

CLINICAL REVIEW

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Applicant	Cephalon
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Dosing Regimen	(b) (4)
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Intended Population	Pediatric patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

[REDACTED] (b) (4)

Based upon the results from this study I would suggest that a double-blind placebo-controlled study be done utilizing 100 mg as the maximum modafinil dose. The current study did demonstrate an apparent objective effect of the 100 mg dose. There is no apparent statistical or clinical benefit to the use of higher doses in treating children with narcolepsy and while there appears to be no studied dose which is free from associated psychiatric adverse events, there is some indication that the risk of such events is greater with higher doses.

Since co-primary endpoints measuring both objective and subjective efficacy should again be used, the participants should have both objective and subjective complaints at study entry. The future study should incorporate teacher's ratings of excessive daytime sleepiness as well as the child's assessment thereof since they are the ones who will see/feel the effects of daytime sleepiness. A total reliance on parental reports of sleepiness will not suffice.

While I do recommend [REDACTED] (b) (4) the results of Study 3027 taken in combination with the results from the attention deficit/hyperactivity (ADHD) database lead me to conclude that future study of modafinil in the treatment of narcolepsy should be restricted to pediatric patients aged 12 years and above, as that is the group in which the potential benefit appears to outweigh the risk. The sponsor asserts that "the safety profile of PROVIGIL demonstrated in this clinical program is consistent with that seen in...other pediatric studies with modafinil (p. 27 of the clinical overview, section 2.5)." I would note that in addition to the most commonly reported adverse event which was headache, the adverse event profile for this development program includes psychosis, hostility and suicidal ideation. While based upon the data from the ADHD safety database I would agree that these findings are consistent with what has been previously described, I do not concur with the sponsor's implication that this is an acceptable level of risk in light of the (modest) potential benefit to be gained from modafinil use. The majority of the pediatric patients who reported psychiatric adverse events in the narcolepsy development program were under 12 years old. I do not think that the benefit of modafinil use will outweigh the risk in that subset of the pediatric population. Since narcolepsy is most commonly diagnosed/treated in early adolescents, age restriction would be clinically appropriate if modafinil were to demonstrate efficacy in an adequately designed placebo-controlled double-blind study. Additionally, it seems appropriate to consider restricting use of this product in patients with past history of psychosis or mania in light of the stimulant effects of the product. It may be prudent to contraindicate the product in persons with a past history of suicidal ideation or gestures.

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If modafinil were to demonstrate efficacy at a maximal dose of 100 mg in the subset of pediatric patients aged 12 years and older, then the sponsor would have to address the risk of Stevens-Johnson syndrome (SJS). In light of a finding of probable Stevens-Johnson syndrome during the ADHD pediatric trials, the Advisory Committee recommended further investigation to ‘cap the risk’ of SJS at 1/1000 with modafinil use. Since, if efficacy could be demonstrated, (b) (4) the concern over SJS related risk remains the same. The risk of SJS should be adequately assessed, so that it can be appropriately factored into the risk/benefit analysis. (b) (4)

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Cephalon did not submit a risk management plan in support of this application. There is no risk management plan for PROVIGIL as currently marketed to adults. However, in light of recent media attention on the misuse of modafinil by high school and college students, a risk management plan might be an appropriate consideration, e.g. <http://www.washingtonpost.com/wp-dyn/content/article/2006/06/10/AR2006061001181.html>.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 requests.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Modafinil (PROVIGIL) is a racemic CNS activating agent with a chemical structure and pharmacology dissimilar to sympathomimetic stimulants such as amphetamine, methylphenidate and ephedrine.

It is indicated for use (in adults) “in excessive sleepiness due to narcolepsy, obstructive sleep apnea and/or shift work sleep disorder.”

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The sponsor provided efficacy data from a single double-blind placebo-controlled study in pediatric patients with narcolepsy: C1538/3027/NA/MN. Safety data was provided from that trial, a trial in pediatric patients with obstructive sleep apnea, as well as a 12 month open-label extension of those two trials and a six-month open-label safety trial conducted abroad in children with narcolepsy or obstructive sleep apnea. Additionally, the sponsor relied upon safety data from trials of modafinil in pediatric patients with attention deficit/hyperactivity disorder (ADHD).

The single efficacy trial submitted enrolled 165 patients. The safety trials specific to this application enrolled a total of 239 patients: 91 patients were enrolled in the 6 month trial, 148 were enrolled in the ongoing 12 month safety extension trial.

1.3.2 Efficacy

The sponsor provided data from a double-blind placebo-controlled efficacy study for review: Study C1538/3027/NA/MN. While the primary efficacy study was intended to be a six-week study with a 12-month open-label safety extension, the sponsor allowed investigators to transfer patients to the open label study after 3 weeks of double blind treatment assuming the given patient had not been withdrawn from the double-blind study due to adverse events. Patients were allowed to transfer due to perceived lack of efficacy, e.g. in an informed consent document for the efficacy study, it was stated that in patients who were perceived to have continued excessive sleepiness, parents could “ask for early termination after 3 weeks of participation and roll-over to the open label study where [the] child [would] be on a known amount of study drug.”

The primary efficacy measures were the Multiple Sleep Latency test (MSLT) and the Clinical Global Impression of Change (CGI-C) ratings for severity of excessive sleepiness (ES) at the last post baseline observation (week 6 or early termination).

The efficacy analysis was based upon all patients who had received at least one dose of study drug and who had at least one post-baseline MSLT or CGI-C; 160 patients in the active treatment arms and 41 in the placebo arm.

The study submitted in support of this application represents a failed trial in that neither of the pre-specified co-primary endpoints achieved statistical significance.

The statistical hypothesis to be tested for MSLT, an objective measure of benefit, was a test for linear trend in the placebo and modafinil treatment groups. The data indicate that there was no linear dose response in the active control group when the results at endpoint were compared to the results at baseline, p-value 0.0604. We have secondary evidence of a modest objective benefit, specifically prolongation of sleep latency with all three doses of modafinil studied: the 100 mg/day group had a mean increase of 3.8 minutes, the 200 mg/day group had a mean increase of 4.8 minutes, the 400 mg/day group had a mean increase of 3.0 minutes, the placebo group had a mean increase of 0.6 minutes. There is no dose response effect so there would be no reason to recommend use of doses higher than 100 mg.

There is no subjective evidence of benefit. On the pre-specified primary endpoint of change in CGI-C from baseline to endpoint, the study failed to demonstrate overall efficacy of active drug as

compared to placebo. While the sponsor was able to demonstrate statistical significance at the 100 mg dose at endpoint, that dose did not show statistical evidence of benefit at the Week 3 evaluation nor did it show benefit in those children who completed the study, i.e. those evaluated at Week 6. Additionally, the secondary endpoint of change from baseline in the pediatric daytime sleepiness scale confirmed the lack of clinical improvement since none of the doses studied were able to distinguish themselves from placebo.

1.3.3 Safety

Safety data was provided from a trial in pediatric patients with narcolepsy, a trial in pediatric patients with obstructive sleep apnea, as well as a 12 month open-label extension of those two trials and a six-month open-label safety trial conducted abroad in pediatric patients with narcolepsy or obstructive sleep apnea. Additionally, the sponsor relied upon safety data from trials of modafinil in pediatric patients with attention deficit/hyperactivity disorder (ADHD). When information from the narcolepsy trials was combined with the data from the ADHD trials, safety data was available from over 1000 patients.

There were no deaths reported during the narcolepsy development program. The majority of the patients who withdrew from the placebo-controlled narcolepsy study due to adverse events were under age 12 years. Psychiatric adverse events such as psychosis, hostility and suicidal ideation were seen predominantly in children under age 12 years and at doses higher than 100 mg/day. Insomnia was also seen more frequently in younger patients as compared to older patients (17% vs. 9%).

Realizing that the data from placebo-controlled trials in children with narcolepsy is based upon 165 patients, adverse events that may be considered common and drug related in this pediatric subset are the following:

- Insomnia
- Hostility/Irritability
- Abdominal pain
- Pharyngitis and Sinusitis

Cataplexy and hypnagogic hallucinations are components of narcolepsy. These symptoms were described by some patients as adverse events, indicating that there may be patients in whom use of modafinil is associated with idiosyncratic worsening of preexisting symptoms.

While no significant rashes were seen in the patients who participated in the narcolepsy development program, concern has been raised about an association between SJS and modafinil usage in the pediatric population. This is an issue which warrants further investigation as well as notification of the potential risk (b) (4).

1.3.4 (b) (4)

(b) (4)

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[Redacted] (b) (4)

1.3.5 [Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted]

1.3.6 [Redacted] (b) (4)

[Redacted] (b) (4)

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Modafinil (PROVIGIL) is a racemic CNS activating agent with a chemical structure and pharmacology dissimilar to sympathomimetic stimulants such as amphetamine, methylphenidate and ephedrine.

In adults it is indicated for use in excessive sleepiness due to narcolepsy, obstructive sleep apnea and/or shift work sleep disorder. (b) (4)

2.2 Currently Available Treatment for Indications

The only other product indicated for the treatment of excessive daytime sleepiness due to narcolepsy is gamma hydroxybutyrate, currently marketed as Xyrem. (b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

Cephalon is the American licensee of Lafon's product Modafinil, which received orphan drug development status [OD 93-737] for the indication "excessive daytime sleepiness associated with narcolepsy" in 1993. Clinical pharmacology trials, safety trials and pivotal efficacy trials were conducted under IND 42,873.

It has been marketed in the US since 1999 and is marketed in 31 other countries worldwide. This product was licensed but never marketed in Ukraine. An application for marketing was submitted in (b) (4) but subsequently withdrawn (b) (4). Applications were rejected in (b) (4). The sponsor did not provide the rationales for the refusals.

The initial US approval was for use in patients with excessive sleepiness due to narcolepsy. The sponsor subsequently applied to extend the indication for use in other conditions associated with excessive sleepiness. An advisory committee was convened to discuss the matter. As of January 2004, the indication was extended to allow for the treatment of excessive sleepiness due to obstructive sleep apnea/hypopnea syndrome and for the treatment of excessive sleepiness due to shift work sleep disorder.

The sponsor reports that there has been a total exposure of 780,000 patient-treatment years: 750,000 patient-treatment years in adults; 30,000 patient-treatment years in children.

Cephalon also reported the following updates to the Provigil labeling:

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- Aganulocytosis as well as symptoms consistent with psychosis and mania were added to the postmarketing reports section in October 2002
- Urticaria and angioedema were added to the postmarketing reports section in February 2004
- Suspected cases of erythema multiforme and suspected cases of Stevens-Johnson syndrome were added to the postmarketing reports section in December 2004

Cephalon reports that modafinil has not been withdrawn from marketing for safety reasons.

2.4 Important Issues With Pharmacologically Related Products

In March of 2006, an FDA Advisory Committee recommended strengthening the warning language on the stimulants as a class to address the possibility of psychosis, specifically hallucinations in the pediatric population. While modafinil is not technically a stimulant but rather a ‘wakefulness-promoting agent,’ it was discussed as a member of this general class and the recommendation was extended to its use.

2.5 Presubmission Regulatory Activity

At the time of this review, the only NDA for this product is NDA 20-717: PROVIGIL (modafinil) indicated for excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder.

There are three related INDs:

42,873: PROVIGIL (modafinil) tablets for narcolepsy

(b) (4)

[Reviewer’s note: The studies performed in response to the Pediatric Written Request (PWR) were performed under this IND.]

(b) (4)

June 5 2003

Cephalon submitted a proposed pediatric study request (S-198 to IND 42,873) comprising a rationale along with 2 synopses of proposed studies: a double blind, placebo-controlled, parallel-group, 6-week study (study 307) followed by a one year open-label extension study (study 308) (b) (4)

The originally proposed populations of interest were patients with narcolepsy, patients with residual sleepiness associated with treated obstructive sleep apnea (OSA) (b) (4)

The proposed primary endpoints were a measure of attention (TOVA) as well as a measure of global clinical benefit (CGIS/C):

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- Test of variables of attention (TOVA) is a continuous performance test which has been used to assess attention and cognitive impairment in children. TOVA has been validated in persons aged 6 to 19 years.
- Clinical global impression of change (CGI-C) is the assessment of change in the patient's overall condition as assessed by the investigator.

The proposed secondary endpoints were chosen to support the findings of the primary efficacy endpoints:

- Pediatric Daytime Sleepiness Scale (PDSS), a self (or parent)-report questionnaire that is similar to the Epworth Sleepiness Scale used in adults.
- Multiple Sleep Latency Test (MSLT). This sponsor argued that this 'should be a secondary endpoint in this study since 1) this procedure may be difficult to execute in children, 2) unlike in adults, it is not yet validated in children to quantify improvement in sleepiness associated with clinical intervention, and 3) the MSLT requires an overnight stay in the sleep laboratory and may be difficult for children...it [was] proposed that a nocturnal polysomnograph and MSLT be conducted at screening for diagnostic and baseline information and again at endpoint (Week 6 /final visit) in order to provide additional supportive efficacy information. (from S-198 the PPSR)'

(b) (4)

June 17, 2004

The Agency issued a Pediatric Written Request (PWR) to Cephalon for studies of modafinil in pediatric patients with narcolepsy and in pediatric patients with obstructive sleep apnea.

Three types of studies were requested:

- Study type 1: A PK and tolerability study of modafinil
- Study type 2: Efficacy and safety studies of modafinil

Obstructive sleep apnea (OSA)

A single multi-center pediatric double-blind, placebo-controlled, randomized parallel-group efficacy and safety study in patients with excessive daytime sleepiness resulting from OSA. This study must be at least 6 weeks in duration.

Narcolepsy

A single multi-center pediatric double-blind, placebo-controlled, randomized parallel-group efficacy and safety study in patients with excessive daytime sleepiness resulting from narcolepsy. This study must be at least 6 weeks in duration.

- Study type 3: One year safety study of modafinil

"We are requesting that at least 100 patients treated with differing therapeutic doses of modafinil be followed for one year with monthly blood counts and differentials." The longer-term safety studies may be open-label or controlled studies. Adequate longer-term safety data must be distributed amongst the different indications studied. For each grouping (by age and indication), the minimum number of patients indicated besides that grouping must be exposed to study drug for 6 months.

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Specific safety concerns include cognitive and behavioral (anxiety, nervousness and symptoms of mania /psychosis) effects of the drug. Monitoring must include interviews by a child psychologist or psychiatrist and a standardized test of behavior (e.g. the Aschenbach Child Behavior Checklist).

Changes in cognition associated with both short and long term use of modafinil must also be determined. Age-appropriate cognitive assessment must also be performed.

Other adverse effects that are of specific interest include effects on growth, potential bone marrow suppression and the hypertensive effect of modafinil. Blood pressure must be monitored throughout all studies.

We have specific concerns related to the occurrence of leukopenia with the use of modafinil in the pediatric and adolescent subjects. We are requesting that at least 100 patients treated with differing therapeutic doses of modafinil be followed for one year with monthly blood counts and differentials.”

September 24, 2004

A meeting was held to discuss proposed changes to the PWR issued on June 17 2004. Cephalon had submitted a request to amend the written request on August 17 2004; said request was submitted to NDA 20-717.

The key agreements were:

1. Cephalon would be allowed to initiate the definitive efficacy and tolerability studies since there appeared to “be sufficient tolerability studies. In the final submission of the WR [Cephalon] should submit data from the tolerability studies in a fashion that justifies the selected doses.
2. Cephalon sought to revise the inclusion criteria for patients with obstructive sleep apnea. The Division stated that it was concerned that the drug would be used as a substitute for CPAP. The Division informed the sponsor that it would be acceptable for CPAP failures to be included in the study if in fact they were true therapeutic failures....The WR wording would be revised to reflect that.
3. Cephalon sought to have the requirement for approximately equal distribution of patients across the two age groups be deleted. The Division stated that a reasonable attempt should be made to recruit an approximately equal distribution of patients across the age ranges (>6 to <12 and ≥ 12 to <17) and any problems in recruiting less than these proportions would be acceptable only if there is adequate documentation that a sufficient effort was made in recruitment.
4. Cephalon sought acknowledgement that the safety data obtained in ADHD studies could contribute to the safety data in pediatric patients with narcolepsy and OSA. The Division agreed that the ADHD studies would contribute to the safety data base.
5. Cephalon sought to remove the requirement that a minimum number of patients be studied in each age group for each disorder. The Division noted that because of the availability of long term ADHD data the requirements for the total number of patients studied long term could be reduced. A minimum of 100 patients should be studied for all disorders combined (narcolepsy and OSA), but an attempt should be made to obtain equal distribution across

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age and indication. The Division agreed to modify the written request to reflect that change.

October 11, 2004

The three protocols for the pediatric exclusivity studies were submitted to IND [REDACTED] (b) (4)

- Study 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
- Study C1538/3028/AP/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 Obstructive sleep apnea /Hypopnea syndrome
- Study C1538/3029/ES/MN: A 1-year open-label, flexible-dosage extension study to assess the safety and continued effectiveness of PROVIGIL (Modafinil) treatment (100, 200 and 400 mg/day) in children and adolescents with excessive sleepiness associated with narcolepsy or Obstructive sleep apnea /Hypopnea syndrome

December 16 2004

The Agency revised the PWR to state that “a minimum of 100 patients should be studied for all disorders combined (narcolepsy and OSA) with an approximate equal distribution across age groups (≥ 6 to < 12 and ≥ 12 to < 17) and diagnoses for a period of at least 6 months. Recruiting unequal proportions across age groups and diagnoses would be acceptable only if there is adequate documentation that a sufficient attempt was made to achieve equal distributions across age and diagnoses during recruitment.

August 10, 2005

The Agency revised the PWR to remove the requirement for a study in pediatric patients with OSA.

2.6 Other Relevant Background Information

Modafinil has been approved for marketing in France by Lafon since 1992. It became commercially available there in 1994 but was originally restricted to prescriptions from public hospital neurologists and hospital pharmacies. In 1995, the French health ministry liberalized the requirement to allow specialists and physicians working in neurology departments and public or private sleep centers to prescribe the drug and allow dispensing by retail pharmacies. General practitioners were to be permitted to renew prescriptions provided that the patients were seen and reevaluated by a specialist yearly with formal testing (PSG , MSLT) every five years.

A marketing application was submitted [REDACTED] (b) (4)
[REDACTED] After supplementation, the application was resubmitted to the Canadian Health Ministry in August 1996 and subsequently approved.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review of this submission was done by Dr. Nallaperumal Chidambaram (b) (4)

3.2 Animal Pharmacology/Toxicology

In the original NDA submission, as reviewed by Dr. Bob Rappaport, the important findings were summarized as follows:

- Studies in the rat and in narcoleptic dogs revealed that modafinil maintained and/or promoted wakefulness in a dose dependent manner.
- Across high dose levels, in preclinical models, body weight loss and increased liver weights were seen. Microscopic analysis revealed hepatocellular hypertrophy and alterations in red cell parameters such as decreased erythrocyte counts, packed red cell volumes, and hemoglobin levels and increased reticulocyte counts and indications of erythropoiesis.
- While lifetime carcinogenicity studies were reported to have no positive findings above what was seen in animals treated with placebo, Dr. Aisar Atrakchi noted that the mouse carcinogenicity study did not reach a maximally tolerated dose. The Center CAC-exec concurred with that assessment.
- There was no evidence of genotoxic or teratogenic potential.
- There was no reproductive or developmental toxicity seen.

According to the approved labeling, while there was no evidence of tumorigenesis seen during the carcinogenicity studies done in mice (78 weeks) and rats (104 weeks) “because the mouse study used an inadequate high dose that was not representative of a maximum tolerated dose, the carcinogenic potential of modafinil has not been fully evaluated.”

The preclinical information from the current application has been reviewed by Dr. Melissa Banks of the Pharmacology/Toxicology staff. The interested reader is referred to her review for discussion of that data.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data used for this review comes from the two double-blind studies performed in response to the PWR, the 6-month open label trial performed in modafinil naïve subjects outside of the USA and Canada, and the ongoing 12-month open-label extension trial in pediatric patients with narcolepsy and OSA.

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In addition, I used safety data from the trials done [REDACTED] (b) (4) [REDACTED] as well as the ODS reviews of psychiatric adverse events seen with the use of stimulant therapy used for ADHD. The latter consults reviewed data from clinical trials as well as postmarketing data.

4.2 Tables of Clinical Studies

Table 1: Studies submitted in support of the Narcolepsy indication (S021)

	Patients	Design	Duration	E/S
Study C1538/ 3027 /NA/MN	165	R, DB, PC	6 weeks-DB phase	E/S
Study C1538/ 3029 /NA/MN	148	OL extension of 3027 and 3028	12 months	S
Study C1538/ 3034 /ES/MN (foreign study)	91	OL	6 months	S
Study C1538/ 3028 /AP/MN	26 with OSAHS	R, DB, PC	6 weeks-DB phase Terminated due to difficulty with recruitment	S

R-randomized; DB-double blind; OL-open label; PC-placebo controlled; E-efficacy; S-safety
The **bold** font indicates the shortened form of the study name, e.g. Study 3027 is equivalent to Study C1538/**3027**/NA/MN. The shortened form will be used throughout this review.

4.3 Review Strategy

The sponsor's submission in response to the Pediatric Written Request (as amended) was emphasized in this review, with particular attention paid to the data provided in support of safety. Information from trials performed in pediatric patients given modafinil for ADHD was included in the safety analysis. The latter trials were formally reviewed by Drs. June Cai and Glenn Mannheim of the Division of Psychiatry.

I, Dr. D. Elizabeth McNeil, was responsible for the synthesis and documentation of the overall conclusions of this application.

Dr. Sharon (Xiaorong) Yan, of the Office of Biostatistics, performed the formal biometrics analyses of the efficacy data.

Dr. V. Atul Bhattaram, of the Office of Clinical Pharmacology and Biopharmaceutics, reviewed the pharmacokinetics, pharmacodynamics and exposure-response data.

Dr. Melissa Banks of the Pharmacology and Toxicology staff reviewed the pharmacology/toxicology data.

Dr. Nallaperumal Chidambaram, of the chemistry, manufacturing and controls (CMC) staff reviewed the CMC data.

4.4 Data Quality and Integrity

In the data quality assurance section of the clinical study report (CSR) for study 3027 (section 9.6, p. 47), the sponsor reports the following information:

“During the review of the data listings after data were unblinded, an error was found in the conversion programming of the NPSG data from the spread sheet (source document) to the SAS data. The conversion programming wrongly applied the decimal format to the data when data were reported in whole numbers (i.e. without decimals) and rounded these data points incorrectly. Subsequently the data on the spread sheets were used to correct these incorrectly rounded values in the derived (analysis) datasets. Since the source data were not changed and the error occurred only in the conversion programming to SAS, this correction after the NPSG data were unblended was not considered to create any bias in these data.”

The Division of Scientific Investigations (DSI) was consulted to inspect the sites with the largest enrollment into the double-blind placebo-controlled trial: sites 004, 014, 066 and 070.

- Site 004: This site (Dr. Bogan-PI) randomized 14 patients according to the clinical study report. The DSI report found that 12 patients completed the study: subject #713 was discontinued due to non-compliance, subject 704 was discontinued due to the SAE of seizures and delirium. No violations were found by the DSI inspector upon review of all of the study subjects' records.
- Site 014: This site (Dr. Makris-PI) randomized 19 patients according to the clinical study report. Two patients were terminated early due to lack of efficacy. One violation was found by the DSI inspector upon review of all of the study subjects' records. Subject 713 was unblinded 'due to a lab error after the 6 week study period.' The investigator noted a memo from the sponsor which indicated that 'unblinding occurred twice during in the study but we have record of the above subject only.'
- Site 066: This site (Dr. Black-PI) randomized 14 patients according to the clinical study report. The DSI reviewer reports that 13 subjects were screened and randomized, with one discontinuing early due to incarceration. Two violations were found by the DSI inspector upon review of the study subjects' records. The study site violated 21 CFR 312.60 by not ensuring that the investigation was conducted according to the investigational plan: Pregnancy testing was not performed at randomization in five patients of childbearing potential. The study site violated 21 CFR 312.62 (b) by not maintaining adequate and accurate case histories that recorded all observations and data pertinent to the investigation: The case report forms for those five patients recorded that the pregnancy testing had been completed prior to the actual testing being done. According to the DSI field inspector, a Form 483 (Inspectional Observations) was not issued since the PI thought that the pregnancy testing was 'done by the central laboratory.'
- Site 070: This site (Dr. Boellner-PI) screened 11 patients and randomized 10 patients, all of whom completed the study. One violation was found by the DSI inspector upon review of all of the study subjects' records. The study site violated 21 CFR 312.60 by not ensuring

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that the investigation was conducted according to the investigational plan: The protocol specified that this was to be a double-blind study. During the DSI inspection, it was noted that the medication kit (#50096) intended for subject #1620, the screening failure, was not accounted for. The field inspector reported being told by the study site coordinator 'that Cephalon instructed Dr. Boellner to dispense that kit to another subject enrolled in the open label study currently underway since as that subject needed the same strength medication and quantity in kit 50096. We note that the blinded study was still ongoing when medication kit #50096 was reassigned.'

[Reviewer's note: The study appears to have been blinded to the investigators (though, as discussed above, Dr. Makris was not fully blinded) and the subjects but by report Cephalon may have had knowledge of the randomization assignments.

The data quality is also worrisome in that there is a discrepancy between the number of patients reported as randomized in the CSR and the number of patients as reported at inspection at least one site, site 066. I also note that the only patient reported not to meet screening criteria at Dr. Boellner's site was a patient with screening ID 070707.

A review of the protocol does not make it clear whether the central laboratory was to be expected to perform the urine human chorionic gonadotropin testing in addition to the urinalysis at screening. There may have been a true misunderstanding about the pregnancy testing responsibility at site 066.]

4.5 Compliance with Good Clinical Practices

The trials appear to have been conducted in accordance with acceptable ethical standards.

During the course of the review, I noted that site 079 enrolled 9 patients: one had only a baseline visit recorded (079707); 7 terminated early leaving patient 079705 as the only patient at this site who completed all 6 weeks. I requested a 'for-cause' investigation of the reasons for early termination in what appeared to be a disproportionately high number of patients. On August 16 2006, I spoke with Dr. Malek (of DSI) about his findings at the site review. In summary he found that the PI appeared to have used the provision in protocol 3029 that allowed early termination (after 3 weeks) for seven of the nine patients who were enrolled in study 3027 at her site; specific details of Dr. Malek's findings may be found in section 7.2.8.

4.6 Financial Disclosures

The sponsor provided financial disclosure information for study (b) (6)

Cephalon submitted certification of the absence of disclosable interests (form 3454) for the majority of the Principal Investigators and their sub-investigators.

(b) (6) a subinvestigator (b) (6) received payment of \$76,550 as part of a Cephalon speaker's bureau consulting agreement. (b) (6) patients were dispensed study drug and treated at site (b) (6)

(b) (6) reported owning (b) (6) shares of Cephalon common stock. The final study enrollment at site (b) (6)

(b) (6) a subinvestigator (b) (6) received payment of \$57,300 as part of a Cephalon speaker's bureau consulting agreement. (b) (6) patients were dispensed study drug and treated at site (b) (6)

Reviewer's summary

The submitted financial information is complete.

The payments made (b) (6) were unlikely to have influenced study outcome. In both instances the data from their sites were consistent with the results from the other sites.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

In the original NDA submission, reviewed by Dr. Bob Rappaport, the important pharmacokinetic (PK) findings in adults were summarized as follows:

- Peak modafinil plasma concentration occurred at 1-4 hours
- Linear pharmacokinetics for modafinil and its major metabolite, modafinil acid, were exhibited over a dose range of 50 to 499 milligrams.
- The elimination half-life was between 9 and 14 hours after a single dose of either 200 or 400 milligrams. After multiple doses of modafinil given daily at 200, 400 and 600 mg, steady state plasma levels were reached at Day 2-4. The elimination half-life after the last dose in a multiple dose regimen was 13-18 hours.
- Modafinil was moderately protein bound, essentially to albumin.
- In a single dose drug-drug interaction study with methylphenidate, no clinically significant alterations in the pharmacokinetic profile of either drug were noted but a delay in oral absorption of modafinil was seen, T max of 2.9 hours vs. 1.9 hours alone.

The above findings were based on 17 Phase I studies, 2 Phase II studies and 2 Phase III studies in adults.

In the sponsor's briefing document (p.19) for the Advisory Committee meeting in March 2006, it was noted that "the pharmacokinetic profile in children/adolescents is characterized by a relatively rapid rate of absorption with a t_{max} of 2 to 3 hours followed by an apparent biexponential decline from peak concentration. The estimated $t_{1/2}$ for the youngest patients (6-7 year olds) is approximately 7 hours and increases with age. The general trend in the data indicates that there is a continuous gradual increase in $t_{1/2}$ with a pronounced shift towards higher values in children between 9 and 11 years of age that are more similar to those observed in adults....data indicate that there is a continuous gradual decrease in concentrations of modafinil sulfone with increase in

age, with a pronounced shift towards lower concentrations in children between 9 and 11 years of age.” While the interested reader is referred to the review by Dr. V. Atul Bhattaram for a detailed discussion of the PK data, at the advisory committee meeting discussing use of this product for the treatment of ADHD in pediatric patients, the following information was presented by Dr. Glenn Mannheim (reproduced below *verbatim*):

Table 2: PK exposure in Pediatric patients vs. Adults with therapeutic doses

Parameter	Analyte	Adults (n=13)	Children and adolescents	
		PROVIGIL normalized to 200 mg QD x 21 days	Weight ≥30 kg	Weight <30 kg
			N=11	N=13
			Modafinil 425 mg QD x 14 days	Modafinil 340 mg QD x 14 days
C _{max}	Modafinil	6.4±0.75	16.0±3.00	19.5±4.44
	Modafinil acid	2.65±0.5	5.4±1.09	4.9±1.28
	Modafinil sulfone	1.85±0.8	11.8±7.25	29.0±15.7
AUC _{tau}	Modafinil	73.5±13.3	177±28.5	199±45.4
	Modafinil acid	26.7±5.0	61.3±11.4	54.7±61.3
	Modafinil sulfone	38.8±1.7	251±154	629±349
Sulfone AUC ratios		1.0	6.5	16.2
Subpopulation: adults				
Maximum daily dose (MDD) mg/kg		2.67	14.2	21.25
MDD ratios		1.0	5.3	8.0

The pediatric data was derived from study C1538a/113/PK/US
The adult data was derived from study C1538a/404/PK/US-dose 400 mg

5.2 Pharmacodynamics

There were no reports of human pharmacodynamic studies submitted in support of this application (NDA section 5.3.4).

5.3 Exposure-Response Relationships

The exposure-response relationship in children was not formally evaluated in preliminary studies prior to this application. The sponsor had information from ongoing studies which indicated that higher exposure was needed for treatment of childhood ADHD. The minimal studied dose of 100 mg mirrored the effective dose for the treatment of excessive sleepiness in adult narcoleptics.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor proposed the following indication for this product:

“PROVIGIL is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder, (b) (4)

6.1.1 Methods

[Reviewer’s note: The interested reader is referred to the review by Dr. Sharon Yan of the Office of Biostatistics for detailed discussion of the statistical analysis.]

The sponsor provided data from a single double-blind placebo-controlled efficacy study for review: Study C1538/3027/NA/MN.

The primary efficacy measures were the Multiple Sleep Latency test (MSLT) and the Clinical Global Impression of Change (CGI-C) ratings for severity of ES at the last post baseline observation (week 6 or early termination). The efficacy analysis was based upon all patients who had received at least one dose of study drug and who had at least one post-baseline MSLT or CGI-C; 160 patients in the active treatment arms and 41 in the placebo arm.

The objective efficacy variable, change from baseline in the mean sleep latency during the first 4 MSLT naps was analyzed using ANCOVA with treatment as a factor and the corresponding baseline value as a covariate. The test of linear trend between the dosages was performed. If a patient did not fall asleep during the 20 minute MSLT trials, the sleep latency was assigned to 20 minutes. The calculations of mean sleep latency were based upon observed and assigned values.

The analysis of the primary subjective efficacy measure, the proportion of patients who had CGI-C ratings which indicated at least minimal improvement in the severity of ES at endpoint (defined as the last post baseline observation at week 6 or early termination), used the Pearson’s chi-square test.

6.1.2 General Discussion of Endpoints

Mirroring the development plan used for the approval in adults, this study designated an objective and a subjective primary endpoint as co-primaries.

Objective

The primary objective endpoint, based upon the MSLT, was the change in baseline for the mean sleep latency over 4 naps, scheduled for 0900, 1100, 1300 and 1500. The MSLT consists of four 20-minute naps. In each of the four nap periods, sleep latency is measured as the time from ‘lights

out’ to the first 16 seconds of elapsed sleep. The mean sleep latency is the average of the sleep latencies at the 4 naps.

Subjective

The primary subjective endpoint was the CGI-C rating for severity of ES at the last post-baseline observation (week 6 or early termination). The clinical global impression-severity (CGI-S) was assessed at baseline. The CGI-C ratings were assessed at the post-baseline visits. At weeks 3 and 6, the physician asked the parent (caregiver) to report on the child’s home behavior over the preceding week. The rating scale is anchored by 1 (very much improved) and 7 (very much worse), with a score of 4 representing no change.

6.1.3 Study Design

This was a double-blind, randomized, placebo-controlled, parallel group study which compared the efficacy and safety of 3 doses of modafinil (100mg, 200mg, 400mg) to placebo in pediatric patients with excessive sleepiness due to narcolepsy. During the first 7 days of the double-blind period, patients were titrated up to their randomized dose, with a 100 mg increase every 2 days; the patients in the placebo group and in the 100 mg group were at their randomized dose at Day 1, the 200 mg group reached their dose by day 3, the 400 mg group reached their dose by day 7. Patients were to stay at their designated dose for the remainder of the 6 week double-blind period. However, the safety extension protocol allowed patients to request early termination from study 3027 after 3 weeks with “rollover” into the 12-month open-label study 3029.

6.1.4 Efficacy Findings

Objective data

The primary objective efficacy measure was the MSLT at the last post baseline observation (week 6 or early termination). The primary statistical analysis for the mean change in MSLT was a linear dose trend test. The test for linear dose response did not reach statistical significance (p=0.0604), however at endpoint each individual dose level studied demonstrated a statistically significant change in mean sleep latency as compared to placebo.

Table 3: Change in mean sleep latency (average of the 4 naps)

	100 mg/day (N=41)	200mg/day (N=41)	400 mg/day (N=37)	Placebo (N=41)
N	40	40	36	40
Mean (SD)	3.8 (4.01)	4.8 (4.34)	3.0 (5.11)	0.6 (3.86)
Median	4.2	3.6	3.1	-0.1
Range	-2.8, 15.6	-1.4, 14.4	-11.0, 10.6	-6.4, 16.6
p-value	0.032	0.0001	0.0473	

Data from Table 9 of study report, summary 15.8 of study report
The p-values represent comparisons with the placebo treatment group, adjusted by Dunnett’s method.

Subjective data

The primary subjective efficacy measure was the proportion of patients who had CGI-C ratings which indicated at least minimal improvement in the severity of ES at endpoint (defined as the last post-baseline observation at week 6 or early termination). The analysis of this variable used the Pearson's chi-square test.

The study failed to demonstrate efficacy on the primary subjective endpoint. When compared to the placebo arm, the active treatment arms combined did not show a statistically significant difference in the proportion of patients with at least minimal improvement, $p=0.0523$.

Since the first step of the hierarchical analysis failed to achieve statistical significance, the statistical analysis plan indicated that the other steps should not be carried out. Nonetheless, the sponsor did analyze the individual doses. When the treatment doses were evaluated individually, the 100 mg dose was the only one that showed a statistically significant difference in favor of active drug.

The table below, a reproduction of table 10 from the study report, shows the proportion of patients with at least minimal improvement at endpoint. This analysis only included patients who had a CGI-C rating at endpoint. In order to be considered as having had 'at least minimal improvement,' patients had to have been rated as very much improved, much improved or minimally improved.

Table 4: Proportion with at least minimal improvement at endpoint

	100 mg/day (N=41)	200mg/day (N=41)	400 mg/day (N=37)	Placebo (N=41)
N (%)	35 (85%)	34 (83%)	27(73%)	27(66%)
p-value	0.0397	0.0766	0.4963	

Data from Table 10 of study report, summary 15.9 of study report

The p-values represent comparisons with the placebo treatment group, from Pearson's chi-square test.

[Reviewer's note: The sponsor's review of the proportion with at least minimal improvement data from the patients in the 100 mg group, the only one to show a statistically significant benefit at endpoint, revealed no statistically significant benefit over placebo at week 3 (p -value=0.8751, $n=40$) or at week 6 (p -value=0.0916, $n=38$). The populations used for the analyses at endpoint, at Week 3 and at Week 6 were different, which may account for the difference in results.]

6.1.5 Clinical Microbiology

This section is not applicable to this review.

6.1.6 Efficacy Conclusions

6.1.6.1 Comments from the statistician's review:

Dr. Yan concluded that “the study failed to demonstrate that there is a linear dose response in the primary efficacy variable of MSLT, which was the designated primary analysis... The treatment difference in the co-primary efficacy variable of CGI-C failed to reach statistical significance. “

6.1.6.2 Clinical reviewer's comment:

The sponsor provided data from a double-blind placebo-controlled efficacy study for review: Study C1538/3027/NA/MN. While the primary efficacy study was intended to be a six-week study with a 12-month safety extension, the sponsor allowed investigators to transfer patients to the open label study after 3 weeks of double blind treatment assuming the given patient had not been withdrawn from the double-blind study due to adverse events. Patients were allowed to transfer due to perceived lack of efficacy, e.g. in an informed consent document for the efficacy study, it was stated that in patients who were perceived to have continued excessive sleepiness, parents could “ask for early termination after 3 weeks of participation and roll-over to the open label study where [the] child [would] be on a known amount of study drug.” The original requirement for routine MSLT testing at Week 3 had been removed in a protocol amendment dated February 2005. This precluded comparison of patients who were terminated early and transferred into the open-label protocol with those who were not terminated early.

The primary efficacy measures were the Multiple Sleep Latency test (MSLT) and the Clinical Global Impression of Change (CGI-C) ratings for severity of excessive sleepiness (ES) at the last post baseline observation (week 6 or early termination).

The efficacy analysis was based upon all patients who had received at least one dose of study drug and who had at least one post-baseline MSLT or CGI-C; 160 patients in the active treatment arms and 41 in the placebo arm.

The study submitted in support of this application represents a failed trial in that neither of the pre-specified co-primary endpoints achieved statistical significance. The subjective co-primary endpoint failed to demonstrate overall statistical or clinical difference from placebo.

The statistical hypothesis to be tested for MSLT, an objective measure of benefit, was a test for linear trend in the placebo and Provigil treatment groups. The data indicate that there was no linear dose response in the active control group when the results at endpoint were compared to the results at baseline, p-value 0.0604. We have secondary evidence of objective benefit, specifically prolongation of sleep latency with all three doses of modafinil studied: the 100 mg/day group had a mean increase of 3.8 minutes, the 200 mg/day group had a mean increase of 4.8 minutes, the 400 mg/day group had a mean increase of 3.0 minutes, the placebo group had a mean increase of 0.6 minutes. There is no dose response effect so there would be no reason to utilize use of higher doses than 100 mg.

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There is no subjective evidence of benefit. On the pre-specified primary endpoint of change in CGI-C from baseline to endpoint, the study failed to demonstrate overall efficacy of active drug as compared to placebo. While the sponsor was able to demonstrate statistical significance at the 100 mg dose when measured at endpoint, that dose did not show statistical evidence of benefit at the Week 3 evaluation nor did it show benefit in those children who completed the study, i.e. those evaluated at Week 6. The secondary endpoint of change from baseline in the pediatric daytime sleepiness scale confirmed the lack of clinical improvement since none of the doses studied were able to distinguish themselves from placebo.

Additionally, the inclusion/exclusion criteria could have been better defined. Patients were permitted to have either objective (MSLT < 10 minutes) or subjective evidence of excessive sleepiness (clinical global impression of severity (CGI-S) rating ≥ 4) as entry criteria. It might have been better to assure that study participants had both objective signs and subjective symptoms as a basis for study entry since both were designated as primary endpoints. It would not be farfetched to assume that someone without much subjective complaint of sleepiness at the onset might not show a great deal of improvement in that symptom even if treated with an effective drug.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths reported during any of the studies submitted in support of this application.

7.1.2 Other Serious Adverse Events (SAEs)

7.1.2.1 Study 3027: A double-blind study in narcoleptic patients

Patient 004704

This 6 year old was titrated to 400 mg modafinil by Study Day 5. Fexofenadine hydrochloride for treatment of seasonal allergies was begun on Day 6. On Day 12, he had nausea and vomiting in association with fever. He was treated with Emetrol and acetaminophen. He reported pharyngitis on Day 13 and received a 7-day course of amoxicillin; the throat cultures done at the time were negative. On Day 15 he took his last dose of study medication. On Day 16, he was hospitalized due to somnolence and confusion. He was found to have an elevated serum ammonia of 145 and hypophosphatemia. On Day 17, he had seizures and delirium with hallucinations. His workup included cerebrospinal fluid analysis, neurological examinations, serum chemistries including liver function tests, toxicology testing and CT scans of his head. There were no positive findings. The patient was withdrawn from the study. While most of the adverse events described resolved without residua, the fever and somnolence persisted until Day 48.

According to Cephalon, there was no known antecedent aspirin use prior to the hospitalization nor did the PI report known outbreaks of varicella or influenza in the community. The patient had normal serum chemistries at baseline; the only abnormal hematologic finding was a borderline low hematocrit of 35% (normal 36-47%). The sponsor had this patient's case reviewed by a pediatrician and a pediatric neurologist. Normal CSF results notwithstanding, the consultants felt that this was a case of viral encephalitis based upon clinical presentation,. They considered but eliminated the following diagnoses based upon the laboratory and CT findings: an inborn error of metabolism, Reye's syndrome, modafinil toxicity.

[Reviewer's note: While the half-life of modafinil might be expected to be 7 hours in a child of this age, we have pharmacokinetic data that suggests that the serum concentrations of modafinil sulfone may be expected to be quite high especially after multiple days of 400 mg/day dosing. His modafinil dosing was stopped on March 25. His delirium, hallucinations and seizures began on March 27. He did not have an assessment of his serum modafinil or modafinil sulfone. While the parent product may have been eliminated by March 27, it is unlikely that the metabolite had been eliminated by that point. I am not certain that drug toxicity, due to the metabolite not the parent compound, can be ruled out.]

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Patient 016704

This 12 year old was randomized to placebo. On Day 28, he had appendicitis diagnosed. He had an appendectomy on Day 29. His study drug was interrupted for the day of surgery but resumed thereafter.

[*Reviewer's note: This adverse event was not related to study drug.*]

7.1.2.2 Study 3028: A double-blind study in patients with OSAHS

There were no serious adverse events reported in Study 3028.

7.1.2.3 Study 3029: An open label extension of studies 3027 and 3028

Patient 026701

This 10 year old patient began receiving 100 mg/day of PROVIGIL but due to continued sleepiness was titrated up to 200 mg/day. She was titrated up to 400mg/day by Week 3. She made a suicidal gesture on Day 75. No psychiatric treatment was given, modafinil was continued at first but she was later withdrawn from the study.

[*Reviewer's note: This adverse event may have been related to study drug.*]

Patient 031704

This 14 year old girl, whose past medical history was significant for having had a kidney transplant in 1998, had been receiving placebo during the double-blind study. She began receiving 100 mg/day of PROVIGIL and was titrated up to 400mg/day by Day 90. She was found to have a kidney infection on Day 2 of this study and was hospitalized until Day 9. Her modafinil dosing was suspended from Day 4 through Day 12. She withdrew consent and discontinued use of modafinil on Day 143.

[*Reviewer's note: Her kidney infection was not related to use of the study drug.*]

7.1.2.4 Study 3034: A 6-month open label study in modafinil naïve patients with either narcolepsy or OSAHS

Patient 066001

This 12 year old with OSAHS was receiving 100 mg/day of modafinil. His past medical history was significant for an osteofibroma detected 2 months prior to study entry. Four days before Day 1, he had hip pain and associated gait abnormality. On Day 8, the osteofibroma was resected and a bone graft was inserted. Study drug was suspended for one day. By day 13, this adverse event was considered to have resolved.

He also had a progressive decline in weight. His baseline was 54.4 kg. On Day 63, his weight was 50 kg. His weight had decreased to 46.8 kg by Day 187 with interval changes to 49.5 kg on Day 91, 47.3 kg on Day 124, and 47.5 kg on Day 155. On Day 155, his diastolic blood pressure was 50 mm Hg down from his baseline value of 65 mm Hg. By Day 187, his diastolic mm Hg had returned to 60 mm Hg. He completed the study as scheduled.

[*Reviewer's note: His osteofibroma was not related to study drug but his weight loss may have been.*]

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

7.1.3.1.1 Study 3027: A double-blind study in patients with narcolepsy

This study enrolled 166 patients; 144 of whom completed the 6 week trial. Seventeen (14%) withdrew from the active treatment arm and 5 (12%) withdrew from the placebo arm. Nine of the 17 patients (53%) who withdrew from the active treatment arm were in the 400 mg group.

The reasons for early termination were as follows:

- Adverse event (AE)-3 (2 in the 400 mg group; 1 in the 200 mg group, though he never received study drug)
- Lack of efficacy-2 (1 in the 400 mg group; 1 in the placebo group)
- Withdrawn consent-4 (1 in each treatment group)
- Noncompliance with study drug-1 (400 mg group)
- Noncompliance with study procedure-1 (placebo group)
- Lost to follow-up-1 (100 mg group)
- Other-10 (2 each in the placebo, 100mg and 200 mg groups; 4 in the 400 mg group)
 - Wished to be on a known dose of medication before the start of the school year (6 patients)
 - Incarcerated (1 patient)
 - Early termination due to school schedule (1 patient)
 - Wished to re-evaluate after beginning school year off medication (1 patient)
 - Decline in school work associated with increase in excessive sleepiness, “need to be on adequate dose of PROVIGIL” (1 patient)

[Reviewer’s note: A decline in schoolwork in this setting may represent a change in function and therefore represent an adverse event.]

7.1.3.1.2 Study 3029: An open-label extension of studies 3027 and 3028

This ongoing study enrolled 132 narcolepsy patients from study 3027; since 144 patients completed that study there are 12 patients unaccounted for. This study also enrolled 16 patients with OSAHS from study 3028 which was ended early due to inadequate enrollment. The total enrollment was 148 patients.

By the time of the 120 day safety update, one patient had completed the study and 41 patients (28%) had discontinued.

The reasons for early discontinuation were as follows:

- Adverse event (AE)-8
- Lack of efficacy-6
- Withdrawn consent-15
- Noncompliance with study drug-2
- Noncompliance with study procedure-2
- Lost to follow-up-5
- Other-3

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7.1.3.1.3 Study 3034: A 6-month open label study in modafinil naïve patients

This study enrolled 92 patients; 84 of whom completed the 6 month trial.

The reasons for early termination were as follows:

- Lack of efficacy-1 with narcolepsy; 2 with OSAHS
- Withdrawn consent-1 with narcolepsy; 3 with OSAHS
- Noncompliance with study drug-1 with OSAHS

7.1.3.2 Adverse events associated with dropouts

7.1.3.2.1 Study 3027: A double-blind study in narcoleptic patients

Patient 004704

This 6 year old patient was discussed in detail in section 7.1.2 and so will not be discussed here.

Patient 016701

This 6 year old patient was randomized to the 400 mg treatment arm. He received 100 mg of study drug on Day 2, 200 mg on Days 3 and 4, and 400 mg on Day 7. On Day 3, his family reported the onset of “uncontrollable behavior” which led to him being withdrawn from the study on Day 7.

The adverse event, which was coded as ‘personality disorder’, resolved on Day 8.

[Reviewer’s note: His behavior was coded as personality disorder though it probably should have been coded as hostility. This adverse event may have been related to study drug.]

Patient 079707

This 13 year old patient was randomized to the 200 mg treatment arm but prior to his first dose of medication he sustained a tear of his right anterior cruciate ligament (coded as accidental in jury) and was withdrawn from the study.

[Reviewer’s note: This adverse event was not related to study drug.]

7.1.3.2.2 Study 3028: A double-blind study in patients with OSAHS

Patient 004802

An 11-year-old patient, who was randomized to receive placebo, was found to have elevated SGOT, SGPT and GGT on Day 23. Study drug was discontinued on Day 32 due to these ongoing adverse events.

[Reviewer’s note: This adverse event was probably not related to study drug.]

Patient 039802

A 9-year-old patient, who was randomized to receive placebo, was found to have worsening ADHD behavior (verbatim term, which was coded as hyperkinesia) on Day 9. Study drug was discontinued on Day 25 with resolution of symptoms noted on Day 32.

[Reviewer’s note: This adverse event was probably not related to study drug.]

7.1.3.2.3 Study 3029: An open label extension of studies 3027 and 3028

Patient 004702

This 15 year old patient had been randomized to the 100 mg/day treatment arm during the double-blind study. By Day 8 of this study, she was receiving 200 mg/day. She had bouts of emesis on

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Days 3, 8, 9, 10, 11 and 12. The dose of study drug was reduced to 100 mg/day on Day 12 but the patient elected to withdraw from the study due to the emesis.

[Reviewer's note: This adverse event was probably drug related, or more specifically dosage related since the advent of daily emesis appears to coincide with the increase in dose.]

Patient 014723

This 10 year old patient who was receiving 400mg/day was withdrawn due to continued irritability. *[Reviewer's note: This adverse event may have been related to study drug.]*

Patient 014724

This 11 year old patient who had been receiving 100 mg/day in the previous study was maintained on that dose in this study. On Day 2 of this study, she had swollen joints bilaterally (coded as arthrosis) and joint tenderness (coded as arthralgia). Her modafinil dosing was discontinued on Day 2 due to the joint swelling. She was given ibuprofen and had resolution of her symptoms by Day 6. Additionally, she was noted to have a rash on her thighs on Day 5, which resolved the next day.

[Reviewer's note: This adverse event may have been drug related.]

Patient 018701

This 8 year old patient had been receiving 200 mg/day in the previous study. She was titrated up to 400 mg/day by Day 22 of this study. On Day 55 she was reported to have what were described as behavior outbursts (coded as hostility). Her modafinil dose was halved on Day 56 and eliminated on Day 69 due to the persistence of this adverse event. The event resolved by Day 88.

[Reviewer's note: This adverse event was probably drug related.]

Patient 026701

This patient was discussed in detail in section 7.1.2.3 and so will not be discussed here.

Patient 028801

This 14 year old patient had been receiving 100 mg/day in the previous study and he remained on that dose in this study. On Day 1 of this study, he was noted to have aggressiveness (coded as hostility). Since the adverse event persisted, he stopped taking modafinil on Day 57. The adverse event was considered to have resolved on Day 69.

[Reviewer's note: This adverse event was probably drug related.]

Patient 070704

This 15 year old patient had been receiving 100 mg/day in the previous study. By Day 22 of this study she was titrated up to 400 mg/day. On Day 64 of this study, she began to complain of headaches; modafinil was discontinued on Day 97, without resolution of the headaches by report.

[Reviewer's note: This adverse event may have been related to study drug.]

Patient 079709

This 7 year old patient had been randomized to the 100 mg treatment arm in the previous study and continued on 100 mg/day in this study. Beginning on Day 3 of the initial study, she had been reported to have hyperactivity (coded as hyperkinesia). She also had increased awakenings at night

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(coded as insomnia), memory loss (coded as amnesia) and poor impulse control manifested as frequent interrupting of conversations. Modafinil was discontinued on Day 13 of this study. [Reviewer's note: This adverse event was probably drug related; the symptoms described sound like hypomania.]

7.1.3.2.4 Study 3034: A 6-month open label study in modafinil naïve patients with either narcolepsy or OSAHS

There were no withdrawals due to adverse events in this study according to the sponsor. However, Patient 066003, a 10 year old boy who was receiving 100 mg /day began to display aggressive behavior at an unspecified point. He withdrew consent on Day 68. [Reviewer's note: It is not clear whether the withdrawal of consent was due to the adverse event or not.]

Reviewer's summary

When evaluated by age, 7 patients who were under 12 years old and 3 patients who were 12 or older who received active drug had SAE or AE which led to withdrawal. Those numbers omit the patients with conditions such as appendicitis and the ACL tear since those are not possibly drug related. This represents a higher percentage of patients in the 6 to 12 year group (7%) as compared to the 12 and older group (2 %).

Additionally, I would note that most of the adverse events which led to withdrawal occurred during the open label extension trial which might lead to the speculation that there was a time related aspect to these events. By the time of entry into trial 3029, patients would have had up to 6 weeks of treatment in the previous double-blind trials.

7.1.3.3 Significant adverse events from the Narcolepsy/OSAHS trials

7.1.3.3.1 Psychiatric adverse events

7.1.3.3.1.1 Patient 004710: Abnormal thinking

This is a 15 year old patient who complained of "difficulty understanding letters" on Day 29 while taking 100 mg/day of modafinil. This event resolved in less than 24 hours. [Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.2 Patient 014703: Hypnagogic hallucinations, aggression

This is an 11 year old patient with a history of hypnagogic hallucinations who was receiving 200 mg/day of modafinil on study 3027. She reported increased episodes of hallucinations at sleep onset (verbatim term, coded as hallucinations) on Day 4. Modafinil treatment was interrupted on Day 6. The modafinil treatments were resumed and the hallucinations resolved on Day 22. Upon entry into the extension study (3029) she noted hypnagogic hallucinations and sleep paralysis (verbatim terms which were coded as sleep disorder) on days 23, 34 and 37. She was noted to have an increase in aggressive behavior on Day 90 which resolved by Day 124. [Reviewer's note: These adverse events were probably related to study drug.]

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7.1.3.3.1.3 Patient 014711: Hypnagogic hallucinations

This 12 year old patient, with a past history of hypnagogic hallucinations, was receiving 400 mg/day. Hypnagogic hallucinations occurred on days 3 and 4 of the study and resolved the same day without residua.

[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.4 Patient 016701: Uncontrollable behavior

This 6 year old patient with uncontrollable behavior was described in Section 7.1.3.2.1.

7.1.3.3.1.5 Patient 071008: Hostility

This is a 16 year old who was taking 400 mg/day of modafinil during study 3034. On Day 123, she exhibited violent behavior. Her dose was reduced to 300 mg/day on the same day. The patient completed the study.

[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.6 Patient 018701: Behavioral outbursts

This is an 8-year old patient who was receiving 200 mg/day of modafinil on study 3027. An increase in behavioral outbursts (temper tantrums), coded as hostility, was reported on Day 26. This was considered to have resolved by Day 40. Upon completion of the initial study she was enrolled in the open-label extension where her modafinil was titrated to 400 mg/day. On Day 55, severe behavioral outbursts were reported which led to a decrease in the modafinil dose to 200 mg/day on Day 56. Modafinil was discontinued on Day 69 due to ongoing hostility and behavioral outbursts.

[Reviewer's note: This adverse event was probably related to study drug.]

7.1.3.3.1.7 Patient 024002: Aggression

This is a 12 year old who was taking 300 mg/day on Study 3034. On Day 98 of the study he had aggressiveness which persisted after study completion.

[Reviewer's note: This adverse event was probably related to study drug.]

7.1.3.3.1.8 Patient 026071: Suicidal gesture

This is a 10 year old patient who was receiving 400 mg of modafinil/day as part of study 3029. She made a suicidal gesture on Day 75. No psychiatric treatment was given. Modafinil was continued at first but she was later withdrawn from the study.

[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.9 Patient 028705: Aggression

This is a 16 year old patient who was taking 100 mg/day on Study 3029. He had aggression noted on Day 9 which resolved by Day 28.

[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.10 Patient 028801: Hostility, aggression

This is a 14 year old with OSAHS who was receiving 100 mg/day on Study 3029, having received the same dose in Study 3028. He began to manifest aggression on Day 1 of the extension study. On Day 57 of the extension, his use of modafinil was stopped due to continued hostility. He had resolution of his hostility by Day 69.

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[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.11 Patient 038703: Hostility, self-injurious behavior

This was not reported as an adverse event but during the psychiatric interview, both at baseline and at endpoint, the 7 year old patient's hostility and self-injurious behavior was noted. He was receiving 200 mg/day.

[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.12 Patient 057701: Aggression

This 6 year old was receiving 100 mg of modafinil when he exhibited aggressive behavior on Day 4 of study 3029. This symptom resolved without residua on Day 12.

[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.13 Patient 061001: Aggression

This 13 year old was taking 100 mg of modafinil on study 3034. She had aggression noted on Day 36 of that study.

[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.14 Patient 063704: Anger

This is a 13 year old patient who was receiving 200 mg/day of modafinil on study 3027. Anger was reported, coded by COSTART as hostility. This symptom was ongoing at study completion.

[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.15 Patient 066003: Aggression

This 10 year old patient, who was receiving 100 mg /day, began to display aggressive behavior at an unspecified point. He withdrew consent on Day 68.

[Reviewer's note: It is not clear whether the withdrawal of consent was due to the adverse event or not. This adverse event may have been related to study drug.]

7.1.3.3.1.16 Patient 066004: Aggression

This 5 year old patient who was receiving 100 mg /day began to display aggressive behavior on day 67 of study 3034. She completed the study after 190 days of modafinil use. By report, her aggression was ongoing.

[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.17 Patient 073703: Hallucinations

This 17 year old patient, who was receiving 200 mg/day, reported hallucinations on days 21 and 33 while participating in study 3029.

[Reviewer's note: This adverse event may have been related to study drug.]

7.1.3.3.1.18 Patient 073705: Agitation

This is a 5 year old patient who was receiving 100 mg/day of modafinil on study 3027. Agitation was reported. This symptom resolved whilst treatment continued.

[Reviewer's note: This adverse event may have been related to study drug.]

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7.1.3.3.1.19 Patient 076802: Emotional lability

This 10 year old patient had “moodiness” coded as emotional lability noted on day 1 of study 3029. At the time he was taking 100 mg/day, the same dose as he had been taking on study 3028. His symptom was persisting at the time of data cut-off for this submission.
[Reviewer’s note: *This adverse event may have been related to study drug.*]

7.1.3.3.1.20 Patient 079709: Possible hypomania

This 7 year old patient with possible hypomania was described earlier in Section 7.1.3.2.3.

Reviewer’s summary

While the study failed to demonstrate efficacy based upon the primary endpoints, there was some objective evidence that sleep latency might be prolonged. If there were to be further investigations of this product for pediatric use performed, the dose investigated should be limited to 100 mg since there is no evidence that higher doses provide any added efficacy and there is some evidence, based on this results of this trial and additional information from the trials in ADHD, that higher doses may be associated with an increased risk for psychiatric AEs.

7.1.3.3.2 Dermatologic adverse events, specifically rashes

7.1.3.3.2.1 Patient 008802: Generalized body rash

This patient had a generalized body rash on Day 65 of Study 3029. This rash was persisting at the time of data cut-off.
[Reviewer’s note: *This adverse event may have been related to study drug.*]

7.1.3.3.2.2 Patient 062001: Neck erythema

This patient had a rash described as neck erythema on Day 83 of study 3034. This adverse event resolved with residua on day 91.
[Reviewer’s note: *This adverse event may have been related to study drug.*]

7.1.3.3.2.3 Patient 066704: Pityriasis rosea

This patient was receiving 200 mg/day when pityriasis rosea developed (COSTART: maculopapular rash). This adverse event began on Day 10 of Study 3027 and resolved on Day 34.
[Reviewer’s note: *This adverse event was not related to study drug.*]

7.1.3.3.2.4 Patient 070701: Desquamative foot rash

This patient was receiving placebo when an exfoliative dermatitis was detected. This adverse event was ongoing at study completion.
[Reviewer’s note: *This adverse event was not related to study drug.*]

7.1.3.3.2.5 Patient 070702: Rash on feet

This patient was receiving 400 mg/day when a pedal rash appeared. This adverse event began on day 40 of Study 3027 and resolved on Day 31 of Study 3029.
[Reviewer’s note: *This adverse event was not related to study drug.*]

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7.1.3.3.2.6 Patient 071011: Urticaria-like rash

This patient had what was described as a “urticaria-like rash on the legs and abdomen” noted on day 20 of study 3034. The PI elected to interrupt study drug on Day 23, resuming therapy on Day 28 after apparent resolution of the event on day 26.

[Reviewer’s note: This adverse event may have been related to study drug.]

7.1.3.3.2.7 Patient 012010: Cutaneous eruption

This patient had a rash, which began on day 10 of Study 3034 and resolved on Day 13.

[Reviewer’s note: This adverse event may have been related to study drug.]

7.1.3.3.2.8 Patient 014708: Eczema

This patient was receiving placebo when eczema developed. This adverse event was ongoing at study completion.

[Reviewer’s note: This adverse event was not related to study drug.]

7.1.3.3.2.9 Patient 014724: Rash

This patient was described in section 7.1.3.2.3 and so will not be discussed further here.

7.1.3.3.2.10 Patient 014711: Pustule on left ear

This patient was receiving 400 mg/day during study 3027 when an ear pustule developed on Day 40. This adverse event was ongoing at the time of data cut-off for study 3029.

[Reviewer’s note: This adverse event was not related to study drug.]

7.1.3.3.2.11 Patient 014715: Fungal dermatitis

This patient was receiving placebo when evidence of ringworm was detected. This adverse event was ongoing at study completion.

[Reviewer’s note: This adverse event was not related to study drug.]

7.1.3.3.2.12 Patient 014719: Diaphoresis

This patient was receiving placebo when diaphoresis was noted. This adverse event was resolved by study completion.

[Reviewer’s note: This adverse event was not related to study drug.]

7.1.3.3.2.13 Patient 027702: Rash

This patient had a rash on day 17 of Study 3029, which was persisting at the time of NDA submission.

[Reviewer’s note: This adverse event may have been related to study drug.]

Reviewer’s summary

The dermatologic events described were, in all likelihood, not related to use of study drug.

7.1.3.4 Selected significant adverse events from the ADHD trials

[Reviewer’s note: I note that the majority of the described psychiatric adverse events occurred in patients who were under 12 years old giving further support to consideration of a potential age restriction. These AEs are included here for the sake of completeness only. The interested reader is

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referred to the reviews by Drs. Cai and Mannheim of the Division of Psychiatry Products (DPP) for detailed descriptions of the adverse events and discontinuations associated with the ADHD trials.]

7.1.3.4.1 Psychiatric adverse events

7.1.3.4.1.1 Patient 15010: Hallucinations

This is a 6 year old patient who was taking 300 mg of modafinil per day as a participant in study 213. On Study Day 6, he had an episode of hallucinations. No treatment was given and modafinil was continued.

7.1.3.4.1.2 Patient 410: Hallucinations

This is an 8 year old patient who was taking 100 mg of modafinil per day as a participant in study 207. On Study Day 18, he complained of formication. This persisted for 2 days and then modafinil was withdrawn.

7.1.3.4.1.3 Patient 40629: Hallucinations

This is an 8 year old patient who taking 425 mg of modafinil per day as a participant in study 310. On Study Day 11, he began complaining of hallucinations. This persisted for 7 days then modafinil was withdrawn.

7.1.3.4.1.4 Patient 11002: Psychosis, Suicidal gesture

This is an 8-year-old patient who participated in trial C1538a/213/AD/US. He had a diagnosis of ADHD with a diagnostic score of 17 out of 18. He received 300 mg of modafinil/day during the double-blind phase of the trial which began on Feb 26 and ended March 26 2002. He began open-label treatment with the same dose on April 6 2002.

On (b) (6) the patient's mother found him attempting to hang himself; he had previously expressed suicidal intent to his sister. Prior to the suicide attempt, psychological testing had been recommended by the school because he had been noted to be talking to himself. On (b) (6) the child was seen by a counselor who had him admitted to a psychiatric hospital. The study medication was stopped (b) (6)

Upon hospital admission (b) (6) the child reported auditory command hallucinations with three different voices, only one of whom was speaking at the time of admission as the other two "were sleeping." No toxicology screening was done. He was treated with nortriptyline (40 mg/day) and risperidone (0.5 mg BID) with good effects and was released from the hospital (b) (6) The hospital discharge summary indicated that "the patient had a history of threatening or attempting suicide, being afraid of many things with highly variable moods"

Prior to study enrollment, he had taken Adderall which was discontinued due to mood swings and Dexedrine which was discontinued due to two episodes of abnormal thought and strange behaviors. While he found Concerta ineffective, there were no reports of psychiatric adverse events in association with its usage. He was the product of a full term uncomplicated pregnancy. He had normal developmental milestones with no reported motor delays. His family medical

history is significant for “three direct family members...[who have] a history of bipolar disorder or psychosis.”

7.1.3.4.1.5 Patient 59271: Ideas of referential control

This is a 7 year old patient who was receiving 340 mg of modafinil as a participant in Study 312. On study day 59, he began complaining of ideas of referential control. These symptoms persisted for more than 10 months. He was not given psychiatric treatment. Modafinil treatment persisted.

7.1.3.4.1.6 Patient 405: Suicidal ideation

This is a 7 year old patient who was receiving 200 mg of modafinil per day on study 207. On Day 22, he gave evidence of suicidal ideation. No psychiatric treatment was given and modafinil was continued.

7.1.3.4.1.7 Patient 411: Suicidal ideation

This is a 10 year old patient who was receiving 200 mg of modafinil per day on study 207. On Study Day 8, he gave evidence of suicidal ideation. No psychiatric treatment was given and modafinil was continued.

7.1.3.4.1.8 Patient 53317: Suicidal ideation

This is an 8 year old patient who was receiving 255 mg of modafinil per day on study 311. On Study Days 13 and 21, he evidenced suicidal ideation. No psychiatric treatment was given and modafinil was continued.

7.1.3.4.1.9 Patient 40178: Suicidal ideation

This is an 8 year old patient who was receiving 340 mg of modafinil per day on study 310. On Study Day 8, she made a suicide threat. She received no psychiatric treatment but modafinil was withdrawn.

7.1.3.4.1.10 Patient 14016: Abnormal behavior

This is a 6 year old patient who was taking 255 mg of modafinil/day on study 312. On study day 93, 24 hours after her last dose of medication, she was noted to have abnormal behavior which persisted for 97 days. She was hospitalized.

7.1.3.4.1.11 Patient 003102: Suicidal ideation, situational depression

This is a 15 year old patient who had been taking 425 mg of modafinil/day for an unspecified amount of time prior to the emergence of symptoms. No treatment was given, modafinil was continued.

7.1.3.4.1.12 Patient 016001: Suicidal ideation

This is a 15 year old patient who was taking 425 mg of modafinil/day. On study day 219, she began to have suicidal ideation which persisted for 8 days. She was hospitalized and later withdrawn from the study for depressive disorder, not otherwise specified.

7.1.3.4.1.13 Patient 02008: Paranoia

This is an 8 year old patient who was receiving 255 mg of modafinil/day on study 3044. He had a paranoid reaction on Day 16, which persisted for 5 days. Modafinil was discontinued.

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Reviewer's comment

The psychiatric events described appear to be associated with the higher doses studied. Consideration should be given to age restriction for all potential modafinil indications since psychiatric events were more commonly described in children under 12 years old within the safety database.

7.1.3.4.2 *Dermatologic adverse events*

7.1.3.4.2.1 Patient 0623: Erythema multiforme/Steven-Johnsons syndrome(SJS)

Patient 062338 is a 7 year old patient who participated in study 311. He was titrated to 340 or 425 mg/day by Study Day 14. On Day 16, he had fever of 101.9 degrees, sore throat and a rash described as red bumps. On day 17, he had a single dose of amoxicillin. On Day 18, the modafinil was stopped. Over the next 4 days the skin reaction progressed from multiple pruritic areas on his arms/stomach (day 19) to involve his face and mucosa (urethral meatus/swollen crusty lips). After a period of extensive skin peeling which included his palms and soles, his skin reaction resolved with no new lesions noted. He was rechallenged with modafinil and the pruritis returned. He was withdrawn from the study on Day 44, after the positive rechallenge.

7.1.3.4.2.2 Patient 315: Erythema multiforme/Stevens-Johnson syndrome

Patient 315 is an 11 year old patient whose past medical history is significant for attention deficit disorder, Turner's syndrome and nocturnal enuresis. On Day 4 she was noted to have fever, abdominal pain, diarrhea. These symptoms lasted for 9 days. On Day 14, she was seen in the Emergency Room for treatment of pruritic urticaria involving her face and chest. Modafinil was stopped. The next day the rash was noted to be worsening so she was hospitalized with a provisional diagnosis of SJS. Her rash resolved in one week.

[Reviewer's note: Ten patients in the active drug group dropped out of the ADHD studies due to rash; there were no patients in the placebo group who dropped out for this reason. There were no placebo patients reported with serious rashes.]

7.1.4 Other Search Strategies

No additional search strategies were used for this review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The protocol for study 3027 called for assessing adverse events in person at screening, at the baseline visit, at the Week 3 visit (visit 3) and at week 6 or early termination (visit 4). Telephone assessments were to be made at weeks 1 and 2 of the double-blind period. In lieu of checklists, the study staff was instructed to ask an open-ended question such as "Have you had any unusual symptoms or medical problems since the last [contact]?"

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor elected to use the COSTART dictionary of preferred terms to report adverse events from the trials. In the adverse event reporting for trial 3027, there were some verbatim terms such as headache or abdominal pain coded to the body system-“body as a whole” as opposed to nervous system and digestive system as I would have expected.

Tourette’s disorder (pt. 027703) and exacerbation of nervous tic (pt 38701) were both coded as twitching and classified as musculoskeletal. *[Reviewer’s note: In the adverse event table below, I have reclassified them as Tourette’s disorder and placed them under nervous system disorders.]*

Interestingly, the sponsor did not code any of the adverse events reported to psychiatric disorders: hallucinations, irritability, and moodiness were all coded as nervous system disorders. In one case the hallucinations were reported as hallucinations; in the other they were reported as a sleep disorder. *[Reviewer’s note: I combined the two patients since they both had hallucinations and added the row to the adverse event table.]*

Irritability was coded as nervousness, which I do not think was an appropriate categorization. *[Reviewer’s comment: I relabeled that row “irritability” and placed an asterisk there to denote that this is not a COSTART preferred term.]*

[Reviewer’s note: In her review of the ADHD safety database, Dr. Cai noted “inappropriate translations/codings from verbatim terms, mostly from uncontrolled trials....She concluded that these instances did not appear to impact the AE analysis of the controlled trials. She hypothesized that the COSTART version 5.0 was not “granular enough to reflect the adverse events...accurately.”

She also noted that the sponsor reported that the incidence of suicidal ideation was zero during the open label ADHD trials but on her review there were three children with suicidal ideation during these trials. She specifically noted the case of subject 16001 (study 312), who was reported as having had an SAE but her acute depression and suicidal ideation were not listed in the JMP file; the symptoms listed in the JMP file under this subject ID # did not match the narrative provided by the sponsor.

Dr. Cai gives multiple examples of incomplete listings of verbatim terms for case report and narrative summaries in the open label data. She warns that while “in summary the AE listing and coding for the three double-blind, placebo-controlled (ADHD) trials are ...basically satisfactory....however deficiencies in listing AEs and problems in AE coding of Phase 2 and open label trials could cause problems if overall safety dataset is used for calculation as denominator (p.11).”]

7.1.5.3 Incidence of common adverse events

Study 3027 was the only placebo-controlled trial that went to completion so it was used to develop the table in section 7.1.5.4. This trial enrolled 165 people: 42 were treated with placebo. Patients

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had a 7-day titration period followed by a 6-week double-blind maintenance period on their randomized dose.

7.1.5.4 Common adverse event tables

The sponsor submitted one short-term placebo controlled trial: Study 3027. The adverse event data from that trial is depicted in the table below.

The tabulated data describes all of the adverse events which were described in 2 or more patients in the active treatment arm and those which occurred in a higher percentage in the active treatment arm than in the placebo group. The denominator for the dysmenorrhea group is different from the rest of the table since males are excluded. The asterisks denote categorizations that I have made which do not represent COSTART preferred terms.

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Table 5: Adverse events seen during the placebo-controlled trial in pediatric patients with narcolepsy

COSTART preferred term	Provigil-100 mg N=42	Provigil-all N=123	Placebo N=42
Body as a whole			
Headache	6 (14%)	22 (18%)	7 (17%)
Abdominal Pain	3 (7%)	9 (7%)	0
Accidental injury	0	4 (3%)	0
Fever	1(2%)	4 (3%)	0
Pain	0	3 (2%)	1 (2%)
Viral infection	1 (2%)	3 (2%)	1 (2%)
Digestive system disorders			
Nausea	2 (5%)	4 (3%)	1 (2%)
Diarrhea	1 (2%)	2 (2%)	0
Dyspepsia	1 (2%)	2 (2%)	0
Nervous system disorders			
Hypnagogic hallucinations (increased)	0	2 (2%)	0
Tourette's syndrome *	0	2 (2%)	0
Insomnia	2 (5%)	7 (6%)	1 (2%)
Somnolence	2 (5%)	4 (3%)	2 (5%)
Irritability/hostility*	1(2%)	6 (5%)	2 (5%)
Cataplexy (increased)	0	2 (2%)	0
Respiratory system disorders			
Rhinitis	3 (7%)	8 (7%)	1 (2%)
Pharyngitis	2 (5%)	5 (4%)	0
Sinusitis	1(2%)	4 (3%)	0
Cough increased	1(2%)	4 (3%)	1(2%)
Urogenital disorders			
Urinary tract infection	1(2%)	2(2%)	0
Dysmenorrhea (56 females received active drug, 19 received 100 mg)	2(11%)	3(5%)	0

7.1.5.5 Identifying common and drug-related adverse events

Realizing that the data from placebo-controlled trials in children with narcolepsy is based upon 165 patients, adverse events that may be considered common and drug related are the following:

- Insomnia
- Hostility
- Abdominal pain
- Pharyngitis and Sinusitis
- Urinary tract infection
- Dysmenorrhea

Insomnia was more frequently seen in the younger patients, those <12 years, as compared to the older patients, 17% vs. 9%.

Cataplexy was described in two children in study 3027 who received 400 mg/day and none who received placebo. Though both children had a past history of unmedicated cataplexy, worsening cataplexy was reported. Patient 038701 had worsening noted on Day 8 which resolved one day after study completion. Patient 079703 had worsening cataplexy beginning on Study day 22 which persisted through early termination from trial 3027 and persisted until Day 15 of open-label study 3029. Patient 31002 had worsening cataplexy which was treated with fluoxetine on Day 132 but persisted at through study completion; this information was not incorporated into the table above because it is data from an open-label study (3034). Cataplexy is a component of narcolepsy and so it is not clear that this symptom can be considered drug related in itself but there may be patients in whom use of modafinil is associated with idiosyncratic reaction, namely worsening of preexisting symptoms.

While no significant rashes were seen in the patients who participated in the narcolepsy development program, concern has been raised about an association between SJS and modafinil usage in the pediatric population due to findings during the ADHD trials. This is an issue which warrants further investigation as well as notification of the potential risk via labeling.

7.1.5.6 Additional analyses and explorations

An additional exploration was performed to assess for allergic reactions including eosinophilia, since those reactions were considered significant adverse events in the pediatric population. One participant (Patient 087704) had eosinophilia noted during screening for study 3027. Seven patients were found to have had allergic symptoms or eosinophilia during treatment:

Patient 066003 (study 3034)

This patient had an eosinophil value of 16% on day 22 (normal range is 0-9%); baseline value had been 18%. By Day 72, the eosinophil value was 9%.

Patient 066004 (Study 3034)

This patient had eosinophilia by report. No start or stop days nor abnormal values were provided. The values provided were all within normal limits. Conjunctivitis was reported on day 50 with resolution by Day 54.

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Patient 004701 (Study 3029)

This patient complained of worsening seasonal allergies on Day 42. The event was continuing at the time when the patients withdrew from the study due to lack of efficacy on day 106.

Patient 049703 (Study 3029)

This patient complained of dust allergies on day 89. The event resolved without intervention.

Patient 079703 (Study 3029)

This patient sustained a spider bite to the right leg with subsequent leg swelling on Day 2. This event resolved by Day 4. Seasonal allergy symptoms were noted on Day 28. The latter symptoms were ongoing at the time of data cutoff.

Patient 031002 (Study 3034)

Hay fever symptoms commenced on day 21. They had resolved by the time of study completion on Day 202.

Patient 012012 (study 3034)

This patient had allergic rhinopharyngitis reported without start or stop dates being given.

Reviewer's summary

The events described were, in all likelihood, not related to use of study drug.

7.1.6 Less Common Adverse Events

The following adverse events, listed by COSTART body system, occurred as isolated events in patients receiving active drug during placebo-controlled trial 3027:

Body as a whole

Asthenia, chest pain

Cardiovascular

Tachycardia, vasodilation

Hematologic and lymphatic

Anemia, ecchymosis, leukopenia

Digestive system disorders

Constipation, gastrointestinal hemorrhage

Metabolic and nutritional system disorders

Hypophosphatemia, NPN increased, SGPT increased, weight gain, hypoglycemia

Musculoskeletal

Leg cramps

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Nervous system disorders

Confusion, convulsion, delirium, hypesthesia, personality disorder, agitation, amnesia, emotional lability, hyperkinesia

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The protocol for study 3027 called for laboratory testing at screening, at the baseline visit (if abnormalities were found during screening), at the Week 3 visit (visit 3) and at week 6 or early termination (visit 4). The specimens were analyzed by (b) (4) a facility (b) (4)

Of the 123 patients who received active drug, all had baseline laboratory values and 120 had endpoint values. Of the 42 patients who received placebo, all had baseline laboratory values and 41 had endpoint values.

Though not included on the table below, urine pregnancy tests were performed at screening, at the baseline visit (if more than 2 weeks since screening), and at week 6 or early termination (visit 4). Urine drug screening was performed at screening, prior to the baseline visit (if abnormalities were found during screening), and at week 6 or early termination (visit 4). Additional urine drug screening and/or pregnancy testing was to be done at non-scheduled intervals if clinically indicated.

Table 6: Laboratory tests performed during Study 3027

Serum chemistry	Hematology	Urinalysis
Sodium	Hemoglobin	Protein
Potassium	Hematocrit	Glucose
Chloride	Red blood cell (RBC) count	Ketones
Bicarbonate or carbon dioxide	Platelet count	Blood (hemoglobin)
Glucose	White blood cell (WBC) count and differential count	pH
Blood urea nitrogen (BUN)	— polymorphonuclear	Specific gravity
Creatinine	— leukocytes (neutrophils)	Microscopic
Calcium	— absolute neutrophil count (ANC)	— bacteria
Phosphorus	— lymphocytes	— red blood cells (RBCs)
Uric acid	— eosinophils	— white blood cells (WBCs)
Total bilirubin	— monocytes	— casts
Total protein	— basophils	— crystals
Albumin	Atypical lymphocytes	
Cholesterol		
Alanine aminotransferase (ALT)		
Aspartate aminotransferase (AST)		
Alkaline phosphatase		
Gamma-glutamyl transpeptidase (GGT)		

(reproduction of Table 2 from the clinical study report)

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

I used the data from the placebo-controlled study of PROVIGIL in pediatric narcolepsy: study 3027.

7.1.7.3 Standard analyses and explorations of laboratory data

The sponsor used the following criteria to determine clinically significant abnormal clinical laboratory values:

Table 7:

Table 3: Criteria for Clinically Significant Abnormal Clinical Laboratory Values

Test	Criterion value
Serum chemistry	
Alanine aminotransferase (ALT)	≥3xULN
Aspartate aminotransferase (AST)	≥3xULN
Alkaline phosphatase	≥2xULN
Gamma-glutamyl transpeptidase (GGT)	≥3xULN
Blood urea nitrogen (BUN)	≥10.71 mmol/L
Creatinine	≥177 μmol/L
Uric acid	Boys Girls
	≥625 μmol/L ≥506 μmol/L
Bilirubin (total)	≥34.2 μmol/L
Hematology	
Hematocrit	<0.30 L/L
Hemoglobin	≤100 g/L
White blood cell (WBC) count	≤3x10 ⁹ /L or ≥ 20x10 ⁹ /L
Eosinophils	≥10%
Absolute neutrophil count (ANC)	≤1x10 ⁹ /L
Platelet counts	≤75x10 ⁹ /L or ≥ 700x10 ⁹ /L

ULN=upper limit of the normal range.

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7.1.7.3.1 Analyses focused on measures of central tendency

Serum chemistry

There were apparent trends in three of the measured variables. In the combined Provigil group, mean increases were noted (measured from baseline to endpoint) in alkaline phosphatase (11.2 U/L compared to 1.0 U/L in placebo) and in gamma-glutamyl transferase (2.1 U/L compared to 0.3 U/L in placebo). An increase was also seen in serum creatinine, 1.2 mmol/L as compared to 1.5 mmol/L for the placebo group.

The sponsor noted that the mean changes in the liver function tests appeared to be dose related with greater increases noted in those patients who received 400 mg/day:

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Alkaline phosphatase, with change as measured from baseline to endpoint

- Placebo group 1.0 U/L
- 100 mg group 2.9 U/L
- 200 mg group 15.0 U/L
- 400 mg group 15.9 U/L

GGT, with change as measured from baseline to endpoint

- Placebo group -0.3 U/L
- 100 mg group 0.1 U/L
- 200 mg group 1.7 U/L
- 400 mg group 4.7 U/L

[Reviewer's note: It appears that the effect is more marked in those patients who received more than 100 mg/day on this small study.]

Serum hematology

There were no significant trends in the hematology values.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Serum chemistry

Seven patients in the active treatment group had shifts from normal to abnormal GGT values: no placebo patients had similar changes. Five of the patients who had changes were in the 400 mg/day group.

Nine patients in the active treatment group had shifts from normal to abnormal cholesterol values: no placebo patients had similar changes. Six of the patients who had changes were in the 200 mg/day group.

Serum hematology

Patient 087704 (400 mg group) had lymphocytosis, leukopenia and eosinophilia noted at screening (Day -9):

- ANC $1.3 \times 10^9/L$ (normal: $\geq 1 \times 10^9/L$)
- Eosinophil value of 16% (normal: $\leq 10\%$)
- WBC of $5.4 \times 10^9/L$ (normal: 3.5 to $10.5 \times 10^9/L$)

On Day 21, the following clinically significant values were detected: an eosinophil value of 16% with an absolute neutrophil count (ANC) of $0.7 \times 10^9/L$.

On day 39, the testing revealed a WBC of $3 \times 10^9/L$, an eosinophil value of 3%, and an ANC of $1.4 \times 10^9/L$. A urinary tract infection and mild sinusitis had been reported as adverse events on Day 37.

[Reviewer's note: Causality cannot be definitely determined, but the use of study drug may have contributed to the hematological abnormalities seen.]

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7.1.7.4 Additional analyses and explorations

No additional analyses were performed.

7.1.7.5 Special assessments: Leukopenia

During these trials, seven patients were noted to have leukopenia:

Patient 004708 (Study 3029)

This patient had an ANC of $1.4 \times 10^9/L$ on Day 67 which resolved on Day 96 when the ANC was measured as $1.8 \times 10^9/L$.

Patient 012003 (Study 3034)

This patient was febrile on Days 10 and 11. A cough began on day 11 but resolved by Day 23. On Day 15 abnormal hematology parameters were noted: eosinophilia, lymphocytosis, ANC of $1.6 \times 10^9/L$. At Day 214 (final visit), all hematology parameters had normalized.

Patient 027701 (Study 3029)

On Day 14, ANC was noted to be $1.9 \times 10^9/L$. By Day 122, the ANC was $1.1 \times 10^9/L$ which led to suspension of modafinil. Since the ANC measured on Day 147 was $2 \times 10^9/L$, the neutropenia was considered to have resolved and treatment with modafinil was resumed on Day 160.

Patient 027702 (Study 3029)

This patient began to have decreased appetite, pharyngitis and intermittent emesis on Day 33 (of the open-label extension) which continued up until the time of data cut-off. On Day 55 (of the open label extension) lymphocytosis, decreased monocytes and an ANC of $0.8 \times 10^9/L$ were noted.

Patient 028701(Study 3029)

This patient had an ANC of $0.8 \times 10^9/L$ on Day 27 which resolved to $2.0 \times 10^9/L$ on day 42.

Patient 084702 (study 3027)

On Day 22, this patient had an absolute neutrophil count (ANC) of $0.8 \times 10^9/L$ as well as rhinitis. When measured on Days 34 and 46, the ANC was within normal limits.

Patient 085703 (Study 3027)

This patient had an ANC of $1.2 \times 10^9/L$ on Day 43. By Day 16 of the open-label extension study 3029, the ANC had resolved to $2.9 \times 10^9/L$.

Patient 087703 (study 3027)

On Day 42, this patient had an absolute neutrophil count (ANC) of $1 \times 10^9/L$. The ANC was within normal limits at baseline.

Patient 087704 (study 3027)

This patient was discussed in section 7.7.7.3 and will not be discussed further here.

Reviewer's summary

We do not have sufficient information to assign causality to the use of study drug. I would note that most of the leukopenia was detected in patients who had been enrolled in Studies 3027/3028 who then went on to participate in the extension study 3029. This may reflect a time-dependent drug effect but again we do not have sufficient information to make a definitive statement.

The sponsor provided additional data on ANC and WBC counts from study 312, a 12-month open-label study in pediatric patients with ADHD. In that analysis, Cephalon found that mean WBC count decreased over the first 4 months of treatment and subsequently increased, stabilizing at the week-2 level. The mean ANC also decreased over the first 4 months of treatment and subsequently increased, but stabilized as a level which was lower than the baseline values.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The protocol for study 3027 called for assessing vital signs at screening, at the baseline visit, at the Week 3 visit (visit 3) and at week 6 or early termination (visit 4).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Data for the analysis came from all submitted studies, though the focus was on data from study 3027 as it was the only placebo-controlled study.

7.1.8.3 Standard analyses and explorations of vital signs data

The sponsor used the following criteria to determine clinically significant abnormal vital signs:
Table 8:

Table 4: Criteria for Clinically Significant Abnormal Vital Signs Measurements

Vital sign	Criterion value	Change relative to baseline
Pulse	≥ 120 bpm	Increase of ≥15 bpm
	≤ 50 bpm	Decrease of ≥15 bpm
Systolic blood pressure	≥ 130 mmHg	Increase of ≥20 mm Hg
	≤ 80 mm Hg	Decrease of ≥20 mm Hg
Diastolic blood pressure	≥ 85 mm Hg	Increase of ≥15 mm Hg
	≤ 50 mm Hg	Decrease of ≥15 mm Hg
Body temperature	≥ 38.3°C	Change of ≥1.1°C
Weight	—	Change of ≥7%

bpm=beats per minute.

7.1.8.3.1 *Analyses focused on measures of central tendencies*

The mean pulse in the modafinil treated group (n=123) was 79.5 beats per minute (SD 12.09) at baseline; when the 120 patients who had both baseline and endpoint data were evaluated, the mean change was -1.3 beats per minute (SD 14.09). The mean pulse in the placebo treated group (n=42) was 77.3 beats per minute (SD 11.04) at baseline; when the 41 patients who had both baseline and endpoint data were evaluated, the mean change was -3.0 beats per minute (SD 12.46).

The mean systolic blood pressure in the modafinil treated group (n=123) was 112.6 mmHg (SD 12.78) at baseline; when the 120 patients who had both baseline and endpoint data were evaluated, the mean change was -0.5 mmHg (SD 10.38). The mean systolic blood pressure in the placebo treated group (n=42) was 112.1 mmHg (SD 10.47) at baseline; when the 41 patients who had both baseline and endpoint data were evaluated, the mean change was 0 mmHg (SD 12.03).

The mean diastolic blood pressure in the modafinil treated group (n=142) was 68.0 mmHg (SD 9.38) at baseline; when the 120 patients who had both baseline and endpoint data were evaluated, the mean change was 0.1 mmHg (SD 9.6). The mean diastolic blood pressure in the placebo treated group (n=42) was 66.1 mmHg (SD 8.58) at baseline; when the 41 patients who had both baseline and endpoint data were evaluated, the mean change was 1.0 mmHg (SD 9.27).

[Reviewer's note: The mean changes were not clinically significant for either group nor were the differences between groups clinically significant.]

7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

The following comments are based upon data from all studies, both placebo-controlled and open-label, submitted in support of this application.

There were 2 patients who had a pulse rate of ≥ 120 bpm and an increase ≥ 15 bpm; both were in the modafinil group. There were 2 patients who had a pulse rate of ≤ 50 bpm and a decrease ≥ 15 bpm; both were in the modafinil group.

There were 6 patients who had a systolic blood pressure of ≥ 130 mmHg and an increase ≥ 20 mmHg in the modafinil group; there were 3 patients who had a systolic blood pressure of ≥ 130 mmHg and an increase ≥ 20 mmHg in the placebo group. In the modafinil group, two patients continued to have clinically significant values at study completion, the other patients had resolution of their blood pressure elevations.

There was 1 patient who had systolic blood pressure of ≤ 80 mmHg and a decrease ≥ 20 mmHg; that patient was in the placebo group.

There were 5 patients who had a diastolic blood pressure of ≥ 85 mmHg and an increase ≥ 15 mmHg in the modafinil group; there were 2 patients who had a diastolic blood pressure of ≥ 85 mmHg and an increase ≥ 15 mmHg in the placebo group. In the modafinil group, two patients continued to have clinically significant values at study completion, the other patients had resolution of their blood pressure elevations.

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There were 2 patients in the modafinil group who had systolic blood pressure of ≤ 50 mmHg and a decrease ≥ 15 mmHg; there was one patient who met this criterion in the placebo group.

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

Patient 004714 (400 mg/day group) was a marked outlier with a heart rate of 91 at baseline. On Day 24, the heart rate had dropped to 48 beats/minute and remained low, with a rate of 47 recorded at the final visit.

Patient 028702 (400 mg/day group) had a systolic blood pressure which increased to 142 mm/Hg from a baseline level of 122 noted on Day 40.

Patient 070709 (400 mg/day group) who had been granted an exemption to enroll despite a baseline blood pressure of 153/96 was noted to have an elevated systolic blood pressure on day 21 to 159 and an elevated diastolic blood pressure to 111 on Day 41.

Patient 041701 (200 mg/day group) had a baseline blood pressure of 110/75 which was increased to 140/90 on Day 42.

7.1.8.4 Additional analyses and explorations

There was an additional exploration done using data from both controlled and uncontrolled studies to assess cardiac related events of syncope, arrhythmia or tachycardia. Eight patients reported these adverse events but none withdrew from the study due to these events.

Patient 004707 (study 3027)

This patient reported tachycardia on Day 30, however no heart rate data is available from that day. Study drug was interrupted due to the adverse event.

Patient 004701(study 3029)

This patient had arrhythmia and tachycardia (HR=106 bpm) on day 106. Her baseline heart rate was 78 bpm. While both symptoms resolved in under 24 hours, the patient withdrew from the study due to lack of efficacy.

Patient 031704 (study 3029)

An episode of syncope on Day 83 resolved the same day.

Patient 067001 (study 3034)

This patient had a heart rate of 72 bpm prior to study entry. Tachycardia was reported on Day 18 but there are no heart rate values available from that day.

Patient 062001 (study 3034)

This patient had tachycardia on Day 44 of the study with a heart rate of 83 bpm; baseline heart rate was 60 bpm. Heart rates were noted to fluctuate between 75 and 90 bpm but the tachycardia was considered resolved on day 175, when the heart rate was recorded as 77 bpm. [Reviewer's note: While this final rate was lower than the 89 bpm recorded on day 140, it was still above baseline. I am not certain that this symptom could be considered to have truly resolved.]

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Patient 072006 (study 3034)

This patient reported palpitations on day 24; no heart rate was recorded. The symptoms continued at the time of last evaluation.

Patient 012009 (study 3034)

An episode described as vagal crisis, coded as syncope, occurred on day 18 and resolved the following day.

Patient 092003 (study 3034)

This patient fainted following a blood draw on Day 56. The syncopal episode resolved without sequelae.

Reviewer's summary

There is insufficient evidence to assess the potential causal relationship between the drug and the symptoms described.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The protocol for study 3027 called for assessing 12-lead ECGs at screening, and at week 6 or early termination (visit 4). The latter study was to be done after the first MSLT nap. The sponsor hired eResearch technology Inc., a central diagnostic center, to interpret the ECGs. Findings that the PIs felt represented a clinically significant change were to be considered adverse events, recorded on the CRFs and monitored until resolution or stabilization occurred.

In study 3027, a minority of patients (n=26, 16%) had abnormal ECGs at baseline; prolonged QTc interval was the most common abnormal finding. Nineteen patients had ECG abnormalities newly diagnosed during the study:

- Prolonged QTc interval: 5 PROVIGIL patients, 4 placebo patients
- Intraventricular conduction defect: 5 PROVIGIL patients, 1 placebo patient
- Sinus bradycardia: 5 PROVIGIL patients, 0 placebo patients

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

I used the data from the placebo-controlled study of PROVIGIL in pediatric narcolepsy, study 3027.

7.1.9.3 Standard analyses and explorations of ECG data

The sponsor provided information on the baseline and endpoint values for the PR, QT, QRS and QTc interval measurements. There were no clinically significant differences between the active drug group and the placebo group.

7.1.9.4 Additional analyses and explorations

The sponsor analyzed the QTc interval using three different methods. There was no evidence that PROVIGIL affected the QTc interval during this study.

Table 9: Calculations of QTc interval, three different methods

Variable	Category	Number (%) of patients				
		PROVIGIL			All PROVIGIL (N=123)	Placebo (N=42)
		400 mg/day (N=40)	200 mg/day (N=41)	100 mg/day (N=42)		
QTc interval (Fridericia)	Maximum increase from baseline (msec)					
	<30	15 (38)	19 (46)	17 (40)	51 (41)	13 (31)
	30 to 60	2 (5)	1 (2)	2 (5)	5 (4)	3 (7)
	>60	0	0	0	0	0
	Maximum value on treatment (msec)					
	<450	38 (95)	40 (98)	39 (93)	117 (95)	40 (95)
QTc interval (Bazett)	Maximum increase from baseline (msec)					
	<30	12 (30)	17 (41)	14 (33)	43 (35)	10 (24)
	30 to 60	8 (20)	3 (7)	7 (17)	18 (15)	4 (10)
	>60	0	0	0	0	1 (2)
	Maximum value on treatment (msec)					
	<450	33 (83)	40 (98)	38 (90)	111 (90)	36 (86)
QTc interval (neuropharm ^a)	Maximum increase from baseline (msec)					
	<30	16 (40)	20 (49)	16 (38)	52 (42)	11 (26)
	30 to 60	2 (5)	1 (2)	3 (7)	6 (5)	4 (10)
	>60	0	0	0	0	0
	Maximum value on treatment (msec)					
	<450	37 (93)	40 (98)	38 (90)	115 (93)	40 (95)

SOURCE: Listing 33.

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

QTc=QT interval corrected for heart rate.

Reproduction of table 30 from the study report

7.1.10 Immunogenicity

This section is not relevant to this application.

7.1.11 Human Carcinogenicity

A 12 year old boy (patient 066001 on study 3034) had an exacerbation related to a preexisting osteofibroma whilst on study. This was unlikely to be associated with drug treatment.

7.1.12 Special Safety Studies/Assessments

7.1.12.1 Child behavior checklist for ages 6-18 (CBCL/6-18)

The CBCL/6-18 is a 113-question parent-rated checklist designed to assess the patient's competencies and behavioral/emotional problems over the preceding 6 weeks. Each question is responded to using the following scale: 0=not true, 1=somewhat or sometimes true, and 2=very true or often true. This checklist was to be completed at the baseline and at the final study visit. Higher scores reflect worse behavior/emotional problems so the goal of treatment is to lower the score on the CBCL/6-18.

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7.1.12.1.1 Study 3027: The double-blind narcolepsy study

All study groups had mean decreases in CBCL/6-18 total scores at endpoint as compared to baseline.

7.1.12.1.2 Study 3034: the 6 month open-label safety study

There is no baseline data available for the CBCL/6-18 from this study, since all patients had been enrolled and administered study drug at the time of the amendment. It is not clear why this is the case since the original PWR, which required age appropriate assessments, was issued on 17 June 2004 and this study began screening subjects on 31 January 2005. The protocol amendment to include the CBCL/6-18 was dated March 2005.

7.1.12.1.3 Study 3029: The 12 month open-label safety study

There is no data available at this time since the study is ongoing.

7.1.12.2 Brief psychiatric interview

This interview was to be conducted by a clinical psychologist /psychiatrist at baseline and at the final study visit to assess for possible anxiety, nervousness, symptoms of mania and/or psychosis.

The following was provided as a sample in appendix 6 of the protocol for guidance:

Sample Questions for Psychiatric Interview
COPYRIGHT MATERIAL

SOURCE: Guy W. ECDEU Assessment Manual for Psychopharmacology (Revised). Rockville, MD: US Department of Health, Education, and Welfare; Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration; National Institute of Mental Health, Psychopharmacology Research Branch; 1976:141-146

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7.1.12.2.1 Study 3027: The double-blind narcolepsy study

The interview was performed inconsistently. A large proportion of patients were missing the baseline and/or the endpoint interview: 7 in the 400 mg group (18%), 9 in the 200 mg group (22%), 9 in the 100 mg group (21%), and 6 in the placebo group (14%). The results of the psychiatric interview, in those instances when it was done, did not appear to provide evidence of any effect of PROVIGIL on mania, psychosis, anxiety or nervousness.

[Reviewer's note: Based only on the 8 questions above, without further details about the psychiatric interview, it is conceivable that subtle psychiatric changes might have been missed.]

7.1.12.2.2 Study 3034: the 6 month open-label safety study

Since all patients had been enrolled and administered study drug prior to the implementation of the protocol amendment, there is not good data for comparison: only two of the 90 patients had baseline interviews. There was data from 52 patients who had endpoint interviews: while 6 patients had abnormalities detected at that timepoint it is not possible to discern whether the abnormalities are in any way related to PROVIGIL therapy.

7.1.12.2.3 Study 3029: The 12 month open-label safety study

There is no data available at this time since the study is ongoing.

7.1.12.3 Kaufman Brief Intelligence Test, second edition (KBIT-2)

This is a 15-30 minute test to evaluate cognitive function. The vocabulary subtest assesses the patient's knowledge of words and their meanings. The matrices subtest assesses problem-solving ability. Total (IQ composite), verbal and nonverbal subscores were to be evaluated.

7.1.12.3.1 Study 3027: The double-blind narcolepsy study

There was no evidence of significant effect on cognition though there was a slight trend towards an improved IQ composite score (as compared to baseline) for the lowest scoring individuals in both the active treatment arm and in the placebo arm.

7.1.12.3.2 Study 3034: the 6 month open-label safety study

There is no baseline data available for the KBIT-2 from this study since all patients had been enrolled and administered study drug at the time of the amendment. It is not clear why this is the case since the original PWR, which required age appropriate assessments, was issued on 17 June 2004 and this study began screening subjects on 31 January 2005. The amendment to include the KBIT-2 was dated March 2005.

KBIT-2 subtests that involved English language comprehension were, for obvious reasons, not conducted in non-English-speaking countries.

The scanty data available does not allow any meaningful analysis to be done.

7.1.12.3.3 Study 3029: The 12 month open-label safety study

There is no data available at this time since the study is ongoing.

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7.1.12.4 Nocturnal polysomnograph (NPSG)

This was to be performed at the baseline visit and at week 6 to document normal nighttime sleep. The study was to begin within 30 minutes of the patient's usual bedtime, but no later than 23:30 and had to last at least 8 hours.

7.1.12.4.1 Study 3027: The double-blind narcolepsy study

There was no evidence of an effect of PROVIGIL on nocturnal sleep initiation or sleep maintenance.

7.1.12.4.2 Study 3029: The 12 month open-label safety study

There is no data available at this time since the study is ongoing.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

During trial 3027, it was noted that Patient 067702 (100 mg group) did not date the study drug card and took an unspecified number of additional tablets on a few occasions. This may or may not represent an episode of abuse. We do not have sufficient evidence to make a determination.

PROVIGIL (modafinil) is listed in Schedule IV of the Controlled Substances Act.

The following information is taken *verbatim* from the approved labeling:

“In addition to its wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants. In *in vitro* binding studies, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release. Modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine...The abuse potential of modafinil (200, 400, and 800 mg) was assessed relative to methylphenidate (45 and 90 mg) in an inpatient study in individuals experienced with drugs of abuse. Results from this clinical study demonstrated that modafinil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). The effects of modafinil withdrawal were monitored following 9 weeks of modafinil use in one US Phase 3 controlled clinical trial. No specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.”

[*Reviewer's note: Since modafinil is reinforcing and produces “psychoactive and euphoric effects and feelings consistent with...methylphenidate,” it is not clear that we should not expect an increase in modafinil abuse as the product has increased availability. Its Schedule IV status may lead to an increase in prescriptions as the ability to avoid the restrictions associated with prescribing Schedule III products is one of the perceived advantages frequently commented on at the Advisory Committee hearing regarding the use of modafinil in the treatment of ADHD.*]

7.1.14 Human Reproduction and Pregnancy Data

While there are no adequate and well-controlled studies in pregnant women, the following comments are made in the approved labeling based upon patient data from trials in adults (reproduced *verbatim*):

- Seven normal births occurred in patients who had received modafinil during pregnancy. One patient gave birth 3 weeks earlier than the expected range of delivery dates (estimated using ultrasound) to a healthy male infant. One woman with a history of spontaneous abortions suffered a spontaneous abortion while being treated with modafinil.
- It is not known whether modafinil or its metabolites are excreted in human milk.

In the briefing document prepared by Cephalon for the Advisory committee meeting in March 2006, they state in a footnote to table 41 (p.94) that “the death of a neonate was reported with adverse events of neonatal respiratory distress and severe intrauterine growth retardation. The mother had been prescribed modafinil tablets throughout her pregnancy.”

[Reviewer’s note: The sponsor was asked to provide us with all available information on the latter patient and its mother. In supplement 21 to this application, the Sponsor provided a MedWatch form from January 2004 as well as an ultrasound report from the same month. Though the letter from the treating physician makes reference to a pregnancy tracking form, that form was not provided for our review. This case originated in the United Kingdom and was first reported to the Agency on November 26 2003 with a final MedWatch follow-up provided on January 29, 2004. In November 2003, a health professional reported ultrasound results of a small 19-week fetus with short femurs and hydronephrosis being carried by a mother who was and had been taking modafinil throughout the pregnancy. The woman had taken clomipramine at some point but the dates of use were not given. A repeat ultrasound done on a unspecified date revealed right kidney dilation, short femur length and a head circumference growing consistently in the 5th percentile. There was no end-diastolic flow on placental doppler which was considered evidence of intra-uterine growth retardation (IUGR). While the mother was not known to be hypertensive, she did smoke 4 cigarettes daily. The child was born (b) (6) While in the hospital, he died with the final diagnoses of respiratory distress and severe intra-uterine growth retardation. The hydronephrosis seen on the antenatal ultrasound was not confirmed. While there is no clear causal correlation, it is not possible to entirely rule out an association between the fetal IUGR and the maternal use of modafinil.]

7.1.15 Assessment of Effect on Growth

There was no evidence of an effect on height/weight parameters during the short placebo-controlled study 3027.

The sponsor combined the height and weight data from all studies to calculate standardized weight z-scores and percentiles. However, the data reflects exposure that ranged from a few days to 6 months and dosages that ranged from 100 to 400 mg. Slight decreases in mean weight percentile were seen with a greater decrease seen in the small subset of patients with OSAHS.

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[Reviewer's note: It is not clear that the data obtained from children in countries outside the US, e.g. data from study 3034, can be appropriately assessed by conversion of said data to standardized z-scores and percentile scores from the National Center for health Statistics which is based upon data from American children. Additionally, the range in duration exposure and dosage exposure makes the change in z-scores difficult to interpret.]

7.1.16 Overdose Experience

No overdoses were reported during the Phase III studies in pediatric patients with narcolepsy or OSAHS. During the Phase III studies in pediatric patients with ADHD, 38 patients received doses higher than the protocol maximum of 425 mg/day, with a range of overdose from 510 mg-850 mg/day. The patient who received 850 mg reported insomnia.

The following information is taken from the approved labeling for PROVIGIL:

“In clinical trials, a total of 151 protocol-specified doses ranging from 1000 to 1600 mg/day (5 to 8 times the recommended daily dose of 200 mg [for adults]) have been administered to 32 subjects, including 13 subjects who received doses of 1000 or 1200 mg/day for 7 to 21 consecutive days.

In addition, several intentional acute overdoses occurred; the two largest being 4500 mg and 4000 mg taken by two subjects participating in foreign depression studies. None of these study subjects experienced any unexpected or life-threatening effects.

Adverse experiences that were reported at these doses included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea and decreased prothrombin time.

From post-marketing experience, there have been no reports of fatal overdoses involving modafinil alone (doses up to 12 grams). Overdoses involving multiple drugs, including modafinil, have resulted in fatal outcomes. Symptoms most often accompanying modafinil overdose, alone or in combination with other drugs have included: insomnia; central nervous system symptoms such as restlessness, disorientation, confusion, excitation and hallucination; digestive changes such as nausea and diarrhea; and cardiovascular changes such as tachycardia, bradycardia, hypertension and chest pain.

Cases of accidental ingestion/overdose have been reported in children as young as 11 months of age. The highest reported accidental ingestion on a mg/kg basis occurred in a three-year-old boy who ingested 800-1000 mg (50-63 mg/kg) of modafinil. The child remained stable. The symptoms associated with overdose in children were similar to those observed in adults.

No specific antidote to the toxic effects of modafinil overdose has been identified to date. Such overdoses should be managed with primarily supportive care, including cardiovascular monitoring. If there are no contraindications, induced emesis or gastric lavage should be considered.

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There are no data to suggest the utility of dialysis or urinary acidification or alkalization in enhancing drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose”.

7.1.17 Postmarketing Experience

In a review of pharmacovigilance reports of incidents in pediatric patients less than 18 years of age done for the March 2006 Advisory Committee, the sponsor found that from January 2000 to June 2005, the total estimated pediatric exposure was 24,700 patient years. The sponsor reports 97 post-marketing case reports in patients under 17 years old, with the most common reports being suicide attempt, mania, hallucinations, intentional misuse and tachycardia. There were seven psychiatric-related reports detected (data from slides 105 and 106 in the sponsor’s presentation at the AC):

- 6 year old girl with night-time awakenings complaining of bugs biting her
- 7 year old boy with visual hallucinations
- 11 year old boy with visual and auditory hallucinations
- 13 year old boy who complained of agitation, feeling terrible and easily angered
- 13 year old girl who complained of anger, a jittery feeling, achiness and loss of appetite
- 14 year old girl who attempted suicide via drug overdose
- 17 year old boy with mania: flight of ideas, sexual excitation, increased irritability

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 10: Studies submitted in support of the Narcolepsy indication (S021)

	Patients	Design	Duration	E/S
Study C1538/ 3027 /NA/MN	165	R, DB, PC	6 weeks-DB phase	E/S
Study C1538/ 3029 /NA/MN	148	OL extension of 3027	12 months	S
Study C1538/ 3034 /ES/MN (foreign study)	91	OL	6 months	S
Study C1538/ 3028 /AP/MN	26 with OSAHS	R, DB, PC	6 weeks-DB phase Terminated due to difficulty with recruitment	S

R-randomized; DB-double blind; OL-open label; PC-placebo controlled; E-efficacy; S-safety
A more detailed table, composed by the sponsor, may be found in appendix 10.1.

Table 11: Demographics

	Narcolepsy N=202	OSAHS N=68	Total (n=270)
Age (years)			
Mean (SD)	12.4 (2.94)	11.7 (3.11)	12.2 (2.99)
Age group, n (%)			
<12 years	67 (33%)	28 (41%)	95 (35%)
≥12 years	135 (67%)	40 (59%)	175 (65%)
Sex			
Male	108 (53%)	47 (69%)	155 (57%)
Female	94 (47%)	21 (31%)	115 (43%)
Ethnicity			
White	122 (60%)	57 (84%)	179 (66%)
Black	69 (34%)	5 (7%)	74 (27%)
Asian	1 (<1%)	1 (1)	2 (<1%)
American Indian	1 (<1%)	0	1 (<1%)
Pacific Islander	1 (<1%)	0	1 (<1%)
Other	8 (4%)	5 (7%)	13 (5%)

(modification of table 12 from the summary of clinical safety)

7.2.1.3 Extent of exposure (dose/duration)

When both OSAHS and narcolepsy patients from all studies are considered, the majority of the patients treated received 400 mg/day. The majority (72%) of patients with narcolepsy received 400 mg/day providing a exposure of 37.8 patient-years. The sponsor had 9.6 patient-years of data on patients who received the proposed doses of 100 mg/day.

At the time of submission, the sponsor provided data from 6 months or less in patients with narcolepsy or OSAHS. The data is presented for all patients combined in the table below with no distinction made between the narcolepsy and the OSAHS patients. The average daily dose was higher for the 91 patients treated in the foreign protocol 3034 with a mean of 229.7 mg/day (range 92.6 to 400, median of 227). In the US protocol 3029, the mean average daily dose for the 148 participants was 169.6 mg/day with a range of 2.3 to 407.1 mg and a median of 152 mg.

Table 12: Extent of exposure during the two long term safety trials (6 mo and 12 mo)

Duration	6 mo trial n=91 (%)	12 mo trial n=148 (%)
< 2 weeks	0	13 (9)
≥2 weeks to < 1 month	0	26 (18)
≥ 1 to <3 months	3 (3)	58 (39)
≥3 to < 6 months	5 (5)	44 (30)
≥6 months	83 (91)	7 (5)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There were no other studies used to provide clinical data.

7.2.2.2 Postmarketing experience

The important postmarketing events have been placed throughout this review in the appropriate places.

7.2.2.3 Literature

The literature search in the combined applications, i.e. the current one as well as the application for modafinil in the treatment of childhood ADHD, was adequate. I did not perform an independent literature review in support of this application.

7.2.3 Adequacy of Overall Clinical Experience

The single placebo-controlled study in conjunction with the data from the open label studies exposed an adequate number of people to the drug though the demographics were skewed towards pubescent males of European ancestry.

The doses studied were adequate. The duration of exposure conformed to the pediatric written request for the most part. The requested 12-month study was not completed at the time of the submission of this supplement.

The study design mirrored that used for the adult approval. It is unclear why there was no evidence of subjective benefit. It may well be that the study design, while adequate for evaluation of adults, needs further modification to adequately assess subjective benefit in the pediatric population.

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Potential class effects were not evaluated.

The exclusion criteria did not limit the relevance of the safety assessments. While pediatric patients who had a history of psychiatric illness were not supposed to participate, it seems appropriate to restrict use of this product in patients with past history of psychosis or mania in light of the stimulant effects of the product. In addition, it may be prudent to contraindicate the product in persons with a past history of suicidal ideation or gestures.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The preclinical testing was adequate.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The sponsor did not perform drug-drug interaction studies in support of this submission.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The potential adverse events of concern for use of modafinil for the narcolepsy indication were 1) behavioral (anxiety, nervousness and symptoms of mania /psychosis) effects of the drug 2) changes in cognition associated with both short and long term use of modafinil, 3) effects on growth, 4) potential bone marrow suppression, 5) potential leukopenia and 6) the hypertensive effect of modafinil.

The sponsor's behavioral (psychiatric) assessments were sub-optimal as they were done inconsistently over the 3 studies.

The data on the short-term effects on cognition derived from Study 3027 were adequate. The results from Studies 3034 and 3029 were not useful for this review for reasons previously discussed.

The data on the short-term effects on growth derived from Study 3027 were adequate. The results from Studies 3034 and 3029 were not useful for this review for reasons previously discussed.

The data on the short-term effects on potential bone marrow suppression and potential leukopenia derived from Study 3027 were adequate. The results from Study 3029, the 12-month study done in the US, are pending as the study is ongoing.

The data on short-term hypertensive effects were adequate.

7.2.8 Assessment of Quality and Completeness of Data

The quality of the data from Study 3027 appears to be satisfactory and complete. However, there is possible evidence of investigator bias at site 079. At that site, which enrolled 9 patients, one patient (079707) discontinued early due to a non-study related adverse event and one patient completed the study. The other 7 patients were all terminated from the study at week 3 and transferred into the open-label study 3029. It appears that the PI was not fully convinced of clinical equipoise at study initiation and hypothesized that inadequate modafinil dosing was the cause of some of the witnessed symptoms.

- Subject 079701: This patient began study drug on 7/7/05. At week 3, the PI wrote “possible early termination visit because patient still sleepier than usual.” At the early termination visit (8/5/05), the PI noted that the symptoms of excessive sleepiness were inadequately controlled on study medication. Dry mouth, sinusitis and cough were also noted as adverse events. Her mean change from baseline on the MSLT was 1.625 minutes. Her CGI-C scores were 3 at week 3 and 3 at early termination. The chart states that “family/patient request early termination to enter open label study on a known dose of drug prior to school starting.” This patient was later changed to Adderall 60 with marked improvement in her EDS.

[Reviewer’s note: Though the reason for discontinuation was classified as other, it should have been classified as lack of efficacy from the 400mg/day of modafinil being administered.]

- Subject 079702: This patient, who was also receiving 400 mg/day, was terminated early for no apparent reason. He had no adverse events reported. His mean change from baseline on the MSLT was 0.75 minutes. His CGI-C scores were 1 at week 3 and 1 at early termination.
- Subject 079703: Worsening cataplexy and anemia were recorded with a single episode of epistaxis after 3 weeks on 400 mg/day of modafinil. Her mean change from baseline on the MSLT was 1.125 minutes. Her CGI-C scores were 1 at week 3 and 2 at early termination (8/2/05). The chart states that “family/patient request early termination to enter open label study on a known dose of drug prior to school starting.”

[Reviewer’s note: Though the reason for discontinuation was classified as other, it should have been classified as adverse events from the 400mg/day of modafinil being administered.]

- Subject 079704: This patient, who was receiving 100 mg/day, was said to have been minimally improved with the parent unsure of the effect of the drug. Her mean change from baseline on the MSLT was 16.125 minutes. Her CGI-C scores were 2 at week 3 and 3 at early termination.
- Subject 079705: This patient, who was receiving 400 mg/day, was the only one from this site to complete the study. At the 3 week visit, the PI noted that the patient had “unacceptable sleepiness on study drug. Sleepiness had been fairly well controlled on modafinil 400 mg prior to starting study.” There were no adverse events reported.

[Reviewer’s note: This patient should have been noted to have lack of efficacy.]

- Subject 079706: This patient, who was receiving placebo, was the only one from this site to complete the study. His family requested early termination because he was felt to be worse

than baseline. His mean change from baseline on the MSLT was 8.125 minutes. His CGI-C scores were 2 at week 3 and 4 at early termination.

- Subject 079707 withdrew due to a non-study related adverse event.
- Subject 079708: This patient, who was receiving 200 mg/day, had decreased appetite and intermittent cough noted. By report he was doing well on the study medication. His family requested early termination in order to be on a known dose of modafinil. His mean change from baseline on the MSLT was 4.375 minutes. His CGI-C scores were 1 at week 3 and 2 at early termination.
- Subject 079709: This patient, who was receiving 100 mg/day, was noted to have hyperactive behavior, memory loss, cough and sleep-walking every other night. Her mean change from baseline on the MSLT was 20.0 minutes. Her CGI-C scores were 2 at week 3 and 3 at early termination. Her family requested early termination in order to be on a known dose of modafinil. Her hyperactivity was noted to be an additional factor in her early termination from Study 3027. While on the open label study, she had unacceptable levels of hyperactivity on 100 mg/day so modafinil was discontinued and Concerta therapy (27 mg) was resumed.

[Reviewer's note: Though the reason for discontinuation was classified as other, it should have been classified as adverse events from the 100mg/day of modafinil being administered.]

Documentation of adverse events and laboratory values was done inconsistently during open-label safety study 3034.

The data from open-label 3029 is apparently complete but I do note Dr. Cai's comments regarding the inadequacy of the open label data from the ADHD safety database as previously commented upon.

7.2.9 Additional Submissions, Including Safety Update

There were (as of July 14, 2006) four additional submissions to supplement 021:

February 7 2006

A request for categorical exclusion (environmental assessment) for this supplement

March 17 2006

The sponsor reported an error in Listing 44 (Nocturnal polysomnography times by treatment group randomized patients) of the study report for Study 3027. "The event labels of lights on and lights off were reversed due to an error in generating the listing." A corrected listing was provided.

April 18 2006

This represented the required 4-month safety update. The sponsor provided a revised summary of clinical safety including the original safety information as well as information accrued through February 21 2006 from the ongoing 12-month study, Study 3029.

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Since 30-day follow-up information was still pending from 39 patients in the 6-month study 3034 at the time of original data submission, that information was also incorporated into this update.

(b) (4)

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

My review of the safety data from the trials in patient with narcolepsy, OSA/HS and ADHD indicates that modafinil is capable of producing adverse effects such as:

- Psychosis manifest as visual, auditory and command hallucinations
- Headache
- Abdominal Pain
- Diarrhea
- Dysmenorrhea
- Insomnia (predominantly seen at doses of 200 mg and higher)

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- Anorexia (predominantly seen at doses of 200 mg and higher)
- Weight Loss (predominantly seen at doses of 200 mg and higher)

While rashes and dermatologic adverse effects are not common, there was at least one case of probable Stevens-Johnson syndrome seen during the ADHD trials.

Cataplexy is a component of narcolepsy and so it is not clear that this symptom can be considered drug related in itself but there may be patients in whom use of modafinil is associated with idiosyncratic reactions, namely worsening of preexisting symptoms such as cataplexy and/or hypnagogic hallucinations.

While causality cannot be definitively determined, modafinil may lead to an exacerbation of the symptoms of Tourette's syndrome.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

I looked at the studies presented individually without pooling the data though I would note that the safety data from ongoing study 3029 represents long-term data from patients on studies 3027 and 3028.

7.4.1.2 Combining data

While I did not formally combine the safety data from the double-blind study and its safety extension, I did evaluate the data to determine whether there were any adverse events that appeared to be time dependent.

I did not combine the data from the safety studies performed since they were done in different populations.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The sponsor did not formally explore dose dependency in these studies though they assert that there was no correlation between the dose and the adverse events seen.

I note that there was an apparent trend toward an increased frequency of adverse events at higher doses, especially at the 400mg dose. Due to the small number of events and enrolled patients, it is difficult to arrive at a definitive conclusion.

7.4.2.2 Explorations for time dependency for adverse findings

The sponsor concluded that the incidence of adverse events was higher in those patients who had received at least 6 months of therapy (85% as compared to 75% in the population overall), with the incidence of headache (28%), anorexia (20%) and nervousness (7%) appearing to increase with prolonged exposure. The incidence of rash also appeared to increase but only among the younger children.

I note that there was an apparent trend toward an increased frequency of reported psychiatric events in the extension studies which would make me question whether this was a time-dependent finding. Due to the small number of events and enrolled patients, it is difficult to arrive at a definitive conclusion.

7.4.2.3 Explorations for drug-demographic interactions

The sponsor did not assess drug-demographic interactions in these studies.

7.4.2.4 Explorations for drug-disease interactions

The sponsor did not assess drug-disease interactions in these studies.

7.4.2.5 Explorations for drug-drug interactions

The sponsor did not assess drug-drug interactions in these studies.

7.4.3 Causality Determination

My review of the safety data from the trials in patient with narcolepsy, OSA/HS and ADHD indicates that modafinil is capable of producing adverse effects such as:

- Psychosis manifest as visual, auditory and command hallucinations
- Headache
- Abdominal Pain
- Diarrhea
- Dysmenorrhea
- Insomnia (predominantly seen at doses of 200 mg and higher)
- Anorexia (predominantly seen at doses of 200 mg and higher)
- Weight Loss (predominantly seen at doses of 200 mg and higher)

While rashes and dermatologic adverse effects are no common, there was at least one case of probable Stevens-Johnson syndrome seen during the ADHD trials.

Cataplexy is a component of narcolepsy and so it is not clear that this symptom can be considered drug related in itself but there may be patients in whom use of modafinil is associated with idiosyncratic reactions, namely worsening of preexisting symptoms such as cataplexy and/or hypnagogic hallucinations.

While causality cannot be definitively determined, modafinil may lead to an exacerbation of the symptoms of Tourette's syndrome.

8 ADDITIONAL CLINICAL ISSUES

8.1

(b) (4)

(b) (4)

8.2 Drug-Drug Interactions

The following drug-drug interaction information is reproduced *verbatim* from the approved labeling for this product:

CNS Active Drugs

Methylphenidate - In a single-dose study in healthy volunteers, simultaneous administration of modafinil (200 mg) with methylphenidate (40 mg) did not cause any significant alterations in the pharmacokinetics of either drug. However, the absorption of PROVIGIL may be delayed by approximately one hour when coadministered with methylphenidate.

Dextroamphetamine - In a single dose study in healthy volunteers, simultaneous administration of modafinil (200 mg) with dextroamphetamine (10 mg) did not cause any significant alterations in the pharmacokinetics of either drug. However, the absorption of PROVIGIL may be delayed by approximately one hour when coadministered with dextroamphetamine.

Clomipramine - The coadministration of a single dose of clomipramine (50 mg) on the first of three days of treatment with modafinil (200 mg/day) in healthy volunteers did not show an effect on the pharmacokinetics of either drug. However, one incident of increased levels of clomipramine and its active metabolite desmethylclomipramine has been reported in a patient with narcolepsy during treatment with modafinil.

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Triazolam – In the drug interaction study between PROVIGIL and ethinyl estradiol (EE₂), on the same days as those for the plasma sampling for EE₂ pharmacokinetics, a single dose of triazolam (0.125 mg) was also administered. Mean C_{max} and AUC_{0-∞} of triazolam were decreased by 42% and 59%, respectively, and its elimination half-life was decreased by approximately an hour after the modafinil treatment.

Monoamine Oxidase (MAO) Inhibitors - Interaction studies with monoamine oxidase inhibitors have not been performed. Therefore, caution should be used when concomitantly administering MAO inhibitors and modafinil.

Other Drugs

Warfarin - There were no significant changes in the pharmacokinetic profiles of R- and S- warfarin in healthy subjects given a single dose of racemic warfarin (5 mg) following chronic administration of modafinil (200 mg/day for 7 days followed by 400 mg/day for 27 days) relative to the profiles in subjects given placebo. However, more frequent monitoring of prothrombin times/INR is advisable whenever PROVIGIL is coadministered with warfarin.

Ethinyl Estradiol - Administration of modafinil to female volunteers once daily at 200 mg/day for 7 days followed by 400 mg/day for 21 days resulted in a mean 11% decrease in C_{max} and 18% decrease in AUC₀₋₂₄ of ethinyl estradiol (EE₂; 0.035 mg; administered orally with norgestimate). There was no apparent change in the elimination rate of ethinyl estradiol.

Cyclosporine - One case of an interaction between modafinil and cyclosporine, a substrate of CYP3A4, has been reported in a 41 year old woman who had undergone an organ transplant. After one month of administration of 200 mg/day of modafinil, cyclosporine blood levels were decreased by 50%. The interaction was postulated to be due to the increased metabolism of cyclosporine, since no other factor expected to affect the disposition of the drug had changed. Dosage adjustment for cyclosporine may be needed.

Potential Interactions with Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes

In *in vitro* studies using primary human hepatocyte cultures, modafinil was shown to slightly induce CYP1A2, CYP2B6 and CYP3A4 in a concentration-dependent manner.

[Reviewer's note: Since sustained high concentrations of the modafinil sulfone metabolite are seen in pediatric patients, induction may be more prominent in children. When modafinil is coadministered with drugs that depend on these three enzymes for their clearance, lower blood levels of the latter drugs could result.]

The exposure of human hepatocytes to modafinil *in vitro* produced an apparent concentration-related suppression of expression of CYP2C9 activity suggesting that there is a potential for a metabolic interaction between modafinil and the substrates of this enzyme (e.g., S-warfarin and phenytoin). (b) (4) in a subsequent (b) (4) clinical study in healthy adult volunteers, chronic modafinil

treatment did not show a significant effect on the single-dose pharmacokinetics of warfarin when compared to placebo.

In vitro studies using human liver microsomes showed that modafinil reversibly inhibited CYP2C19 at pharmacologically relevant concentrations of modafinil. CYP2C19 is also reversibly inhibited, with (b) (4) potency, by a circulating metabolite, modafinil sulfone. (b) (4)

Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin, omeprazole or S-mephenytoin may have prolonged elimination upon coadministration with modafinil and may require dosage reduction and monitoring for toxicity. *Tricyclic antidepressants* - CYP2C19 also provides an ancillary pathway for the metabolism of certain tricyclic antidepressants (e.g., clomipramine, (b) (4) and desipramine) that are primarily metabolized by CYP2D6. In tricyclic-treated patients deficient in CYP2D6 (i.e., those who are poor metabolizers of debrisoquine; 7-10% of the Caucasian population; similar or lower in other populations), the (b) (4) of (b) (4) via CYP2C19 may be substantially increased. PROVIGIL may cause elevation of the levels of the tricyclics in this subset of patients. Physicians should be aware that a reduction in the dose of tricyclic agents might be needed in these patients.

In addition, due to the partial involvement of CYP3A4 in the metabolic elimination of modafinil, coadministration of potent inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole) could alter the plasma levels of modafinil.

8.3 Special Populations

8.3.1 Ethnicity

The number of non-white study participants was too low to make any definite comments about efficacy or safety in those patients.

8.3.2 Gender

While the majority of the study participants were males, the numbers are too small to make definitive comments about differential efficacy/safety.

8.3.3 Hepatic insufficiency

The product was not evaluated in persons with hepatic insufficiency so no comments may be made about efficacy/safety in that group.

8.3.4 Renal insufficiency

The product was not evaluated in persons with renal insufficiency so no comments may be made about efficacy/safety in that group.

8.4 Pediatrics

This submission was performed in response to a Pediatric Written Request (PWR).

8.5 Advisory Committee Meeting

A meeting of the Psychopharmacologic Drugs Advisory Committee was convened on March 23 2006 to discuss the proposed use of modafinil for the treatment of Attention Deficit/Hyperactivity disorder (ADHD, proposed doses 85 mg, 100 mg, 170 mg, 200 mg, 255 mg, 340 mg and 425 mg tablets). The interested reader is referred to the transcripts of that meeting for further details of the committee findings and to the reviews by the Division of Psychiatry Products (DPP) for further details of the clinical background.

In summary the following information was presented to the committee:

A total of 933 pediatric patients received modafinil in Phase II-III studies for this indication. The studies comprised a myriad of designs ranging from open label to double-blind studies with study durations from a single day up to 12 months. The doses ranged from 100 mg to 425 mg/day.

The safety results (summarized by Drs. Paul Andreason and Glenn Mannheim of DPP) were as follows:

- There were no deaths.
- Adverse events
 - Stevens/Johnson syndrome/erythema multiforme: 2 cases in the modafinil treated group, none in the placebo group
 - Suicide related adverse events: 6 in the modafinil treated group, none in the placebo group
 - Psychosis: 5 in the modafinil treated group, none in the placebo group
 - Weight changes: 0.7 kg loss in the modafinil treated group, 1 kg gain in the placebo treated group

Dr. Mannheim quoted a background rate for EM/SJS of 1-2/1,000,000 per year (0.00015%) as compared to the range of risk seen in the ADHD studies of 0.2% to 1.3%.

The specific questions posed to the committee were the following:

- Has modafinil been shown to be effective for the treatment of ADHD in children and adolescents?
- Has modafinil been shown to be acceptably safe in the treatment of ADHD in children and adolescents?
- If modafinil were to be considered for approval:

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- What sort of risk management plan should be implemented with regard to the signal for serious skin rashes in the ADHD program?
- How should the concern about serious skin rashes be addressed in product labeling?
- Should there be a requirement for a post-marketing study(ies) to better understand the serious skin rashes and what sort of study(ies) should be considered?

The committee voted unanimously that modafinil had been shown to be effective in the treatment of ADHD in children and adolescents. In an 11-1 vote, they voted that modafinil had not been shown to be safe in the treatment of ADHD in children and adolescents: the consulting dermatologist was the only dissenter. At that time the sponsor was told that safety could be established by additional study to ‘cap’ the SJS risk, or by additional information on the sentinel case (patient 062338). They elected to provide additional information. Upon review of the submitted material, the Division of Psychiatric Products decided that further study to ‘cap’ the risk was still warranted.

8.6 Literature Review

I did not perform a literature review in support of this application.

8.7 Postmarketing Risk Management Plan

Cephalon did not submit a postmarketing plan in support of this application.

8.8 Other Relevant Materials

8.8.1 Original NDA review

I utilized information from the original review of modafinil (NDA 20-717), completed September 30 1997, performed by Dr. Bob Rappaport. I have incorporated information from his original evaluation of efficacy and safety throughout the current review.

8.8.2 ODS consult on clinical trial data-March 2006

This review, entitled “Psychiatric adverse events in clinical trials for ADHD” was written by Dr. Andrew Mosholder of ODS in response to questions raised at an Advisory Committee meeting (June 30 2005) regarding adverse events seen in association with Concerta use.

“This consult [summarized] the data from approximately 90 clinical trials that was submitted in response to the agency’s request. Sponsors of marketed products for ADHD and drugs under review for that indication were asked to search their clinical trial databases for adverse psychiatric events in three primary categories: psychosis and mania, suicidal events, and aggression. This search was conducted electronically using selected, prespecified adverse event terms. They were also asked to search their databases for additional miscellaneous psychiatric events if the outcome was serious.

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Data on the duration of exposure to treatment in the trials and subject characteristics were also requested, as were clinical descriptions of the events and descriptions of the clinical trials in the ADHD development programs. Data were pooled within development programs to estimate the rates of the events of interest.

The findings are subject to the usual limitations of such safety analyses, which include potential lack of consistency of ascertainment of adverse events across the various trials, the possibility of misclassification of cases, and statistical power limitations imposed by the sample sizes.”

The sponsor provided the following data from the pediatric clinical trials in ADHD:
Table 13:

Treatment	N	Person-years	Psychosis	Suicidal event	Aggression event
DB-Placebo	308	32.55	0	0	5
DB-Modafinil	664	75.11	2	4	9 [11]
OL-Modafinil	799	369.95	2	0	14

[Reviewer’s note: The reviews by Drs. Cai and Mannheim of DPP revealed that the number of aggression events should be 11 not 9 as stated by the sponsor.]

After review of the results from all provided information of AE during trials of medications indicated for ADHD, Dr. Mosholder came to the following conclusions (reproduced verbatim from his consult, p. 25):

“With respect to psychosis and mania events although the numbers of such events with drug treatment were small, the complete absence of such events with placebo treatment was notable. For 4028 pediatric ADHD patients in these trials, there were no such events in 425 person-years of aggregated placebo treatment. Statistically, observing no events in 425 person-years yields an upper one-sided 97.5% confidence limit to the “true” event rate of 0.9 per 100 person-years. (Similarly, there were no psychosis or mania events in these trials among 578 adult ADHD patients receiving placebo for a total exposure time of 111.5 person-years in the adult age group.) Psychosis/mania events occurred during double-blind treatment with every compound except[one]. Furthermore, as noted above, some subjects in Phase I studies of these drugs experienced this type of event.

Patients and physicians should be aware of the possibility that these events, when they arise in the course of drug treatment of ADHD may represent adverse reactions to drugs.

In terms of future clinical trial designs, it should be borne in mind that short-duration trials and trials which exclude subjects who are naïve to this class of drug, while they may be efficient for determining efficacy, have limitations for defining the safety profile of the drug.”

8.8.3 ODS consult on postmarketing data-March 2006

The following is taken verbatim from the consult performed by Dr. Gelperin and Ms. Phelan of ODS.

“Information pertaining to selected psychiatric adverse event reports received since January 1, 2000 was requested from the manufacturers of products approved or with pending applications for the treatment of ADHD. Sponsors were asked to provide information regarding four broad categories of psychiatric adverse events: 1) signs and/or symptoms of psychosis or mania; 2) suicidal ideation and behavior; 3) aggression and violent behavior; and, 4) miscellaneous serious adverse psychiatric events. In addition, searches of the FDA AERS safety database were conducted covering the same time period, and the identified cases were assessed by a DDRE Review Team. Duplicates and reports which were considered to be of poor quality or highly unlikely to be related to the drug of interest were excluded from this analysis.

Cases received from Sponsors, as well as those identified from the FDA AERS safety database, were systematically reviewed and analyzed to assess the probability of adverse drug reactions and to describe characteristics or risk factors observed in these reports.

This review focuses on postmarketing safety data from the first three search categories.

The miscellaneous category was considered to be beyond the scope of this current analysis due to the large volume of data for review.

The most important finding of this review is that signs and symptoms of psychosis or mania, particularly hallucinations, can occur in some patients with no identifiable risk factors, at usual doses of any of the drugs currently used to treat ADHD. Current approved labeling for drug treatments of ADHD does not clearly address the risk of drug induced signs or symptoms of psychosis or mania (such as hallucinations) in patients without identifiable risk factors, and occurring at usual dosages. In addition, current labeling does not clearly state the importance of stopping drug therapy in any patient who develops hallucinations, or other signs or symptoms of psychosis or mania, during drug treatment of ADHD. We recommend that these issues be addressed.

A substantial proportion of psychosis-related cases were reported to occur in children age ten years or less, a population in which hallucinations are not common. The occurrence of such symptoms in young children may be particularly traumatic and undesirable, both to the child and the parents. The predominance in young children of hallucinations, both visual and tactile, involving insects, snakes and worms is striking, and deserves further evaluation....In many patients, the events resolved after stopping the drug. In the FDA AERS review, resolution of the events after stopping the drug was reported in ...60% of modafinil cases.... (Note: Outcome of the psychiatric adverse events was not reported in ...9% of modafinil cases....)

For drugs currently approved for ADHD treatment, no risk factors were identified which could account for the majority of reports of psychosis-related events. For instance, drug abuse was reported in fewer than 3% of overall cases from the FDA AERS analysis of psychosis-related events. Also of note, in the overwhelming majority of cases (roughly 90% overall), the patient had no prior history of a similar condition.

Numerous postmarketing reports of aggression or violent behavior during drug therapy of ADHD have been received, most of which were classified as non-serious, although approximately 20% of cases overall were considered life-threatening or required hospital admission. In addition, a few cases resulted in incarceration of juveniles. The majority of the reports of aggression for drugs currently approved for the treatment of ADHD were in children and adolescents, with a striking male predominance. No specific risk factors for aggression or violent behavior were identified in this analysis. For instance, drug abuse was reported in fewer than 5% of overall cases identified from the FDA AERS search. Also of note, a striking majority (80 to 90% overall) of patients identified in this review had no prior history of similar events. Several cases describing positive rechallenge were reported for each of the drugs included in this analysis. Consideration should be given to stopping the medication in patients who develop aggressive or violent behavior during drug therapy of ADHD....”

[Reviewer’s note: The emphasis conveyed by bolded font is a reproduction of the executive summary in the consult as filed. While I did not add additional emphasis, I think that the findings/conclusions of the ODS consult are particularly important in the risk-benefit analysis of the use of this product in the pediatric population.]

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy

Study 3027, the only double-blind placebo-controlled study submitted in support of this NDA, represents a failed study in that neither of the pre-specified co-primary endpoints achieved statistical significance. The subjective co-primary endpoint failed to demonstrate overall statistical or clinical difference from placebo.

The sponsor chose to focus on the performance of the individual doses as compared to placebo and assert efficacy on that basis however, the study failed to achieve significance on the pre-specified primary objective efficacy endpoint which was the performance of active drug (with all doses combined) versus placebo. We have secondary objective evidence of benefit, specifically prolongation of sleep latency, with all three doses of modafinil studied. There is no dose response effect so there would be no reason to approve use of higher doses than 100 mg based upon the objective evidence.

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There is no subjective evidence of benefit. On the pre-specified primary endpoint of change in CGI-C from baseline to endpoint, the study failed to demonstrate overall efficacy of active drug as compared to placebo. While the sponsor was able to demonstrate statistical significance at the 100 mg dose, that dose did not show statistical evidence of benefit at the Week 3 evaluation nor did it show benefit in those children who completed the study, i.e. those evaluated at Week 6. Additionally, the secondary endpoint of change from baseline in the pediatric daytime sleepiness scale confirmed the lack of clinical improvement since none of the doses studied were able to distinguish themselves from placebo.

Patients were permitted to have either objective (MSLT < 10 minutes) or subjective evidence of excessive sleepiness (clinical global impression of severity (CGI-S) rating ≥ 4) as entry criteria. It might have been better to assure that study participants had both objective signs and subjective symptoms as a basis for study entry since both were designated as primary endpoints. It would not be farfetched to assume that someone without much subjective complaint of sleepiness at the onset might not show a great deal of improvement in that aspect even if treated with an effective drug.

Safety

There were no deaths during the studies submitted in support of this application. The majority of the patients who withdrew from the study due to adverse events were under age 12 years. Psychiatric adverse events such as psychosis, hostility and suicidal ideation were seen, predominantly in children under age 12 years and at doses higher than 100 mg/day.

Overall the most commonly reported adverse events were insomnia, rhinitis, headache and abdominal pain. Modafinil is capable of producing adverse effects such as:

- Psychosis manifest as visual, auditory and command hallucinations
- Headache
- Abdominal Pain
- Diarrhea
- Dysmenorrhea
- Insomnia (predominantly seen at doses of 200 mg and higher)
- Anorexia (predominantly seen at doses of 200 mg and higher)
- Weight Loss (predominantly seen at doses of 200 mg and higher)

While rashes and dermatologic adverse effects are not common, there was at least one case of probable Stevens-Johnson syndrome seen during the ADHD trials.

Cataplexy is a component of narcolepsy and so it is not clear that this symptom can be considered drug related in itself but there may be patients in whom use of modafinil is associated with idiosyncratic reactions, namely worsening of preexisting symptoms such as cataplexy and/or hypnagogic hallucinations.

While causality cannot be definitively determined, modafinil may lead to an exacerbation of the symptoms of Tourette's syndrome.

9.2 Recommendation on Regulatory Action

[REDACTED] (b) (4)

Based upon the results from this study I would suggest that a double-blind placebo-controlled study be done utilizing 100 mg as the maximum modafinil dose. The current study did demonstrate an apparent objective effect of the 100 mg dose. There is no apparent statistical or clinical benefit to the use of higher doses in treating children with narcolepsy and while there appears to be no studied dose which is free from associated psychiatric adverse events, there is some indication that the risk of such events is greater with higher doses.

Since co-primary endpoints measuring both objective and subjective efficacy should again be used, the participants should have both objective and subjective complaints at study entry. The future study should incorporate teacher's ratings of excessive daytime sleepiness as well as the child's assessment thereof since they are the ones who will see/feel the effects of daytime sleepiness. A total reliance on parental reports of sleepiness will not suffice.

While I do recommend [REDACTED] (b) (4) the results of Study 3027 taken in combination with the results from the attention deficit/hyperactivity (ADHD) database lead me to conclude that future study of modafinil in the treatment of narcolepsy should be restricted to pediatric patients aged 12 years and above, as that is the group in which the potential benefit appears to outweigh the risk. The sponsor asserts that "the safety profile of PROVIGIL demonstrated in this clinical program is consistent with that seen in...other pediatric studies with modafinil (p. 27 of the clinical overview, section 2.5)." I would note that in addition to the most commonly reported adverse event which was headache, the adverse event profile for this development program includes psychosis, hostility and suicidal ideation. While based upon the data from the ADHD safety database I would agree that these findings are consistent with what has been previously described, I do not concur with the sponsor's implication that this is an acceptable level of risk in light of the (modest) potential benefit to be gained from modafinil use. The majority of the pediatric patients who reported psychiatric adverse events in the narcolepsy development program were under 12 years old. I do not think that the benefit of modafinil use will outweigh the risk in that subset of the pediatric population. Since narcolepsy is most commonly diagnosed/treated in early adolescents, age restriction would be clinically appropriate if modafinil were to demonstrate efficacy in an adequately designed placebo-controlled double-blind study. Additionally, it seems appropriate to consider restricting use of this product in patients with past history of psychosis or mania in light of the stimulant effects of the product. It may be prudent to contraindicate the product in persons with a past history of suicidal ideation or gestures.

If modafinil were to demonstrate efficacy at a maximal dose of 100 mg in the subset of pediatric patients aged 12 years and older, then the sponsor would have to address the risk of Stevens-Johnson syndrome (SJS). In light of a finding of probable Stevens-Johnson syndrome during the ADHD pediatric trials, the Advisory Committee recommended further investigation to 'cap the

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risk' of SJS at 1/1000with modafinil use. Since, if efficacy could be demonstrated, (b) (4)
the concern over SJS related risk remains the same. The risk of SJS should be adequately assessed, so that it can be appropriately factored into the risk/benefit analysis. (b) (4)

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Cephalon did not submit a risk management plan in support of this application. However, in light of recent media attention on the misuse of modafinil by high school and college students, a risk management plan might be an appropriate consideration: (<http://www.washingtonpost.com/wp-dyn/content/article/2006/06/10/AR2006061001181.html>).

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 requests.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 (b) (4)

(b) (4)

9.5 Comments to Applicant

1. Perform a double-blind study limited to patients aged 12 years and older, utilizing a maximal dose of 100 mg. This study should be at least 6 weeks in duration without the option to terminate early and rollover to an open label study after 3 weeks. Patients should retain the right to terminate early and cease medication use at any point.

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2. Create inclusion/exclusion criteria that will better allow assessment of change in the co-primary endpoints.
3. Incorporate CGI-C ratings by the patient and the teachers into the study design.

(b) (4)



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10 APPENDICES

- 10.1 Tabular listing of all clinical studies included in this submission (as provided by the sponsor)
- 10.2 Review of individual study reports

10.1 Tabular listing of all clinical studies as provided by the sponsor (NDA section 5.2 from 09/05 submission)

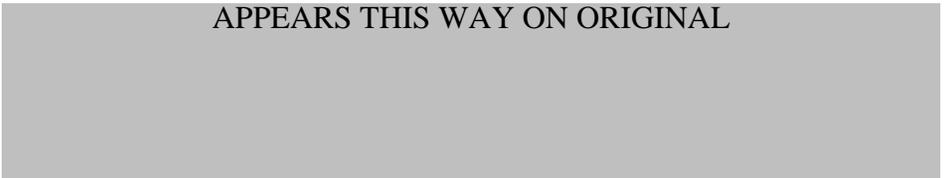
Study number Study title (design) Phase	No. of centers Location	Status Dates*	Study population Variables	Dose regimen ^b Duration of treatment	Formulation (Lot no.)	No. treated Age (yr): mean (range) M/F (%) W/NW/U (%) Weight (kg) mean (range)
Efficacy and Safety Studies: Controlled Clinical Studies						
<p>Study C1538/3027/NA/MN</p> <p>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</p> <p>Phase 3</p>	<p>5 in Canada</p> <p>41 in US</p>	<p>Completed</p> <p>21Dec04-10Oct05</p>	<p>Patients from 6 through 16 years of age with ES associated with narcolepsy</p> <p>Primary efficacy variables: The change from baseline to the last postbaseline observation (week 6 or early termination) in mean sleep latency from the MSLT, and the percentage of patients with at least minimal improvement on the CGI-C ratings at the last postbaseline observation (week 6 or early termination)</p> <p>Secondary efficacy variables: The percentage of patients with at least minimal improvement in the CGI-C rating (for severity of ES) at weeks 3 and 6, the change from baseline for the total score from the PDSS at weeks 3 and 6, and at the last postbaseline observation, the change from baseline to week 6, for the mean sleep latency from the MSLT</p> <p>Safety variables: Adverse events and concomitant medication usage throughout the study; clinical laboratory test results and vital signs measurements at weeks 3 and 6 or early termination; 12-lead ECG findings, physical examination findings (including body weight), CBCL/6-18 scores, brief psychiatric interview, KBIT-2 scores, and NPSG at week 6 or early termination</p>	<p>PROVIGIL 100 to 400 mg once daily</p> <p>Placebo</p> <p>Approximately 8 weeks to include a 1- to 2-week screening period, and 6 weeks double-blind treatment</p>	<p>100 mg PROVIGIL tablets (04106B5a, 04185B5a, and 05B003A502)</p> <p>Placebo tablets (03163B5a, 04107B5a, 04186B5a, 04208B5a, and 05B004A502)</p>	<p>N=165</p> <p>12.5 (5-17)</p> <p>94/71 (57/43)</p> <p>84/81/0 (51/49/0)</p> <p>63.4 (18.8-156.5)</p>

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Study number Study title (design) Phase	No. of centers Location	Status Dates ^a	Study population Variables	Dose regimen ^b Duration of treatment	Formulation (Lot no.)	No. treated Age (yr): mean (range) M/F (%) W/NW/U (%) Weight (kg) mean (range)
Efficacy and Safety Studies: Controlled Clinical Studies (Continued)						
Study C1538/3028/AP/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 Obstructive Sleep Apnea/Hypopnea Syndrome Phase 3	1 in Canada 15 in US	Completed ^c 15Jan05-9Sep05	Patients from 6 through 16 years of age with ES associated with OSAHS Primary efficacy variables: The change from baseline to the last postbaseline observation (week 6 or early termination) in mean sleep latency from the MSLT, and the percentage of patients with at least minimal improvement on the CGI-C ratings at the last postbaseline observation (week 6 or early termination) Secondary efficacy variables: The percentage of patients with at least minimal improvement in the CGI-C rating (for severity of ES) at weeks 3 and 6, the change from baseline for the total score from the PDSS at weeks 3 and 6, and at the last postbaseline observation, the change from baseline to week 6, for the mean sleep latency from the MSLT Safety variables: Adverse events and concomitant medication usage throughout the study; clinical laboratory test results and vital signs measurements at weeks 3 and 6 or early termination; 12-lead ECG findings, physical examination findings (including body weight), CBCL/6-18 scores, brief psychiatric interview, KBIT-2 scores, and NPSG at week 6 or early termination	PROVIGIL 100 to 400 mg once daily Placebo Approximately 8 weeks to include a 1- to 2-week screening period and 6 weeks double-blind treatment	100 mg PROVIGIL tablets (lot numbers not available) Placebo tablets	NA ^c NA ^c NA/NA ^c W/NW/U NA ^c NA ^c

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Study number Study title (design) Phase	No. of centers Location	Status Dates ^a	Study population Variables	Dose regimen ^b Duration of treatment	Formulation (Lot no.)	No. treated Age (yr): mean (range) M/F (%) W/NW/U (%) Weight (kg) mean (range)
Efficacy and Safety Study: Uncontrolled Clinical Study (Continued)						
Study C1538/3034/ES/MN A 6-Month Open-Label, Flexible-Dosage Study to Assess the Safety and Effectiveness of PROVIGIL [®] (Modafinil) Treatment in Children and Adolescents With Excessive Sleepiness Associated With Narcolepsy or Obstructive Sleep Apnea/Hypopnea Syndrome Phase 3	1 in Australia 1 in Czech Republic 3 in Finland 3 in France 3 in Israel 5 in Italy 6 in Spain 1 in United Kingdom	Completed ^d 21Dec04- 9Oct05	Patients from 6 through 16 years of age with ES associated with narcolepsy, presumed narcolepsy, or OSAHS Efficacy variables: CGI-C in severity of ES and total score on the PDSS, both at months 3 and 6 or early termination Safety variables: Adverse events and concomitant medication usage throughout the study; clinical laboratory test results and vital signs measurements, body weight and height and pregnancy (HCG) screening (if appropriate) at all monthly visits (months 1–6); 12-lead ECG findings, physical examination findings, CBCL/6-18 scores, brief psychiatric interview, and KBIT-2 scores at months 3 and 6 or early termination	PROVIGIL 100 to 400 mg once daily Approximately 6 months to include a 1- to 2-week screening period, 6 months treatment, and a 4-week follow-up period	100 mg PROVIGIL tablets (04256B5a)	91 12.2 (5-17) 53/38 (58/42) 86/5/0 (95/5/0) 55.7 (19.8-114.0)

^a Study dates are from first patient enrolled to last patient last visit unless otherwise noted.

^b Study drug was administered orally in all studies.

^c Enrollment in this study was terminated prematurely because of the difficulty in finding patients who met the eligibility criteria. Data have not been reported separately at this time but are integrated in the all-patients safety database.

^d Date of data cut-off for submission.

^e Does not include final telephone contact for 39 patients at the time of data cut-off for submission.

CBCL/6-18=Child Behavior Checklist for Ages 6-18; CGI-C=Clinical Global Impression of Change; ECG=electrocardiogram; ES=excessive sleepiness; HCG=human chorionic gonadotropin; KBIT-2=Kaufman Brief Intelligence Test, Second Edition; MSLT=Multiple Sleep Latency Test; NPSG=nocturnal polysomnography; NA=Not available; NW/U=Nonwhite/unknown; OSAHS=obstructive sleep apnea/hypopnea syndrome; PDSS=Pediatric Daytime Sleepiness Scale; W=white.

10.2 Review of Individual Study Reports

10.2.1 Study C1538/3027/NA/MN: A Phase III, 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

10.2.1.1 Objectives

Primary

To determine the effectiveness of PROVIGIL treatment, compared to placebo treatment, in children and adolescents with excessive sleepiness associated with narcolepsy, as assessed by the following co-primary measures:

- Mean sleep latency from the Multiple Sleep Latency Test (average of 4 naps performed at 0900, 1100, 1300 and 1500) at the last post baseline observation (week 6 or early termination)
- Clinical Global Impression of Change (CGI-C) for excessive sleepiness at the last post baseline observation (week 6 or early termination)

Secondary

To determine the effect of PROVIGIL treatment, compared with placebo treatment, on

- CGI-C ratings for excessive sleepiness at weeks 3 and 6
- Total score from the Pediatric Daytime Sleepiness Score (PDSS) at weeks 3 and 6
- Mean sleep latency from the MSLT (average of 4 naps performed at 0900, 1100, 1300 and 1500) at week 6

To assess the safety and tolerability of PROVIGIL treatment by evaluating

- Adverse events
- Clinical laboratory parameters (serum chemistry, hematology and urinalysis) at weeks 3 and 6
- Vital signs at weeks 3 and 6
- Body weight, electrocardiography and physical examinations at week 6 or early termination
- The effect of PROVIGIL on anxiety, nervousness, and symptoms of mania and psychosis as assessed by a psychiatric interview at week 6 or early termination
- The effect of PROVIGIL treatment on competencies and behavioral/emotional problems as assessed by the Child Behavior Checklist for Ages 6-18 (CBCL/6-18) at week 6 or early termination
- The cognitive effect of PROVIGIL as assessed by the Kaufman Brief Intelligence Test, second edition (KBIT-2) at week 6 or early termination
- The effect of PROVIGIL treatment on nighttime sleep as assessed by a nocturnal polysomnograph (NPSG) at week 6 or early termination
- To investigate the dose-response relationship of PROVIGIL, including the identification of a no-effect level

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- To assess the population pharmacokinetics and the pharmacokinetic/pharmacodynamic relationship

10.2.1.2 Study design

This was a randomized, double-blind, placebo-controlled, parallel-group study.

10.2.1.3 Study population and procedures

10.2.1.3.1 Study duration

There were to be 6 weeks of double-blind treatment per patient.

10.2.1.3.2 Entry criteria

Inclusion criteria

1. Boy or girl between 6 and 16 years old, inclusive
2. Met the minimal criteria established by the International Classification of Sleep Disorders manual of the American Academy of Sleep Medicine for narcolepsy (or presumed narcolepsy) as assessed by all of the following
 - Clinical history
 - NPSG to rule out other sleep disorders, i.e. obstructive sleep apnea/Hypopnea or periodic limb movement with sleep
 - Narcolepsy (or presumed narcolepsy) as identified by at least one of the following
 - i. MSLT with a mean sleep latency [from 4 naps] of < 10 minutes
 - ii. 2 sleep-onset REM (SOREM)
 - iii. Cataplexy
 - iv. Sleep paralysis
 - v. Hypnagogic hallucinations

OR

A previous diagnosis of narcolepsy on the basis of NPSG and/or MSLT at any time before the screening visit

3. Excessive sleepiness (MSLT < 10 minutes and/or CGI-S > 4) that is not a direct result of inadequate sleep hygiene or other medical disorder
4. Good health as determined by a medical and psychiatric history, physical examination, ECG and clinical laboratory tests
5. Blood pressure values less than the 95th percentile for age on the National High Blood Pressure Education Program guidelines for blood pressure levels boys and girls ages 6-16 years
6. Girls who are postmenarche or sexually active must have had a negative urine pregnancy test prior to the baseline visit, were to use a medically acceptable form of birth control and must have agreed to use the chosen method throughout the study and for 30 days after the study ended. Acceptable methods of birth control included barrier method with spermicide, steroidal contraceptives in conjunction with a barrier method, intrauterine device or abstinence.

7. Patients had to be able to swallow a placebo tablet which was the same shape and size as the study drug tablet.
8. Patients had to have a negative urine drug screen for any illicit drug, ethanol, stimulants or modafinil at screening; if positive for stimulants or modafinil (prescribed for excessive sleepiness) at the screening visit, the urine drug screen was to be repeated after a washout period and before the baseline visit
9. Signed informed consent/assent document at screening
10. Patients had to have a parent who was willing to participate in the study.

Exclusion criteria

1. Presence of any other sleep disorder that might be considered the cause of excessive sleepiness, e.g. self-induced sleep deprivation
2. Pregnancy or lactation
3. An average of 5 or more apneic or hypopneic episodes per hour of nocturnal sleep as assessed by NPSG at the baseline visit.
4. Known clinically significant drug sensitivity to stimulants such as amphetamine, dextroamphetamine, methylphenidate, or pemoline; and/or modafinil or any of its components
5. Use of any prescription (e.g. clonidine, guanfacine) or nonprescription [OTC] medications, including dietary supplements with psychoactive properties (e.g. any OTC medications or supplements containing ephedrine, pseudoephedrine, caffeine or phenylpropanolamine) or sedating properties (i.e. sedating antihistamines or sedative-hypnotics) within 1 week of the baseline visit. Medications for the treatment of cataplexy were allowed if the patient had been on a stable dose for at least one month.
6. History of seizures (except for history of a single febrile seizure), psychosis, clinically significant head trauma with brain damage, or past neurosurgery.
7. History of past suicide attempts or currently at risk for suicide
8. Use of any MAO inhibitors or SSRIs within 2 weeks of the baseline visit (unless used for cataplexy)
9. receipt of any investigational drug (except modafinil) within 4 weeks of the baseline visit
10. Any disorder that could interfere with drug absorption, distribution, metabolism or excretion (including previous gastrointestinal surgery)
11. History of drug addiction or drug abuse
12. Evidence of an active clinically significant illness including neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary or metabolic disease
13. Any clinically significant deviation from the normal range in physical examination, ECG findings or clinical laboratory test results at the screening or baseline visit
14. ANC (at the screening visit) below the lower limit of normal and greater than $1.0 \times 10^9/L$, which the investigator considers clinically significant; the medical monitor will be consulted.
15. Seated pulse outside the range of 60 through 115 bpm after resting for 5 minutes
16. A total daily intake of more than 250 mg of caffeine per day within 1 week of the baseline visit
17. A clinically significant illness within 4 weeks of the baseline visit
18. Symptomatic clinically significant illness at the screening or baseline visit

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10.2.1.3.3 Study medications

Prohibited concurrent therapy

The use of the following medications was to be prohibited during the study: methylphenidate, neuroleptic agents, amphetamines, pemoline, monoamine oxidase inhibitors, anticonvulsants, barbiturates, benzodiazepines, zolpidem, as well as tricyclic and all other antidepressants.

A urine drug screen was to be performed at the screening visit and prior to the baseline (if positive at the screening visit for stimulants or modafinil), at week 6 or early termination, at as needed if drug use/abuse was suspected.

The use of steroidal contraception alone was not to be permitted since PROVIGIL treatment has the potential to increase hepatic enzyme induction and increase the metabolism of this type of contraception.

Patients were not to use any OTC medications with psychoactive properties or sedating properties or any prescription medications within 1 week of the baseline visit. Stimulant therapy was not to be permitted during either the washout period or during the study.

Patients were not to use any MAO inhibitors or SSRIs within 2 weeks of the baseline visit or any other prescription medications for ADHD with psychoactive properties after Day -10. While use of prescription and OTC medications with psychoactive properties was to be permitted on an as needed basis for allergies and flu symptoms, they were to be avoided within 1 week of clinic visits.

10.2.1.3.4 Study procedures

Patients were to come for a screening visit between 7 and 14 days prior to Study Day 1. At that visit, they were to provide a complete medical history. An examination including assessment of body weight and vital signs was to be done along with clinical laboratory evaluation. Urine was to be obtained for pregnancy screening and drug screening. A 12-lead ECG was to be performed. During the screening period (up to 14 days), medications for excessive sleepiness (ES) were to be discontinued. At selected centers, a blood sample for drug assay would be performed assuming that no washout was needed.

Eligible patients were to come to the study site for a baseline visit (Visit 2) which was to include an overnight polysomnograph with next-day MSLT. The following testing was to be done to obtain a baseline: CBCL/6-18, brief psychiatric interview, KBIT-2, CGI-S, PDSS. If more than 14 days had elapsed since the screening visit.

After the baseline visit, patients were to be randomized into one of the four treatment arms: placebo, 100 mg PROVIGIL, 200 mg PROVIGIL, 400 mg PROVIGIL. The tablets were to be taken one daily in the morning. During the first 7 days of the double-blind period, patients were titrated up to their randomized dose, with a 100 mg increase every 2 days; the patients in the placebo group and in the 100 mg group were at their randomized dose at Day 1, the 20 mg group reached their dose by day 3, the 400 mg group reached their dose by day 7. Patients were to stay at their designated dose for the remainder of the 6 week double-blind period.

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Patients were to be contacted by telephone at weeks 1 and 2 to determine tolerability with clinic visits scheduled for weeks 3 and 6 to include assessments for efficacy and safety.

After 6 weeks of double-blind treatment, patients were to return to the clinic for their final visit. Patients who completed this study were eligible to enroll in the planned open-label extension study: C1538/3029/ES/MN.

10.2.1.3.5 Efficacy parameters

The primary efficacy measures were the MSLT and the CGI-C ratings for severity of ES at the last post baseline observation (week 6 or early termination).

The secondary efficacy parameters were:

- CGI-C ratings for severity of ES at weeks 3 and 6
- The PDSS at weeks 3 and 6, and last post baseline observation
- The MSLT at week 6.

10.2.1.3.6 Safety parameters

- Adverse events were to be assessed throughout the study.
- Serum chemistries, hematology values and urinalysis were to be performed at weeks 3 and 6 or early termination.
- Electrocardiography, physical examinations, CBCL/6-18, brief psychiatric interview and the KBIT-2 were to be scheduled for week 6.
- A polysomnograph, measuring standard sleep parameters, was scheduled for week 6 to assess potential drug effect on nighttime sleep.

10.2.1.3.7 Statistical analysis

10.2.1.3.7.1 Sample size

The sponsor calculated the sample size for this study based upon the results from the adult studies in this indication. That data indicated that 140 patients would provide 80% power to detect an average difference of 2.5 minutes (SD 4.5 minutes) in the change from baseline in mean sleep latency from the maintenance of wakefulness test (MWT) and >80% power to detect a 25% difference in the percentage of patients with at least minimal improvement in the CGI-C assuming a placebo rate of 37%. The sponsor elected to use the MSLT since the MWT “has not been sufficiently studied in children.”

10.2.1.3.7.2 Efficacy analysis

The efficacy analysis was to be based upon all patients who had received at least one dose of study drug and who had at least one post-baseline assessment. The primary efficacy variable, change from baseline in the mean sleep latency during the first 4 MSLT naps was to be analyzed using ANCOVA with treatment as a factor and the corresponding baseline value as a covariate. The test of linear trend between the dosages was to be performed. If there was evidence of treatment by covariate interaction, the primary analysis was to be replaced by ANOVA with treatment as a factor.

10.2.1.3.7.3 Safety analysis

The safety analysis was to be based upon all patients who had received at least one dose of study drug. Descriptive statistics were to be provided for all continuous variables. Frequency and percentages were to be provided for all categorical variables.

10.2.1.3.7.4 Pharmacokinetics/pharmacodynamic analyses

Plasma concentration data for parent product and metabolites was to be summarized in tabular form. Modafinil plasma concentration versus sleep latency times were to be graphically presented.

10.2.1.3.8 Protocol amendments

The protocol amendment dated 06 August 2004 made the following substantive changes in addition to minor administrative changes:

- The second screening visit was deleted.
- Vital signs were to be measured before the NPSG and after the last MSLT nap.
- NPSG and MSLT were to be conducted at the baseline visit instead of at the second screening visit. Each investigator was responsible for evaluating the NPSG and MSLT results for patient eligibility.
- The requirement for the Diagnostic Interview Schedule for Children, 4th edition was removed.
- Patients were permitted to meet a single criterion for excessive sleepiness; they could have either MSLT < 10 minutes or a Clinical global impression of severity (CGI-S) rating ≥ 4
- Transdermal steroidal contraceptives were considered acceptable methods of contraception
- Patients with absolute neutrophil counts below the lower limit of normal for age instead of the previously defined value of $1000/\text{mm}^3$ were to be excluded.

The protocol amendment dated 29 November 2004 made the following substantive changes in addition to minor administrative changes:

- The central nocturnal polysomnogram (NPSG) and multiple sleep latency test (MSLT) scored was to be Dr. Richard Bogan of SleepMed. Dr Thomas Roth of Henry Ford Hospital will perform a quality review of 10% of the test results.
- The previous diagnosis of narcolepsy on the basis of NPSG and/or MSLT could have been made at any time prior to the screening visit.

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- Pharmacokinetic blood sampling was to be performed at only those centers with personnel qualified to perform the task.
- At each sampling time point, one 2-3 ml blood sample was to be obtained.

The protocol amendment dated 10 February 2005 made the following substantive changes in addition to minor administrative changes:

- The number of planned study centers was increased from 60 to 100 in order to enroll the required number of patients in the allotted time.
- This study was restricted to centers in the USA and Canada, with a separate open label study planned to enroll patients world-wide.
- The study enrollment period was extended with study completion planned for September 2005.
- Telephone contacts were substituted for clinic visits at weeks 1 and 2.
- The screening visit may occur up to the day before the baseline visit. Since the baseline visit is overnight, any center which had the capability to perform the assessments and receive the results during the stay was permitted to do so.
- Patients who completed this study were eligible to participate in an open label extension study provided that they met the inclusion criteria for that study, C1538/3029/ES/MN.
- The exclusion criteria for periodic limb movements with arousals was deleted
- The MSLT previously scheduled for Week 3 was removed.
- The clinical global impression of change and the pediatric daytime sleepiness scales which were to be measured in Weeks 1 and 2 were removed since those clinic visits were eliminated.
- Adverse events that are continuing at the time of a patient's final visit will be followed until resolution or stabilization occurs.
- A psychiatric interview to assess behavioral effects of the drug was added at the baseline and final visits.
- The Kaufman Brief Intelligence Test, second edition (KBIT-2) will be performed at the baseline and final visits to evaluate cognition.
- The NPSG and the blood draw scheduled for visit 3 was eliminated.

The protocol amendment dated 22 August 2005 made the following substantive changes in addition to minor administrative changes:

- Clarified that the nocturnal polysomnography (NPSG) and multiple sleep latency test (MSLT) were to be evaluated using the Morpheus electronic sleep scoring system. Equipment at the study centers were to record the data onto a computer disk which was then to be sent to SleepMed for evaluation using their Morpheus system.
- The instructions for possible dose adjustments at the Week 1 and 2 telephone contacts were removed. Patients who were unable to tolerate study drug during the titration phase were removed from the study without attempts at dose adjustment.
- An NPSG and an MSLT were no longer required at the baseline visit if they had been performed for diagnostic purposes at the screening visit.
- A time interval (0700-0730) was given for study drug administration at the Week 6 visit.

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- The patient enrollment period was extended with completion of the study scheduled for October 2005.
- Post-baseline clinic visits were defined as relative to the baseline visit. A week was defined, for the purposes of this protocol as 7+/- 2 days.
- The duration of patient participation is defined as 8 weeks.
- Procedures/assessments, other than the NPSG and the MSLT, scheduled for the final visit will be conducted on the day of the MSLT before the patient leaves the clinic.
- The medical monitor was to be consulted before exclusion of patients with an absolute neutrophil count (at the screening visit) below the lower limit of normal and greater than $1.0 \times 10^9/l$ which the investigator considered clinically significant.
- Hypotensive patients were not to be excluded from the study.
- Vital signs were to be collected at the baseline visit and at week 6 in the evening before the NPSG and on the following day after the last MSLT nap. Additional vital sign measurements were to be collected at the screening visit and at week 3.

10.2.1.4 Study results

10.2.1.4.1 Trial characteristics

This study began screening subjects on 21 December 2004. The last patient completed the study on 10 October 2005. A total of 166 patients were enrolled and randomized; 165 of whom received at least one dose of study drug. A total of 144 patients completed the study.

10.2.1.4.2 Demographics

The majority of the participants were White (51%), male (57%) and aged 12 years or older (70%). There were no statistically significant differences between the groups in age, weight or BMI. The 100 mg/day group had a greater percentage of older children and fewer Black children than the other two active treatment arms. There were no clinically or statistically significant differences in the prior medication usage between the groups.

While there were no statistically significant differences at baseline in terms of illness severity, the highest percentage of patients considered markedly, severely or extremely ill on the CGI-S was in the PROVIGIL 400 mg/day group (58% as compared to 50% (placebo), 43% (100 mg), 44% (200 mg). Five children who were considered slightly ill, as rated by the CGI-S, were included because they were found to have MSLT sleep latency of <10 minutes at baseline. At least one of these children was included in each treatment arm; two were in the 200 mg arm.

Four patients who did not meet the protocol specified age restrictions were given exemptions and allowed to participate in the study:

Patient 073705, a 5 year old who was randomized to PROVIGIL 100 mg
Patient 038702, a 17 year old who was randomized to PROVIGIL 400 mg
Patient 073703, a 17 year old who was randomized to PROVIGIL 200 mg
Patient 039701, a 17 year old who was randomized to placebo

Table: Demographics for study 3027

	Placebo N=42	Provigil 100 mg N=42	Provigil 200 mg N=41	Provigil 400 mg N=40
Age (years)				
Mean (SD)	12.6 (2.55)	12.9 (2.74)	12.2 (3.12)	12.3 (2.94)
Age group, n(%)				
<12 years	11 (26%)	11 (26%)	14 (34%)	14 (35%)
≥12 years	34 (74%)	31 (74%)	27 (66%)	26 (65%)
Sex				
Male	27 (64%)	23 (55%)	21 (51%)	23 (58%)
Female	15 (36%)	19 (45%)	20 (49%)	17 (43%)
Ethnicity				
White	20 (48%)	26 (62%)	19 (46%)	19 (48%)
Black	19 (45%)	13 (31%)	20 (49%)	16 (40%)
Asian	0	0	0	1 (3%)
American Indian/Alaskan native	0	1 (2%)	0	0
Pacific islander	0	0	1 (2%)	0
Other	3 (7%)	1 (2%)	1 (2%)	4 (10%)

(modification of table 7 from the study report)

10.2.1.4.3 Protocol violations

Four patients were noted to have had incorrectly administered study drug:

- Patient 038701 (400 mg) did not take study drug for approximately one week prior to taking a single dose before the MSLT at the final visit.
- Patient 067702 (100 mg) did not date the study drug card and took an unspecified number of additional tablets on a few occasions.
- Patient 014708 (placebo) took study drug prior to the first MSLT nap at the final visit as opposed to 11.5 to 2 hours prior to the first nap.
- Patient 073704 (placebo) forgot to take study drug prior to the first MSLT nap at the final visit but took it at 1430 before the last MSLT nap at that visit.

10.2.1.4.4 Efficacy endpoints

The efficacy analyses were performed on the full analysis set (FAS) which included those patients in the safety analysis set who had at least one post baseline MSLT or CGI-C; 160 patients in the active treatment arms and 41 in the placebo arm.

Primary endpoints

Analyses of the data related to the primary efficacy variables for this trial may be found in section 6 of this review.

Secondary endpoints

- CGI-C ratings for excessive sleepiness (ES) at weeks 3 and 6
The CGI-C is the clinician's assessment of change in the severity of ES during the course of the study. The physician asks the parent or legal guardian to assess the patient's home behavior over the past week. The clinician then assigns a rating based upon a 7 point scale anchored by "very much improved" (scored as 1) and "very much worse" (scored as 7), with no change represented by a score of 4.

To analyze this data the sponsor grouped the ratings into two categories: at least minimal improvement, which included scores of 1-3; and "no improvement", which included scores of 4-7.

There was a statistically significant difference in favor of PROVIGIL for the 100 mg group only, $p=0.0397$. When an overall comparison of active treatment versus placebo was done, there was no statistically significant difference at week 3, at week 6 or at endpoint. When individual groups were compared to placebo, only the 100 mg group had a statistically significant result.

- Total score from the Pediatric Daytime Sleepiness Score (PDSS) at weeks 3 and 6
The PDSS is a self-report 8 item questionnaire designed to examine the relationship between daytime sleepiness and school-related outcomes. The protocol called for the PDSS to be completed by the parent or legal guardian within 24 hours of the scheduled visit based upon the patient's behavior since the last visit/assessment.

The sponsor evaluated the change from baseline in total PDSS score. There was no statistically significant change seen when the active treatment group was compared to the placebo group at endpoint. Additionally there was no statistically significant change, seen at any time point, when the individual treatment arms were compared to placebo.

- Mean sleep latency from the MSLT (average of 4 naps performed at 0900, 1100, 1300 and 1500) at week 6

The sponsor analyzed the MSLT data from just those patients who completed all six weeks of double-blind treatment, comparing baseline results to those at week 6. In all groups the mean MSLT latency was seen to increase in a statistically significant manner:

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placebo (n=37) increased 0.7 minutes; 100 mg group (n=38) increased 3.8 minutes; 200 mg group (n=38) increased 5.1 minutes; 400 mg group (n=31) increased 3.3 minutes.

- To investigate the dose-response relationship of PROVIGIL, including the identification of a no-effect level

There is not a consistently demonstrated increase in efficacy with increased dose. The 100 mg dose, which was the lowest studied, demonstrated efficacy so there was not a no-effect dose established in this study.

The interested reader is referred to the review performed by Dr. V. Atul Bhattaram of Pharmacometrics for a detailed discussion of these findings.

- To assess the population pharmacokinetics and the pharmacokinetic/pharmacodynamic relationship

The interested reader is referred to the review performed by Dr. V. Atul Bhattaram of Pharmacometrics for a discussion of these findings.

10.2.1.4.5 Safety

The protocol's secondary objectives included assessment of the safety and tolerability of PROVIGIL treatment by evaluation of the following parameters:

- Adverse events
- Clinical laboratory parameters (serum chemistry, hematology and urinalysis) at weeks 3 and 6
- Vital signs at weeks 3 and 6
- Body weight, electrocardiography and physical examinations at week 6 or early termination
- The effect of PROVIGIL treatment on nighttime sleep as assessed by a nocturnal polysomnograph (NPSG) at week 6 or early termination
- The effect of PROVIGIL on anxiety, nervousness, and symptoms of mania and psychosis as assessed by a psychiatric interview at week 6 or early termination
- The effect of PROVIGIL treatment on competencies and behavioral/emotional problems as assessed by the Child Behavior Checklist for Ages 6-18 (CBCL/6-18) at week 6 or early termination
- The cognitive effect of PROVIGIL as assessed by the Kaufman Brief Intelligence Test, second edition (KBIT-2) at week 6 or early termination

The safety data have been discussed in section 7 of this review.

10.2.1.5 Reviewer's Summary

By parental report, the 100 mg dose of modafinil decreased excessive sleepiness at home (as measured by the CGI-S) though there was no effect upon school-reported outcomes (as measured by the PDSS). When the results from the study completers, a potentially skewed population,

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were reviewed, the 100 mg group had a change of 3.8 minutes as compared to the 0.7 minutes seen in the placebo group. It is noted that the patients in the 100 mg group tended to be white males over age 12 years which may or may not indicate a subpopulation with a better response.

There is no dose-response relationship so there is no reason why doses over 100 mg should be used for the treatment of excessive sleepiness in children with narcolepsy.

10.2.2 Study C1538/3028/NA/MN: A Phase III, 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 OSAHS

This study was almost identical to study Study C1538/3027/NA/MN: A Phase III, 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. The only difference was the study population: this study enrolled patients who had OSAHS. The study was terminated early due to difficulties with recruitment.

The enrollment (n=26) was too small to adequately assess efficacy in this population but the safety data from these patients was incorporated into the overall analysis.

10.2.3

10.2.4 Study C1538/3034/ES/MN: A 6-Month Open-Label Flexible-Dosage Study To Assess The Safety And Effectiveness Of PROVIGIL (Modafinil) Treatment In Children And Adolescents With Excessive Sleepiness Associated With Narcolepsy Or Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS)

10.2.4.1 Objectives

Primary

To determine the safety and tolerability of PROVIGIL treatment in children and adolescents with excessive sleepiness associated with narcolepsy or OSAHS when administered for up to 6 months, as assessed by the following measures:

- Adverse events
- Clinical laboratory parameters (serum chemistry, hematology and urinalysis)
- Vital signs
- Body weight and height
- 12-lead electrocardiography and physical examinations
- Concomitant medication usage
- The effect of PROVIGIL treatment on competencies and behavioral/emotional problems as assessed by the Child Behavior Checklist for Ages 6-18 (CBCL/6-18) at months 3 and 6 or early termination
- The cognitive effect of PROVIGIL as assessed by the Kaufman Brief Intelligence Test, second edition (KBIT-2) at months 3 and 6 or early termination

[Reviewer's note: The latter two objectives were added in response to the pediatric written request but in actuality, all patients had been enrolled and administered study drug at the time of the amendment. There is no baseline data available for the CBCL/6-18 or the KBIT-2 from this study. It is not clear why this is the case since the original PWR was issued on 17 June 2004 and this study began screening subjects on 31 January 2005. The amendment to include the CBCL/6-18 and the KBIT-2 was dated March 2005.]

Secondary

To determine the effect of PROVIGIL treatment, compared with placebo treatment, on

- CGI-C ratings for excessive sleepiness at months 3 and 6
- Total score from the Pediatric Daytime Sleepiness Score (PDSS) at months 3 and 6

10.2.4.2 Study design

This was an open-label safety study conducted outside the United States.

10.2.4.3 Study population and procedures

10.2.4.3.1 Study duration

There were to be 6 months of open-label treatment per patient.

10.2.4.3.2 Entry criteria

Inclusion criteria

1. Boy or girl between 6 and 16 years old, inclusive
2. Met the minimal criteria established by the International Classification of Sleep Disorders manual of the American Academy of Sleep Medicine for narcolepsy (or presumed narcolepsy) or OSAHS OR had a previous diagnosis of narcolepsy or OSAHS before the screening visit
3. Patient has a complaint of excessive sleepiness
4. Good health as determined by a medical and psychiatric history, physical examination, ECG and clinical laboratory tests
5. Blood pressure values greater than those for the 5th percentile and less than the 95th percentile for age on the National High Blood Pressure Education Program guidelines for blood pressure levels for boys and girls ages 6-16 years
6. Girls who were postmenarche or sexually active must have had a negative urine pregnancy test prior to the baseline visit, were to use a medically acceptable form of birth control and must have agreed to use the chosen method throughout the study and for 2 cycles after study participation. Acceptable methods of birth control included barrier method with spermicide, steroidal contraceptives in conjunction with a barrier method, intrauterine device or abstinence.
7. Patients had to be able to swallow a placebo tablet which was the same shape and size as the study drug tablet.
8. Patients had to have a negative urine drug screen for any illicit drug, ethanol, or stimulants at screening; if positive for stimulants (prescribed for excessive sleepiness) at the screening visit, the urine drug screen was to be repeated after a washout period and before the baseline visit
9. Patients had to have a parent or legal representative who was willing to participate in the study.
10. Written informed consent/assent must have been obtained.

Exclusion criteria

11. Presence of any other sleep disorder that might be considered the cause of excessive sleepiness, e.g. self-induced sleep deprivation
12. Pregnancy or lactation
13. Known clinically significant drug sensitivity to stimulants such as amphetamine, dextroamphetamine, methylphenidate, and/or modafinil or any of its components
14. History of seizures (except for history of a single febrile seizure), psychosis, clinically significant head trauma with brain damage, or past neurosurgery.
15. History of past suicide attempts or currently at risk for suicide
16. Use of any MAO inhibitors or SSRIs within 2 weeks of the baseline visit although patients who had been on a stable dose (one month or longer) of an SSRI for cataplexy would be eligible
17. receipt of any investigational drug (except modafinil) within 4 weeks of the baseline visit
18. Any disorder that could interfere with drug absorption, distribution, metabolism or excretion (including previous gastrointestinal surgery)
19. History of drug addiction or drug abuse

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20. Evidence of an active clinically significant illness including neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary or metabolic disease
21. Any clinically significant deviation from the normal range in physical examination, ECG findings or clinical laboratory test results at the screening or baseline visit
22. ANC (at the screening visit) below the lower limit of normal; the medical monitor was to be consulted.
23. Seated pulse outside the range of 60 through 115 bpm after resting for 5 minutes
24. A total daily intake of more than 500 mg of caffeine per day within 1 week of the baseline visit
25. A clinically significant illness within 4 weeks of the baseline visit or symptomatic clinically significant illness at the baseline visit

10.2.4.3.3 Study medications

Prohibited concurrent therapy

The use of the following medications was to be prohibited during the study: methyphenidate, neuroleptic agents, amphetamines, monoamine oxidase inhibitors, anticonvulsants, barbiturates, benzodiazepines, zolpidem, as well as tricyclic and all other antidepressants. A urine drug screen was to be performed at the screening visit and prior to the baseline (if positive at the screening visit for stimulants or modafinil), at months 3 and 6 or early termination, and as needed if drug use/abuse was suspected.

The use of steroidal contraception alone was not to be permitted since PROVIGIL treatment has the potential to increase hepatic enzyme induction and increase the metabolism of this type of contraception.

Use of prescription and OTC medications with psychoactive and/or sedating properties was to be permitted on an as needed basis for allergies and flu symptoms.

10.2.4.3.4 Study procedures

Patients were to come for a screening visit between 7 and 14 days prior to Study Day 1. At that visit, they were to provide a complete medical history. Patients who were receiving or who had tried the current standard treatments for OSAHS but still had excessive sleepiness and those who were awaiting CPAP were eligible for study inclusion. Patients who were currently being maintained on PROVIGIL were eligible to enter the study and would resume their usual dose after a 1 week washout to obtain a baseline. An examination including assessment of body weight and vital signs was to be done along with clinical laboratory evaluation. Urine was to be obtained for pregnancy screening and drug screening. A 12-lead ECG was to be performed. During the screening period (up to 14 days), medications for excessive sleepiness (ES) were to be discontinued.

After the baseline visit, patients were to be administered study drug. The tablets were to be taken one daily in the morning. Patients were to be titrated up to their optimal dose, with a 100 mg increase allowed every 7 days up to a maximum of 400 mg. Patients were to stay at their optimal dose for the remainder of the 6 month period, although the protocol did allow for decreases in dose if the study drug was not well-tolerated.

Patients were to be contacted by telephone at weeks 1 and 3 to determine tolerability with clinic visits scheduled for weeks 2 and 4 to include assessments for efficacy and safety. Thereafter, the patients were scheduled for monthly clinic visits.

10.2.4.3.5 Efficacy parameters

The primary efficacy measures were the PDSS and the CGI-C ratings for severity of ES at the month 3 and month 6 (or early termination).

10.2.4.3.6 Safety parameters

- Adverse events were to be assessed throughout the study.
- Body weight and height were to be assessed at all monthly visits
- Electrocardiography, physical examinations, CBCL/6-18, brief psychiatric interview and the KBIT-2 were to be scheduled for months 3 and 6.

10.2.4.3.7 Statistical analysis

The safety and efficacy analyses were to be based upon all patients who had received at least one dose of study drug. Descriptive statistics were to be provided for all continuous variables. Frequency and percentages were to be provided for all categorical variables.

10.2.4.3.8 Protocol amendment

The protocol amendment dated 16 March 2005 made the following substantive changes in addition to minor administrative changes:

- Previously the diagnosis of narcolepsy or obstructive sleep apnea/hypopnea syndrome had to have been made within 2 years of the beginning of the study. The time aspect of this requirement was removed and patients who had been diagnosed at any time were allowed to participate.
- The use of SSRIs for cataplexy was allowed.
- A psychiatric interview at baseline and at months 3 and 6 (or at early termination) was added as per the terms of the pediatric written request.
- The Kaufman Brief Intelligence Test (KBIT-2) was to be performed at baseline and at months 3 and 6 (or at early termination) as per the terms of the pediatric written request.

10.2.4.4 Study results

10.2.4.4.1 Trial characteristics

This study began screening subjects on 31 January 2005. The study completion date was 27 October 2005. A total of 92 patients were enrolled; 91 of whom received at least one dose of study drug. The majority (90%) completed 6 months of treatment.

10.2.4.4.2 Demographics

The majority of the participants were White (95%), male (58%) and aged 12 years or older (66%).

Table: Demographics for study 3034

	Narcolepsy N=46	OSAHS N=45	Total (n=91)
Age (years)			
Mean (SD)	12.0 (3.16)	12.4 (3.04)	12.2 (3.09)
Age group, n(%)			
<12 years	18 (39%)	13 (29%)	31 (34%)
≥12 years	28 (61%)	32 (71%)	60 (66%)
Sex			
Male	19 (41%)	34 (76%)	53 (58%)
Female	27 (59%)	11 (24%)	38 (42%)
Ethnicity			
White	42 (91%)	44 (98%)	86 (95%)
Black	4 (9%)	0	4 (4%)
Other (Hispanic, biracial)	0	1 (2%)	1 (1%)

(modification of table 6 from the study report)

10.2.4.4.3 Protocol violations

The majority of the protocol violations were noncompliance with study drug procedures, n=33 (36%).

According to the sponsor, three patients were in violation of GCP guidelines. In all three cases, the patients were allowed to continue study participation.

- Patient 071003/LRD: On study day 79, this patient was reported to be taking zolpidem 5mg once a week due to difficulty falling asleep.
- Patient 031002/L-H: On study day 83, it was noted that the drug compliance had been 73% between month 1 and 2. On study day 112, it was again noted that the drug compliance had been 73% between month 2 and 3.
- Patient 031003/J-G: On study day 95, it was noted that the drug compliance had been 122% between month 2 and 3 and that the patient had a positive screen for cannabinoids. On study day 187, it was again noted that the patient had a positive screen for cannabinoids.

10.2.4.4.4 Efficacy endpoints

The efficacy analyses were performed on the full analysis set (FAS) which included those patients in the safety analysis set who had at least one post baseline efficacy assessment.

- CGI-C ratings for excessive sleepiness (ES) at weeks 3 and 6
The CGI-C is the clinician's assessment of change in the severity of ES during the course of the study. The physician asks the parent or legal guardian to assess the patient's home behavior over the past week. The clinician then assigns a rating based upon a 7 point scale anchored by "very much improved" (scored as 1) and "very much worse" (scored as 7), with no change represented by a score of 4.

To analyze this data the sponsor grouped the ratings into two categories: at least minimal improvement, which included scores of 1-3; and "no improvement", which included scores of 4-7.

The majority, over 90%, had at least minimal improvement at all time points assessed. The sponsor reported that "a greater percentage of patients with narcolepsy than patients with OSAHS were reported in the category of very much improved (28 vs. 18%) and much improved (57% vs. 48%), while a greater percentage of OSAHS patients than narcolepsy patients were reported in the categories of minimally improved (20% vs. 11%) and non change (14% vs. 2%)."

- Total score from the Pediatric Daytime Sleepiness Score (PDSS) at weeks 3 and 6
The PDSS is a self-report 8 item questionnaire designed to examine the relationship between daytime sleepiness and school-related outcomes. The protocol called for the PDSS to be completed by the parent or legal guardian within 24 hours of the scheduled visit based upon the patient's behavior since the last visit/assessment.

The mean PDSS score at baseline was 19.5. The mean PDSS score at endpoint was 13.0, representing a change of 6.5 points overall.

10.2.4.4.5 Safety

The protocol included an assessment of the safety and tolerability of PROVIGIL treatment. The safety data have been discussed in section 7 of this review.

10.2.4.5 Reviewer's Summary

This was a safety study. Since it was performed without a control group, no comments may be made about comparative safety and/or efficacy.

10.2.5 Study C1538/3029/ES /MN: INTERIM REPORT: A 1-Year Open-Label , Flexible-Dose, Extension Study To Assess The Safety And Continued Effectiveness Of PROVIGIL (Modafinil) Treatment In Children And Adolescents With Excessive Sleepiness Associated With Narcolepsy Or Obstructive Sleep Apnea/Hypopnea Syndrome

10.2.5.1 Objectives

Primary

To determine the safety and tolerability of PROVIGIL treatment in children and adolescents with excessive sleepiness associated with narcolepsy or OSAHS when administered for up to 6 months, as assessed by the following measures:

- Adverse events
- Clinical laboratory parameters (serum chemistry, hematology and urinalysis)
- Vital signs
- Body weight and height
- 12-lead electrocardiography at study termination
- Quarterly physical examinations
- Concomitant medication usage
- The effect of PROVIGIL treatment on competencies and behavioral/emotional problems as assessed by the Child Behavior Checklist for Ages 6-18 (CBCL/6-18)
- The cognitive effect of PROVIGIL as assessed by the Kaufman Brief Intelligence Test, second edition (KBIT-2)
- A brief psychiatric interview

Secondary

To determine the effect of PROVIGIL treatment, compared with placebo treatment, on

- CGI-C ratings for excessive sleepiness
- Total score from the Pediatric Daytime Sleepiness Score (PDSS)

10.2.5.2 Study design

This was an open-label safety extension study.

10.2.5.3 Study population and procedures

10.2.5.3.1 Study duration

There were to be 12 months of open-label treatment per patient.

10.2.5.3.2 Entry criteria

Inclusion criteria

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1. Boy or girl who participated in either study C1538/3027/MA/MN or C1538/3028/AP/MN and was between 6 and 16 years old, inclusive, at the start of the previous double-blind study
2. Met the minimal criteria established by the International Classification of Sleep Disorders manual of the American Academy of Sleep Medicine for narcolepsy (or presumed narcolepsy) or OSAHS OR had a previous diagnosis of narcolepsy or OSAHS before the screening visit
3. Good health as determined by a medical and psychiatric history, physical examination, ECG and clinical laboratory tests
4. Blood pressure values less than the 95th percentile for age on the National High Blood Pressure Education Program guidelines for blood pressure levels for boys and girls ages 6-16 years
5. Girls who were postmenarche or sexually active must have had a negative urine pregnancy test prior to the baseline visit, were to use a medically acceptable form of birth control and must have agreed to use the chosen method throughout the study and for 2 cycles after study participation. Acceptable methods of birth control included barrier method with spermicide, steroidal contraceptives in conjunction with a barrier method, intrauterine device or abstinence.
6. Patients had to have a negative urine drug screen for any illicit drug, ethanol, or stimulants at the baseline visit; if a false positive was suspected, the urine drug screen was to be repeated after a washout period and before baseline
7. Patients had to have a parent or legal representative who was willing to participate in the study.
8. Written informed consent/assent must have been obtained from the parent or legal guardian

Exclusion criteria

1. Presence of any other sleep disorder that might be considered the cause of excessive sleepiness, e.g. self-induced sleep deprivation
2. Pregnancy or lactation
3. Known clinically significant drug sensitivity to stimulants such as amphetamine, dextroamphetamine, methylphenidate or pemoline; and modafinil or any of its components
4. History of seizures (except for history of a single febrile seizure), psychosis, clinically significant head trauma with brain damage, or past neurosurgery.
5. History of past suicide attempts or currently at risk for suicide
6. Any disorder that could interfere with drug absorption, distribution, metabolism or excretion (including previous gastrointestinal surgery)
7. Evidence of an active clinically significant illness including neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary or metabolic disease
8. Any clinically significant deviation from the normal range in physical examination, ECG findings or clinical laboratory test results at the screening or baseline visit
9. ANC (at the screening visit) below the lower limit of normal and greater than $1 \times 10^9/L$ which the investigator considers clinically significant; the medical monitor was to be consulted.

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10. Seated pulse outside the range of 60 through 115 bpm after resting for 5 minutes
11. A total daily intake of more than 500 mg of caffeine per day within 1 week of the baseline visit

10.2.5.3.3 Study medications

Prohibited concurrent therapy

The use of the following medications was to be prohibited during the study: methylphenidate, neuroleptic agents, amphetamines, monoamine oxidase inhibitors, anticonvulsants, barbiturates, benzodiazepines, zolpidem, as well as tricyclic and all other antidepressants. Medications for cataplexy and serotonin reuptake inhibitors were to be permitted if the patients has been on a stable dose for at least one month. A urine drug screen was to be performed at the screening visit and prior to the baseline (if positive at the screening visit for stimulants or modafinil), at months 3, 6, 9 and 12 (or early termination), and as needed if drug use/abuse was suspected.

The use of steroidal contraception alone was not to be permitted since PROVIGIL treatment has the potential to increase hepatic enzyme induction and thereby increase the metabolism of this type of contraception.

Use of prescription and OTC medications with psychoactive and/or sedating properties was to be permitted on an as needed basis for allergies and flu symptoms.

10.2.5.3.4 Study procedures

Patients were to come for a screening visit within 14 days of the final double-blind visit. If more than 14 days had elapsed, patients would be required to have a screening/washout period before entering the open-label study.

After the baseline visit, patients were to be administered study drug. The tablets were to be taken one daily in the morning. Patients were to be titrated up to their optimal dose, with a 100 mg increase allowed every 7 days up to a maximum of 400 mg. Patients were to stay at their optimal dose for the remainder of the 12 month period, although the protocol did allow for decreases in dose if the study drug was not well-tolerated. The minimum allowed dose was 100 mg.

Patients were to be contacted by telephone at weeks 1 and 3 to determine tolerability with clinic visits scheduled for weeks 2 and 4 to include assessments for efficacy and safety. Thereafter, the patients were scheduled for monthly clinic visits.

10.2.5.3.5 Efficacy parameters

The primary efficacy measures were the PDSS and the CGI-C ratings for severity of ES.

10.2.5.3.6 Safety parameters

- Adverse events were to be assessed throughout the study.
- Vital signs were to be assessed at each visit
- Body weight and height were to be assessed beginning at month 1 and monthly thereafter
- 12-lead Electrocardiography was to be done at month 12 for patients in the US and at months 3 and 12 for Canadian participants

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- Physical examinations were to be done at months 3, 6, 9 and 12,
- CBCL/6-18 was to be done at months 3, 6, 9, 12 and early termination
- Brief psychiatric interview
- KBIT-2

10.2.5.3.7 Statistical analysis

The safety and efficacy analyses were to be based upon all patients who had received at least one dose of study drug. Descriptive statistics were to be provided for all continuous variables. Frequency and percentages were to be provided for all categorical variables.

10.2.5.3.8 Protocol amendments

The protocol amendment dated 29 November 2004 made the following substantive changes in addition to minor administrative changes:

- The references to the CGI-S were removed since that assessment was not to be performed in this study.
- The 12-lead electrocardiograms previously scheduled for months 3, 6 and 9 were removed from the protocol because “there [had] been no ECG findings of concern in earlier studies of PROVIGIL.

The protocol amendment dated 14 February 2005 made the following substantive changes in addition to minor administrative changes:

- The number of planned study centers was increased to 100.
- The study sites were limited to the USA and Canada.
- The protocol formerly called for a directed telephone contact 4 weeks after the final study visit. This was removed from the protocol.
- A 12-lead ECG was added at the 3-month visit for Canadian participants in response to a request by Health Canada.
- The psychiatric interview and KBIT-2 were to be performed at months 3, 6, 9 and 12 in the FDA PWR.
- The study completion date was scheduled for September 2006

The protocol amendment dated 22 August 2005 made the following substantive changes in addition to minor administrative changes:

- The study completion date was scheduled to be October 2006.
- The automatic exclusion for neutropenia was modified. Children who had ANC that were below the lower limit of normal but above $1 \times 10^9/L$ would be considered for possible study participation.
- Hypotensive patients were not to be excluded from the study.

10.2.5.4 Study results

10.2.5.4.1 Trial characteristics

This study, which enrolled patients from the USA and Canada, began screening subjects on 1 February 2005. The data cut-off date was 21 October 2005. A total of 92 patients were enrolled

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and randomized, all from centers outside of the USA. Almost all (n=91, 99%) received at least one dose of study drug. A total of 83 patients completed 6 months of treatment.

10.2.5.4.2 Demographics

The majority of the participants were White (51%), male (58%) and aged 12 years or older (64%).

Table: Demographics for study 3029

	Narcolepsy N=132	OSAHS N=16	Total (n=148)
Age (years)			
Mean (SD)	12.4 (2.83)	10.3 (3.05)	12.2 (2.92)
Age group, n(%)			
<12 years	43 (33%)	10 (63%)	53 (36%)
≥12 years	89 (67%)	6 (38%)	95 (64%)
Sex			
Male	77 (58%)	9 (56%)	86 (58%)
Female	55 (42%)	7 (44%)	62 (42%)
Ethnicity			
White	65 (49%)	10 (63%)	75 (51%)
Black	58 (44%)	4 (25%)	62 (42%)
Asian	1 (<1%)	0	1 (<1%)
American Indian or Pacific Islander	1 (<1%)	0	1 (<1%)
Other (Hispanic, biracial)	6 (5%)	2 (13)	5 (8%)

(modification of table 7 from the study report)

10.2.5.4.3 Protocol violations

The majority of the protocol exceptions reported represented inclusion of patients whose ANC was below the normal criterion: 11 patients.

There were 5 protocol violations reported:

- Patient 070702-Restarted excluded concomitant medication

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- Patient 049702-Positive urine drug screen, though it was negative on repeat one month later
- Patient 045701-Pulse outside the criteria
- Patient 070704-Drug was dispensed prior to receipt of clinical laboratory results
- Patient 039802-Mother did not follow the titration schedule (This patient was withdrawn from the study. This patient had withdrawn from study 3028 due to an adverse event, so participation in this study represented a second protocol violation)

10.2.5.4.4 Efficacy endpoints

No efficacy information was presented in this interim report.

10.2.5.4.5 Safety

The protocol included an assessment of the safety and tolerability of PROVIGIL treatment. The safety data have been discussed in section 7 of this review.

10.2.5.5 Reviewer's Summary

This was a safety study. Since it was performed without a control group, no comments may be made about comparative safety and/or efficacy.

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