safety Studies: Controlled Clinical Studies (Continued)							
C1538d/309/AD/US A 9-Week, Randomized, Double-Blind, Placebo- Controlled, Flexible-Dosage (up to 425 mg/day), Parallel- Group Study to Evaluate the Efficacy and Safety of Modafinil (Film-Coated Tablet) in Children and Adolescents With Attention- Deficit/Hyperactivity Disorder Phase 3	18 centers Arnold Montgomery- Barefield Boellner Chandler Dean Ferguson Lee Levine Lipetz Padilla Northam Pahl Reichler Rugino Sangal Sarkis Schub Molina USA	Completed 8Nov03- 27May04	Pediatric ADHD Efficacy: ADHD-RS-IV (School Version) ADHD-RS-IV (Home Version) TOVA CGI-C Safety: AEs laboratory tests serum chemistry hematology urinalysis vital signs ECGs physical examination concomitant medications Pharmacokinetics: modafinil, modafinil metabolite(s), plasma levels, weekly	Modafinil: once daily (AM) d1, d2: 85 mg/d d3 - d7: 170 mg/d d8 - d14: 255 mg/d d15 - d21: 340 mg/d d22+: 425 mg/d (dose was then adjusted from 170 to 425 mg/d based on individual patient evaluations) placebo: once daily (AM) 9 wks	Modafinil 85-mg film- coated tablets (03033B5a) placebo tablets (03034B5a)	N=198 (131 modafinil, 67 placebo) 9.9 (6-16) 144/54 (73/27) 142/56(72/28) 40.1 (18.6-87.1)	NA

* Modafinil was administered orally in all studies.
 Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen ^a Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Efficacy and Safety Studies: Controlled Clinical Studies (Continued)							
C1538d/310/AD/US A 9-Week, Randomized, Double-Blind, Placebo-Controlled, Fixed-Dosage (340 or 425 mg/day), Parallel-Group Study to Evaluate the Efficacy and Safety of Modafinil (Film-Coated Tablet) in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder, Including a 2-Week (Blinded) Withdrawal Period Phase 3	17 centers Biederman Couch McKnight Horwitz Knutson Lopez Lundt McCarty McConville Miller Palumbo Pliszka Rieser Rubin Schexnayder Sedillo Vince USA	Completed 8Nov03- 2Jun04	Pediatric ADHD Efficacy: ADHD-RS-IV (School Version) ADHD-RS-IV (Home Version) TOVA CGI-C Safety: AEs laboratory tests serum chemistry hematology vital signs ECGs physical examination concomitant medications STESS (withdrawal period) Pharmacokinetics: modafinil, modafinil metabolite(s), plasma levels, weekly	Modafinil: once daily (AM) d1, d2: 85 mg/d d3, d4: 170 mg/d d5, d6: 255 mg/d patients <30kg, d7 – wk 7: 340 mg/d patients ≥30kg, d9 – wk 7: 425 mg/d placebo: once daily (AM) wk 8 and wk 9 (withdrawal period) per randomized sequence: modafinil/ modafinil; modafinil/placebo; placebo/placebo 9 wks	Modafinil 85-mg film-coated tablets (03033B5A) placebo tablets (03034B5A)	N=189 (125 modafinil, 64 placebo) 10.0 (6–17) 135/54 (71/29) 151/38 (80/20) 40.3 (19.6–98.4)	NA

^a Modafinil was administered orally in all studies.
 Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen* Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) MF (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Efficacy and Safety Studies: Controlled Clinical Studies (Continued)							
C1538d/311/AD/US A 9-Week, Randomized, Double-Blind, Placebo-Controlled, Flexible-Dosage (up to 425 mg/day), Parallel-Group Study to Evaluate the Efficacy and Safety of Modafinil (Film-Coated Tablet) in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder Phase 3	24 centers Ahmann Kliewer Cecil DePriest Greenhill Grimm Hedrick Kratovich McBurnett McCarthy Owens Waxmonsky Moore Reisinger Rosenthal Saylor Smith Wigal Wynn Sperry Boellner Arnold Ball Hassman USA	Completed 11Nov03- 11Jun04	Pediatric ADHD Efficacy: ADHD-RS-IV (School Version) ADHD-RS-IV (Home Version) TOVA CGI-C Safety: AEs laboratory tests serum chemistry hematology urinalysis vital signs ECGs physical examination concomitant medications Pharmacokinetics: modafinil, modafinil metabolite(s), plasma levels, weekly	Modafinil: once daily (AM) d1, d2: 85 mg/d d3 – d7: 170 mg/d d8 – d14: 255 mg/d d15 – d21: 340 mg/d d22+: 425 mg/d (dose was then adjusted from 170 to 425 mg/d based on individual patient evaluations) placebo: once daily (AM) 9 wks	Modafinil 85-mg film-coated tablets (03033B5a) placebo tablets (03034B5a)	N=246 (164 modafinil, 82 placebo) 10.3 (6–17) 174/72 (71/29) 190/56 (77/23) 42.9 (18.6–85.4)	NA

* Modafinil was administered orally in all studies.
 Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen ^a Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) MF (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Efficacy and Safety Studies: Uncontrolled Clinical Studies							
C1538a/207/AD/US (Open-Label Extension Period) Phase 2	3 centers Wigal Spencer Greenhill USA	Completed 5Jul00- 6Sep00	Pediatric ADHD ADHD RS-IV (Home Version) CGL-C laboratory tests chemistry hematology urinalysis vital signs ECG physical examination AEs	Modafinil: once or twice daily 100 to 400 mg/d (dose adjusted at investigator's discretion) up to 8 wks	PROVIGIL (modafinil) 100-mg tablet (99017B5)	N=30 9.5 (6-13) 24/6 (80/20) 14/16 (47/53) 34.8 (19.3-62.1)	NA

^a Modafinil was administered orally in all studies.
 Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen ^a Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Efficacy and Safety Studies: Uncontrolled Clinical Studies (Continued)							
C1538a/213/AD/US (Open-Label Extension Period) Phase 2	28 centers Apter Boellner Chandler Connor Couch Hartman McCarthy DePriest Lopez McCarty Lee Pahl Plizka Hedrick Rugino Keating Smith Wigal Biederman Helfing (2 centers) Repass Northam Cecil Ingenito Levine McConville Wynn USA	Completed 19Mar02- 5Aug02	Pediatric ADHD Efficacy: ADHD RS-IV (Home Version) CADS-P CGI-C CSWS Safety: laboratory tests WBC count ANCs serum chemistry hematology urinalysis AEs physical examination vital signs 12-lead ECGs	Modafinil: twice daily (AM/PM) beginning at 100 mg/d and titrated to optimal dosage (up to 400 mg/d) 8 wks	PROVIGIL (modafinil) 100-mg tablet (00018B5a, 01022B5a)	N=220 9.2 (6-14) 159/61 (72/28) 180/40 (82/18) 37.2 (19.5-89.4)	NA

^a Modafinil was administered orally in all studies.
 Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen ^a Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Efficacy and Safety Studies: Uncontrolled Clinical Studies (Continued)							
C1538d/312/AD/US A 1-Year, Open-Label, Flexible-Dosage Study to Evaluate the Safety and Continued Efficacy of Modafinil (Film-Coated Tablet Formulation) in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder Includes patients previously enrolled in the following studies: C1538d/113/BA/US C1538d/213/AD/US C1538d/309/AD/US C1538d/310/AD/US C1538d/311/AD/US Phase 3	56 centers All investigators from the previous 5 studies enrolled patients except the following: Apter Connor Hartman Keating Helfing Repass Ingenito McKnight USA	Ongoing Interim safety: 12Sep03- 5Oct04	Pediatric ADHD Safety: AEs physical examination vital signs body weight and height 12-lead ECGs laboratory tests Efficacy: ADHD-RS-IV (Home Version) CGI-S CHQ Pharmacokinetics: modafinil, modafinil metabolite(s), plasma levels, monthly	Modafinil: once daily (AM) d1, d2: 85 mg/d d3, 4, 5: 170 mg/d d6 – d9: 255 mg/d d10 – d14: 340 mg/d (dose was then adjusted from 170 to 425 mg/d based on individual patient evaluations) Up to 12 months	Modafinil 85-mg film-coated tablet (03033B5a)	N=533 10.2 (6–17) 391/142 (73/27) 411/122 (77/23) 42.0 (18.6–98.4)	NA

^a Modafinil was administered orally in all studies.
 Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen ^a Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Other Completed Clinical Studies							
EI044 (Lafon-sponsored study) Pilot Study of Modafinil in Attention-Deficit Hyperactivity Disorder in Children. Double-Blind Placebo-Controlled Trial Phase 2	4 centers Bouvard Laurent Le Heuzey Revol France	Completed Oct1996- May1998	Pediatric ADHD Conners 10-item questionnaire Conners 28-item questionnaire Conners 48-item questionnaire CGI-C VAS vital signs laboratory tests hematology chemistry AEs	Modafinil: twice daily 50 mg, AM 50 mg, PM 100 mg/d (after d28, dose could be adjusted to 50 mg/d or 200 mg/d at investigator's discretion) placebo: twice daily 56 days	Modafinil tablets (batch no. 112 108) placebo tablets (batch no. 112 109)	N=48 24 modafinil: 9.7 (NA) 24/0 (100/0) NA 31.1 (NA) 24 placebo: 9.9 (NA) 22/2 (92/8) NA 34.4 (NA)	NA

^a Modafinil was administered orally in all studies. Abbreviations on last page.

(Continued)

Table 1: Tabular Listing of All Clinical Studies Included in This Submission (Continued)

Study number Study title (design) Phase	No. of centers Investigator(s) Location	Status Dates	Study population Variables	Dose regimen ^a Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (y): mean (range) M/F (%) W/NW (%) Weight (kg): mean (range)	Review copy Volume Number
Other Completed Clinical Studies (Continued)							
E1047 (Lafon-sponsored study) Pilot Trial of Modafinil in Childhood Attention Deficit Disorder with Hyperactivity. Open Trial in Children Responsive to Methylphenidate Phase 2	1 center Marescaux France	Completed 1Sep97– 30Oct97	Pediatric ADHD Conners 10-item questionnaire Conners 48-item questionnaire CPT Rey 15-word Test VAS-hyperactivity VAS-efficacy/safety CGL-C neurologic examination vital signs AEs	Modafinil: twice daily 50 mg, AM 50 mg, noon 100 mg/d (dose could be adjusted at d14 to 200 mg/d and at d28 to 300 mg/d at investigator's discretion) 42-49 days	NA	N=14 9.1 (6-13) 13/1 (93/7) NA 32.9 (21.0-69.0)	NA

^a Modafinil was administered orally in all studies.

Abbreviations:

ADHD	attention-deficit/hyperactivity disorder	CGL-S	Clinical Global Impression of Severity	λ_z	terminal elimination rate constant	STESS	Subject's Treatment Emergent Symptom Scale
ADHD-RS-IV	ADHD Rating Scale, Fourth Edition	CHQ	Children's Health Questionnaire	M	males	t _{1/2}	half-life
AEs	adverse events	CLF	total plasma clearance	mg	milligram	t _{max}	time to maximum concentration
AM	morning	CPT	Continuous Performance Test	NA	not available	TOVA	Test of Variables of Attention
ANC	absolute neutrophil count	CSWS	Children's Sleep Wake Scale	No.	number	USA	United States of America
AUC	area under the plasma concentration-time curve	d	day	NW	non-White	VAS	visual analogue scale
C _{max}	maximum plasma concentration	DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition	PD	pharmacodynamics	V/F	volume of distribution
CADS-P	Conner's ADHD/DSM-IV Scales-Parent	ECG	electrocardiogram	PK	pharmacokinetics	W	white (Caucasian)
		F	females	PM	evening	WBC	white blood cell
CGL-C	Clinical Global Impression of Change	GSI	General Sleep Information	po	oral	wk	week(s)
		kg	kilogram	SKAMP	Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale	y	year(s)

10.3 List of proposed labeling changes

Labeling Section	Description of Change(s)
General	Incorporated ATTENACE throughout
Description	Added text to describe use for new indication; revised modafinil solubility statements in accordance with USP; incorporated new strengths and revisions to inactive ingredients
Clinical Pharmacology	Revised throughout for relevance to pediatric population; added pediatric data
Clinical Trials	Replaced sleep disorder data with ADHD data
Indications and Usage	Replaced sleep disorder information with ADHD information
Warnings	Replaced warnings related to sleepiness/drowsiness with warnings related to growth in pediatric patients
Precautions	Removed precautions related to sleep disorders; revised throughout for relevance to pediatric population and related dose changes; added results from preclinical development study to Pediatric Use subsection
Adverse Reactions	Replaced sleep disorder data with ADHD data
Drug Abuse and Dependence	Replaced sleep disorder withdrawal data with ADHD withdrawal data
Overdosage	Revised text based on pediatric dose data
Dosage and Administration	Replaced sleep disorder information with ADHD information
How Supplied	Replaced information for currently approved formulation and strengths with information for new formulation and strengths
Patient Information Leaflet	Revised completely for ADHD indication and patients

10.4 History of changes since last approved labeling

Component Code	Description of Change(s)	Submission	
		Type	Date
PROV-007	Added copyright information to Patient Information Leaflet	Annual Report	Pending
PROV-008	Added information regarding rare reports of serious skin reactions to the Postmarketing Reports subsection of Adverse Reactions	CBE	02-Dec-2004
	Revised introductory text to Postmarketing Reports subsection of Adverse Reactions		
	Corrected typographical error in Pregnancy subsection of Precautions		

10.5 List of Investigators

No. 1047

NEUROLOGY FEDERATION

Professor Christian MARESCAUX, Neurologist, PU-PH
Head of Dept.: Professor Maurice COLLARD

Doctor Sonja FINCK*, Pediatrician, Hospital Physician
Head of Dept.: Professor Maurice COLLARD

Doctor Christophe PETIAU, Neurologist, CCA
Head of Dept.: Professor Jean KRIEGER

Neurology Clinic – Civilian Hospital – Strasbourg University Hospitals [S.U.H.]
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DEPT. OF CHILD AND ADOLESCENT PSYCHOTHERAPY

Head of Dept.: Professor Claude BURSZTEJN

Professor Anne DANION-GRILLIAT, Pediatric Psychiatrist, PU-PH

Doctor Eve BECACHE, Pediatric Psychiatrist, CCA

Miss Caroline SEEGMULLER, Psychologist

Miss Lyne PELLETIER, Psychologist

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* Doctor Sonja FINCK is also on the staff of Haguenu Hospital Center in the Pediatric Department of Doctor Marie-Odile VUILLEMIN

Study 309

List of Investigators and Patient Enrollment

Center number	Investigator and affiliation	Number of patients enrolled/given study drug
01	Valerie Arnold, MD Clinical Neuroscience Solutions, Inc. 6401 Poplar Avenue Suite 420 Memphis, Tennessee 38119 USA	18/18
02	Laura Montgomery-Barefield, MD University of Alabama at Birmingham 1700 Seventh Ave South Smolian Building, Room 243 Birmingham, Alabama 35025 USA	12/12
03	Samuel Boellner, MD Clinical Study Centers, LLC 9601 Lile Drive Suite 900 Little Rock, Arkansas 72205 USA	18/18
04	Mark Chandler, MD North Carolina Neuropsychiatry Clinic 1829 E. Franklin St. 400 Franklin Square Chapel Hill, North Carolina 27514 USA	12/12
05	Raymond Dean, PhD Midwest Neurology, Inc. 100 Meadow Drive Danville, Indiana 46122 USA	4/4
06	James Ferguson, MD Radiant Research, Salt Lake City- 64th South 448 East 6400 South Suite 200 Salt Lake City, Utah 84107 USA	7/7

09	James Lee, MD Piedmont Neuropsychiatry 7731 Little Avenue Suite 100 Charlotte, North Carolina 28226 USA	5/5
10	Alan Levine, MD Alpine Clinical Research 1000 Alpine Avenue Suite 2000 Boulder, Colorado 80304 USA	6/6
11	Robert Lipetz, DO Encompass Clinical Research 10225 Austin Drive Suite 203 Spring Valley, California 91978 USA	12/12
12	Americo Padilla, MD Miami Research Associates 7500 SW 87th Avenue Suite 202 Miami, Florida 33173 USA	8/8
13	Ralph Northam, MD Monarch Medical Research 850 Southampton Avenue Third Floor Norfolk, Virginia 23510 USA	6/6
14	Jorg Pahl, MD Pahl Brain Associates, Inc 3909 N. Classen Oklahoma City, Oklahoma 73118 USA	17/17
15	Robert J. Reichler, MD Pacific Institute of Mental Health 2150 North 107th Street Suite 510 Seattle, Washington 98133-9009 USA	9/9
16	Thomas Rugino, MD Children's Specialized Hospital 94 Stevens Road	10/10

Clinical Review

Glenn B. Mannheim, M.D.

NDA 20-717 (S-019)

SPARLON (Proposed Trade Name) and Provigil (Generic Name)

	Toms River, New Jersey 08755 USA	
17	Bart Sangal, MD Clinical Neurophysiology Services, PC 44199 Dequindre Suite 311 Troy, Michigan 48085 USA	15/14
18	Elias H. Sarkis, MD Sarkis Family Psychiatry 529 NW 60th Street Gainesville, Florida 32607 USA	15/14
19	Howard Schub, MD Child Neurology Associates 5505 Peachtree Dunwoody Road Suite 500 Atlanta, Georgia 30342 USA	16/16
20	Marino Molina, Jr., MD Amedica Research Institute, Inc. 625 East 49th Street Hialeah, Florida 33013 USA	10/10

Study 310

List of Investigators and Patient Enrollment

Center number	Investigator and affiliation	Number of patients enrolled/given study drug
21	Joseph Biederman, MD Massachusetts General Hospital Department. of Pediatric Psychopharmacology 185 Alewife Brook Parkway, Suite 2000 Cambridge, Massachusetts 02138 USA	6/6
22	Steven Couch, MD Vanderbilt University 2100 Pierce Avenue, Room 426 Nashville, Tennessee 37232 USA	4/4
23	James McKnight, MD Mountainview Center for Medical Research 1456 McLendon Drive, Suite B Decatur, Georgia 30033 USA	10/10
24	Alexander A. Horwitz, MD OCCI, Inc. 700 Bellevue Street SE, Suite 240 Salem, Oregon 97301 USA	10/10
26	PI: James A. Knutson, MD 512 6 th Street South, Suite 101 Kirkland, Washington 98033 USA	21/21
27	Frank Lopez, MD Children's Development Center, P.A. 600 S. Orlando Ave, Suite 102 Maitland, Florida 32751 USA	14/14
28	Leslie Lundt, MD Foothills Psychiatry 223 West State Street Boise, Idaho 83702 USA	5/5

Center number	Investigator and affiliation	Number of patients enrolled/given study drug
29	Joseph McCarty, MD River Valley Neurology Center 600 Lexington Ave Fort Smith, Arkansas 72901 USA	16/16
30	Brian McConville, MD Psychiatric Professional Services, Inc. 231 Albert Sabin Way PO Box 6700559 Cincinnati, Ohio 45267 USA	5/5
31	Janice Miller, MD Clinical Neuroscience Solutions, Inc. 5601 Corporate Way, Building 2, Suite #210 West Palm Beach, Florida 33407 USA	16/15
32	Donna R. Palumbo, PhD University of Rochester, School of Medicine and Dentistry 601 Elmwood Avenue, Room 5-5210 Rochester, New York 14642 USA	7/7
33	Steven Pliszka, MD UT Health Science Center Department of Psychiatry MC 7792 7703 Floyd Curl Drive San Antonio, Texas 78229-3900 USA	3/3
34	Michael J. Rieser, MD 2801 Palumbo Drive, Suite 202 Lexington, Kentucky 40509 USA	11/11
35	Richard L. Rubin, MD Otter Creek Clinical Studies 789 Pine Street Burlington, Vermont 05401 USA	8/8

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Glenn B. Mannheim, M.D.
NDA 20-717 (S-019)
SPARLON (Proposed Trade Name) and Provigil (Generic Name)

Center number	Investigator and affiliation	Number of patients enrolled/given study drug
36	Donald A. Schexnayder, MD, PhD Dolby Providers, Inc. 6030 Bullard Avenue, Suite 250 New Orleans, Louisiana 70128 USA	10/10
37	Andrew C.A. Sedillo, MD Pedia Research, LLC 920 Frederica Street, Suite 1010 Owensboro, Kentucky 42301 USA	24/24
40	Bradley D. Vince, DO Vince and Associates Clinical Research 6600 College Blvd. Suite 330 Overland Park, Kansas 66211 USA	20/20

Study 311

List of Investigators and Patient Enrollment

Center number	Investigator and affiliation	Number of patients enrolled/given study drug
041	Peter Ahmann, MD Marshfield Clinic 9601 Towne Line Road Minocqua, Wisconsin 54548 USA	1/1
042	Vernon Kliewer, MD Cientifica at Prairie View 1901 East 1st Street Newton, Kansas 67114 USA	14/14
043	John Cecil, Jr, MD Four Rivers Clinical Research, Inc. 81 Lakeview Drive Paducah, Kentucky 42001 USA	21/21
044	Michael DePriest, MD Radiant Research, Las Vegas 2940 South Jones Blvd., Suite C Las Vegas, Nevada 89146-5611 USA	1/1
046	Laurence L. Greenhill, MD New York State Psychiatric Institute 1051 Riverside Drive, Room 2307 New York, New York 10032 USA	4/4
047	James Grimm, MD OCCI, Inc. 572 West 11th Avenue Eugene, Oregon 97401 USA	5/5
048	James Hedrick, MD Kentucky Pediatric/Adult Research 201 South 5th Street, Suite 102 Bardstown, Kentucky 40004 USA	21/21

049	Chris Kratochvil, MD University of Nebraska Medical Center Department of Psychiatry 985581 Nebraska Medical Center Omaha, Nebraska 68198 USA	14/14
050	R. Keith McBurnett, PhD University of California at San Francisco 401 Parnassus Avenue, Box CAS-0984 Room 140 San Francisco, California 94143 USA	17/16
051	Craig McCarthy, MD Pivotal Research Center 1220 S Alma School Road, Suite 206 Mesa, Arizona 85210 USA	6/6
052	Judith Owens, MD, MPH Department of Pediatrics, Rhode Island Hospital Potter Building 593 Eddy Street Suite 200 Providence, Rhode Island 02903 USA	7/7
053	James Waxmonsky, PhD University of Buffalo, Center for Children and Families 318 Diefendorf Hall 3435 Main Street, Building 20 Buffalo, New York 14214 USA	4/4
054	Dennis Moore, MD Clinical Research Center of Nevada 6301 Mountain Vista Las Vegas, Nevada 89014 USA	11/11
055	Keith S. Reisinger, MD, MPH Primary Physicians Research, Inc. (PPR) 1580 McLaughlin Run Road Pittsburgh, Pennsylvania 15241 USA	3/3

Clinical Review

Glenn B. Mannheim, M.D.

NDA 20-717 (S-019)

SPARLON (Proposed Trade Name) and Provigil (Generic Name)

063	Valerie Arnold, MD Clinical Neuroscience Solutions, Inc. 6401 Poplar Avenue, Suite 420 Memphis, Tennessee 38119 USA	9/9
064	Roberta R. Ball, DO CNS Research Institute, PC 2827 Tyson Avenue Philadelphia, Pennsylvania 19149 USA	13/13
065	Howard A. Hassman, DO CNS Research Institute, PC 130 White Horse Pike Clementon, New Jersey 08021 USA	18/17

Study 312

Center number	Investigator and affiliation	Number of patients enrolled/given study drug
010	Alan Levine, MD Alpine Clinical Research 1000 Alpine Avenue Suite 2000 Boulder, Colorado 80304 USA	4/4
011	Robert Lipetz, DO Encompass Clinical Research 10225 Austin Drive Suite 203 Spring Valley, California 91978 USA	11/11
012	Americo Padilla, MD Miami Research Associates 7500 SW 87th Avenue Suite 202 Miami, Florida 33173 USA	8/8
013	Ralph Northam, MD Monarch Medical Research 850 Southampton Avenue Third Floor Norfolk, Virginia 23510 USA	7/7
014	Jorg Pahl, MD Pahl Brain Associates, Inc 3909 N. Classen Oklahoma City, Oklahoma 73118 USA	14/14
015	Robert J. Reichler, MD Pacific Institute of Mental Health 2150 North 107th Street Suite 510 Seattle, Washington 98133-9009 USA	9/9
016	Thomas Rugino, MD Children's Specialized Hospital 94 Stevens Road Toms River, New Jersey 08755 USA	9/9
017	Bart Sangal, MD Clinical Neurophysiology Services, PC 44199 Dequindre Suite 311 Troy, Michigan 48085 USA	11/12
018	Elias H. Sarkis, MD Sarkis Family Psychiatry 529 NW 60th Street Gainesville, Florida 32607 USA	13/13

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 SPARLON (Proposed Trade Name) and Provigil (Generic Name)

Center number	Investigator and affiliation	Number of patients enrolled/given study drug
030	Brian McConville, MD Psychiatric Professional Services, Inc. 231 Albert Sabin Way PO Box 6700559 Cincinnati, Ohio 45267 USA	3/3
031	Janice Miller, MD Clinical Neuroscience Solutions, Inc. 5601 Corporate Way, Building 2, Suite #210 West Palm Beach, Florida 33407 USA	12/12
032	Donna R. Palumbo, PhD University of Rochester, School of Medicine and Dentistry 601 Elmwood Avenue, Room 5-5210 Rochester, New York 14642 USA	6/6
033	Steven Pliszka, MD UT Health Science Center Department of Psychiatry MC 7792 7703 Floyd Curl Drive San Antonio, Texas 78229-3900 USA	2/2
034	Michael J. Rieser, MD 2801 Palumbo Drive, Suite 202 Lexington, Kentucky 40509 USA	9/9
035	Richard L. Rubin, MD Otter Creek Clinical Studies 789 Pine Street Burlington, Vermont 05401 USA	8/8
036	Donald A. Schexnayder, MD, PhD Dolby Providers, Inc. 6030 Bullard Avenue, Suite 250 New Orleans, Louisiana 70128 USA	10/10
037	Andrew C.A. Sedillo, MD Pedia Research, LLC 920 Frederica Street, Suite 1010 Owensboro, Kentucky 42301 USA	17/17

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Center number	Investigator and affiliation	Number of patients enrolled/given study drug
040	Bradley D. Vince, DO Vince and Associates Clinical Research 6600 College Blvd. Suite 330 Overland Park, Kansas 66211 USA	16/16
041	Peter Ahmann, MD Marshfield Clinic 9601 Towne Line Road Minocqua, Wisconsin 54548 USA	1/1
042	Vernon Kliewer, MD Cientifica at Prairie View 1901 East 1st Street Newton, Kansas 67114 USA	12/12
043	John Cecil, Jr, MD Four Rivers Clinical Research, Inc. 81 Lakeview Drive Paducah, Kentucky 42001 USA	18/18
044	Michael DePriest, MD Radiant Research, Las Vegas 2940 South Jones Blvd., Suite C Las Vegas, Nevada 89146-5611 USA	2/2
046	Laurence L. Greenhill, MD New York State Psychiatric Institute 1051 Riverside Drive, Room 2307 New York, New York 10032 USA	1/1
047	James Grimm, MD OCCI, Inc. 572 West 11th Avenue Eugene, Oregon 97401 USA	4/4
048	James Hedrick, MD Kentucky Pediatric/Adult Research 201 South 5th Street, Suite 102 Bardstown, Kentucky 40004 USA	18/18
049	Chris Kratochvil, MD University of Nebraska Medical Center Department of Psychiatry 985581 Nebraska Medical Center Omaha, Nebraska 68198 USA	11/11

Center number	Investigator and affiliation	Number of patients enrolled/given study drug
050	R. Keith McBurnett, PhD University of California at San Francisco 401 Parnassus Avenue, Box CAS-0984 Room 140 San Francisco, California 94143 USA	14/14
051	Craig McCarthy, MD Pivotal Research Center 1220 S Alma School Road, Suite 206 Mesa, Arizona 85210 USA	5/5
052	Judith Owens, MD, MPH Department of Pediatrics, Rhode Island Hospital Potter Building 593 Eddy Street Suite 200 Providence, Rhode Island 02903 USA	7/7
053	James Waxmonsky, PhD University of Buffalo, Center for Children and Families 318 Diefendorf Hall 3435 Main Street, Building 20 Buffalo, New York 14214 USA	2/2
054	Dennis Moore, MD Clinical Research Center of Nevada 6301 Mountain Vista Las Vegas, Nevada 89014 USA	10/10
055	Keith S. Reisinger, MD, MPH Primary Physicians Research, Inc. (PPR) 1580 McLaughlin Run Road Pittsburgh, Pennsylvania 15241 USA	2/2
056	Murray Rosenthal, DO BMR Healthquest 3625 Ruffin Road, Suite 100 San Diego, California 92123 USA	9/9
057	Keith E. Saylor, MD NeuroScience, Inc. 5612 Spruce Tree Avenue Third Floor Bethesda, Maryland 20814 USA	10/10
058	Ward Smith, MD Summit Research Network Inc., Oregon 1849 NW Kearney, Suite 201 Portland, Oregon 97209 USA	7/8

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 Glenn B. Mannheim, M.D.
 NDA 20-717 (S-019)
 SPARLON (Proposed Trade Name) and Provigil (Generic Name)

Center number	Investigator and affiliation	Number of patients enrolled/given study drug
059	Sharon Wigal, PhD University of California, Irvine Child Development Center 19722 MacArthur Blvd. Irvine, California 92612 USA	17/17
060	Daniel Wynn, MD Consultants in Neurology, Ltd. 1535 Lake Cook Road, Suite 601 Northbrook, Illinois 60062 USA	6/6
061	David Sperry, MD Dallas Pediatric Neurology Associates Medical City Dallas Suite A3077777 Forest Lane Dallas, Texas 75230 USA	9/9
064	Roberta R. Ball, DO CNS Research Institute, PC 2827 Tyson Avenue Philadelphia, Pennsylvania 19149 USA	8/9
065	Howard A. Hassman, DO CNS Research Institute, PC 130 White Horse Pike Clementon, New Jersey 08021 USA	14/14

10.6 Study 312: 4 Mth Safety Update, Subject Disposition

C1538d/312/AD/US

Summary 15.1
 Patient Disposition
 All Enrolled Patients

Analysis group, n (%)	Modafinil
Enrolled	536 (100)
from C1538d/113/PA/US	13 (2)
from C1538a/213/AD/US	15 (3)
from C1538d/309/AD/US	170 (32)
from C1538d/310/AD/US	133 (25)
from C1538d/311/AD/US	205 (38)
Enrolled, not treated	3 (<1)
Safety analysis set	533 (>99)
Full analysis set	505 (94)
Completed study	48 (9)
Discontinued study	279 (52)
Adverse event	37 (7)
Lack of efficacy	101 (19)
Consent withdrawn	43 (8)
Protocol violation	2 (<1)
Lost to follow-up	57 (11)
Non-compliance to study medication	12 (2)
Non-compliance to study procedure	9 (2)
Other	18 (3)

10.7 Study 312: 4 Mth Safety Update, Safety Analysis Set

C1538d/312/AD/US

Summary 15.2
 Demographics
 Safety Analysis Set

Variable Statistic	Modafinil (N=533)
Age (yrs)	
n	533
Mean	10.2
SD	2.81
Median	10.0
Min, max	6.0, 17.0
Sex	
Male	391 (73)
Female	142 (27)
Race	
White	411 (77)
Black	70 (13)
Asian	2 (<1)
American Indian or Alaskan Native	7 (1)
Pacific Islander	1 (<1)
Other	42 (8)
Weight (kg)	
n	533
Mean	42.0
SD	16.64
Median	38.1
Min, max	18.6, 98.4
Height (cm)	
n	533
Mean	143.6
SD	17.40
Median	141.7
Min, max	110.2, 195.6

10.8 Study 312: 4 Mth Safety Update, Study Drug Administration

Variable Statistic, n (%)	Modafinil (N=533)
Time treated	
<=2 weeks	38 (7)
>2 weeks - <= 1 month	38 (7)
>1 - <=2 months	48 (9)
>2 - <=3 months	20 (4)
>3 - <=4 months	29 (5)
>4 - <=5 months	26 (5)
>5 - <=6 months	29 (5)
>6 - <=7 months	17 (3)
>7 - <=8 months	11 (2)
>8 - <=9 months	11 (2)
>9 - <=10 months	105 (20)
>10 - <=11 months	65 (12)
>11 - <=12 months	58 (11)
>12 months	38 (7)
Duration of treatment (months)	
n	533
Mean	6.9
SD	4.27
Median	9.0
Min, max	0.0, 15.0

C1538d/312/AD/US

Summary 15.14
 Stable Dose of Study Drug
 Safety Analysis Set

Variable Statistic, n (%)	Modafinil (N=533)
Number of patients with stable dose	
85 (mg/day)	12 (2)
170 (mg/day)	27 (5)
255 (mg/day)	54 (10)
340 (mg/day)	167 (31)
425 (mg/day)	267 (50)
510 (mg/day)	6 (1)
Stable dose of treatment (mg/day)	
n	533
Mean	361.5
SD	84.58
Median	425.0
Min, max	85.0, 510.0

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Summary 15.15
 Adverse Events by Body System and Preferred Term
 Safety Analysis Set

Body system COSTART preferred term, n (%)	Modafinil (N=533)
Number of patients with at least 1 AE	437 (82)
BODY AS A WHOLE	282 (53)
HEADACHE	109 (20)
INFECTION	101 (19)
ACCIDENTAL INJURY	65 (12)
ABDOMINAL PAIN	57 (11)
FEVER	30 (6)
PAIN	23 (4)
ALLERGIC REACTION	22 (4)
INFECTION BACTERIAL	20 (4)
FLU SYNDROME	19 (4)
ASTHENIA	14 (3)
VIRAL INFECTION	7 (1)
BACK PAIN	6 (1)
PHOTOSENSITIVITY REACTION	5 (<1)
FACE EDEMA	3 (<1)
INFECTION PARASITIC	3 (<1)
ANAPHYLACTOID REACTION	1 (<1)
CELLULITIS	1 (<1)
CHEST PAIN	1 (<1)
CHILLS	1 (<1)
CYST	1 (<1)
HALITOSIS	1 (<1)
HERNIA	1 (<1)
NECK PAIN	1 (<1)
NEOPLASM	1 (<1)
CARDIOVASCULAR	18 (3)
SYNCOPE	8 (2)
MIGRAINE	4 (<1)
VASODILATATION	2 (<1)
AV BLOCK FIRST DEGREE	1 (<1)
BRADYCARDIA	1 (<1)
ELECTROCARDIOGRAM ABNORMAL	1 (<1)
HYPERTENSION	1 (<1)

Notes: Preferred terms are sorted by descending order of incidence within body system.
 Patients are counted only once in each preferred term category, and only once in each body system category.

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Summary 15.15
 Adverse Events by Body System and Preferred Term
 Safety Analysis Set

Body system COSTART preferred term, n (%)	Modafinil (N=533)
TACHYCARDIA	1 (<1)
DIGESTIVE	159 (30)
ANOREXIA	69 (13)
VOMITING	35 (7)
GASTROENTERITIS	20 (4)
NAUSEA	20 (4)
DIARRHEA	19 (4)
DYSPEPSIA	10 (2)
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	9 (2)
INCREASED APPETITE	8 (2)
CONSTIPATION	7 (1)
DRY MOUTH	7 (1)
TOOTH DISORDER	3 (<1)
GASTROINTESTINAL DISORDER	2 (<1)
THIRST	2 (<1)
TOOTH CARIES	2 (<1)
APHTHOUS STOMATITIS	1 (<1)
DYSPHAGIA	1 (<1)
FECAL INCONTINENCE	1 (<1)
GASTRITIS	1 (<1)
GINGIVITIS	1 (<1)
LIVER FUNCTION TESTS ABNORMAL	1 (<1)
PERIODONTAL ABSCESS	1 (<1)
STOMACH ULCER	1 (<1)
TONGUE DISORDER	1 (<1)
HEMIC AND LYMPHATIC	28 (5)
ECCHYMOSIS	10 (2)
LEUKOPENIA	6 (1)
LYMPHADENOPATHY	6 (1)
LYMPHOCYTOSIS	3 (<1)
LEUKOCYTOSIS	2 (<1)
ANEMIA	1 (<1)
COAGULATION DISORDER	1 (<1)
THROMBOCYTOPENIA	1 (<1)

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Summary 15.15
 Adverse Events by Body System and Preferred Term
 Safety Analysis Set

Body system COSTART preferred term, n (%)	Modafinil (N=533)
METABOLIC AND NUTRITIONAL	62 (12)
WEIGHT LOSS	30 (6)
WEIGHT GAIN	12 (2)
SGOT INCREASED	8 (2)
SGPT INCREASED	8 (2)
HYPOGLYCEMIA	4 (<1)
HYPERCHOLESTEREMIA	3 (<1)
HYPERGLYCEMIA	3 (<1)
ACIDOSIS	2 (<1)
DEHYDRATION	2 (<1)
ALKALINE PHOSPHATASE INCREASED	1 (<1)
EDEMA	1 (<1)
HYPERKALEMIA	1 (<1)
HYPERURICEMIA	1 (<1)
KETOSIS	1 (<1)
MUSCULOSKELETAL	21 (4)
TWITCHING	12 (2)
MYALGIA	7 (1)
CHONDRODYSSTROPHY	1 (<1)
LEG CRAMPS	1 (<1)
MUSCULOSKELETAL CONGENITAL ANOMALY	1 (<1)
NERVOUS	205 (38)
INSOMNIA	138 (26)
NERVOUSNESS	30 (6)
DIZZINESS	15 (3)
EMOTIONAL LABILITY	14 (3)
PERSONALITY DISORDER	14 (3)
SOMNOLENCE	13 (2)
HOSTILITY	10 (2)
AGITATION	8 (2)
HYPERKINESIA	8 (2)
ANXIETY	6 (1)
THINKING ABNORMAL	5 (<1)
TREMOR	4 (<1)

Notes: Preferred terms are sorted by descending order of incidence within body system.
 Patients are counted only once in each preferred term category, and only once in each body system category.

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Summary 15.15
 Adverse Events by Body System and Preferred Term
 Safety Analysis Set

Body system COSIARI preferred term, n (%)	Modafinil (N=533)
DEPRESSION	3 (<1)
HYPERTONIA	3 (<1)
NEUROSIS	3 (<1)
DYSTONIA	2 (<1)
ABNORMAL DREAMS	1 (<1)
APATHY	1 (<1)
DEPERSONALIZATION	1 (<1)
HALLUCINATIONS	1 (<1)
NEUROPATHY	1 (<1)
SPEECH DISORDER	1 (<1)
RESPIRATORY	146 (27)
COUGH INCREASED	50 (9)
RHINITIS	50 (9)
PHARYNGITIS	37 (7)
SINUSITIS	18 (3)
ASTHMA	17 (3)
BRONCHITIS	14 (3)
EPISTAXIS	7 (1)
DYSPNEA	3 (<1)
PNEUMONIA	3 (<1)
LARYNGITIS	2 (<1)
RESPIRATORY DISORDER	1 (<1)
SKIN AND APPENDAGES	69 (13)
RASH	19 (4)
CONTACT DERMATITIS	12 (2)
PRURITUS	8 (2)
ECZEMA	5 (<1)
HERPES ZOSTER	5 (<1)
URTICARIA	5 (<1)
PUSTULAR RASH	4 (<1)
DRY SKIN	3 (<1)
FUNGAL DERMATITIS	3 (<1)
HERPES SIMPLEX	3 (<1)
SKIN BENIGN NEOPLASM	3 (<1)

Notes: Preferred terms are sorted by descending order of incidence within body system.
 Patients are counted only once in each preferred term category, and only once in each body system category.

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Summary 15.15
 Adverse Events by Body System and Preferred Term
 Safety Analysis Set

Body system COSTART preferred term, n (%)	Modafinil (N=533)
ALOPECIA	2 (<1)
NAIL DISORDER	2 (<1)
ACNE	1 (<1)
HAIR DISORDER	1 (<1)
MILIARIA	1 (<1)
SKIN DISCOLORATION	1 (<1)
SWEATING	1 (<1)
VESICULOBULLOUS RASH	1 (<1)
SPECIAL SENSES	34 (6)
CONJUNCTIVITIS	8 (2)
OTITIS MEDIA	7 (1)
EAR PAIN	5 (<1)
EAR DISORDER	3 (<1)
VESTIBULAR DISORDER	3 (<1)
EYE DISORDER	2 (<1)
OTITIS EXTERNA	2 (<1)
AMBLYOPIA	1 (<1)
ANISOCORIA	1 (<1)
DRY EYES	1 (<1)
REFRACTION DISORDER	1 (<1)
RETINAL DISORDER	1 (<1)
TASTE PERVERSION	1 (<1)
UROGENITAL	26 (5)
URINARY TRACT INFECTION	9 (2)
URINARY INCONTINENCE	5 (<1)
URINE ABNORMALITY	4 (<1)
DYSMENORRHEA	3 (<1)
HEMATURIA	2 (<1)
CYSTITIS	1 (<1)
DYSURIA	1 (<1)
KIDNEY CALCULUS	1 (<1)
MENORRHAGIA	1 (<1)
PYURIA	1 (<1)
VAGINAL MONILIASIS	1 (<1)

Notes: Preferred terms are sorted by descending order of incidence within body system.
 Patients are counted only once in each preferred term category, and only once in each body system category.

10.9 Listing 4.1.3 (Clinical Significant Abnormal Values for Selected Chemistry Laboratory Parameters for All Studies of Randomized Patients)

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Listing 4.1.3
 Clinically Significant Abnormal Values for Selected Chemistry Laboratory Parameters
 All Studies
 Randomized Patients

Test	Patient ID	Study	Treatment Group	Sex/Age	Study Day ^a	Lab		Lab		Abnormal Flag*	SI		Criteria for Significance
						Value	Unit	High	Low		Value	Unit	
URIC ACID	311_050218	312	ALL MODAFINIL	FEMALE/14	120	10.1	MG/DL	6.4	2.2	H	600.75	UMOL/L	SEX='F' / >=506
SGOT (AST)	213_05001	213OL	ALL MODAFINIL	MALE/8	76	229	U/L	42	0	H	229	U/L	>=3*ULN
	311_056180	312	ALL MODAFINIL	MALE/9	13	409	U/L	41	0	H	409	U/L	>=3*ULN
	311_056183	312	ALL MODAFINIL	MALE/17	139	128	U/L	41	0	H	128	U/L	>=3*ULN
	311_063329	312	ALL MODAFINIL	MALE/17	98	453	U/L	41	0	H	453	U/L	>=3*ULN
SGPT (ALT)	207_313	207OL	ALL MODAFINIL	FEMALE/11	32	122.00	U/L	20	5	H	122	U/L	>=3*ULN
	213_02012	312	ALL MODAFINIL	FEMALE/9	833	74	U/L	20	5	H	74	U/L	>=3*ULN
	309_006120	312	ALL MODAFINIL	MALE/9	275	262	U/L	30	5	H	262	U/L	>=3*ULN
	310_029109	310	ALL MODAFINIL	MALE/7	-21	103	U/L	30	5	H	103	U/L	>=3*ULN
	310_030639	310	ALL MODAFINIL	FEMALE/16	-16	65	U/L	20	5	H	65	U/L	>=3*ULN
	310_030639	310	ALL MODAFINIL	FEMALE/16	13	100	U/L	20	5	H	100	U/L	>=3*ULN
	310_037583	310	ALL MODAFINIL	MALE/12	48	97	U/L	30	5	H	97	U/L	>=3*ULN
	310_040627	312	ALL MODAFINIL	MALE/15	152	97	U/L	30	5	H	97	U/L	>=3*ULN
	311_042309	311	ALL MODAFINIL	MALE/8	52	95	U/L	30	5	H	95	U/L	>=3*ULN
	311_056180	312	ALL MODAFINIL	MALE/9	13	517	U/L	30	5	H	517	U/L	>=3*ULN
	311_056180	312	ALL MODAFINIL	MALE/9	22	210	U/L	30	5	H	210	U/L	>=3*ULN
	311_063329	312	ALL MODAFINIL	MALE/17	98	269	U/L	30	5	H	269	U/L	>=3*ULN
	311_063329	312	ALL MODAFINIL	MALE/17	103	117	U/L	30	5	H	117	U/L	>=3*ULN
	ALK PHOS	207_203	207OL	ALL MODAFINIL	MALE/7	94	281.00	IU/L	110	26	H	281	U/L
207_205		207OL	ALL MODAFINIL	MALE/11	108	243.00	IU/L	110	26	H	243	U/L	>=2*ULN
207_206		207OL	ALL MODAFINIL	MALE/7	56	269.00	IU/L	110	26	H	269	U/L	>=2*ULN
207_209		207OL	ALL MODAFINIL	MALE/6	115	279.00	IU/L	110	26	H	279	U/L	>=2*ULN
207_210		207OL	ALL MODAFINIL	MALE/9	89	232.00	IU/L	110	26	H	232	U/L	>=2*ULN
207_212		207OL	ALL MODAFINIL	FEMALE/8	89	410.00	IU/L	110	26	H	410	U/L	>=2*ULN
207_214		207OL	ALL MODAFINIL	MALE/7	40	275.00	IU/L	110	26	H	275	U/L	>=2*ULN
207_414		207OL	ALL MODAFINIL	MALE/11	116	262.00	IU/L	110	26	H	262	U/L	>=2*ULN
207_417		207DB	ALL MODAFINIL	FEMALE/7	-1	335.00	IU/L	110	26	H	335	U/L	>=2*ULN
GGT	309_006120	312	ALL MODAFINIL	MALE/9	275	95	U/L	22	3	H	95	U/L	>=3*ULN
	309_006120	312	ALL MODAFINIL	MALE/9	282	70	U/L	22	3	H	70	U/L	>=3*ULN
	309_016228	309	ALL MODAFINIL	MALE/9	62	68	U/L	22	3	H	68	U/L	>=3*ULN
	310_031558	312	ALL MODAFINIL	MALE/12	223	90	U/L	22	3	H	90	U/L	>=3*ULN

^aStudy Day: Day relative to the start of treatment for the individual pertinent study.
 L=Low; H=High; N=Normal

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Listing 4.1.3
 Clinically Significant Abnormal Values for Selected Chemistry Laboratory Parameters
 All Studies
 Randomized Patients

Test	Patient ID	Study	Treatment Group	Sex/Age	Study Day ^a	Lab		Lab		Abnormal Flag*	SI		Criteria for Significance
						Value	Unit	High	Low		Value	Unit	
GGT	310_031558	312	ALL MODAFINIL	MALE/12	230	70	U/L	22	3	H	70	U/L	>=3*ULN
	310_034582	312	ALL MODAFINIL	MALE/12	195	66	U/L	22	3	H	66	U/L	>=3*ULN
	310_034582	312	ALL MODAFINIL	MALE/12	230	77	U/L	22	3	H	77	U/L	>=3*ULN
	311_061341	312	ALL MODAFINIL	FEMALE/10	127	77	U/L	22	3	H	77	U/L	>=3*ULN
TOTAL BILIRUBIN	310_023550	310	ALL MODAFINIL	MALE/13	-21	2.1	MG/DL	1.2	0.1	H	35.91	UMOL/L	>=34.2
	311_043251	311	ALL MODAFINIL	MALE/15	-13	3.2	MG/DL	1.2	0.1	H	54.72	UMOL/L	>=34.2
	311_043251	311	ALL MODAFINIL	MALE/15	-9	2.4	MG/DL	1.2	0.1	H	41.04	UMOL/L	>=34.2
	311_052195	312	ALL MODAFINIL	MALE/14	110	2.5	MG/DL	1.2	0.1	H	42.75	UMOL/L	>=34.2
	311_058156	311	ALL MODAFINIL	MALE/15	-1	2	MG/DL	1.2	0.1	H	34.2	UMOL/L	>=34.2

10.10 Listing 4.1.1(Clinical Significant Abnormal Values for Selected Chemistry Laboratory Parameters for Phase 3 Double-Blind Studies, Randomized Patients)

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Listing 4.1.1
 Clinically Significant Abnormal Values for Selected Chemistry Laboratory Parameters
 Phase 3 Double-Blind Studies
 Randomized Patients

Test	Patient ID	Study	Treatment Group	Sex/Age	Study Day ^x	Lab		Lab		Abnormal Flag*	SI		Criteria for Significance
						Value	Unit	High	Low		Value	Unit	
SGPT (ALT)	309_017319	309	PLACEBO	MALE/8	-8	131	U/L	30	5	H	131	U/L	>=3*ULN
	310_029109	310	340 MG	MALE/7	-21	103	U/L	30	5	H	103	U/L	>=3*ULN
	310_030639	310	425 MG	FEMALE/16	-16	65	U/L	20	5	H	65	U/L	>=3*ULN
	310_030639	310	425 MG	FEMALE/16	14	100	U/L	20	5	H	100	U/L	>=3*ULN
	310_037583	310	425 MG	MALE/12	49	97	U/L	30	5	H	97	U/L	>=3*ULN
	311_042309	311	425 MG	MALE/8	53	95	U/L	30	5	H	95	U/L	>=3*ULN
	311_056183	311	PLACEBO	MALE/17	62	160	U/L	30	5	H	160	U/L	>=3*ULN
	GGT	309_016228	309	425 MG	MALE/9	63	68	U/L	22	3	H	68	U/L
TOTAL BILIRUBIN	310_023550	310	425 MG	MALE/13	-21	2.1	MG/DL	1.2	0.1	H	35.91	UMOL/L	>=34.2
	311_043251	311	425 MG	MALE/15	-13	3.2	MG/DL	1.2	0.1	H	54.72	UMOL/L	>=34.2
	311_043251	311	425 MG	MALE/15	-9	2.4	MG/DL	1.2	0.1	H	41.04	UMOL/L	>=34.2
	311_058156	311	<=255 MG	MALE/15	-1	2	MG/DL	1.2	0.1	H	34.2	UMOL/L	>=34.2

10.11 Portion of Sponsor’s Table 22: Liver Function Chemistry Values, Change from Baseline to Endpoint by Treatment Group for All Phase III Trials

Table 22: Serum Chemistry Variables and Change From Baseline to Endpoint by Treatment Group

Serum chemistry variable	Statistic	Phase 3 double-blind, placebo-controlled studies				All studies	
		Modafinil (N=420)		Placebo (N=213)		All Modafinil (N=933)	
		Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
Albumin (g/L)	n	419	382	213	197	906	810
	Mean	44.2	0.3	44.2	-0.4	44.3	0.5
	SD	2.41	2.62	2.40	2.85	2.31	2.59
	Median	44.0	0.0	44.0	0.0	44.0	0.0
	Min, max	36.0, 55.0	-10.0, 10.0	37.0, 52.0	-8.0, 9.0	36.0, 55.0	-10.0, 10.0
Uric acid (umol/L)	n	419	382	213	197	890	808
	Mean	241.3	-19.4	243.2	3.1	232.4	-5.0
	SD	69.82	43.25	65.47	41.36	66.39	48.06
	Median	232.0	-17.8	232.0	0.0	226.0	-5.9
	Min, max	89.2, 511.5	-184.4, 130.9	101.1, 463.9	-136.8, 130.9	89.2, 511.5	-184.4, 279.6
AST (U/L)	n	419	382	213	197	907	811
	Mean	26.7	2.0	27.2	2.2	27.0	1.7
	SD	7.59	8.07	6.62	7.89	7.12	8.62
	Median	26.0	2.0	26.0	2.0	26.0	1.0
	Min, max	4.0, 65.0	-37.0, 46.0	11.0, 48.0	-16.0, 69.0	4.0, 81.0	-58.0, 103.0
ALT (U/L)	n	419	382	213	197	906	811
	Mean	18.9	1.2	19.4	1.5	18.5	0.4
	SD	7.83	10.34	9.08	12.37	8.18	10.69
	Median	17.0	1.0	17.0	1.0	17.0	0.0
	Min, max	6.0, 57.0	-43.0, 70.0	2.0, 72.0	-33.0, 123.0	2.0, 87.0	-74.0, 88.0
Alkaline phosphatase (U/L)	n	419	382	213	197	906	810
	Mean	261.1	16.8	270.0	7.6	266.7	13.1
	SD	88.32	42.27	100.18	44.60	91.35	60.28
	Median	253.0	15.0	256.0	5.0	256.0	9.0
	Min, max	55.0, 697.0	-224.0, 206.0	58.0, 865.0	-155.0, 154.0	55.0, 865.0	-392.0, 482.0

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(Continued)

Table 22: Serum Chemistry Variables and Change From Baseline to Endpoint by Treatment Group

Serum chemistry variable	Statistic	Phase 3 double-blind, placebo-controlled studies				All studies	
		Modafinil (N=420)		Placebo (N=213)		All Modafinil (N=933)	
		Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
GGT (U/L)	n	419	382	213	197	857	792
	Mean	13.3	6.3	13.5	-0.1	13.5	5.9
	SD	4.71	6.01	4.51	2.94	5.06	6.17
	Median	12.0	6.0	12.0	0.0	12.0	5.0
	Min, max	5.0, 40.0	-8.0, 49.0	7.0, 35.0	-9.0, 23.0	5.0, 83.0	-10.0, 58.0
Total bilirubin (umol/L)	n	419	382	213	197	906	810
	Mean	6.1	-2.0	6.0	-0.5	6.2	-1.3
	SD	4.30	3.73	4.15	2.67	3.96	3.62
	Median	5.1	-1.7	5.1	0.0	5.1	-0.9
	Min, max	0.0, 41.0	-25.7, 5.1	1.7, 27.4	-12.0, 12.0	0.0, 41.0	-27.4, 18.8

SOURCE: Summaries 5.1.1 and 5.1.3.

Min=minimum; max=maximum; SD=standard deviation; GGT=gamma-glutamyl transpeptidase.

10.12 Sponsor's Table 23: Changes from Baseline in GGT and alkaline Phosphatase by Time interval in Phase III Trials

Table 23: Mean Changes From Baseline in GGT and Alkaline Phosphatase by Time Interval in Phase 3 Studies

Time Point	All modafinil (N=626)					
	GGT (U/L)			Alkaline phosphatase (U/L)		
	n	Mean (SD)	Min, max	n	Mean (SD)	Min, max
Baseline	621	13.3 (4.60)	5.0, 40.0	621	265.3 (93.1)	55.0, 865.0
Mean change from baseline to:						
≤2 weeks	156	1.7 (3.83)	-5.0, 29.0	156	7.3 (45.68)	-151.0, 163.0
≤1 month	238	4.0 (5.40)	-6.0, 50.0	238	15.6 (46.14)	-144.0, 183.0
≤3 months	595	5.5 (5.27)	-9.0, 35.0	592	15.2 (55.78)	-347.0, 482.0
≤6 months	596	6.1 (6.36)	-9.0, 52.0	593	11.8 (59.34)	-392.0, 482.0

SOURCE: Summaries 9.4.2 and 9.5.2.

Min=minimum; max=maximum; SD = standard deviation; GGT=gamma-glutamyl transpeptidase.

10.13 Table 13: Number of Patients with the Most Frequently Occurring Adverse Events ($\geq 5\%$ of Patients in the All Modafinil or Placebo Treatment Groups) by Body System and Adverse Event Type Phase 3 Double-Blind, Placebo-Controlled Studies

Table 13: Number of Patients With the Most Frequently Occurring Adverse Events ($\geq 5\%$ of Patients in the All Modafinil or Placebo Treatment Groups) by Body System and Adverse Event Type Phase 3 Double-Blind, Placebo-Controlled Studies

Body system Adverse event	Number (%) of patients				
	Modafinil			All modafinil (N=420)	Placebo (N=213)
	≤ 255 mg/day (N=62)	340 mg/day (N=102)	425 mg/day (N=256)		
No. of patients with any AE	49 (79)	84 (82)	195 (76)	328 (78)	135 (63)
Body as a whole					
Headache	13 (21)	23 (23)	46 (18)	82 (20)	27 (13)
Infection	7 (11)	9 (9)	30 (12)	46 (11)	28 (13)
Abdominal pain	6 (10)	9 (9)	25 (10)	40 (10)	17 (8)
Fever	6 (10)	6 (6)	9 (4)	21 (5)	7 (3)
Digestive					
Anorexia	12 (19)	22 (22)	33 (13)	67 (16)	6 (3)
Vomiting	2 (3)	9 (9)	10 (4)	21 (5)	13 (6)
Nervous					
Insomnia	21 (34)	37 (36)	57 (22)	115 (27)	8 (4)
Nervousness	6 (10)	9 (9)	4 (2)	19 (5)	9 (4)
Respiratory					
Cough increased	5 (8)	7 (7)	20 (8)	32 (8)	16 (8)
Rhinitis	4 (6)	7 (7)	20 (8)	31 (7)	21 (10)
Pharyngitis	5 (8)	6 (6)	19 (7)	30 (7)	15 (7)

SOURCE: Summary 4.1.1.

AE=adverse event.

10.14 Table 15: Number of Patients With the Most Frequently Occurring Adverse Events ($\geq 5\%$ of Patients) by Body System and Adverse Event Type All Phase 3 Studies and All Studies Combined (All Modafinil)

Table 15: Number of Patients With the Most Frequently Occurring Adverse Events ($\geq 5\%$ of Patients) by Body System and Adverse Event Type All Phase 3 Studies and All Studies Combined (All Modafinil)

Body system Adverse event	Number (%) of patients	
	All Phase 3 studies (N=626)	All studies (N=933)
No. of patients with at least 1 AE	545 (87)	794 (85)
Body as a whole		
Headache	170 (27)	235 (25)
Infection	137 (22)	160 (17)
Abdominal pain	90 (14)	130 (14)
Accidental injury	78 (12)	103 (11)
Fever	50 (8)	73 (8)
Pain	34 (5)	38 (4)
Flu syndrome	30 (5)	35 (4)
Infection bacterial	29 (5)	38 (4)
Digestive		
Anorexia	116 (19)	165 (18)
Vomiting	55 (9)	79 (8)
Nausea	35 (6)	59 (6)
Metabolic and nutritional		
Weight loss	37(6)	43 (5)
Nervous		
Insomnia	202(32)	277 (30)
Nervousness	45 (7)	61 (7)
Emotional lability	28 (4)	46 (5)
Somnolence	21 (3)	42 (5)
Respiratory		
Cough increased	73 (12)	102 (11)
Rhinitis	72 (12)	97 (10)
Pharyngitis	66 (11)	78 (8)
Skin and appendages		
Rash	34 (5)	49 (5)

SOURCE: Summaries 4.1.2 and 4.1.3.

AE=adverse event.

10.15 Primary Efficacy Instrument: ADHD-RS-IV School Version

Cephalon - C1538d/310/AD/US eCRF v1.13.15, 2004-05-17 -- Worksheet Printed 17 May 2004

Page 1 of 2

Center: _____ PID: _____ Initials: _____ Visit: _____

ADHD RATING SCALE-IV SCHOOL VERSION

NOT DONE

DATE OF ASSESSMENT	V	
DOES TEACHER SEE PATIENT BETWEEN NOON AND 2 PM?	<input type="radio"/> Yes <input type="radio"/> No	INTERVIEWER'S INITIAL
DAY OF ASSESSMENT:	<input type="radio"/> MON <input type="radio"/> TUES <input type="radio"/> WED <input type="radio"/> THURS <input type="radio"/> FRI	TEACHER'S INITIALS

Check the most appropriate box that best describes the frequency of each behavior.

ITE	Never or Rarely	Sometimes	Often	Very Often
1. Fails to give close attention to details or makes careless mistakes in schoolwork.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Fidgets with hands or feet or squirms in seat.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Has difficulty sustaining attention in tasks or play activities.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Leaves seat in classroom or in other situations in which remaining seated is expected.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Does not seem to listen when spoken to directly.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Runs about or climbs excessively in situations in which it is inappropriate.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Does not follow through on instructions and fails to finish work.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Has difficulty playing or engaging in leisure activities quietly.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

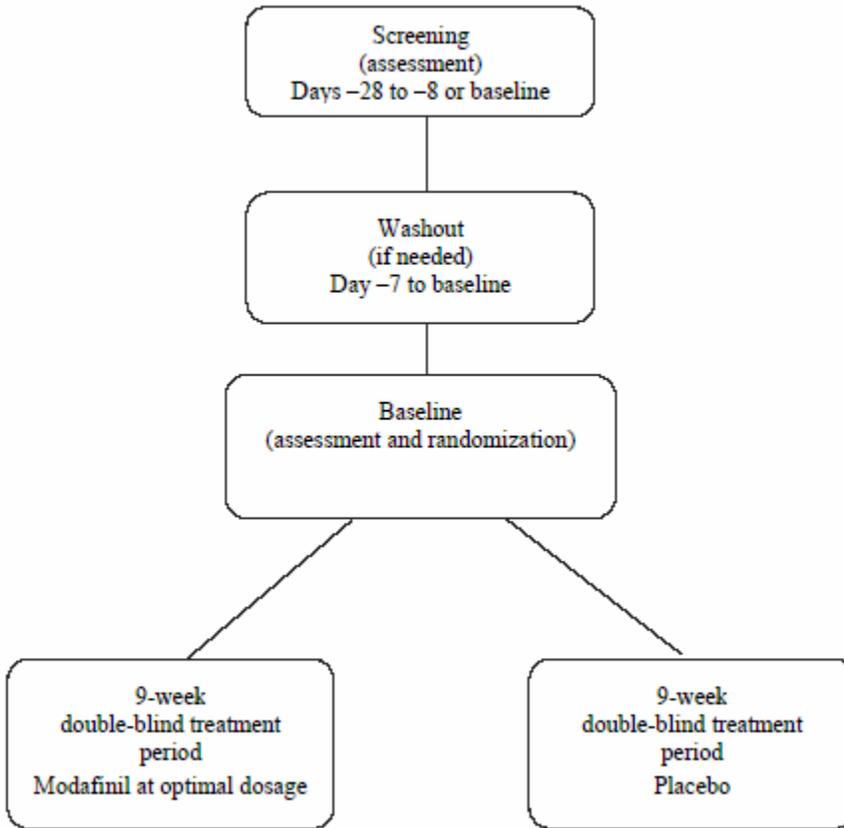
Center: _____ PID: _____ Initials: _____ Visit: _____

9. Has difficulty organizing tasks and activities.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Is "on the go" or acts as if "driven by a motor".	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. Avoids tasks (e.g., schoolwork, homework) that requires sustained mental effort.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. Talks excessively.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13. Loses things necessary for tasks or activities.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
14. Blurts out answers before questions have been completed.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15. Is easily distracted.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
16. Has difficulty awaiting turn.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
17. Is forgetful in daily activities.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18. Interrupts or intrudes on others.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

From ADHD Rating Scale - IV: Checklists, Norms, and Clinical Interpretation by George J. DuPaul, Thomas J. Power, Arthur D. Anastopoulos, and Robert Reid. Copyright 1998 by the authors. Permission to photocopy this scale is granted by purchasers of ADHD Rating Scale -IV for personal use only (see copyright page for details). ADHD criteria are adapted by permission from DSM-IV. Copyright 1994 by the American Psychiatric Association.

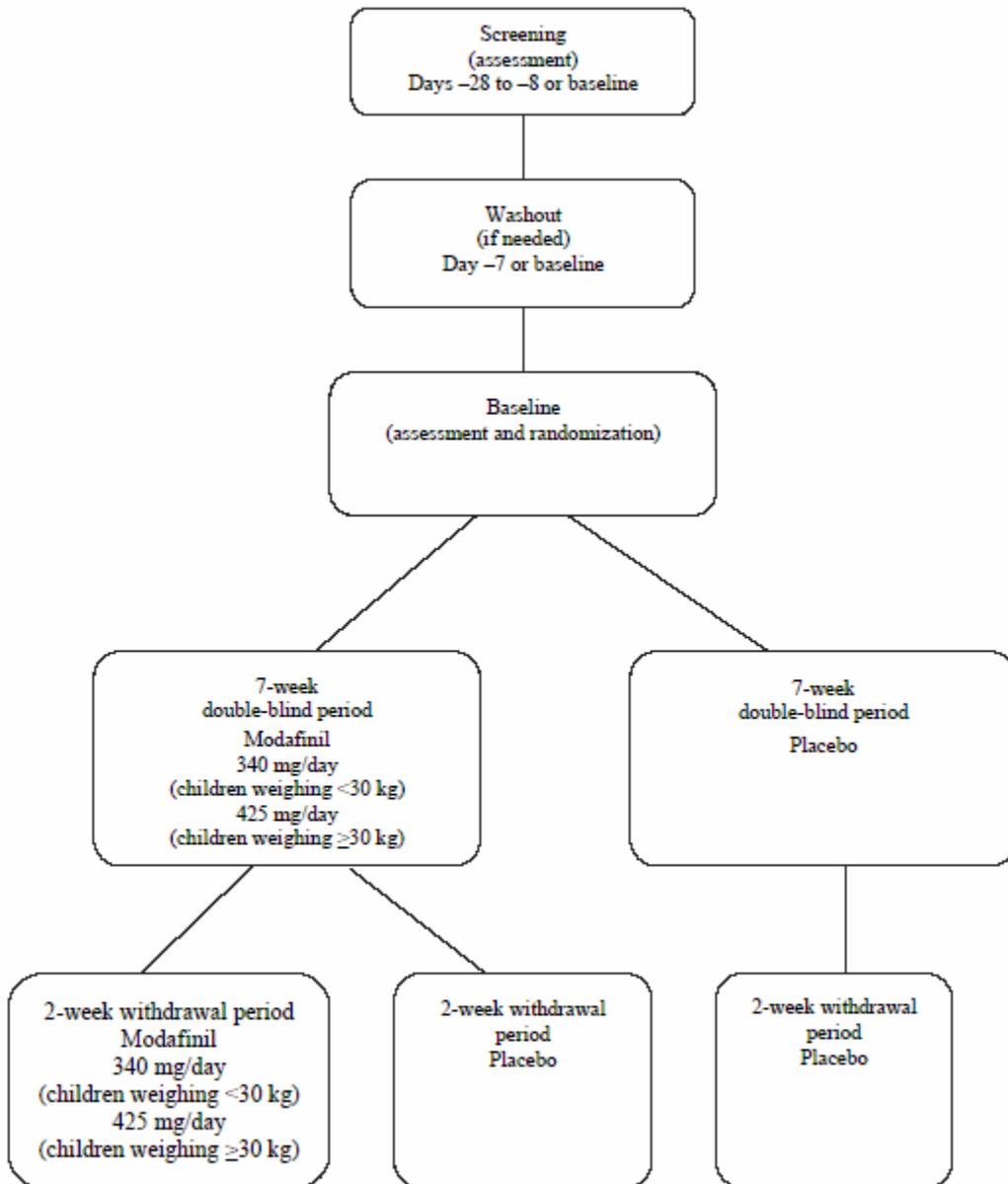
10.16 Overall Study Schema: Study 309, 311

Figure 1: Overall Study Schema



10.17 Overall Study Schema: Study 310

Figure 1: Overall Study Schema



10.18 Study Procedures and Assessments: Study 309, 311

Table 1: Study Procedures and Assessments

Procedures and assessments	Pretreatment			Double-blind treatment period					
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Days -28 to -8 Screening	Day -3 Washout	Day 0 Baseline	Week 1	Week 2	Week 3	Week 5	Week 7	Week 9/early termination
Informed consent	X								
Medical and psychiatric history	X								
Prior medication history	X								
Inclusion and exclusion criteria	X		X						
Diagnostic Interview Schedule for Children, Fourth Edition (DISC-IV)	X								
Wechsler Intelligence Scale for Children, Third Edition (WISC-III)	X								
Wechsler Individual Achievement Test, Second Edition, abbreviated (WIAT-II-A)	X								
Clinical laboratory tests	X		X	X ^a	X ^a	X ^a	X ^a	X ^a	X
Blood sample for drug assay	X		X ^b	X	X	X	X	X	X
Pregnancy test ^c	X		X				X		X
Urine drug screen (UDS)	X	X ^d							X
Body weight and height ^e	X	X	X	X	X	X	X	X	X
Vital signs measurement	X	X	X	X	X	X	X	X	X
12-lead Electrocardiography	X		X ^f						X
Physical examination	X								X
Adverse event inquiry	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry		X ^g	X	X	X	X	X	X	X
Teacher/physician-completed Rating Scale-IV (ADHD-RS-IV) (School Version)	X ^h			X	X	X	X	X	X
Test of Variables of Attention (TOVA)			X			X		X	X
Parent/physician-completed ADHD ADHD-RS-IV (Home Version)			X	X	X	X	X	X	X
Clinical Global Impression ⁱ	X ^h			X	X	X	X	X	X
Social Skills Rating Scale (SSRS)			X			X		X	X
Conners' Parent-Rated Scales-Revised, short form (CPRS-R-5)			X			X		X	X
Child Health Questionnaire (CHQ)			X						X
Dispense/collect study drug			X	X	X	X	X	X	X

Footnotes for this table are presented on the following page.

Footnotes for Table 1.

- ^a Hematology only to be conducted at weeks 1, 2, 3, 5, and 7.
^b For patients requiring a washout period, blood samples for drug assay will be collected at the baseline visit instead of the screening visit.
^c Human chorionic gonadotropin (HCG) for girls of child-bearing potential or all girls 8 years of age and older, only (to be performed at the screening and baseline visits and at weeks 5 and 9 [or early termination], and if clinically indicated thereafter).
^d Urine drug screen (UDS) to be performed after washout and 3 days before baseline only if positive for ADHD medications at the screening visit.
^e Height to be measured only at the screening and baseline visits and at week 9 (or early termination).
^f Electrocardiography to be performed at the baseline visit if more than 2 weeks have elapsed since the screening visit.
^g Any medications taken during the washout period are reported as prior medications.
^h For patients requiring a washout period, the ADHD-RS-IV (School Version) and the Clinical Global Impression of Severity (CGI-S) are to be performed after the washout period. The ADHD-RS-IV (School Version) will be performed no more than 3 days before the baseline visit and the CGI-S will be performed at the baseline visit.
ⁱ The CGI-S will be assessed at the screening/baseline visit; the Clinical Global Impression of Change (CGI-C) will be assessed at weeks 1, 2, 3, 5, 7, and 9 (or early termination).

ADHD=attention-deficit/hyperactivity disorder; ADHD-RS-IV=ADHD Rating Scale, Fourth Edition.

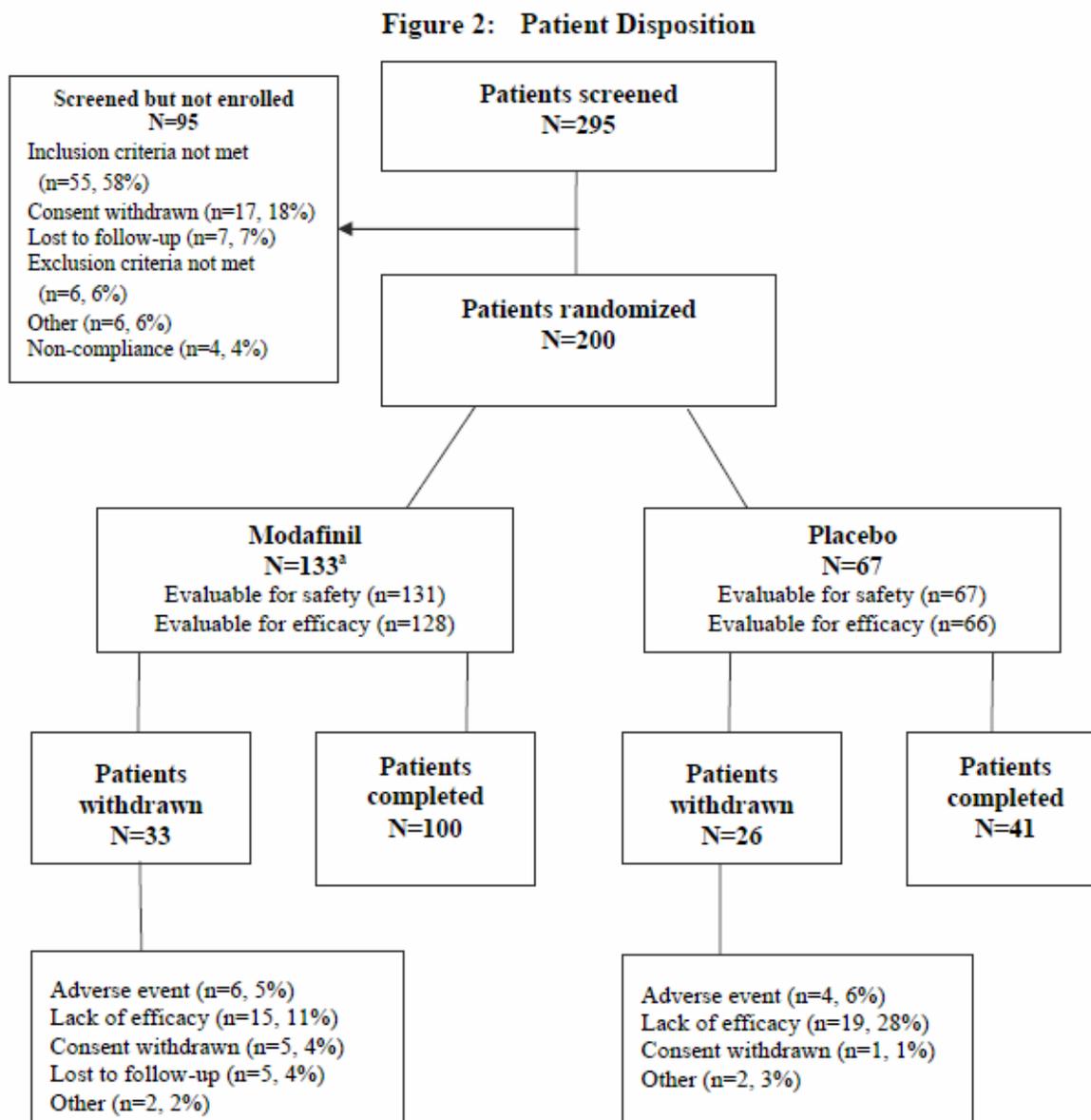
10.19 Study Procedures and Assessments: Study 310

Table 1: Study Procedures and Assessments

Procedures and assessments	Pretreatment			Double-Blind treatment period					Withdrawal period	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Telephone contact	Visit 9
	Days -28 to -8 Screening	(if necessary) Days -7 to baseline Without	Day 0 Baseline	Week 1	Week 2	Week 3	Week 5	Week 7/ early termination	Week 8	Week 9
Informed consent	X									
Medical and psychiatric history	X									
Prior medication history	X									
Inclusion and exclusion criteria	X		X							
Diagnostic Interview Schedule for Children, Fourth Edition (DISC-IV)DISC	X									
Wechsler Intelligence Scale for Children, Third Edition (WISC-III)	X									
Wechsler Individual Achievement Test, Second Edition, abbreviated (WIAT-II-A)	X									
Clinical laboratory tests	X		X	X*	X*	X*	X*	X		X
Blood sample for drug assay	X		X*	X	X	X	X	X		X
Pregnancy test	X		X					X		X
Urine drug screen (UDS)	X	X*						X		X
Body weight and height	X	X	X	X	X	X	X	X		X
Vital signs measurement	X	X	X	X	X	X	X	X		X
12-lead electrocardiography	X		X*					X		X
Physical examination	X							X		
Adverse event inquiry	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry		X*	X	X	X	X	X	X	X	X
Teacher/physician-completed ADHD-RS-IV (School Version)	X*			X	X	X	X	X		X
Test of Variables of Attention (TOVA)			X					X		X
Parent/physician-completed ADHD-RS-IV (Home Version)			X	X	X	X	X	X		X
Clinical Global Impression ¹	X*			X	X	X	X	X		X
Social Skills Rating Scale (SSRS)			X			X		X		X
Conners' Parent-Rated Scales Revised, short form (CPRS-R-S)			X			X		X		X
Child Health Questionnaire (CHQ)			X					X		X
Subject's Treatment Emergent Symptom Scale (STESS)			X						X	X
Dispense/collect study drug			X	X	X	X	X	X		X

Footnotes for this table are provided on the following page.

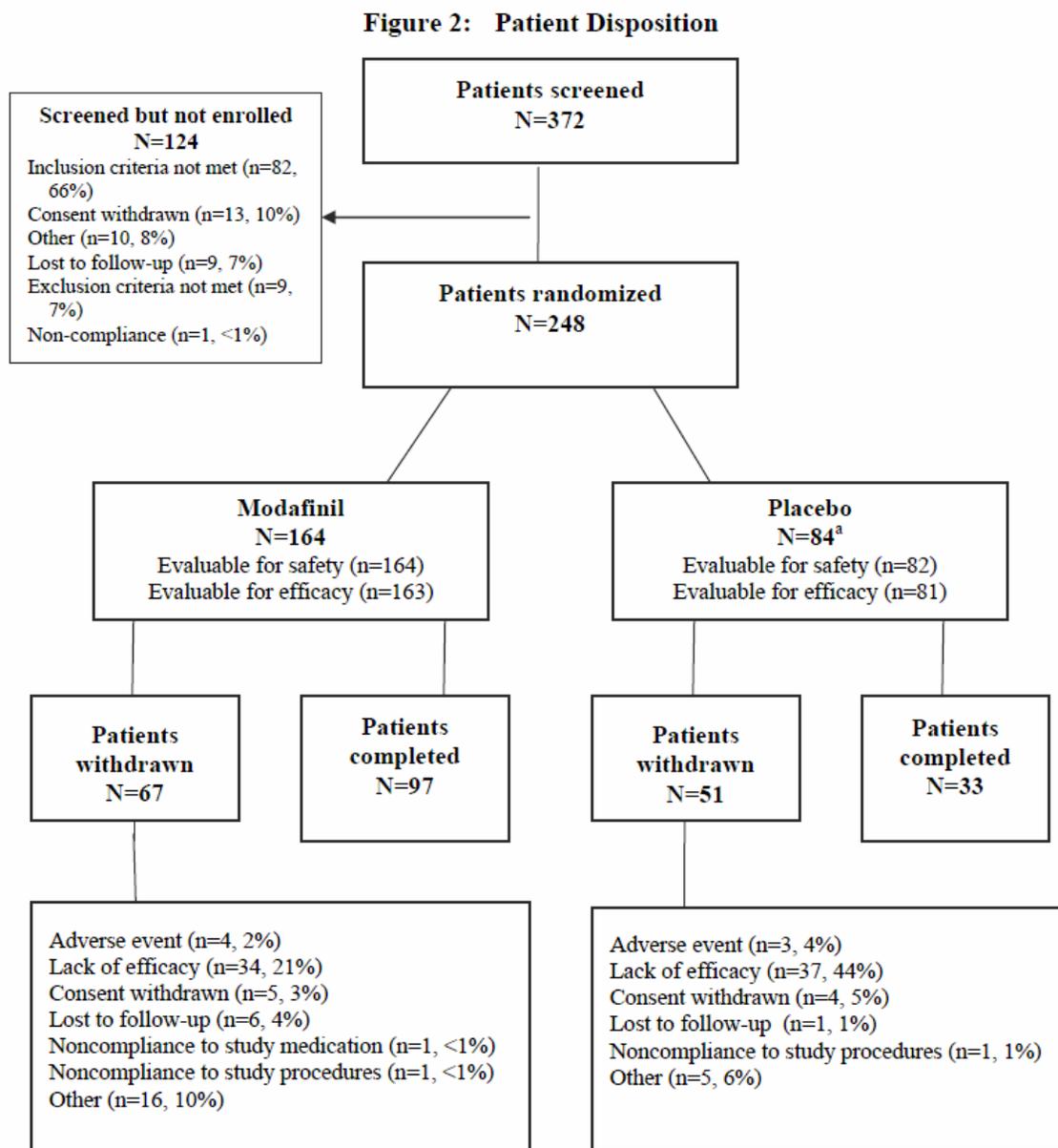
10.20 Subject Disposition: Study 309



SOURCE: Summary 15.1, Listing 2 and Listing 3.

^a Two patients randomized to the modafinil treatment group did not receive study drug.

10.21 Subject Disposition: Study 311

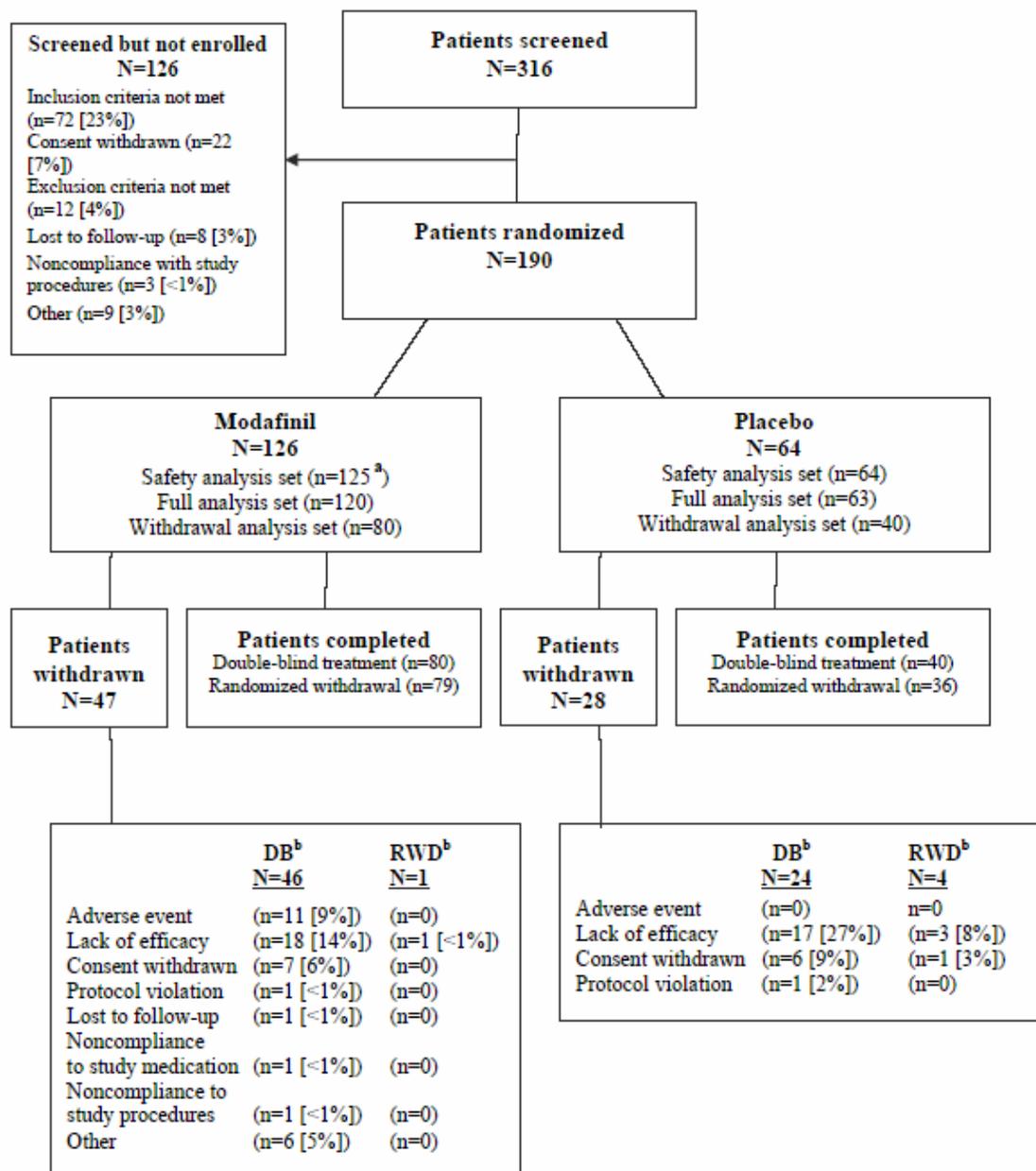


SOURCE: Summary 15.1, Listing 2 and Listing 3.

^a Two patients randomized to the placebo group did not receive study drug.

10.22 Subject Disposition: Study 310

Figure 2: Patient Disposition



SOURCE: Summary 15.1, Listing 2 and Listing 3.

^a One randomized patient did not take any study drug.

^b Percent is based on the total number of patients in the treatment group.

DB=double-blind; RWD=randomized withdrawal.

10.23 Disposition of All Subjects: Study 309

Table 6: Disposition of Patients (All Patients)

Patient disposition	Number (%) of patients		
	Modafinil	Placebo	Total
Screened	NA	NA	295
Randomized	133 (100)	67 (100)	200 (100)
Randomized, not treated	2 (2)	0	2 (1)
Safety analysis set	131 (98)	67 (100)	198 (99)
Full analysis set ^a	128 (96)	66 (99)	194 (97)
Completed	100 (75)	41 (61)	141 (71)
Discontinued study	33 (25)	26 (39)	59 (30)
Death	0	0	0
Adverse event	6 (5)	4 (6)	10 (5)
Lack of efficacy	15 (11)	19 (28)	34 (17)
Consent withdrawn	5 (4)	1 (1)	6 (3)
Protocol violation	0	0	0
Lost to follow-up	5 (4)	0	5 (3)
Noncompliance	0	0	0
Other	2 (2)	2 (3)	4 (2)
Enrolled into open-label study	113 (85)	57 (85)	170 (85)

SOURCE: Summary 15.1, Listing 2.

^a Three patients in the modafinil safety analysis set and 1 patient in the placebo safety analysis set were not evaluable for efficacy.

NA=not applicable.

10.24 Disposition of All Subjects: Study 311

Table 6: Disposition of Patients (All Patients)

Patient disposition	Number (%) of patients		
	Modafinil	Placebo	Total
Screened	NA	NA	372
Randomized	164 (100)	84 (100)	248 (100)
Randomized, not treated	0	2 (2)	2 (<1)
Safety analysis set	164 (100)	82 (98)	246 (>99)
Full analysis set ^a	163 (>99)	81 (96)	244 (98)
Completed	97 (59)	33 (39)	130 (52)
Discontinued study	67 (41)	51 (61)	118 (48)
Death	0	0	0
Adverse event	4 (2)	3 (4)	7 (3)
Lack of efficacy	34 (21)	37 (44)	71 (29)
Consent withdrawn	5 (3)	4 (5)	9 (4)
Protocol violation	0	0	0
Lost to follow-up	6 (4)	1 (1)	7 (3)
Noncompliance to study medication	1 (<1)	0	1 (<1)
Noncompliance to study procedures	1 (<1)	1 (1)	2 (<1)
Other	16 (10) ^b	5 (6)	21 (8)
Enrolled into open-label protocol	133 (81)	72 (86)	205 (83)

SOURCE: Summary 15.1, Listing 2.

^a One patient in the safety analysis set for each treatment group was not evaluable for efficacy.

^b According to the termination page of the case report form (CRF), "other" was the reason for withdrawal for 16 patients in the modafinil treatment group, however, according to the adverse event page of the CRF, 1 of these patients was withdrawn due to adverse events.

NA=not applicable.

10.25 Disposition of All Subjects: Study 310

Table 6: Disposition of Patients (All Patients)

Patient disposition	Number (%) of patients				
	Modafinil 340 mg/day (N=44)	Modafinil 425 mg/day (N=82)	All modafinil (N=126)	Placebo (N=64)	Overall (N=190)
Screened	NA	NA	NA	NA	316
Randomized	44 ^a	82 ^b	126	64	190
Completed double-blind treatment period	26 (59)	54 (66)	80 (63)	40 (63)	120 (63)
Withdrawn during double-blind treatment period	18 (41)	28 (34)	46 (37)	24 (38)	70 (37)
Adverse event	5 (11)	6 (7)	11 (9)	0	11 (6)
Lack of efficacy	8 (18) ^c	10 (12)	18 (14)	17 (27)	35 (18)
Consent withdrawn	1 (2)	6 (7)	7 (6)	6 (9)	13 (7)
Protocol violation	1 (2)	0	1 (<1)	1 (2)	2 (1)
Lost to follow-up	1 (2)	0	1 (<1)	0	1 (<1)
Noncompliance to study medication	1 (2)	0	1 (<1)	0	1 (<1)
Noncompliance to study procedures	0	1 (1)	1 (<1)	0	1 (<1)
Other	1 (2)	5 (6)	6 (5)	0	6 (3)
Completed randomized withdrawal period	26 (59)	53 (65)	79 (63)	36 (56)	115 (61)
Withdrawn during randomized withdrawal period	0	1 (1)	1 (<1)	4 (6)	5 (3)
Lack of efficacy	0	1 (1)	1 (<1)	3 (5)	4 (2)
Consent withdrawn	0	0	0	1 (2)	1 (<1)
Full analysis set	41 (93)	79 (96)	120 (95)	63 (98)	183 (96)
Safety analysis set	44 (100)	81 (99)	125 (>99)	64 (100)	189 (>99)
Withdrawal analysis set	26 (59)	54 (66)	80 (63)	40 (63)	120 (63)
Enrolled into open-label extension study	27 (61)	57 (70)	84 (67)	49 (77)	133 (70)

SOURCE: Summary 15.1, Listing 2, Listing 3, Listing 21, and Listing 22.

NA=not applicable; CRF=case report form.

^a Patient 023615 was properly assigned the 425 mg/day dosage of modafinil, but according to treatment records only took 340 mg of modafinil on days 13 through 60.

^b Patient 027609 who was assigned to, and received, 425 mg of modafinil on days 9 through 63, should have been assigned to receive 340 mg of modafinil (based on body weight).

^c According to the termination page of the CRF, lack of efficacy was the reason for withdrawal for 8 patients receiving 340 mg of modafinil; however, according to the adverse event page of the CRF, 1 of these patients was withdrawn due to adverse event.

10.26 Baseline Characteristics: Study 309

Table 8: Demographic Information (Safety Analysis Set)

Demographic variable	Modafinil (N=131)	Placebo (N=67)	Overall (N=198)
Age, years			
n	131	67	198
Mean	9.9	9.9	9.9
SD	2.64	2.90	2.72
Median	9.0	10.0	9.0
Min, max	6.0, 16.0	6.0, 16.0	6.0, 16.0
Sex, n (%)			
Male	95 (73)	49 (73)	144 (73)
Female	36 (27)	18 (27)	54 (27)
Race, n (%)			
White	95 (73)	47 (70)	142 (72)
Black	24 (18)	12 (18)	36 (18)
Asian	0	1 (1)	1 (<1)
American Indian or Alaskan Native	2 (2)	0	2 (1)
Pacific Islander	1 (<1)	1 (1)	2 (1)
Other	9 (7)	6 (9)	15 (8)
Weight, kg			
n	131	67	198
Mean	39.7	40.9	40.1
SD	15.88	16.50	16.06
Median	36.3	36.7	36.3
Min, max	18.6, 87.1	20.0, 85.3	18.6, 87.1
Height, cm			
n	131	67	198
Mean	141.1	143.3	141.8
SD	16.72	18.52	17.33
Median	136.7	140.5	137.2
Min, max	114.3, 186.2	118.1, 184.2	114.3, 186.2

SOURCE: Summary 15.2, Listing 5.

Min=minimum; max=maximum

Table 9: Baseline Characteristics for All Patients (Safety Analysis Set)

Characteristic	Number (%) of patients		
	Modafinil (N=131)	Placebo (N=67)	Overall (N=198)
CGI-S rating			
Normal	0	0	0
Borderline ill	0	0	0
Slightly ill	0	0	0
Moderately ill	47 (36)	29 (43)	76 (38)
Markedly ill	58 (44)	29 (43)	87 (44)
Severely ill	25 (19)	9 (13)	34 (17)
Among the most extremely ill patients	0	0	0
Not assessed	1 (<1)	0	1 (<1)
Current ADHD subtype*			
Inattentive	28 (21)	19 (28)	47 (24)
Hyperactive/impulsive	9 (7)	1 (1)	10 (5)
Combined	93 (71)	46 (69)	139 (70)

SOURCE: Summary 15.3, Listing 6 and Listing 10.

* Current ADHD subtype was not specified for patient 012197 in the modafinil group and patient 012198 in the placebo treatment group; both patients were granted exceptions to enter the study.

ADHD=attention-deficit/hyperactivity disorder; CGI-S=Clinical Global Impression of Severity.

10.27 Baseline Characteristics: Study 311

Table 8: Demographic Information (Safety Analysis Set)

Demographic variable	Modafinil (N=164)	Placebo (N=82)	Overall (N=246)
Age, years			
n	164	82	246
Mean	10.4	10.1	10.3
SD	2.88	2.86	2.87
Median	10.0	10.0	10.0
Min, max	6.0, 17.0	6.0, 17.0	6.0, 17.0
Sex, n (%)			
Male	113 (69)	61 (74)	174 (71)
Female	51 (31)	21 (26)	72 (29)
Race, n (%)			
White	127 (77)	63 (77)	190 (77)
Black	17 (10)	8 (10)	25 (10)
Asian	3 (2)	1 (1)	4 (2)
American Indian or Alaskan Native	2 (1)	0	2 (<1)
Other	15 (9)	10 (12)	25 (10)
Weight, kg			
n	164	82	246
Mean	43.6	41.4	42.9
SD	16.34	15.96	16.21
Median	41.0	36.7	39.4
Min, max	20.2, 85.4	18.6, 82.1	18.6, 85.4
Height, cm			
n	164	82	246
Mean	145.1	142.3	144.2
SD	17.61	16.92	17.40
Median	146.7	142.1	144.8
Min, max	115.5, 195.6	110.2, 179.1	110.2, 195.6

SOURCE: Summary 15.2, Listing 5.
 Min=minimum; max=maximum.

Table 9: Baseline Characteristics for All Patients (Safety Analysis Set)

Characteristic	Number (%) of patients		
	Modafinil (N=164)	Placebo (N=82)	Overall (N=246)
CGI-S rating			
Normal	0	0	0
Borderline ill	0	0	0
Slightly ill	0	0	0
Moderately ill	72 (44)	43 (52)	115 (47)
Markedly ill	66 (40)	27 (33)	93 (38)
Severely ill	25 (15)	12 (15)	37 (15)
Among the most extremely ill patients	1 (<1)	0	1 (<1)
Not assessed	0	0	0
Current ADHD subtype			
Inattentive	61 (37)	33 (40)	94 (38)
Hyperactive/impulsive	6 (4)	1 (1)	7 (3)
Combined	97 (59)	48 (59)	145 (59)

SOURCE: Summary 15.3, Listing 6 and Listing 10.
 ADHD=attention-deficit/hyperactivity disorder; CGI-S=Clinical Global Impression of Severity.

10.28 Baseline Characteristics: Study 310

Table 8: Demographic Information (Safety Analysis Set)

Demographic variable	Modafinil 340 mg/day (N=44)	Modafinil 425 mg/day (N=81)	All modafinil (N=125)	Placebo (N=64)	Overall (N=189)
Age, years					
Mean	7.5	11.6	10.1	9.7	10.0
SD	1.41	2.56	2.98	3.07	3.01
Min, max	6.0, 11.0	7.0, 17.0	6.0, 17.0	6.0, 17.0	6.0, 17.0
Sex, n (%)					
Male	30 (68)	63 (78)	93 (74)	42 (66)	135 (71)
Female	14 (32)	18 (22)	32 (26)	22 (34)	54 (29)
Race, n (%)					
White	33 (75)	67 (83)	100 (80)	51 (80)	151 (80)
Black	5 (11)	10 (12)	15 (12)	6 (9)	21 (11)
American Indian or Alaskan Native	0	1 (1)	1 (<1)	1 (2)	2 (1)
Other	6 (14)	3 (4)	9 (7)	6 (9)	15 (8)
Weight, kg					
Mean	25.2	48.8	40.5	39.9	40.3
SD	2.92	15.26	16.76	18.43	17.29
Min, max	19.6, 29.9	30.5, 98.4	19.6, 98.4	20.1, 91.2	19.6, 98.4
n (%) <30 kg	43 (98)	1 (1) ^a	44 (35)	24 (38)	68 (36)
n (%) ≥30 kg	1 (2) ^b	80 (99)	81 (65)	40 (63)	121 (64)
Height, cm					
Mean	124.5	151.6	142.0	141.0	141.7
SD	5.80	14.56	17.80	17.22	17.56
Min, max	112.0, 137.2	123.2, 185.0	112.0, 185.0	113.0, 172.7	112.0, 185.0

SOURCE: Summary 15.2, Listing 5.

^a Patient 027609 weighed 66 pounds at screening, was assigned to the 425 mg treatment group using a conversion factor of 2.2 performed at the study center.

^b Patient 023615 who weighed 45.8 kg at screening was assigned to receive 425 mg/day of modafinil; however, this

**Table 9: Baseline Characteristics for All Patients
 (Safety Analysis Set)**

Characteristic	Number (%) of patients ^a				
	Modafinil 340 mg/day (N=44)	Modafinil 425 mg/day (N=81)	All modafinil (N=125)	Placebo (N=64)	Overall (N=189)
CGI-S					
Normal	0	0	0	0	0
Borderline ill	0	0	0	0	0
Slightly ill	0	0	0	0	0
Moderately ill	29 (66)	50 (62)	79 (63)	38 (59)	117 (62)
Markedly ill	7 (16)	25 (31)	32 (26)	23 (36)	55 (29)
Severely ill	8 (18)	6 (7)	14 (11)	3 (5)	17 (9)
Among the most extremely ill	0	0	0	0	0
Current ADHD subtype					
Inattentive	11 (25)	24 (30)	35 (28)	16 (25)	51 (27)
Hyperactive/impulsive	4 (9)	1 (1)	5 (4)	5 (8)	10 (5)
Combined	29 (66)	55 (68)	84 (67)	42 (66)	126 (67)
Total number of symptoms					
Inattention					
n	41	78	119	63	-
Mean	21.4	22.2	21.9	21.0	ND
SD	3.90	3.91	3.91	4.25	ND
Median	22.0	23.0	23.0	22.0	ND
Min, max	10.0, 27.0	10.0, 27.0	10.0, 27.0	7.0, 27.0	ND
Hyperactive/impulsive					
n	41	78	119	63	-
Mean	17.5	15.1	15.9	15.7	ND
SD	7.94	7.56	7.75	7.12	ND
Median	20.0	16.0	17.0	16.0	ND
Min, max	0, 27.0	0, 27.0	0, 27.0	0, 27.0	ND
Combined					
n	41	78	119	63	-
Mean	38.9	37.3	37.8	36.6	ND
SD	9.39	8.68	8.93	9.24	ND
Median	41.0	37.0	39.0	38.0	ND
Min, max	18.0, 54.0	18.0, 53.0	18.0, 54.0	16.0, 54.0	ND

SOURCE: Summary 15.3 and Summary 15.10, and Listing 11 and Listing 14.

^a Except as otherwise indicated, percentages are based on safety analysis set; values may not have been obtained for all children.

ADHD=attention-deficit/hyperactivity disorder; ND=not determined.

10.29 Adverse Events Leading to Discontinuation: Study 309

Study	Pt No	Age	Sex	Race	Dose	SAE	WAE	Event
309	3102	9	M	B	85 mg		X	Cough, rhinorrhea, abdominal pain, malaise, drowsiness (somnolence)
	6123	8	M	Milano	255 mg		X	Severe decreased appetite (anorexia), twitching (nose, mouth), abdominal pain, emotional lability
	9127	9	M	W	255 mg		X	Cold, conjunctivitis, moderate insomnia
	14301	6	M	W	170 mg		X	Moderate mood swings (emotional lability), agitation
	16227	8	M	W	425 mg		X	URI, accidental injury (abrasion) moderate insomnia
	19137	10	F	W	255 mg		X	URI, pharyngitis followed by weight loss, indigestion (dyspepsia), rash, headache, fever, tremor, panic attacks (agitation)
	1114	8	M	B	Placebo		X	Cough, sore throat, moderate anxiety, tachycardia, severe insomnia
	2259	14	M	B	Placebo		X	Fever, sore throat, leukopenia, neutropenia,

								monocytosis; sedation, lethargy (somnia), difficulty focusing (abnormal thinking), muscle pain-soreness (legs, back)
	2282	13	M	W	Placebo		X	Increased irritability (nervousness)
	10176	12	M	W	Placebo		X	Rage (hostility)
XXX	Suggestions of Relation to Infection							
XXX	Psychiatric Worsening							
XXX	Dermatological							
XXX	Unusual Cases							

10.30 Adverse Events Leading to Discontinuation: Study 311

Study	Pt No	Age	Sex	Race	Dose	SAE	WAE	Event
311	42309	8	M	W	425 mg	X		Fever, vomiting, nausea, rash, dehydration, abdominal pain; diagnosed with duodenal ulcer, duodenitis (peptic ulcer) with spasm (hypertonia); sweating, insomnia, night terror (abnormal dreams), functional heart murmur
	62338	7	M	Asian	340 mg		X	Insomnia, fever, sore throat; rash over entire body, extensive skin peeling; moderate skin blistering; burning on urination; upper and lower lips (Steven Johnson Syndrome); erythema multiforme by history, and SJ by definition
	43190	8	M	W	340 mg		X	Cough, insomnia, lethargy (somnia)
	48361	10	F	W	170 mg		X	Possible allergic reaction; dystonic (dystonia) reaction
	49327	10	F	W	425 mg		X	Palpitations, moderate tachycardia, amblyopia, flushed face (vasodilatation)
	48210	8	F	W	Placebo		X	Pharyngitis, nausea, irritability (nervousness), moodiness (emotional lability)
	51138	7	M	W	Placebo		X	Anger (hostility), behavioral disturbance (personality disorder)
	59198	6	M	H	Placebo		X	Hyperactivity (hyperkinesia), increased baseline impulsivity
XXX	Suggestions of Relation to Infection							
XXX	Psychiatric Worsening							
XXX	Dermatological							
XXX	Unusual Cases							

10.31 Adverse Events Leading to Discontinuation: Study 310

Study	Pt No	Age	Sex	Race	Dose	SAE	WAE	Event
310	21191	9	M	W	340 mg	X		Moderate difficulty breathing on day 5; collapsed at school, stopped breathing momentarily on day 8, possible acute asthma attack (wheezing, reddened face, rapid breathing); ? allergic reaction
	34187	6	M	W	340 mg		X	Moderate flu syndrome, dehydration followed by fear of eating (anorexia), then 1 month later headaches, vomiting, 7% increase in weight and then a 7% decrease in weight
	21679	9	M	W	425 mg		X	Increased cough, insomnia, agitation, irritability
	31149	8	F	Brazilian	340 mg		X	Irritability (nervousness), amblyopia, headache, insomnia, dry mouth, confusion, pruritus, conjunctivitis

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SPARLON (Proposed Trade Name) and Provigil (Generic Name)

34132	9	M	M	340 mg	X	Moodiness (emotional lability), hostility, stuttering, incoordination, dyspepsia
21697	9	F	W	425 mg	X	Headache, anorexia, abdominal pain, severe insomnia
23552	11	F	B	425 mg	X	URI, leukopenia, neutropenia
28121	8	M	H	340 mg	X	Insomnia, lack of efficacy
30638	17	F	W	425 mg	X	Intermittent racing pulse (tachycardia), breathing difficulties (dyspnea), muscle tension (hypertonia), anxiety, abdominal pain
31142	6	M	W	340 mg	X	Emotional lability, insomnia, diaphoresis (sweating), headache
37688	9	M	W	425 mg	X	Moderate change in mental status (thinking abnormal), cough
40178	8	F	H	340 mg	X	Suicidal threat (suicidality)
40629	8	F	W	425 mg	X	Insomnia, headaches, mild hallucinations

SAE=Serious Adverse Event; WAE=Adverse Event Leading to Withdrawal

XXX= Adverse Event Term Identified By Sponsor

XXX Suggestions of Relation to Infection

XXX Psychiatric Worsening

XXX Dermatological

XXX Unusual Cases

10.32 Primary Efficacy, Full Analysis Set for Studies 301, 311 and 310

Table 7: Change From Baseline to Endpoint for the Total Score From the ADHD Rating Scale-IV (School Version) for the Phase 3 Placebo-Controlled Studies (Full Analysis Set)

Time point Statistic	Study 309		Study 310		Study 311		Combined	
	Modafinil (N=128)	Placebo (N=66)	Modafinil (N=120)	Placebo (N=63)	Modafinil (N=163)	Placebo (N=81)	Modafinil (N=411)	Placebo (N=210)
Baseline								
n	128	66	119	63	163	81	410	210
Mean	38.6	37.8	37.8	36.6	35.7	35.3	37.2	36.5
SD	8.81	9.02	8.93	9.24	9.25	8.75	9.09	9.00
SE of mean	0.78	1.11	0.82	1.16	0.72	0.97	0.45	0.62
Median	39.0	39.0	39.0	38.0	36.0	35.0	38.0	37.0
Min, max	12.0, 53.0	10.0, 53.0	18.0, 54.0	16.0, 54.0	6.0, 53.0	14.0, 54.0	6.0, 54.0	10.0, 54.0
Endpoint								
n	128	66	120	63	163	81	411	210
Mean	21.1	28.0	20.7	28.4	20.7	28.0	20.8	28.1
SD	13.57	12.70	13.05	12.71	13.86	12.69	13.51	12.64
SE of mean	1.20	1.56	1.19	1.60	1.09	1.41	0.67	0.87
Median	20.0	26.5	19.5	28.0	19.0	26.0	19.0	27.0
Min, max	0.0, 52.0	2.0, 50.0	0.0, 50.0	0.0, 50.0	0.0, 53.0	3.0, 54.0	0.0, 53.0	0.0, 54.0
Endpoint change from baseline								
n	128	66	119	63	163	81	410	210
Mean	-17.5	-9.7	-17.2	-8.2	-15.0	-7.3	-16.4	-8.3
SD	13.11	10.28	12.76	10.27	11.78	9.66	12.51	10.05
SE of mean	1.16	1.27	1.17	1.29	0.92	1.07	0.62	0.69
Median	-19.0	-8.5	-17.0	-8.0	-15.0	-6.0	-17.0	-7.5
Min, max	-46.0, 16.0	-32.0, 14.0	-50.0, 6.0	-32.0, 13.0	-43.0, 17.0	-31.0, 13.0	-50.0, 17.0	-32.0, 14.0
LS mean	-17.7	-10.3	-17.2	-8.2	-14.3	-6.4	-16.5	-8.5
SE of LS mean	1.14	1.57	1.12	1.51	0.94	1.26	0.57	0.79
p-value ^a	<0.0001	-	<0.0001	-	<0.0001	-	<0.0001	-
Effect estimate ^b	-7.4	-	-9.0	-	-8.0	-	-7.9	-
95% CI	(-11.1, -3.8)	-	(-12.7, -5.3)	-	(-10.9, -5.1)	-	(-9.8, -6.0)	-

SOURCE: Summary 4.0.

^a Each p-value is based on an analysis of covariance (ANCOVA) with baseline as the covariate. Factors for studies 309 and 311 are treatment and center. Factors for study 310 are treatment, strata, and treatment by strata. Factors for the combined analysis are treatment and study.

^b The effect estimate is the difference between treatment groups in the LS mean values.

LS mean=least squares mean; min=minimum; max=maximum.

10.33 Table 26 Hematology Variables and Change from Baseline to Endpoint by Treatment Group

Table 26: Hematology Variables and Change From Baseline to Endpoint by Treatment Group

Hematology variable	Statistic	Phase 3 double-blind, placebo-controlled studies				All studies	
		Modafinil (N=420)		Placebo (N=213)		All modafinil (N=933)	
		Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
WBC (10 ⁹ /L)	n	419	413	212	209	913	836
	Mean	7.4	-0.9	7.4	-0.1	7.1	-0.8
	SD	2.06	1.91	2.02	1.93	2.00	2.02
	Median	7.1	-0.8	7.2	-0.3	6.9	-0.8
	Min, max	3.8, 18.6	-8.9, 4.9	3.2, 14.3	-9.2, 8.1	3.0, 18.6	-11.1, 9.9
RBC (10 ¹² /L)	n	419	413	212	209	914	838
	Mean	4.7	-0.2	4.7	-0.1	4.6	-0.1
	SD	0.34	0.26	0.34	0.27	0.37	0.28
	Median	4.7	-0.2	4.7	-0.0	4.7	-0.1
	Min, max	3.9, 6.0	-1.0, 0.5	3.8, 6.0	-0.9, 0.9	3.5, 6.0	-1.0, 1.0
Hemoglobin (g/L)	n	419	413	212	209	914	837
	Mean	135.0	-3.8	134.0	-1.3	131.8	-0.9
	SD	9.56	7.50	9.57	7.66	10.01	7.78
	Median	134.0	-4.0	134.0	-1.0	131.0	-1.0
	Min, max	109.0, 174.0	-28.0, 24.0	110.0, 156.0	-24.0, 25.0	103.0, 174.0	-27.0, 28.0
Hematocrit (l/l)	n	419	413	212	209	914	839
	Mean	0.4	-0.0	0.4	-0.0	0.4	0.0
	SD	0.03	0.03	0.03	0.03	0.03	0.03
	Median	0.4	-0.0	0.4	-0.0	0.4	0.0
	Min, max	0.3, 0.5	-0.1, 0.1	0.3, 0.5	-0.1, 0.1	0.3, 0.5	-0.1, 0.1
ANC (10 ⁹ /L)	n	419	413	212	209	912	837
	Mean	4.0	-0.4	4.0	-0.1	3.8	-0.4
	SD	1.61	1.62	1.53	1.64	1.54	1.67
	Median	3.7	-0.5	3.7	-0.2	3.5	-0.4
	Min, max	1.4, 12.2	-8.0, 6.3	1.3, 9.7	-7.6, 7.2	0.4, 12.2	-7.6, 9.0

Footnotes on last page (continued)

Table 26: Hematology Variables and Change From Baseline to Endpoint by Treatment Group

Hematology variable	Statistic	Phase 3 double-blind, placebo-controlled studies				All studies	
		Modafinil (N=420)		Placebo (N=213)		All modafinil (N=933)	
		Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
Lymphocytes (%)	n	419	413	212	209	914	839
	Mean	35.4	-0.6	35.4	0.3	36.9	-0.7
	SD	9.11	8.68	9.02	8.48	9.47	9.89
	Median	35.4	-0.5	34.9	-0.1	36.7	-0.6
	Min, max	9.4, 60.0	-29.9, 27.5	15.2, 60.0	-30.4, 28.4	9.4, 83.0	-35.4, 33.5
Monocytes (%)	n	419	413	212	209	914	839
	Mean	5.7	0.1	5.8	0.5	5.8	0.3
	SD	1.56	2.15	1.78	2.39	1.98	2.61
	Median	5.5	-0.1	5.5	0.2	5.6	0.1
	Min, max	2.0, 12.9	-11.9, 14.2	1.4, 12.5	-6.2, 16.2	0.2, 16.0	-11.9, 17.0
Basophils (%)	n	419	413	212	209	912	838
	Mean	0.6	0.0	0.6	-0.0	0.5	0.1
	SD	0.31	0.43	0.35	0.41	0.35	0.43
	Median	0.6	0.0	0.6	0.0	0.5	0.1
	Min, max	0.0, 2.0	-1.6, 2.5	0.0, 2.0	-1.7, 1.2	0.0, 2.0	-2.0, 2.5
Eosinophils (%)	n	419	413	212	209	914	839
	Mean	3.1	-0.2	3.0	-0.0	3.3	-0.0
	SD	2.15	2.01	2.18	1.79	2.50	2.29
	Median	2.3	-0.2	2.3	0.0	2.5	-0.1
	Min, max	0.4, 12.5	-6.4, 13.2	0.5, 12.5	-5.9, 10.8	0.0, 20.7	-13.8, 11.7
Platelets (10 ⁹ /L)	n	419	413	212	209	914	839
	Mean	308.8	-25.8	308.4	-15.5	306.5	-30.1
	SD	66.90	52.12	69.29	49.01	65.95	56.21
	Median	304.0	-25.0	296.0	-13.0	301.0	-26.0
	Min, max	167.0, 594.0	-287.0, 160.0	166.0, 522.0	-144.0, 156.0	149.0, 594.0	-287.0, 210.0

SOURCE: Summaries 5.2.1 and 5.2.3.

Min=minimum; max=maximum; SD=standard deviation.

10.34 Sponsors Table 31 entitled Vital Signs and Changes from Baseline to Endpoint by Treatment Group

Table 31: Vital Signs and Changes From Baseline to Endpoint by Treatment Group

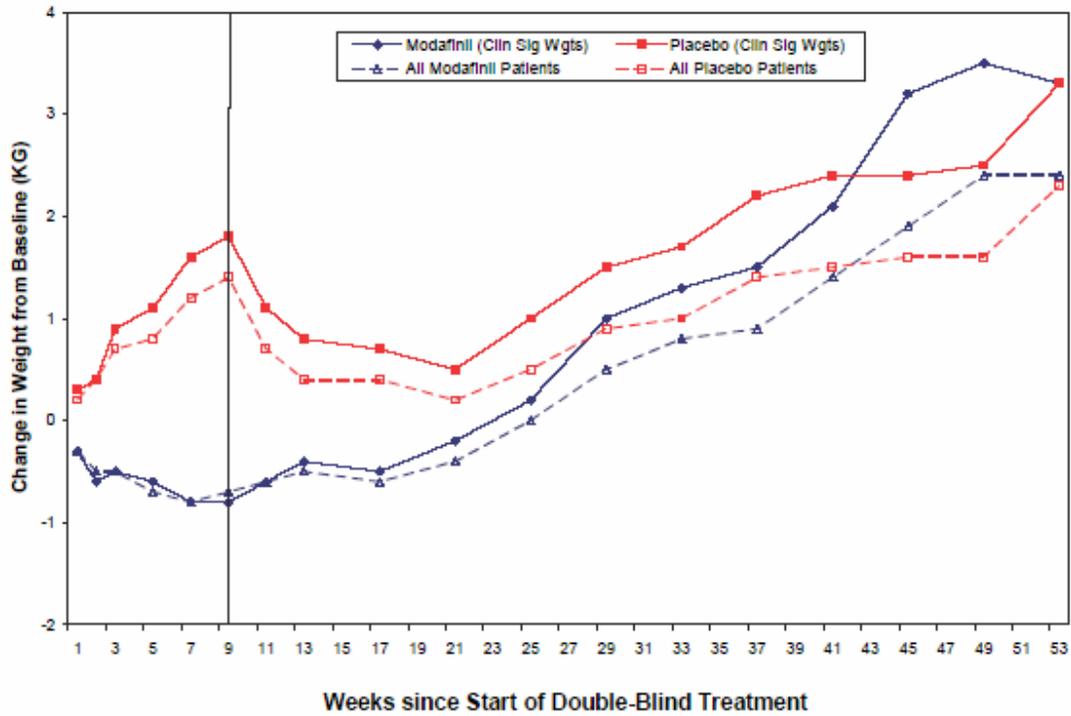
Vital sign variable	Statistic	Phase 3 double-blind, placebo-controlled studies				All studies	
		Modafinil (N=420)		Placebo (N=213)		All modafinil (N=933)	
		Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
Pulse (bpm)	n	420	416	213	212	924	876
	Mean	81.1	1.5	82.2	1.1	82.1	2.0
	SD	10.62	10.88	10.74	11.24	10.83	12.29
	Median	80.0	1.0	81.0	0.0	81.0	2.0
	Min, max	56.0, 110.0	-41.0, 36.0	53.0, 115.0	-28.0, 42.0	56.0, 119.0	-48.0, 42.0
Sitting systolic BP (mm Hg)	n	420	416	213	212	925	876
	Mean	105.5	-1.2	104.9	-0.9	105.2	0.4
	SD	10.09	9.19	10.19	9.99	10.11	10.08
	Median	104.0	-1.0	102.0	0.0	104.0	0.0
	Min, max	80.0, 134.0	-31.0, 22.0	80.0, 133.0	-31.0, 35.0	78.0, 134.0	-49.0, 34.0
Sitting diastolic BP (mm Hg)	n	420	416	213	212	925	876
	Mean	65.0	-0.6	65.2	-0.3	64.5	0.0
	SD	7.28	7.71	7.42	8.59	7.71	8.71
	Median	64.0	0.0	64.0	0.0	64.0	0.0
	Min, max	46.0, 82.0	-28.0, 22.0	46.0, 82.0	-24.0, 46.0	41.0, 86.0	-32.0, 38.0
Weight (kg)	n	420	416	213	212	905	858
	Mean	41.5	-0.7	40.8	1.0	39.9	1.0
	SD	16.38	1.63	16.83	1.26	15.58	3.36
	Median	38.2	-0.5	35.6	0.9	36.1	0.4
	Min, max	18.6, 98.4	-7.8, 4.8	18.6, 91.2	-2.3, 7.3	13.2, 98.4	-14.0, 25.8
Body temperature (°C)	n	420	416	213	212	897	850
	Mean	36.6	0.1	36.6	-0.0	36.6	0.01
	SD	0.47	0.53	0.53	0.59	0.52	0.58
	Median	36.7	0.0	36.7	0.0	36.7	0.0
	Min, max	34.5, 37.8	-1.9, 2.3	33.1, 38.1	-1.7, 3.4	33.1, 38.1	-1.7, 3.2

SOURCE: Summaries 6.1.1 and 6.1.3.

Min=minimum; max=maximum; SD=standard deviation; BP=blood pressure.

10.35 Mean Changes from Baseline in Body Weight during Double Blind and Open Label Periods

Figure 1: Mean Change From Baseline in Body Weight During Double-Blind and Open-Label Periods of Study by Double-Blind Treatment Group: Patients with Clinically Significant Changes in Body Weight During the Open-Label Period and All Patients in the Open-Label Study (C1538d/312/AD/US)



Clin sig wgt=clinically significant weight change during open-label treatment.

10.36 Absolute Values and Changes from Baseline to Endpoint in Electrocardiogram Intervals by Treatment Group Phase 3

Table 33: Absolute Values and Changes From Baseline to Endpoint in Electrocardiogram Intervals by Treatment Group Phase 3 Double-Blind, Placebo-Controlled Studies

ECG parameter	Statistic	Modafinil (N=420)			Placebo (N=213)		
		Baseline	Endpoint	Change	Baseline	Endpoint	Change
PR interval (msec)	n	420	399	399	213	201	201
	Mean	140.3	141.1	0.8	139.9	140.2	0.4
	SD	17.62	17.54	12.52	17.84	16.76	10.57
	Median	138.0	140.0	0.0	139.0	140.0	0.0
	Min, max	91.0, 203.0	95.0, 195.0	-55.0, 43.0	95.0, 223.0	102.0, 201.0	-23.0, 42.0
QRS interval (msec)	n	420	399	399	213	202	202
	Mean	78.0	79.6	1.4	77.3	78.9	1.5
	SD	7.24	7.14	6.02	6.97	7.23	6.19
	Median	77.0	78.0	2.0	77.0	78.0	1.0
	Min, max	63.0, 101.0	64.0, 110.0	-16.0, 20.0	63.0, 96.0	63.0, 105.0	-16.0, 23.0
QT interval (msec)	n	420	399	399	213	202	202
	Mean	356.7	355.1	-1.9	354.7	358.3	3.1
	SD	25.39	24.61	22.16	26.55	25.10	18.05
	Median	355.0	353.0	-1.0	353.5	356.5	4.0
	Min, max	292.0, 444.0	296.0, 432.0	-115.0, 66.0	301.0, 441.0	293.0, 430.0	-49.0, 49.0
QTc interval Bazett (msec)	n	420	399	399	213	202	202
	Mean	406.9	407.7	1.1	404.9	405.0	0.5
	SD	20.97	19.85	22.54	20.28	21.51	20.14
	Median	407.0	408.0	3.0	404.0	405.0	1.0
	Min, max	349.0, 464.0	347.0, 470.0	-62.0, 62.0	359.0, 483.0	351.0, 500.0	-59.0, 51.0
QTc interval Fridericia (msec)	n	420	399	399	213	202	202
	Mean	389.0	389.0	0.0	387.2	388.5	1.5
	SD	18.01	15.83	17.13	17.44	18.06	15.20
	Median	389.0	389.0	1.0	385.0	387.0	2.0
	Min, max	333.0, 456.0	329.0, 436.0	-48.0, 55.0	343.0, 468.0	346.0, 475.0	-39.0, 37.0
QTc interval Neuropharm ^a (msec)	n	419	399	398	213	201	201
	Mean	392.9	393.0	0.4	391.0	391.9	1.1
	SD	18.19	16.09	17.92	17.51	18.38	16.00
	Median	393.0	393.0	1.0	390.0	390.0	1.0
	Min, max	336.0, 457.0	333.0, 441.0	-48.0, 57.0	348.0, 471.0	347.0, 480.0	-42.0, 39.0

SOURCE: Summary 7.1.1.

^a Based on calculation defined by the FDA Division of Neuropharmacological Drug Products.

ECG=electrocardiogram; SD=standard deviation; min=minimum; max=maximum; QTc=QT interval corrected for heart rate.

10.37 Maximum Absolute Value and Change from Baseline in QTc Interval by Treatment Group Phase 3 Double- Blind

Table 34: Maximum Absolute Value and Change From Baseline in QTc Interval by Treatment Group Phase 3 Double-Blind, Placebo-Controlled Studies

Variable	Category	Number (%) of patients	
		Modafinil (N=420)	Placebo (N=213)
QTc interval Bazett	Maximum absolute change from baseline (msec)		
	<30	325 (77)	175 (82)
	30 - 60	69 (16)	27 (13)
	>60	6 (1)	0
	Maximum value on treatment (msec)		
	<450	387 (92)	197 (92)
450 - 500	13 (3)	5 (2)	
>500	0	0	
QTc interval Fridericia	Maximum absolute change from baseline (msec)		
	<30	367 (87)	188 (88)
	30 - 60	33 (8)	14 (7)
	>60	0	0
	Maximum value on treatment (msec)		
	<450	400 (95)	201 (94)
450 - 500	0	1 (<1)	
>500	0	0	
QTc interval Neuropharm ^a	Maximum absolute change from baseline (msec)		
	<30	362 (86)	185 (87)
	30 - 60	37 (9)	16 (8)
	>60	0	0
	Missing	1 (<1)	1 (<1)
	Maximum value on treatment (msec)		
<450	400 (95)	200 (94)	
450 - 500	0	1 (<1)	
>500	0	0	
Missing	0	1 (<1)	

SOURCE: Summary 7.3.1.

^a Based on calculation defined by the FDA Division of Neuropharmacological Drug Products.

QTc=QT interval corrected for heart rate.

10.38 Tables of Subgroup Analysis: Gender, Race, Age

**Table 36: Adverse Events Occurring in $\geq 5\%$ of Patients by Subgroup
 According to Gender
 Phase 3 Double-Blind, Placebo-Controlled Studies**

Body system Adverse event	Number (%) of patients			
	Boys		Girls	
	Modafinil (N=301)	Placebo (N=152)	Modafinil (N=119)	Placebo (N=61)
Number of patients with at least 1 AE	229 (76)	98 (64)	99 (83)	37 (61)
Body as a whole				
Headache	55 (18)	22 (14)	27 (23)	5 (8)
Infection	32 (11)	21 (14)	14 (12)	7 (11)
Abdominal pain	26 (9)	14 (9)	14 (12)	3 (5)
Accidental injury	15 (5)	5 (3)	3 (3)	4 (7)
Fever	12 (4)	5 (3)	9 (8)	2 (3)
Pain	7 (2)	3 (2)	7 (6)	2 (3)
Digestive				
Anorexia	42 (14)	4 (3)	25 (21)	2 (3)
Vomiting	15 (5)	8 (5)	6 (5)	5 (8)
Nausea	11 (4)	2 (1)	4 (3)	3 (5)
Nervous				
Insomnia	78 (26)	4 (3)	37 (31)	4 (7)
Emotional lability	14 (5)	5 (3)	3 (3)	3 (5)
Nervousness	12 (4)	5 (3)	7 (6)	4 (7)
Somnolence	9 (3)	4 (3)	1 (<1)	3 (5)
Respiratory				
Cough increased	18 (6)	11 (7)	14 (12)	5 (8)
Pharyngitis	23 (8)	11 (7)	7 (6)	4 (7)
Rhinitis	20 (7)	17 (11)	11 (9)	4 (7)
Skin and appendages				
Rash	10 (3)	4 (3)	8 (7)	1 (2)

SOURCE: Summary 4.7.1.

AE=adverse event.

**Table 37: Adverse Events Occurring in $\geq 5\%$ of Patients by Subgroup
 According to Race
 Phase 3 Double-Blind, Placebo-Controlled Studies**

Body system Adverse event	Number (%) of patients			
	White		Other	
	Modafinil (N=322)	Placebo (N=161)	Modafinil (N=98)	Placebo (N=52)
Number of patients with at least 1 AE	253 (79)	105 (65)	75 (77)	30 (58)
Body as a whole				
Headache	64 (20)	24 (15)	18 (18)	3 (6)
Infection	36 (11)	20 (12)	10 (10)	8 (15)
Abdominal pain	30 (9)	12 (7)	10 (10)	5 (10)
Fever	18 (6)	5 (3)	3 (3)	2 (4)
Accidental injury	13 (4)	6 (4)	5 (5)	3 (6)
Digestive				
Anorexia	52 (16)	3 (2)	15 (15)	3 (6)
Vomiting	14 (4)	10 (6)	7 (7)	3 (6)
Nausea	8 (2)	4 (2)	7 (7)	1 (2)
Nervous				
Insomnia	90 (28)	4 (2)	25 (26)	4 (8)
Nervousness	15 (5)	7 (4)	4 (4)	2 (4)
Emotional lability	13 (4)	8 (5)	4 (4)	0
Respiratory				
Pharyngitis	25 (8)	12 (7)	5 (5)	3 (6)
Rhinitis	25 (8)	19 (12)	6 (6)	2 (4)
Cough increased	22 (7)	12 (7)	10 (10)	4 (8)
Skin and appendages				
Rash	15 (5)	4 (2)	3 (3)	1 (2)

SOURCE: Summary 4.8.1.

AE=adverse event.

**Table 38: Adverse Events Occurring in ≥5% of Patients by Subgroup
 According to Age
 Phase 3 Double-Blind, Placebo-Controlled Studies**

Body system Adverse event	Number (%) of patients			
	<12 years		≥12 years	
	Modafinil (N=279)	Placebo (N=142)	Modafinil (N=141)	Placebo (N=71)
Number of patients with at least 1 AE	222 (80)	94 (66)	106 (75)	41 (58)
Body as a whole				
Headache	47 (17)	19 (13)	35 (25)	8 (11)
Infection	31 (11)	22 (15)	15 (11)	6 (8)
Abdominal pain	28 (10)	16 (11)	12 (9)	1 (1)
Fever	16 (6)	5 (4)	5 (4)	2 (3)
Accidental injury	9 (3)	6 (4)	9 (6)	3 (4)
Asthenia	5 (2)	3 (2)	2 (1)	4 (6)
Digestive				
Anorexia	51 (18)	1 (<1)	16 (11)	5 (7)
Vomiting	18 (6)	7 (5)	3 (2)	6 (8)
Metabolic and nutritional				
Weight loss	8 (3)	0	8 (6)	1 (1)
Nervous				
Insomnia	87 (31)	5 (4)	28 (20)	3 (4)
Nervousness	16 (6)	5 (4)	3 (2)	4 (6)
Emotional lability	14 (5)	8 (6)	3 (2)	0
Somnolence	6 (2)	2 (1)	4 (3)	5 (7)
Respiratory				
Cough increased	27 (10)	10 (7)	5 (4)	6 (8)
Rhinitis	23 (8)	12 (8)	8 (6)	9 (13)
Pharyngitis	21 (8)	8 (6)	9 (6)	7 (10)
Skin and appendages				
Rash	13 (5)	4 (3)	5 (4)	1 (1)

SOURCE: Summary 4.9.1.
 AE=adverse event.

**Table 39: Adverse Events Occurring in ≥5% of Patients by Subgroup
 According to Weight
 Phase 3 Double-Blind, Placebo-Controlled Studies**

Body system Adverse event	Number (%) of patients			
	<30 kg		≥30 kg	
	Modafinil (N=128)	Placebo (N=75)	Modafinil (N=292)	Placebo (N=138)
Number of patients with at least 1 AE	102 (80)	49 (65)	226 (77)	86 (62)
Body as a whole				
Headache	20 (16)	10 (13)	62 (21)	17 (12)
Accidental injury	6 (5)	3 (4)	12 (4)	6 (4)
Fever	9 (7)	4 (5)	12 (4)	3 (2)
Infection	13 (10)	14 (19)	33 (11)	14 (10)
Infection bacterial	6 (5)	2 (3)	4 (1)	2 (1)
Abdominal pain	11 (9)	10 (13)	29 (10)	7 (5)
Flu syndrome	7 (5)	2 (3)	5 (2)	4 (3)
Digestive				
Anorexia	24 (19)	1 (1)	43 (15)	5 (4)
Vomiting	10 (8)	4 (5)	11 (4)	9 (7)
Metabolic and nutritional				
Weight loss	2 (2)	0	14 (5)	1 (<1)
Nervous				
Insomnia	44 (34)	2 (3)	71 (24)	6 (4)
Emotional lability	7 (5)	7 (9)	10 (3)	1 (<1)
Nervousness	7 (5)	2 (3)	12 (4)	7 (5)
Respiratory				
Cough increased	14 (11)	5 (7)	18 (6)	11 (8)
Pharyngitis	8 (6)	2 (3)	22 (8)	13 (9)
Rhinitis	10 (8)	7 (9)	21 (7)	14 (10)

SOURCE: Summary 4.10.1.
 AE=adverse event.

10.39 Treatment Emergent Symptom Scale

Table 41: Change From Baseline to the Last Withdrawal Visit for Total Scores From the Subject's Treatment Emergent Symptom Scale Study C1538d/310/AD/US (Withdrawal Analysis Set)

Timepoint Statistic	Modafinil-after-modafinil (N=43)	Placebo-after-modafinil (N=37)	Placebo-after-placebo (N=40)
Baseline			
n	43	37	40
Mean	15.6	13.4	15.3
SD	6.97	7.62	10.30
Median	15.0	11.0	13.0
Min, max	4.0, 38.0	3.0, 40.0	0, 55.0
Last withdrawal visit			
n	42	37	39
Mean	12.4	7.8	11.7
SD	9.40	4.43	6.43
Median	10.0	7.0	10.0
Min, max	0, 45.0	0, 21.0	0, 27.0
Change from baseline to last withdrawal visit			
n	42	37	39
SD	-3.1	-5.5	-3.6
Median	10.55	8.13	9.04
Median	-4.5	-5.0	-3.0
Min, max	-25.0, 34.0	-35.0, 6.0	-35.0, 12.0

SOURCE: Summary 9.8.

Min=minimum; max=maximum; SD=standard deviation.

10.40 Postmarketing Reports of Congenital, Familial and Genetic Disorders

Listing of All Reports of Serious Adverse Events (Non-United States) and United States Postmarketing Reports of Serious Adverse Events (Continued)

10010331 - Congenital, familial and genetic disorders:										
UK000410	*	GB	Spont.	NI	M			Pyloric stenosis	Recovered/resolved	Infant may have been exposed to modafinil transplacentally during initial four weeks of gestation. Mother additionally experienced pre-eclampsia at 34 weeks. Ref: UK000430.
US009300	*	US	Spont.	0 days	F	100 mg	9 months	Pulmonary atresia, Transposition of the aorta and pulmonary artery, Ventricular septal defect, Hypoglycemia, Malrotation of intestines	Recovering/resolving	02-Apr-02: Physician unsure of relationship between mother's gestational modafinil use and events experienced by infant.
US009577	*	US	Spont.	0 days	F	200 mg		Choroid plexus cyst right side brain, Umbilical cord around neck, Reflux, Colic, Projectile vomiting	Unknown outcome	Prospective pregnancy report. Follow-up information regarding outcome of pregnancy. Case US009786 refers to maternal experience.

Footnotes and abbreviations appear at the end of the table.

(continued)

MedDRA system organ class Cephalon reference number	Country	Source	Age	Gender	Dosage of PROVIGIL	Time to onset	Description of reaction(s)	Outcome	Comments
US013508 *	US	Spont.	0 days	M	200 mg	1 year 7 months	Mild hypotonia, Chordee	Unknown outcome	Indication for use: drug induced sedation Modafinil therapy discontinued at approximately 1 month gestation Additional suspect drugs: OXYCODONE HYDROCHLORIDE NI

10.41 Postmarketing Reports of Pregnancy, Puerperium and Perinatal Conditions

Listing of All Reports of Serious Adverse Events (Non-United States) and United States Postmarketing Reports of Serious Adverse Events (Continued)

10036585 - Pregnancy, puerperium and perinatal conditions

CEPH-1538-99-5279 *	US	Spont.	37 yrs	F	200 mg	0 days	Spontaneous abortion, Chest pain, Palpitations, Nervousness	Recovered/resolved	Indication for use: idiopathic hypersomnia Absence of fetal heart sounds on ultrasound, dilation and curettage performed. Patient had a history of mitral valve prolapse Cardiac symptoms: positive dechallenge
UK000430 *	GB	Spont.	26 yrs	F	400 mg		Pre-eclampsia	Recovered/resolved	Patient experienced pre-eclampsia at 34 weeks of pregnancy. She was induced at 37 weeks and gave birth to a male infant with pyloric stenosis. Ref: UK000410.

Footnotes and abbreviations appear at the end of the table.

(continued)

MedDRA system organ class Cephalon reference number	Country	Source	Age	Gender	Dosage of PROVIGIL	Time to onset	Description of reaction(s)	Outcome	Comments
UK000470 *	GB	Spont.	32 yrs	F	500 mg	2 years 27 weeks 4 days	Spontaneous abortion	Recovered/resolved	Event happened at 24 weeks of pregnancy. Treatment with modafinil was discontinued at week 8; concomitant medication clomipramine was taken throughout pregnancy. Physician attribution: Possibly related to both modafinil and clomipramine Additional suspect drugs: CLOMIPRAMINE 250 mg
US007613 *	US	Spont.	37 yrs	F		19 weeks	Missed abortion	Recovered/resolved	Modafinil therapy continues. Hypothyroidism. 3 spontaneous abortions within the past year, 1 previous therapeutic abortion, and 3 previous spontaneous abortions.
US008075 *	GB	Spont.	25 yrs	F	400 mg	9 months	Spontaneous abortion	Recovered/resolved	
US009299 *	US	Spont.	37 yrs	F	200 mg	2 years	Pre-term labor, Low glucose in breast milk	Recovering/resolving	
US009784 *	US	Spont.	0 days	F	200 mg	1 year	Premature birth	Recovered/resolved	Prospective pregnancy information. Event reported on follow up. Attribution received from the physician revealed an unlikely relationship between the event and modafinil therapy since the mother has a prior history of premature delivery.

Footnotes and abbreviations appear at the end of the table.

(continued)

10.42 Post-Marketing, Most Frequently Reported ADR's

Table 42: Most Frequently Reported Adverse Drug Reactions (≥ 25 Occurrences) With Modafinil Treatment

Adverse drug reaction	Number of occurrences
Headache	255
Nausea	146
Insomnia	122
Drug interaction	82
Drug ineffective	82
Somnolence	75
Anxiety	71
Nervousness	67
Dry mouth	66
Dizziness	65
Diarrhea	65
Drug tolerance	63
Fatigue	60
Depression	49
Weight decreased	46
Blood pressure increased	46
Tremor	44
Palpitations	42
Asthenia	41
Chest pain	40
Dyspnea	38
Agitation	37
Heart rate increased	35
Irritability	34
Rash	33
Hyperhidrosis	31
Paresthesia	29
Vision blurred	28
Dyskinesia	28
Feeling abnormal	27
Confusional state	27
Weight increased	27
Vomiting	26
Feeling jittery	26
Pruritus	25
Anorexia	25
Arthralgia	25
Urine odor abnormal	25

10.43 Post-Marketing Reports of Leukopenia and Neutropenia, ADR's

Table 43: Postmarketing Reports of Leukopenia and Neutropenia

MedDRA preferred term	Number of serious events	Number of nonserious events	Total number of events
Agranulocytosis	1	0	1
Bone marrow depression	1	0	1
Febrile neutropenia	1	0	1
Leukopenia	2	0	2
Neutropenia	2	1	3
Pancytopenia	2	0	2
Full blood count abnormal	1	0	1
White blood cell count decreased	0	1	1

MedDRA=Medical Dictionary of Regulatory Activities.

11 LINE-BY-LINE LABELING REVIEW

The labeling review will be filed as an Addendum Review if the determination is subsequently made by others in the Agency that they find that this drug is approvable for the indication.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Glenn Mannheim
9/29/2005 12:27:43 PM
MEDICAL OFFICER

Paul Andreason
10/12/2005 09:39:09 AM
MEDICAL OFFICER

I disagree with the recommendation for a Not Approved
Action. I believe that more information is needed
before taking a final action on this NDA
Supplement. Please see my memo to the file
dated 10/12/2005.