Modafinil (CEP-1538) Tablets

Supplemental NDA 20-717/S-019

ADHD Indication

Briefing Document
for
Psychopharmacologic Drugs Advisory Committee Meeting

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Sponsor
Cephalon, Inc.
41 Moores Road
Frazer, Pennsylvania 19355
USA

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LIST OF ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADHD-RS-IV	ADHD Rating Scale, Fourth Edition
ADR	adverse drug reaction
AE	adverse event
AER	adverse event report
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
AUC_{0-24}	area under the plasma concentration time curve from zero to 24 hours after study drug administration
BMI	body mass index
BP	blood pressure
Bpm	beats per minute
CGI–C	Clinical Global Impression of Change
CHQ	Child Health Questionnaire
CL/F	clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
CPRS:R-S	Conners' Parent Rating Scale, Revised, Short Form
CYP	cytochrome
DAT	dopamine transporter gene
DB	double-blind randomized clinical study
DBH	dopamine beta-hydroxylase gene
DISC-IV	Diagnostic Interview for Children, 4th Edition
DRD4	dopamine D4 receptor gene
DRD5	dopamine D5 receptor gene
DSM–IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECG	electrocardiography, electrocardiogram
EM	erythema multiforme
FDA	US Food and Drug Administration
FOI	Freedom of Information
GABA	gamma aminobutyric acid
GGT	gamma-glutamyl transpeptidase
HAFC	Haight Ashbury Free Clinics
HTR1B	serotonin 1B gene
5-HTT	serotonin transporter gene
LS	least squares
MAO	monoamine oxidase
max	maximum
MedDRA	Medical Dictionary of Regulatory Activities
min	minimum
mo	month
MPE	maculopapular exanthema
NA	not applicable
NOS	not otherwise specified
NR	no remarkable history

NCHS	National Center for Health Statistics
NIMH	National Institute of Mental Health
ODD	oppositional defiant disorder
OL	open-label
OSAHS	obstructive sleep apnea/hypopnea syndrome
OTC	over-the-counter
PDS	Phoenix Data Systems
PK	pharmacokinetics
PT	preferred term
RAST	radioallergosorbent test
SBP	systolic blood pressure
SCARs	severe cutaneous adverse reactions
SD	standard deviation
SE	standard error
SJS	Stevens-Johnson Syndrome
SNAP25	synaptosomal-associated protein 25 gene
sNDA	Supplemental New Drug Application
SOC	system organ class
SSRI	selective serotonin-reuptake inhibitor
SSRS	Social Skills Rating Scale
SWSD	shift work sleep disorder
TEN	toxic epidermal necrolysis
t_{max}	time to peak plasma
TOVA	Test of Variables of Attention
Unk	unknown
US	United States
V/F	volume of distribution
VT	verbatim term
WBC	white blood cell

1 EXECUTIVE SUMMARY

PROVIGIL® (modafinil) Tablets [C-IV] have been marketed in the United States (US) for the treatment of adults with excessive sleepiness associated with narcolepsy since February 1999. In January 2004, PROVIGIL was approved in the US for improving wakefulness in adults with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome (OSAHS) and shift work sleep disorder (SWSD). In all, the product is marketed in 28 countries worldwide; it was first approved in France in 1992. Since its initial marketing launch in 1994, the worldwide postmarketing usage of modafinil constitutes 673,000 patient-treatment years.

Cephalon is now seeking marketing approval for modafinil as SPARLON™ tablets for the treatment of children and adolescents with attention-deficit/hyperactivity disorder (ADHD). SPARLON tablets contain the same active ingredient as PROVIGIL tablets (ie, modafinil), but are film-coated and smaller than the PROVIGIL tablet and come in 5 dose strengths, 85, 170, 255, 340, and 425 mg. Over 930 boys and girls (6 to 17 years old) with ADHD have participated in clinical studies sponsored by Cephalon, with 244 treated for at least 1 year and 164 treated for at least 18 months. The supplemental New Drug Application (sNDA) for modafinil in ADHD was submitted to the US Food and Drug Administration (FDA) on 21 December 2004. An approvable letter was issued by FDA on 20 October 2005.

ADHD is a serious chronic neurobehavioral disorder that affects approximately 4% to 12% of school-age children. Characteristic symptoms include inattention, hyperactivity, and impulsivity. Comorbidities include mood and anxiety disorders, oppositional defiant disorder (ODD), developmental and learning disabilities, and substance abuse. Pharmacologic treatment remains the mainstay of therapy for ADHD; however, despite treatment with currently approved medications, it is reported that about 40% of children are suboptimally treated. Thus, there is a need for additional treatments that are safe and effective.

The efficacy of modafinil for the treatment of children and adolescents with ADHD was clearly and reproducibly demonstrated in 3 placebo-controlled Phase 3 studies that included 621 efficacy-evaluable patients. Data from these studies, an additional 4 Phase 1 and 2 studies, and a treatment extension study form the basis of the safety evaluation of modafinil in this patient population (933 children with ADHD). In addition, another 690 pediatric patients with other disorders (eg, narcolepsy, OSAHS) have been treated with modafinil in clinical studies, providing for an even broader safety evaluation.

This briefing document contains information regarding the pharmacology, clinical pharmacokinetics, and data on the efficacy and safety of modafinil in children and adolescents with ADHD. Safety information includes a detailed examination of 3 specific areas of interest, ie, cardiovascular, psychiatric, and dermatologic adverse events. This document concludes with an assessment of the benefits and risks of modafinil and shows that modafinil is a safe and effective treatment for children and adolescents with ADHD.

2 INTRODUCTION

Cephalon is seeking marketing approval for modafinil as SPARLON Tablets for the treatment of children and adolescents wit ADHD. Modafinil has been marketed in 28 countries worldwide for a number of indications. In the US, modafinil is marketed under the trade name PROVIGIL® (modafinil) Tablets [C-IV] and is approved for the treatment of adult patients with excessive sleepiness associated with narcolepsy, OSAHS, and SWSD.

Since the first marketing launch of modafinil in France in 1994 worldwide postmarketing usage is estimated to be 673,000 patient-treatment years (through 31 August 2005).

A new, film-coated tablet formulation of modafinil was developed for use in children and adolescents with ADHD. The proposed formulation has a higher drug/excipient ratio compared to the current marketed product, PROVIGIL, thus allowing for the smaller tablet size. These tablets contain 85, 170, 255, 340, or 425 mg of modafinil and the following inactive ingredients: lactose, croscarmellose sodium, povidone, and magnesium stearate. The film coating for all tablet strengths contains: hypromellose, titanium dioxide, lactose, polyethylene glycol, and triacetin. In addition, the 170- and 340-mg tablets contain iron oxide yellow, and the 255- and 425-mg tablets contain FD&C Blue#2. Cephalon has requested the brand name SPARLON for this tablet formulation of modafinil.

Modafinil is a racemic compound. Modafinil activates the central nervous system (CNS), as do amphetamines, methylphenidate, and caffeine. However, its chemistry and pharmacology clearly distinguish it from the traditional sympathomimetic CNS stimulants such as the amphetamines and methylphenidate.

Although no difference in the pharmacokinetic profile of modafinil was observed as a result of underlying disease state, the systemic exposures associated with a pharmacodynamic effect do differ in children and adolescents with narcolepsy as compared to those with ADHD. In children and adolescents with ADHD, weight-adjusted daily doses (340 mg of modafinil in patients weighing less than 30 kg and 425 mg of modafinil in patients weighing at least 30 kg) are required to achieve a sustained systemic exposure associated with a clinically significant effect (approximately 150 µg•hr/mL). In contrast, in children and adolescents with narcolepsy, lower systemic exposure is needed for treatment of excessive sleepiness (approximately 36 µg•hr/mL). This exposure in children and adolescents with narcolepsy is achieved with a daily dose as low as 100 mg/day.

In clinical studies, modafinil has been evaluated in more than 4000 healthy subjects/patients (adults and children), of which more than 2000 were patients with narcolepsy, OSAHS, SWSD, and ADHD (double-blind and open-label studies combined) conducted by Cephalon and other sponsors in the US, United Kingdom (UK), France, Ireland, Germany, and Canada. A total of 1076 patients with ADHD (adults, n=143; children, n=933) received modafinil in double-blind and open-label studies. Across all clinical studies in adults (all indications), mean duration of exposure was 211 days for a total of 2284 patient-treatment years. In clinical studies, nearly 700 patients have

received modafinil for more than 1 year, and 309 patients have received modafinil for more than 2 years.

Modafinil has been evaluated in 8 clinical studies in children and adolescents with ADHD. Across these studies, 933 patients received treatment with modafinil. The mean duration of exposure was 225 days, for a total of 575 patient-treatment years. A total of 244 patients have received modafinil for at least 12 months, and 164 patients have received modafinil at least 18 months. A Phase 3b study is ongoing in 303 children and adolescents with ADHD.

In addition to the children and adolescents with ADHD, modafinil has also been evaluated in 4 clinical studies in 270 children and adolescents with narcolepsy or OSAHS and in 116 children and adolescents with various disorders in clinical studies performed prior to the ADHD clinical program (legacy studies).

3 REVIEW OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

ADHD is a complex neurobehavioral condition characterized by inattention, hyperactivity, and impulsivity. Neuropsychological and imaging studies have shown that ADHD is associated with alterations in the prefrontal cortex and its connections to the striatum and cerebellum. Research in animals, in combination with observations of patients with cortical lesions, has shown that the prefrontal cortex is critical for the regulation of behavior and attention, and affects using representative knowledge (Arnsten 2006). Traditional CNS stimulant medications may have some of their therapeutic effects by increasing endogenous stimulation of alpha-2a adenoceptors and dopamine D1-receptors in the prefrontal cortex, optimizing prefrontal cortex regulation of behavior and attention (Arnsten 2006). A growing body of behavioral and molecular genetics literature has also indicated that the development of ADHD may be attributed to both genetic and environmental factors. Statistically significant evidence of the association of 7 genes with ADHD has been shown on the basis of pooled odds ratios across studies (the dopamine D4-receptor gene [DRD4], the dopamine D5 receptor gene [DRD5], the dopamine transporter gene [DAT], the dopamine beta-hydroxylase gene [DBH], the serotonin transporter gene [5-HTT], the serotonin 1B gene [HTR1B], and the synaptosomal-associated protein 25 gene [SNAP25] (Faraone and Khan 2006).

ADHD is a common (4% to 12% of children), chronic condition that is associated with significant functional impairments in school, family, and social interactions (American Academy of Pediatrics 2000) and is a major public health problem. The direct cost of medical care for patients with ADHD is double that of the cost of medical care for the rest of the population (Birnbaum et al 2005). Decades of research have demonstrated that medication, alone or in combination with psychotherapy, has a robust impact on the symptoms of the disorder in the short term and after 1 to 2 years of treatment (Spencer et al 1996).

During the past decade, evidence has been accumulating regarding a high incidence of comorbidity associated with ADHD. A number of disorders including ODD, conduct disorder, mood disorder, and anxiety disorder may be associated with ADHD (Spencer 2006). ADHD is most likely a group of conditions, rather than a single homogeneous clinical entity, with potentially different etiologic and modifying risk factors and different outcomes. Follow-up studies of children with ADHD indicate that subgroups of patients with ADHD and comorbid disorders have poorer outcomes as evidenced by significantly greater social, emotional, and psychological difficulties (Spencer 2006). Most commonly, comorbidity with ADHD in youth includes ODD/conduct disorder (30%-50%), mood disorders (15%-75%), and anxiety disorders (25%) (Biederman et al 1991). Learning disabilities and substance abuse disorders have also been implicated.

Several therapeutic mechanisms have demonstrated effectiveness in treating patients with ADHD. There appears to be some commonality in the physiologic mechanisms of action of these agents relevant to the treatment of patients with ADHD. Either direct or indirect attenuation of dopamine and norepinephrine neurotransmission appears related to efficacy of both the traditional stimulant and nonstimulant medications in the treatment of patients with ADHD. However, important differences exist both between and within the specific classes of agents (Wilens 2006).

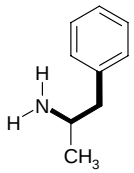
While traditional CNS stimulants are the most commonly used treatments for patients with ADHD, approximately 40% of children with ADHD do not respond positively to the stimulants, have unacceptable side effects, or have concurrent depressive or anxiety disorders that traditional CNS stimulant medications may exacerbate (Wilens and Biederman 1992). Thus there remains a need for additional well tolerated pharmacological agents that are effective in treating the symptomatology of ADHD.

4 PHARMACOLOGY OF MODAFINIL

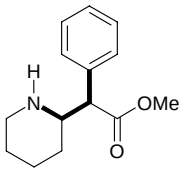
Modafinil is a racemic compound. Like the amphetamines, methylphenidate, and caffeine, modafinil activates the CNS, however, its chemistry and pharmacology clearly distinguish it from the traditional sympathomimetic CNS stimulants.

As a class, sympathomimetic agents activate the sympathetic nervous system through adrenergic receptors either directly (eg, ephedrine, isoproterenol) or indirectly (eg, amphetamine, methylphenidate, monoamine oxidase inhibitors).

CNS-active sympathomimetic agents, such as ephedrine, amphetamine, and methylphenidate, contain the core phenethylamine substructure known from structure-activity studies to be essential for sympathomimetic activity (Goodman et al 2006). Key to this pharmacophore is a basic amine, protonatable at physiologic pH and positioned 2-3 bond lengths from an aromatic ring (phenyl in this case). Modafinil has no such substructure. The NH_2 group in modafinil is attached to a carbonyl (constituting an amide) and is not protonatable at physiologic pH (see below).



amphetamine



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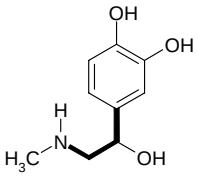
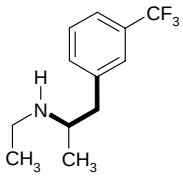
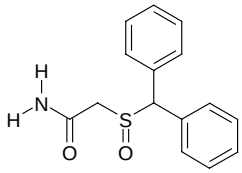


ephedrine



fenfluramine



modafinil

Classification of direct or indirect acting sympathomimetics can be elaborated on the basis of their pharmacology in that the activity of direct-acting sympathomimetics (eg, ephedrine) is not abolished by prior transmitter-depleting agents, such as reserpine, while the pharmacology of the indirect class (eg, methylphenidate) is abolished.

The pharmacology of modafinil is not affected by neurotransmitter-depleting agents and modafinil does not bind to, nor interact indirectly with, adrenergic receptors. This suggests that modafinil is not a sympathomimetic-like CNS stimulant as its pharmacology is not consistent with the typical sympathomimetic pharmacologic profile.

Consistent with a nonsympathomimetic profile, modafinil, in nonclinical models, produces signs of CNS activation (consistent with its primary pharmacology of increased attention and wakefulness promotion (Shelton et al 1995, Touret et al 1995, Panckeri et al 1996, Edgar and Seidel 1997, Hou and Lin 1999, Lin et al 2000, Hendricks et al 2003),

but has minimal effects on cardiovascular, respiratory, renal, or gastrointestinal systems (see below).

Modafinil, therefore, cannot be classified as a traditional sympathomimetic CNS stimulant, as it is chemically and pharmacologically distinct.

The precise molecular targets(s) of modafinil are not yet known, but at pharmacologically relevant concentrations, modafinil has not shown an affinity for a variety or receptors (or their subtypes) including adenosine, benzodiazepines, GABA (gamma aminobutyric acid), histamine, hypocretin/orexin, melatonin, norepinephrine, dopamine, or serotonin. Modafinil does not inhibit the activities of MAO-B (monoamine oxidase type B) or phosphodiesterases II-IV. Modafinil is not a direct or indirect α_1-adrenergic agonist. Although modafinil-induced wakefulness can be attenuated by the α_1-adrenergic receptor antagonist prazosin, in assay systems known to be responsive to α-adrenergic agonists, modafinil does not display adrenergic activity.

Unlike the wakefulness induced by traditional CNS stimulants (eg, amphetamine, methylphenidate), modafinil-induced wakefulness appears not to be mediated by dopamine. Modafinil-induced wakefulness is not blocked by the dopamine antagonist, haloperidol or the neurotransmitter depleting agent alpha-methyl-para-tyrosine (as are the effects of traditional sympathomimetic CNS stimulants) and does not affect the firing rates of dopaminergic or noradrenergic neurons (Lin et al 1992, Ferraro et al 1997). It is not a direct or indirect acting dopamine agonist either in vitro or in vivo (Akaoka et al 1991, De Sereville et al 1994, Ferraro et al 1997). Modafinil has only a weak affinity for the dopamine reuptake site, leading to a small increase in extracellular dopamine but no increase in dopamine release (Mignot et al 1994).

Increases in the expression of c-fos, an immediate-early gene product, which is a marker of neuronal activation, were used to identify sites of action of amphetamine, methylphenidate, and modafinil. In the cat brain, amphetamine and methylphenidate caused widespread stimulation of neuronal activity. Modafinil appears to selectively increase neuronal activity in discrete areas of the brain, especially the anterior hypothalamus (Lin et al 1996, Engber et al 1998, Scammell et al 2000). Studies utilizing 2-deoxyglucose autoradiography as a marker for neuronal activation in the rat brain yielded similar regionally localized results for modafinil (Engber et al 1998). Importantly, areas of the brain thought to be involved in the reinforcing properties of CNS stimulants are not activated. These data are consistent with the low abuse potential of modafinil.

Modafinil is currently listed in Schedule IV of the Controlled Substances Act, and since its introduction in the US market place for excessive sleepiness in 1999, a variety of clinical studies and postmarketing surveillance have reinforced the minimal potential for abuse (Myrick et al 2004). Chemical and pharmacologic profiles of modafinil are not favorable for abuse. In nonclinical models, modafinil displays minimal addiction potential depending on the animal model utilized and the extent of previous stimulant experience. In several human studies involving both nonsubstance-abusing subjects and those using cocaine, once again the results indicate a low potential for abuse. Consistent with the lack of reinforcing properties of modafinil, it is being studied as a possible

treatment for cocaine abuse since it blunts the euphoric effects of cocaine (Dackis et al 2005). The Haight Ashbury Free Clinics (HAFC) Behavioral Research Group is engaged to conduct active surveillance of modafinil abuse and misuse. For the purposes of surveillance of modafinil use, the HAFC Behavioral Research Group has implemented a broad monitoring methodology, gathering information from a large number of sources. HAFC Behavioral Research Group continues to conclude that the abuse liability of modafinil, if it exists, is low. Finally, no safety signals or data of concern regarding abuse or diversion have been identified through postmarketing surveillance.

5 SUMMARY OF CLINICAL PHARMACOLOGY AND JUSTIFICATION OF DOSE SELECTION

The pharmacokinetics of modafinil have been well characterized. In adults, plasma concentrations of modafinil increase in a dose-proportional manner over the dose range of 200 to 600 mg. The time to peak plasma concentration (t_{max}) is, on average, approximately 2 to 4 hours. Food has no effect on overall bioavailability; however, t_{max} may be delayed by approximately 1 hour if modafinil is taken with food. In general, modafinil exhibits an apparent biexponential decline from peak plasma concentration, with a mean terminal half-life ($t_{1/2}$) of approximately 15 hours. Modafinil is lipophilic in nature and is distributed beyond the vascular system (oral volume of distribution [V/F] ~0.9 L/kg). Modafinil is almost exclusively metabolized in the liver, with less than 10% of the administered dose excreted unchanged in the urine. Metabolism occurs primarily via a hydrolytic pathway and, to a lesser extent, via oxidative pathways. Modafinil metabolism involves multiple cytochrome P450 (CYP) enzymes, including CYP3A4/5. Although potent inducers of CYP3A enzymes could increase clearance and reduce systemic exposure to modafinil, the existence of multiple pathways for metabolism of modafinil indicates a low potential for significant effects of CYP inhibitors.

Studies performed to evaluate the pharmacokinetics of modafinil in children and adolescents indicate that although the pharmacokinetic profile of modafinil in young children is similar to that in adults, the elimination rate is markedly different. No evidence of qualitative differences in metabolism has been observed between children/adolescents and adults, but the rates of metabolism are clearly higher in the younger population. 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 (aged 6 to 7 years) studied is approximately 7 hours and increases with increase in age. The general trend in the data indicates that there is a continuous gradual increase in $t_{1/2}$ with a pronounced shift toward higher values in children between 9 and 11 years of age that are more similar to those observed in adults. Due to the shorter $t_{1/2}$ in children/adolescents, carryover between successive daily doses is less in this population, resulting in a lower level of accumulation than that in adults.

Higher plasma concentrations of the metabolite modafinil sulfone were seen in children and adolescents compared to those seen 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.

To guide the selection of the dosage regimens for the Phase 3 studies in this clinical program, pharmacokinetic modeling/simulations of data from initial (Phase 2) studies in children and adolescents with ADHD were used to assess the exposure-response relationship of modafinil following different dose regimens. A population pharmacokinetic model was developed on the basis of data from studies in which patients received daily doses of 200 to 400 mg. This model, coupled with Phase 2 clinical efficacy results, predicted that a systemic exposure (area under the plasma drug concentration by time curve from time zero to 24 hours after study drug administration

[AUC_{0-24}]) of approximately 150 µg•hr/mL would be associated with a consistent pharmacodynamic response.

In selecting the dosage regimens for the Phase 3 program, the apparent decrease in plasma levels of modafinil observed at day 14 relative to day 1 in a multiple-dose Phase 1 study needed to be taken into account. The increase in clearance (CL/F) of modafinil over time reaches steady state by week 6 of treatment. Once steady-state CL/F is reached, the pharmacokinetic parameters of modafinil do not appear to change with continued treatment of up to 1 year.

Dosage regimens selected for the Phase 3 program were predicted to provide a sustained systemic exposure approximating the target value. The more marked shift in clearance of modafinil in children between 9 and 11 years of age coincides with the 30-kg breakpoint in weight used for dose selection in the ADHD population. Hence, taking into account the weight and differences in clearance, the doses selected for further evaluation were 340 mg (weight <30 kg) and 425 mg (weight ≥30 kg) to ensure a sustained systemic exposure within the target range of 150 µg•hr/mL at the time steady state was reached (ie, after 5 to 6 weeks of exposure). The results of the Phase 3 studies have confirmed the appropriateness of the dose selection based on this approach.

In summary, the pharmacokinetic profile of modafinil has been extensively characterized in adults and in children/adolescents. The results for the 2 populations were generally qualitatively similar, although the rate of elimination differs as reflected by the shorter $t_{1/2}$ in the pediatric population as compared to adults. The recommended dosage for treatment of children and adolescents with ADHD (340 mg/day in those weighing <30 kg and 425 mg/day in those weighing ≥30 kg) achieved sustained systemic exposures associated with a significant clinical response to treatment.

6 SUMMARY OF CLINICAL EFFICACY

6.1 Overview of Studies and Study Designs for the Evaluation of Efficacy in Children and Adolescents

Results from 3 Phase 3 randomized, double-blind, placebo-controlled, parallel-group studies are presented here as the primary basis of the efficacy of modafinil when used for the treatment of children and adolescents with ADHD. A total of 621 patients received study drug and were evaluated for efficacy in these 3 studies. Studies C1538d/**309**/AD/US and C1538d/**311**/AD/US (hereafter referred to as studies 309 and 311, respectively) were identically designed flexible-dosage studies with 9-week double-blind treatment periods. Study C1538d/**310**/AD/US (hereafter referred to as study 310) had a fixed-dosage design with a 7-week double-blind treatment period followed by a 2-week randomized-withdrawal period. In all 3 studies, the primary measure of efficacy was the teacher/physician-completed ADHD Rating Scale, Fourth Edition (ADHD-RS-IV) (School Version).

A long-term (>12 months), open-label, extension, safety study (study C1538d/**312**/AD/US, hereafter referred to as study 312) is currently ongoing. Patients participating in this study are children and adolescents with ADHD who had previously received treatment with modafinil or a placebo in a Cephalon-sponsored clinical study (ie, a Phase 1 and a Phase 2 study and the 3 Phase 3 placebo-controlled studies) and who did not withdraw from the previous study due to an adverse event.

The flexible-dosage design (studies 309 and 311) was chosen to allow the study drug (modafinil or placebo) to be titrated for each child to an optimal dosage (170, 255, 340, or 425 mg/day) on the basis of a balance of efficacy and tolerability, reflective of medical practice. A fixed-dosage design (study 310) was chosen to evaluate the effect of treatment with 340 mg/day of modafinil in lighter (<30 kg) patients and 425 mg/day of modafinil in heavier (≥30 kg) patients, the doses predicted to provide optimal plasma exposure of 150 µg•hr/mL. In this study, a 2-week randomized, placebo-controlled, double-blind withdrawal period was conducted after 7 weeks of treatment to evaluate the effect of abrupt withdrawal of modafinil.

Patients in these 3 studies were children or adolescents (6 to 17 years of age, inclusive) who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association 2000) criteria for ADHD at screening, as manifested by a psychiatric/clinical evaluation and the results of the Diagnostic Interview Schedule for Children, Fourth Edition (DISC-IV). The Clinical Global Impression Severity of Illness (CGI–S) rating of was required to be 4 (moderately ill) or greater, as completed by the investigator at the baseline visit. The teacher/physician-completed ADHD-RS-IV (School Version) total and/or subscale score was required to be at least 1.5 standard deviations above the age/sex norm. Patients may have had prior stimulant use prior to enrolling in this study. Throughout the study, patients were to attend a full-time school (not home school) and have a teacher and parent/legal guardian who were willing and able to participate in the appropriate study assessments for the duration of the study.

Evaluation of efficacy included diagnostic interviews with the patients, parents (guardians), and teachers; behavior rating scales completed by parents (guardians) and teachers; direct observations of school behavior; and clinic-based testing. The specific instruments used to evaluate the efficacy of modafinil in these 3 studies are described briefly below.

The ADHD-RS-IV is a validated instrument allowing clinicians to obtain parent and teacher ratings regarding the frequency of each of the symptoms of ADHD on the basis of DSM-IV criteria. Teacher ratings of ADHD symptoms (ADHD-RS-IV [School Version]) correlate classroom behavioral observations and the patient's academic performance; whereas the parent ratings (ADHD-RS-IV [Home Version]) captures behavioral observations at home (primarily in the early evening). The Clinical Global Impression of Change (CGI-C) is a widely used rating scale completed by the physician/clinician on the basis of information obtained from the parent/guardian, teacher, and patient, and on personal observation regarding changes in the patient's global clinical condition. The Conners' Parent Rating Scale, Revised, Short Form (CPRS:R-S), Social Skills Rating Scale (SSRS), and the Child Health Questionnaire (CHQ) are 3 validated scales used to assess the effect of the study drug on problem behaviors, in addition to ADHD symptoms, that are commonly observed in this patient population. The Test of Variables of Attention (TOVA) is a standardized computerized test used to assess attention, response time, and hyperactivity/impulsivity.

6.2 Results of Efficacy Evaluation

6.2.1 Patient Disposition and Demographic/Baseline Characteristics

In these 3 studies, 638 patients were randomized to treatment, 633 patients received at least 1 dose of study drug, and 621 patients were evaluable for efficacy (ie, had at least 1 postbaseline primary efficacy assessment). A total of 391 patients completed the 7- or 9-week double-blind treatment period of their respective study. More patients in the placebo treatment group withdrew from the study before the end of the double-blind treatment period when compared with patients in the modafinil treatment group (47% of placebo-treated patients versus 35% of modafinil-treated patients). The most frequent reason for withdrawal indicated by the investigators in both treatment groups was lack of efficacy (16% of patients in the modafinil treatment group and 34% of patients in the placebo treatment group). Patient disposition is summarized in Table 1.

Table 1: Disposition of Patients by Treatment Group for the Pooled Data From the Phase 3 Placebo-Controlled Studies (Randomized Patients)

	Number (%) of patients		
Patient disposition	**Modafinil**	**Placebo**	**Total**
Randomized	423 (100)	215 (100)	638 (100)
Randomized, not treated	3 (<1)	2 (<1)	5 (<1)
Safety analysis set	420 (99)	213 (99)	633 (99)
Efficacy analysis set	411 (97)	210 (98)	621 (97)
Completed double-blind period	277 (65)	114 (53)	391 (61)
Discontinued double-blind period	146 (35)	101 (47)	247 (39)
Death	0	0	0
Adverse event	21 (5)	7 (3)	28 (4)
Lack of efficacy	67 (16)	73 (34)	140 (22)
Consent withdrawn	17 (4)	11 (5)	28 (4)
Protocol violation	1 (<1)	1 (<1)	2 (<1)
Lost to follow-up	12 (3)	1 (<1)	13 (2)
Noncompliance to study drug administration	2 (<1)	0	2 (<1)
Noncompliance to study procedures	2 (<1)	1 (<1)	3 (<1)
Other	24 (6)	7 (3)	31 (5)

The demographic and baseline characteristics of the population in these 3 studies are representative of those observed in the general population with ADHD and were similar for patients in the modafinil and placebo treatment groups. Of the 621 patients who were evaluable for efficacy, 71% were boys, and 76% of the patients were white. The mean age of the patients was 10.1 years (range 6 to 17 years), and most patients (66%) were less than 12 years of age. The mean weight was 41.4 kg (range 18.6 to 98.4 kg), with 68% of the patients weighing at least 30 kg. On the basis of the CGI-S ratings at baseline, 86% of the patients were moderately or markedly ill and 14% of the patients were severely ill. According to the DISC-IV criteria, 65% of the patients had the combined subtype, 30% had the inattentive subtype, and 4% had the hyperactive/impulsive subtype of ADHD. Approximately half of the randomized patients (330 [52%] of 633 patients) were stimulant naïve.

6.2.2 Analysis of Efficacy Data From Phase 3 Placebo-Controlled Studies

The efficacy analysis set included patients who received at least 1 dose of study drug and had at least 1 postbaseline assessment for the ADHD-RS-IV (School Version). The primary efficacy variable was the change from baseline to endpoint (last postbaseline assessment) in the total score from the teacher/physician-completed ADHD-RS-IV (School Version). Secondary variables that were assessed as changes from baseline to each scheduled visit were the following: total and subscale scores from the teacher/physician-completed ADHD-RS-IV (School Version) and from the parent (guardian)/physician-rated ADHD-RS-IV (Home Version), CGI-C ratings, and TOVA scores. Additional efficacy variables were scores from the SSRS, the CPRS:R-S, and the CHQ.

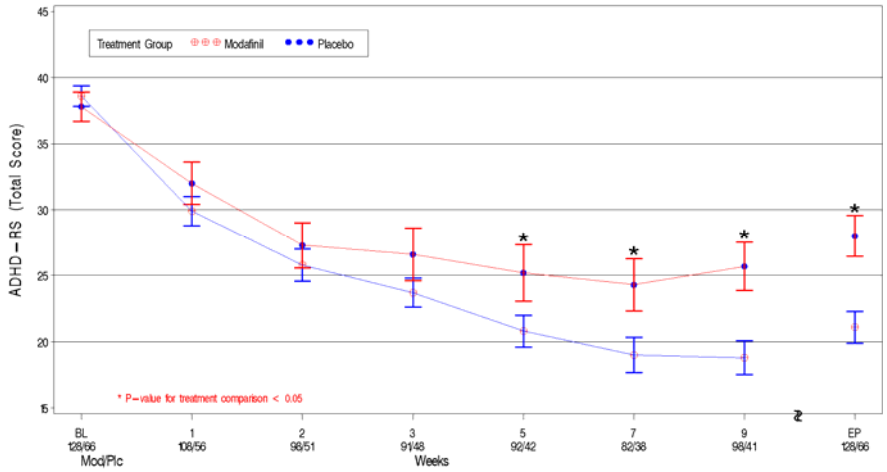
For continuous data, the changes from baseline to each time point and endpoint were analyzed using an analysis of covariance (ANCOVA) model with treatment and study as factors, and the baseline value as a covariate. TOVA scores were analyzed as ranks because of non-normality. Discrete variables for CGI-C ratings and CGI-C responders were analyzed using the chi-square test.

6.2.3 Primary Efficacy Variable

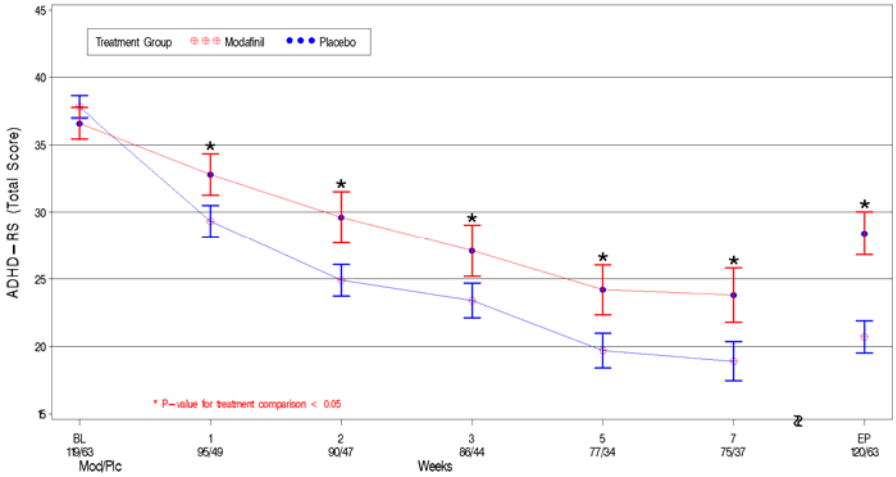
In all 3 studies, analysis of the primary efficacy variable was the change from baseline to the last double-blind treatment period visit (endpoint) in the total score from the teacher-/physician-completed ADHD-RS-IV (School Version). In each of the studies, statistical evidence ($p<0.0001$) in each individual study and in pooled data from all studies) demonstrated that patients treated with modafinil showed a significantly greater improvement than patients treated with placebo (Table 2). The mean decrease in study 309 was 17.5 points for the modafinil treatment group and 9.7 points for the placebo treatment group, with an effect estimate (the difference between treatment groups in the least squares mean values) of –7.4 points. The mean decrease in study 310 was 17.2 points for the modafinil treatment group and 9.2 points for the placebo treatment group, with an effect estimate of –9.0 points. The mean decrease in study 311 was 14.3 points for the modafinil treatment group and 6.4 points for the placebo treatment group, with an effect estimate of –7.9 points. The mean decrease in the pooled data from the Phase 3 studies was 16.4 points for the modafinil treatment group and 8.3 points for the placebo treatment group with an effect estimate (the difference between treatment groups in the least squares mean values) of –7.9 points. Given the magnitude of the changes from baseline values, which reflect the severity of symptoms at the time of entry into the study, these changes are clinically meaningful. The individual study results from the Phase 3 placebo-controlled studies are graphically displayed in Figure 1. (NOTE: The last double-blind treatment period visit was week 9 or early termination in studies 309 and 311, and week 7 or early termination in study 310.)

Figure 1: Changes From Baseline to Each Time Point and Endpoint for the Total Scores From the ADHD Rating Scale-IV (School Version) for Placebo-Controlled Studies

Study 309



Study 310



Study 311

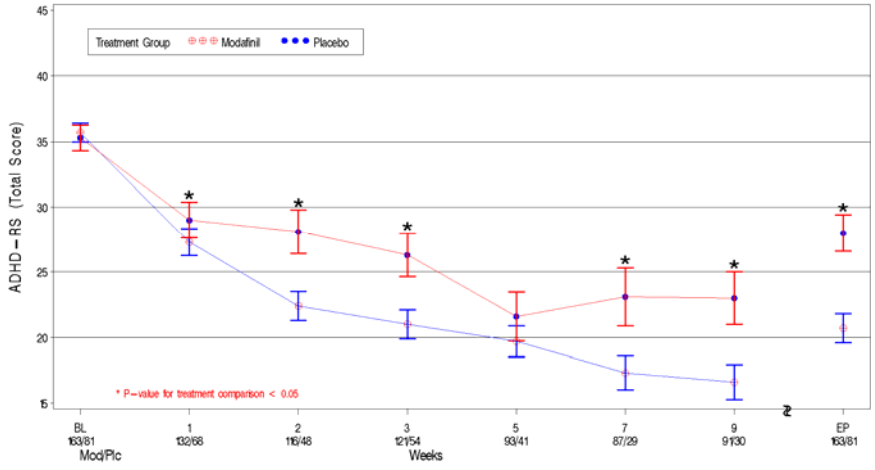


Table 2: Change From Baseline to Endpoint for the Primary Variable of the Total Score From the ADHD Rating Scale-IV (School Version) for the Phase 3 Placebo-Controlled Studies (Efficacy Analysis Set)

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

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

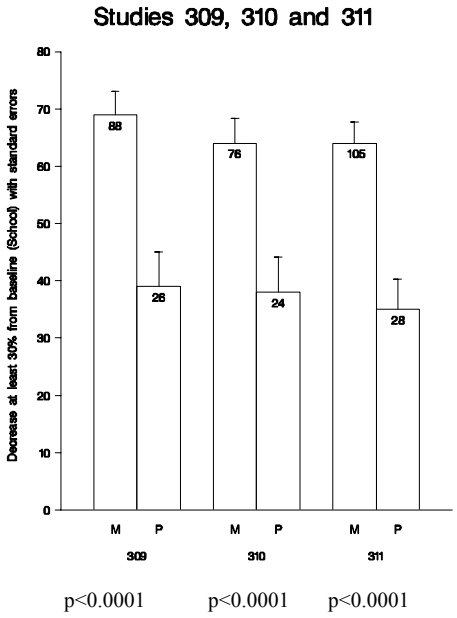
[b] The effect estimate is the difference between treatment groups in the LS mean values.

SD=standard deviation; SE=standard error; min=minimum; max=maximum; LS mean=least squares mean; CI=confidence interval.

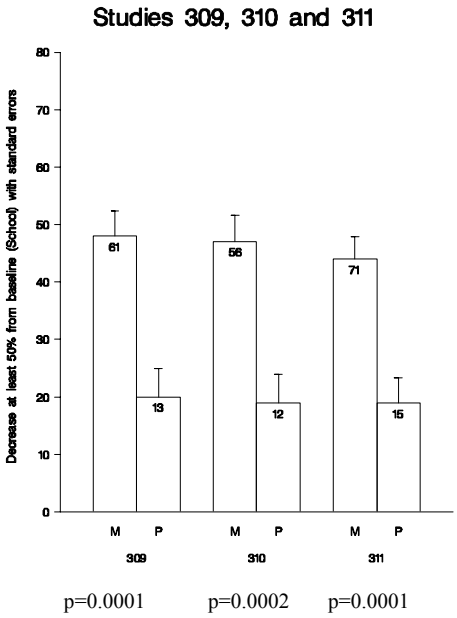
NOTE: Endpoint was week 9 or early termination in studies 309 and 311, and week 7 or early termination in study 310.

Analyses of the total score from the ADHD-RS-IV (School Version) showed the percentages of patients with at least 30% (range 64% to 69% of patients) or 50% (range 44% to 48% of patients) reduction in symptoms were similar across the 3 studies (Figure 2).

Figure 2: Percentage of Patients With 30% or 50% Reduction in ADHD Symptoms in Phase 3 Placebo-Controlled Studies



p<0.0001 p<0.0001 p<0.0001



p=0.0001 p=0.0002 p=0.0001

6.2.4 Secondary Efficacy Variables

Results from secondary assessments evaluating multiple aspects of the patients' conditions (eg, ADHD symptoms at home, global condition, problem behaviors other than those related to ADHD symptoms, and objective assessments of attention) were consistent with the positive results of the effect of modafinil treatment as compared to placebo. Thus, the results from these secondary assessments strongly supported the findings from the primary efficacy assessment, the total score from the School Version of the ADHD-RS-IV at the end of treatment.

6.2.4.1 ADHD-RS-IV (School Version)

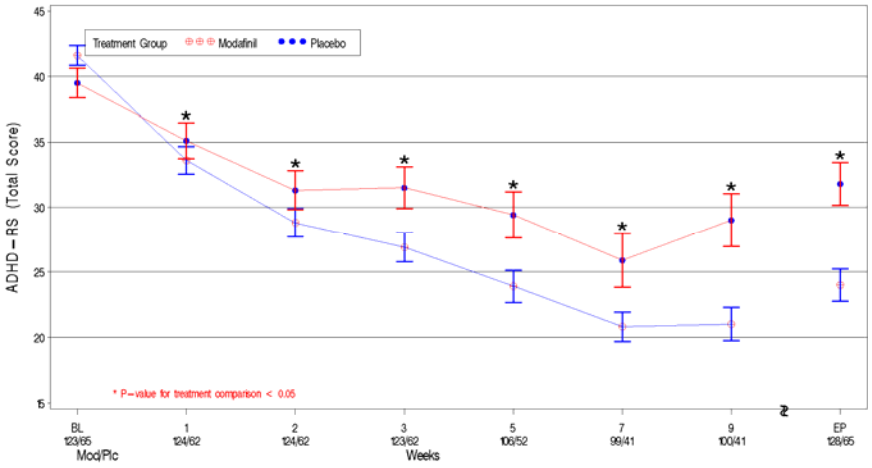
Secondary variables from the ADHD-RS-IV (School Version) included the total scores from each time point and the subscale scores (hyperactivity/impulsivity and inattention) at endpoint and at each time point. Results were consistent with the results seen for the total score at endpoint (primary efficacy variable). In the 3 placebo-controlled studies individually, statistically significant differences in the ADHD-RS-IV (School Version) were observed as early as week 1 (week 5 in study 309) and were maintained throughout the course of the studies (see Figure 1). Statistically significant differences were seen in the individual studies ($p<0.01$) for both the inattentive and hyperactive subscales, demonstrating that treatment with modafinil is effective in alleviating symptoms of both inattention and hyperactivity/impulsivity.

6.2.4.2 ADHD-RS-IV (Home Version)

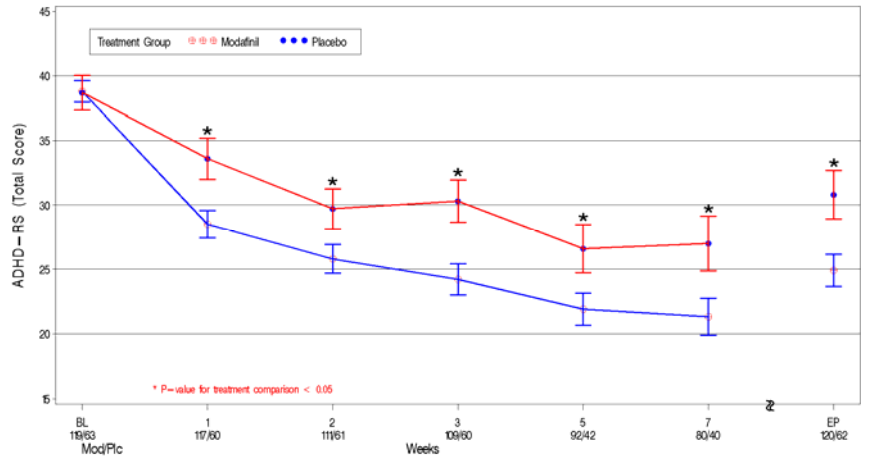
The parent/physician-completed Home Version of the ADHD-RS-IV was conducted between 6 pm and 8 pm in order to evaluate the sustained effect of modafinil treatment over the course of the day and into the early evening. Results were consistent with the results seen in the primary efficacy measure. Statistically significant improvements at endpoint in favor of modafinil were demonstrated in the individual Phase 3 studies ($p\leq0.001$) and in all 3 studies pooled in the total score from the parent/physician-completed Home Version of the ADHD-RS-IV (Figure 3).

Figure 3: Changes From Baseline to Each Time Point and Endpoint for the Total Scores From the ADHD Rating Scale-IV (Home Version) for the Phase 3 Placebo-Controlled Studies

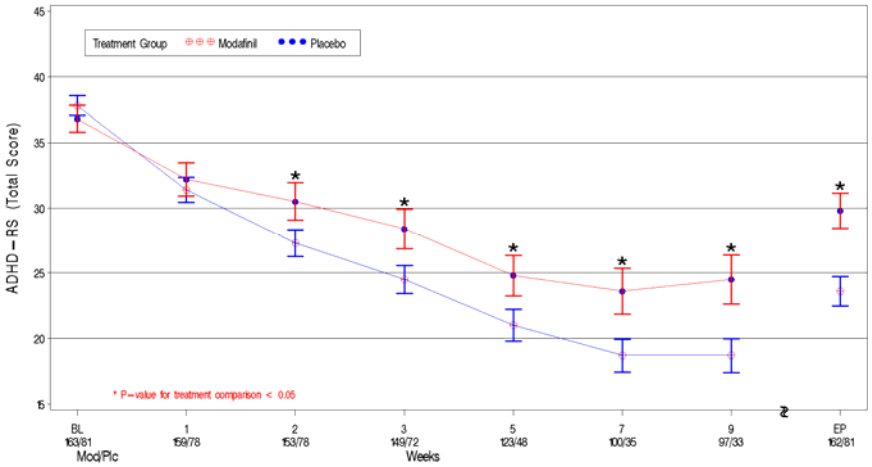
Study 309



Study 310



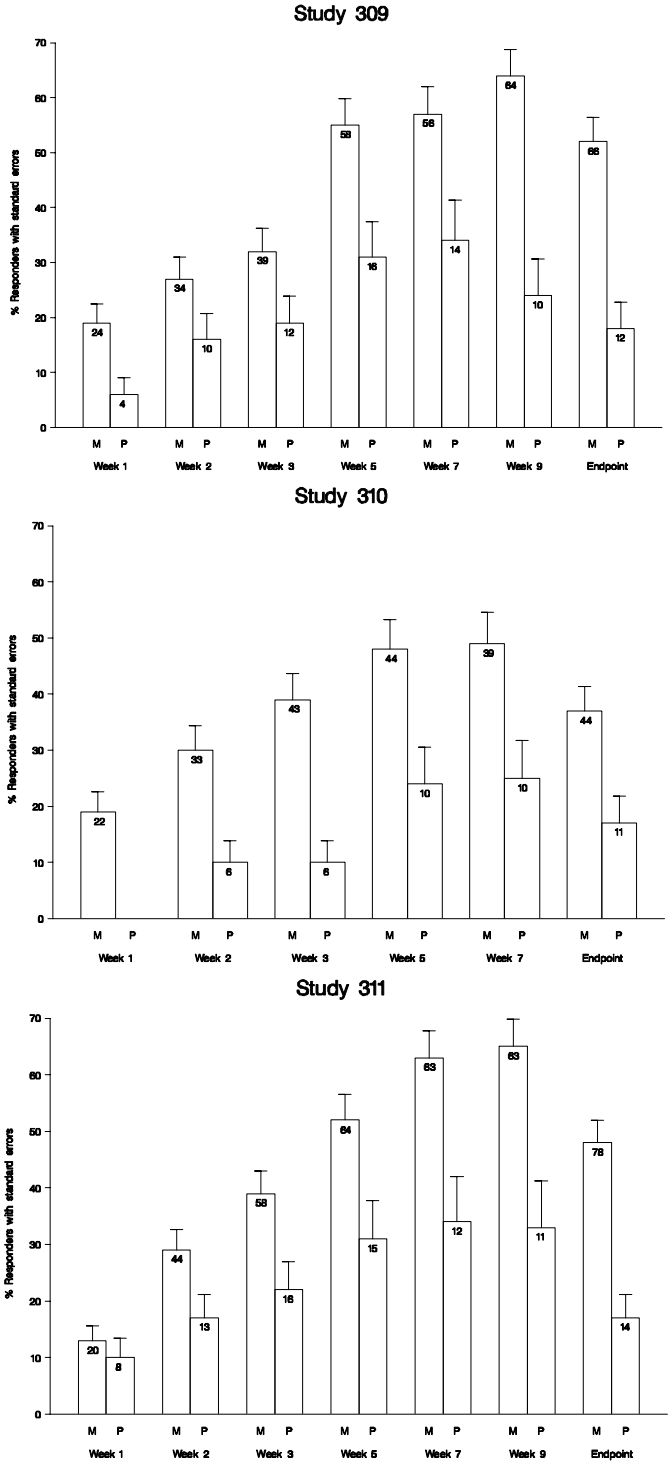
Study 311



6.2.4.3 Clinical Global Impression of Improvement

Results of the CGI-C were consistent with the results from the primary analysis. Analysis of each of the individual studies demonstrated statistically significant improvement (defined as much improved or very much improved) in symptoms at endpoint ($p<0.01$) and at most time points during the studies (Figure 4). In the analysis of the pooled data from all studies, statistically significant improvement was seen at endpoint and at every time point (weeks 1 through 9) for patients in the modafinil treatment group when compared with patients in the placebo treatment group.

Figure 4: Percentage of Responders (Much or Very Much Improved) at Each Time Point for Clinical Global Impression of Change Ratings From the Phase 3 Placebo-Controlled Studies

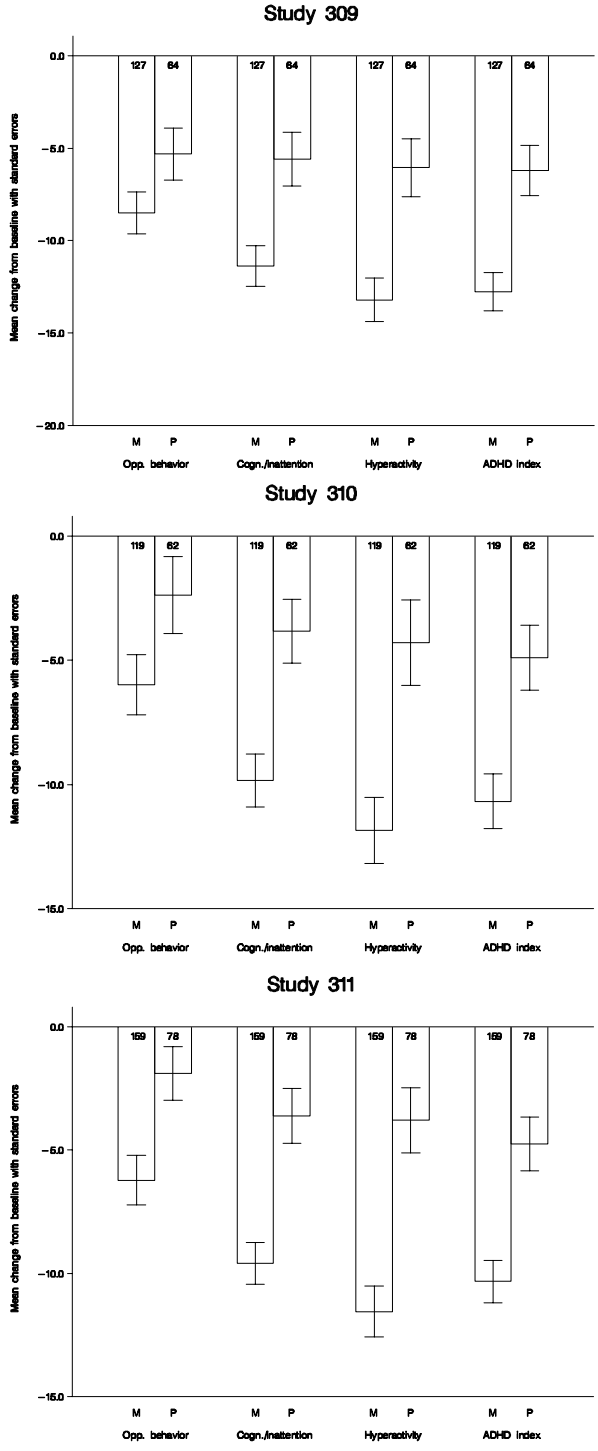


NOTE: With the exception of week 1in study 311, $p<0.05$ at all time points in all studies

6.2.4.4 Conners' Parent Rating Scale: Revised, Short Form

The raw oppositional, cognitive problems/inattention, hyperactivity, and ADHD index scores as assessed by the CPRS:R-S were calculated and converted to T-scores on the basis of the patient's sex and age. Results from all 3 clinical studies were consistent with the results seen in the primary efficacy analysis. Statistically significant improvements in the CPRS:R-S in all 3 studies were observed at endpoint for the modafinil treatment group compared with the placebo treatment group in cognitive problems/inattention ($p<0.05$), hyperactivity ($p<0.001$), and ADHD index T-scores ($p\leq0.001$). Additionally, statistically significant ($p=0.0039$) improvement in oppositional score at endpoint was demonstrated in study 311; quantitative differences favoring modafinil in oppositional behavior were observed at endpoint in studies 309 and 310, and statistical significance ($p=0.0004$) was observed in the pooled analysis.

Figure 5: Changes From Baseline to Endpoint for the Scores From the Connor's Parent Rating Scale:Revised, Short Form for the Phase 3 Placebo-Controlled Studies



NOTE: With the exception of oppositional behavior in studies 309 and 310, $p<0.05$ in all studies.

6.2.4.5 Social Skills Rating Scale

Many children with ADHD have poor peer relationships and have problems socializing. Results from analysis of the SSRS in all 3 clinical studies were consistent with the results seen in the primary efficacy analysis. Statistically significant improvement was seen at endpoint for the modafinil treatment group compared to the placebo treatment group for the problem behaviors total score ($p<0.05$) and for some, but not all, subscores in each individual study. In the analysis of pooled data, there was statistically significant improvement at endpoint in the externalizing ($p=0.0043$), internalizing ($p=0.0021$), and hyperactivity ($p<0.0001$) subscale scores and in the problem behaviors total score ($p<0.0001$). There was also statistically significant improvement at the last postbaseline visit in the cooperation ($p=0.0061$), assertion ($p=0.0331$), responsibility ($p=0.0088$), and self-control ($p=0.0056$) subscale scores, and in the social skills total score ($p=0.0011$) compared to the placebo treatment group. These improvements were seen only in elementary level (kindergarten-grade 6) school children; no significant differences were observed in the secondary level (grades 7-12) school children.

6.2.4.6 Child Health Questionnaire

Results from the CHQ, a quality-of-life instrument, were consistent with the results seen in the primary efficacy measure. In each of the individual studies, statistically significant differences ($p<0.05$) were seen between the treatment groups in favor of modafinil on the psychosocial summary score. Several of the behavioral and psychosocial domain scores either showed a statistically significant difference or a trend toward a significant difference. In the analysis of pooled data, there were statistically significant differences between the treatment groups in favor of modafinil on a majority of the behavioral and psychosocial domains ($p<0.01$), but not on any of the physical or health domains, which were already within the normal range at baseline.

6.2.4.7 Test of Variables of Attention

Results from the TOVA, an objective continuous performance test that assesses attention, failed to show a consistent benefit of treatment either within group or when compared to placebo. However, in each study, statistically significant differences at endpoint were seen between the treatment groups in favor of modafinil on the calculated ADHD score ($p<0.05$).

6.2.5 Subgroup Analyses

The effects of the demographic and baseline characteristics listed below on the efficacy of modafinil treatment were evaluated using the mean change from baseline to endpoint in the total score from the ADHD-RS-IV (School Version). These subgroup analyses are based on the pooled Phase 3 data in order to have sufficient patient numbers to assess evidence of trends.

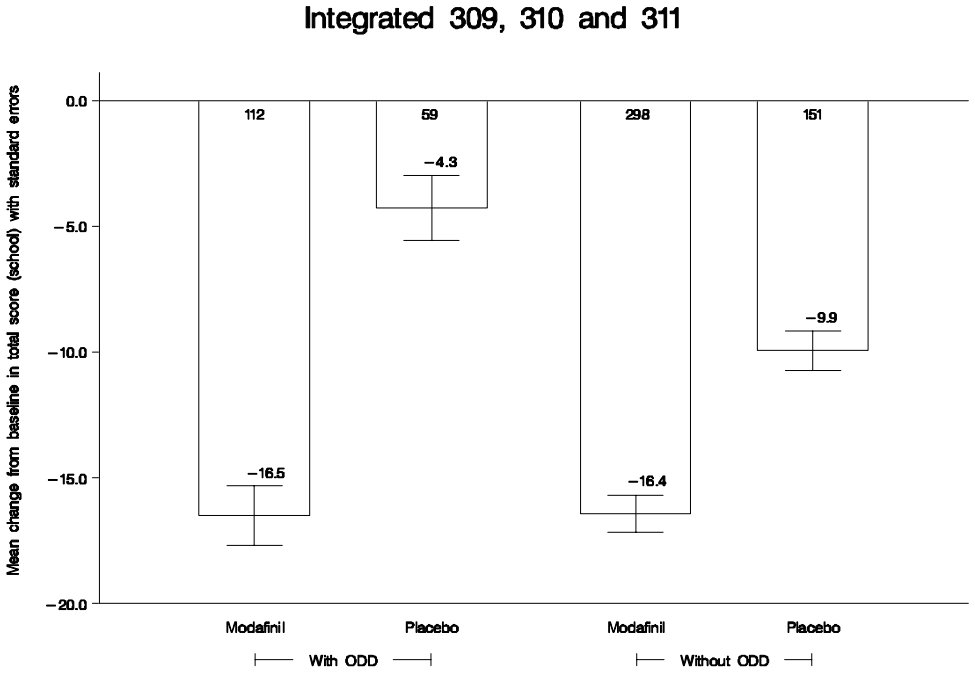
- demographic characteristics (age, race, sex, weight)
- ADHD subtype

- patients with comorbid ODD
- stimulant-naïve patients
- patients with previous stimulant treatment

There were no apparent effects of race, sex, weight, ADHD subtype, or comorbidity of ODD on the response to modafinil treatment. There was some indication of increased efficacy for patients less than 12 years of age (n=279) when compared with patients at least 12 years of age (n=141), with a slightly larger decrease in scores for the younger modafinil-treated patients.

Patients with (n=112) and without (n=298) a comorbidity of ODD showed similar response to treatment with modafinil (Figure 6).

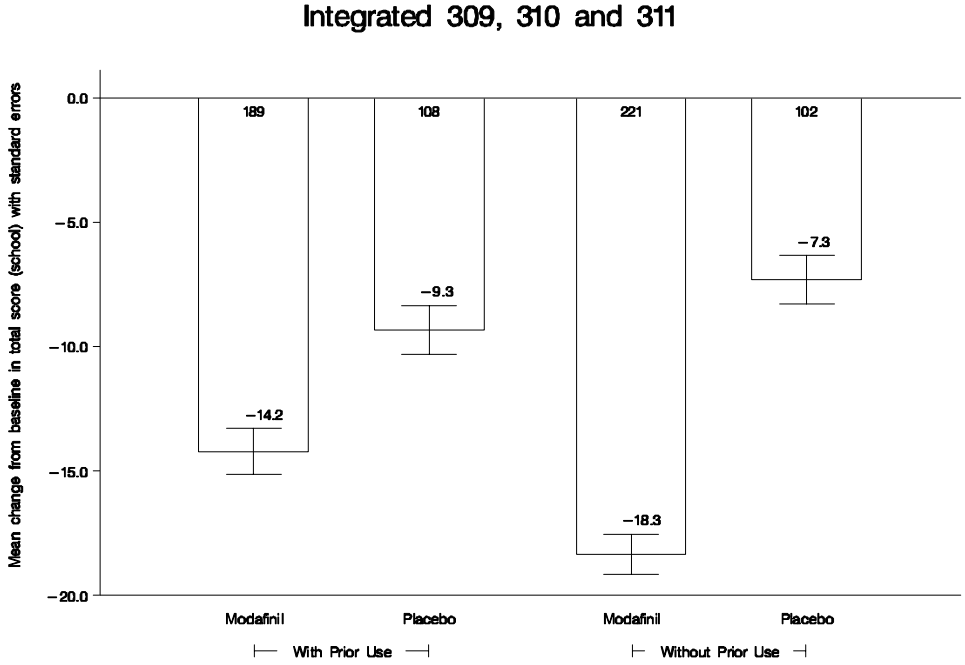
Figure 6: Relationship of Comorbid Oppositional Defiant Disorder to Treatment With Modafinil or Placebo in Children and Adolescents With Attention-Deficit Hyperactivity Disorder



NOTE: p<0.05 for patients with and without oppositional defiant disorder.

Modafinil was efficacious in stimulant-naïve patients and in patients who had received prior stimulant treatment. However, patients treated with modafinil who had not previously used stimulant treatment for their symptoms of ADHD (n=221) showed more improvement (change from baseline –18.3) in the total score from the ADHD-RS-IV (School Version) than did patients who had previously used stimulant treatment (n=189) (change from baseline –14.2) (Figure 7). Total scores from the ADHD-RS-IV (Home Version) also showed slightly more improvement (change from baseline –15.8) for patients without previous stimulant treatment than did patients who had previously used stimulant treatment (change from baseline –14.4).

Figure 7: Relationship of Previous Stimulant Usage to Treatment With Modafinil or Placebo in Children and Adolescents With Attention-Deficit Hyperactivity Disorder



NOTE: $p<0.05$ for patients with and without prior stimulant use.

6.3 Summary of Efficacy Results

Modafinil was shown to be efficacious in the treatment of children and adolescents with ADHD. For the primary efficacy variable, the change from baseline to the last double-blind treatment period visit (endpoint) in the total score from the teacher/physician-completed ADHD-RS-IV (School Version), provided very robust statistical evidence ($p<0.0001$) in each individual study and in the analysis of pooled data.

Results for the secondary variables were consistent with the results for the primary variable, and included ratings by teachers, physicians, and parents. For the ADHD-RS-IV (School Version), statistically significant differences observed early were maintained throughout the course of the studies, and demonstrated that treatment with modafinil is effective in alleviating symptoms of both inattention and hyperactivity/impulsivity. For the Home Version of the ADHD-RS-IV (parent/physician-completed), statistically significant improvements at endpoint and at most time points during treatment in favor of modafinil were demonstrated in the 3 individual studies and in pooled data from all 3 studies. For the CGI-C

(physician-completed), statistically significant improvement (defined as much improved or very much improved) was seen at endpoint and at weeks 1 through 9 in pooled data from all 3 studies. At endpoint, 46% of the patients who received modafinil treatment were rated as much or very much improved in their global clinical condition compared with 18% of the patients who received placebo treatment (pooled data from all studies).

Analyses of the total score from the ADHD-RS-IV (School Version) showed the percentage of modafinil-treated patients with at least 30% (range 64% to 69% of patients) or 50% (range 44% to 48% of patients) reduction in symptoms were similar across the 3 studies and was much higher when compared with placebo-treated patients (ranges 35% - 39% and 19% - 20%, respectively).

No apparent effects of race, sex, weight, ADHD subtype, or comorbidity of ODD were seen in the response to modafinil treatment. More improvement was seen in patients less than 12 years of age than was seen in older patients. Modafinil was efficacious in treating both stimulant-naïve patients and those who had received prior stimulant therapy. However, there appeared to be a greater improvement in those patients without previous stimulant treatment than in patients who had previously used stimulant treatment.

Results from additional analyses show improvement in children with ADHD across multiple domains: the Social Skills Rating Scale, the Conners' Parent Rating Scale: Revised, Short Form, the Child Health Questionnaire, and the Test of Variables of Attention. These results are also consistent with the other secondary variables and measure improvement in different settings (eg, school and home).

6.4 Clinical Relevance of Efficacy Results

The data across all studies for all measures demonstrate clinical improvement in ADHD symptoms for children and adolescents. The magnitude of the treatment differences in the primary variable, the ADHD-RS-IV (School Version) total score (difference of –7.9 points) and the analysis of CGI-C demonstrate that these results are clinically meaningful. In summary, the following aspects of efficacy are supported by the data:

- consistent and reproducible efficacy results in the treatment of core ADHD symptoms and behaviors across the 3 pivotal studies for children and adolescents receiving modafinil compared to those receiving placebo
- consistent and reproducible improvement of ADHD symptoms and behaviors as evaluated by multiple raters (teachers in the school setting, physicians in the clinical setting, and parents in the home setting through the early evening hours)
- consistent and reproducible trends toward improvement in other psychosocial domains as well as the core ADHD symptoms and behaviors
- consistent and reproducible efficacy results in the treatment of ADHD symptoms and behaviors in both treatment-naive patients and patients with prior stimulant experience
- consistent and reproducible efficacy results in the treatment of ADHD symptoms and behaviors results in patients with comorbid ODD.

7 SUMMARY OF SAFETY

7.1 Modafinil Exposure to Children and Adolescents in Clinical Studies

In clinical studies, a total of 1622 children and adolescents have received treatment with modafinil for ADHD (1236 patients), excessive sleepiness associated with narcolepsy or OSAHS (270 patients), or in legacy studies (116 patients) (Table 3).

Table 3: Overview of Modafinil Exposure to Children and Adolescents in Clinical Studies

	Number of patients		
	Randomized controlled studies		All studies
Study population	**Modafinil**	**Placebo**	**Modafinil**
Studies in children and adolescents with ADHD			
Phase 1	—	—	24
Phase 2	244	95	311
Phase 3	420	213	598
Total patients included in the sNDA	664	308	933
Phase 3b			303
Total patients with ADHD			1236
Other studies in children and adolescents			
Patients with narcolepsy or OSAHS	142	52	270
Patients with other conditions (legacy)	—	—	116
Total children and adolescents in clinical studies	—		1622

ADHD=attention-deficit/hyperactivity disorder; sNDA=Supplemental New Drug Application; OSAHS=obstructive sleep apnea/hypopnea syndrome.

A total of 933 children and adolescents with ADHD have received treatment with modafinil in Cephalon-sponsored Phase 1, 2, and 3 clinical studies (Table 4). Three Phase 3 placebo-controlled, parallel-group studies (studies 309, 310, and 311) are presented as the primary basis to demonstrate the safety of modafinil tablets for use in the treatment of children and adolescents with ADHD. In these 3 studies, 420 patients received modafinil at dosages up to 425 mg/day. Patients who participated in previous Cephalon-sponsored studies with modafinil could enroll in a Phase 3 long-term (>12 months) open-label extension study (study 312), which is ongoing. The mean duration of modafinil treatment in Phase 1, 2, and 3 studies combined was 177.1 days, including 12-months of exposure data from study 312. A total of 244 of 933 (26%) patients received modafinil for more than 12 months, and 164 of 933 (18%) patients received modafinil for more than 18 months. In addition, a Phase 3b open-label study (study C1538/3044/AD/US) in 303 children and adolescents with ADHD who have not previously participated in a Cephalon-sponsored study with modafinil is ongoing.

In addition to children and adolescents with ADHD, modafinil (100-mg tablet formulation) treatment has also been evaluated in clinical studies in 270 children and

adolescents with excessive sleepiness associated with narcolepsy or obstructive sleep apnea/hypopnea syndrome (OSAHS) (Table 4). A total of 270 patients received treatment with modafinil at dosages of 100, 200, 300, or 400 mg/day in these studies. Across these studies, a majority (63%, 171 of 270) of patients received 3 months or more of modafinil treatment, and 103 (38%) patients had at least 6 months exposure to modafinil.

Table 4: Clinical Studies With Modafinil in Children and Adolescents

Study number	Study design	Duration[a]	Modafinil dosage	N[b]
Phase 1, 2, and 3 studies in children and adolescents with ADHD				
Phase 1 study				
C1538d/113/BA/US	Open-label, crossover	Single dose	170 or 200 mg/day	24
	Open-label, multiple dose	14 days	340 or 425 mg/day	
Phase 2 studies				
C1538a/206/PK/US	Open-label, dose-ranging	12 weeks	100 to 400 mg/day	20
C1538a/207/AD/US	Double-blind, crossover (4-period)	4 weeks	100 to 400 mg/day	47
	Open-label, treatment extension	8 weeks	100 to 400 mg/day	
C1538a/213/AD/US	Double-blind, parallel-group	4 weeks	300 to 400 mg/day	197
	Open-label, treatment extension	8 weeks	100 to 400 mg/day	47[c]
Phase 3 studies				
C15398d/309/AD/US	Double-blind, flexible-dosage, parallel-group	9 weeks	255 to 425 mg/day	131
C15398d/310/AD/US	Double-blind, fixed-dosage, parallel-group	9 weeks[d]	<255 to 425mg/day	125
C15398d/311/AD/US	Double-blind, flexible-dosage, parallel-group	9 weeks	255 to 425 mg/day	164
C1538d/312/AD/US[e]	Open-label, treatment extension	>12 months	170 to 425 mg/day	178[c]
Total patients in Phase 1, 2, and 3 studies				**933**
Other studies in children and adolescents				
C1538/3027/NA/MN	Double-blind, parallel-group (narcolepsy)	6 weeks	100 to 400 mg/day	123
C1538/3028/AP/MN	Double-blind, parallel-group (OSAHS)	6 weeks	100 to 400 mg/day	19
C1538/3029/ES/MN[e]	Open-label, treatment extension (narcolepsy or OSAHS)	12 months	100 to 400 mg/day	37[c]
C1538/3034/ES/MN	Open-label, flexible dosage (narcolepsy or OSAHS)	6 months	100 to 400 mg/day	91
C1538/3044/AD/US[e]	Open-label, flexible dosage (ADHD)	>6 months	85 to 425 mg/day	303
Children and adolescents in legacy studies				116
Total patients in other studies				**689**
Total number of children and adolescents treated with modafinil				**1622**

[a] Maximum duration of modafinil treatment.
[b] Number of patients who received modafinil; patients who received modafinil during double-blind and open-label treatment are counted only once.
[c] Numbers for studies 213, 312, and 3029 indicate patients who switched from placebo during double-blind treatment periods to modafinil during open-label treatment; total numbers of patients who received open-label treatment in these studies were 220, 533, and 148, respectively.
[d] Includes a 2-week randomized withdrawal period.
[e] Ongoing study.
ADHD=attention-deficit/hyperactivity disorder; OSAHS=obstructive sleep apnea/hypopnea syndrome.

7.2 General Safety Evaluation

7.2.1 Nonclinical Studies

Modafinil has been assessed in a standard series of in vitro and in vivo nonclinical safety (toxicology) tests. The testing consisted of general toxicity evaluations in rodents (principally rats) and nonrodents (principally dogs) of an acute (single-dose) or repeated-dose regimen (up to 1 year in rats and dogs utilizing consecutive daily dose administrations); a cardiovascular (hemodynamic) study in dogs; mutagenicity/genetic toxicology tests; developmental and reproductive tests (fertility and general reproductive performance; teratology; perinatal and postnatal development); and lifetime (2-year) carcinogenicity bioassays (rats and mice), including an alternative (dermal) bioassay in Tg.AC (transgenic) mice. Although the majority of the in vivo toxicity tests were carried out in sexually mature (adult) animals, a series of nonclinical safety evaluations were also performed in neonatal/weanling and prejuvenile rats and prejuvenile dogs in support of the ADHD indication in children and adolescents. Additionally, a 4-week oral toxicity study of modafinil sulfone, a principal circulating metabolite of modafinil, was conducted in rats.

Collectively, in the nonclinical safety evaluations conducted in vitro or in standard laboratory species, no significantly adverse, untoward, or alarming toxicities were identified. Overt signs reflective of exaggerated primary pharmacologic (CNS) effects occurred at the higher doses. Repeat-dose administration also resulted in an elevation in liver weights, microscopic evidence of centrilobular hepatocellular hypertrophy, and a decrease in concentrations of modafinil and its circulating metabolites over the course of the dosing period. These alterations were associated with hepatic enzyme induction with repeated dosing. Modafinil was not shown to affect mating or fertility, had no adverse effects on embryo-fetal development, including skeletal or soft tissue abnormalities, and was nonmutagenic/nongenotoxic and noncarcinogenic. Overall, under the conditions of all studies conducted as described, modafinil was generally well tolerated and no definitive target organs of toxicity were apparent.

In all of the multiple-dose nonclinical systemic toxicity studies carried out in rats and dogs, a complete gross and histopathologic examination of the heart was conducted. Additionally, ECGs were undertaken and heart rate and blood pressure were measured predose and during study weeks 6 and 12 in a 12-week multiple-dose oral toxicology study in mature beagle dogs. In the 13-week study in prejuvenile beagle dogs, multilead (leads I, II, III, aVR, aVL, aVF) ECGs were conducted predose and during study weeks 13 and 17 (recovery). In the cardiovascular (hemodynamic) study conducted in the beagle dog, a series of cardiac functions were assessed following single-dose intraduodenal administration of modafinil to anesthetized animals.

No morphologic treatment-related gross or histopathologic changes in the heart were noted in any of the multiple-dose nonclinical toxicology studies in adult animals with modafinil after consecutive daily dosing by the oral (clinical) route for 4 weeks (rats

given doses up to 400 mg/kg/day), 12 weeks (rats given doses up to 200 mg/kg/day and dogs given doses up to 100/75 mg/kg/day [dose reduction from 100 to 75 mg/kg/day on study day 15 due to the elicitation of marked CNS effects]), 26 weeks (rats given doses up to 200 mg/kg/day), or 52 weeks (rats given doses up to 60 mg/kg/day and dogs given doses up to 40 mg/kg/day). In the 12-week toxicity evaluation in dogs, no adverse treatment-related alterations were seen in ECG findings (QRS, QTc intervals) or blood pressure measurements. In this study, heart rates were moderately reduced approximately 30% lower (study weeks 6 and 12) relative to concurrent control values at the high-dose level; this change was not present in the low- (20 mg/g/day) or mid-dose (50 mg/kg/day) groups. No treatment-induced alterations in the ECG data (including heart rate) were evident in the 13-week study carried out in the prejuvenile beagle dogs. Additionally, gross and microscopic examination of the heart from a 6-week oral toxicity study in weanling rats given modafinil at doses up to 400 mg/kg/day and in a 13-week oral toxicity study in prejuvenile beagle puppies given modafinil at doses up to 90→75 mg/kg/day (dose reduction from 90 to 75 mg/kg/day due to morbidity in some animals during study week 2) revealed no compound-induced cardiac alterations.

In the cardiovascular (hemodynamic) study of modafinil in male beagle dogs (5/group), modafinil did not produce any biologically relevant changes in systolic/diastolic or mean arterial pressure, heart rate, left ventricular pressure, left ventricular end diastolic pressure, + dp/dt at 40 mm Hg intraventricular pressure, cardiac output, contractile force, or ECG (PR, QRS, QTc) intervals after administration of single intraduodenal doses of 20 and 60 mg/kg. The hemodynamic parameters were assessed at predose and at 30-minute intervals up to 2 hours postdose in the dogs.

In summary, no potential cardiac liabilities were identified on the basis of the nonclinical safety/toxicity testing performed with modafinil.

7.2.2 Clinical Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

The safety information for children and adolescents with ADHD will be presented in 2 ways; first for the Phase 3 placebo-controlled studies and, secondly, for all studies (which includes pooled data from all Phase 1, 2, and 3 studies and their open-label extensions).

In the Phase 3 placebo-controlled studies, a total of 633 patients received either modafinil (N=420) or placebo (N=213). The mean age was 10.2 years for modafinil-treated patients and 9.9 years for placebo-treated patients. Of the 420 patients in the modafinil treatment group, 66% (279 patients) were less than 12 years of age, 72% (301 patients) were boys, and 77% (322 patients) were white. Demographic characteristics for the 213 patients in the placebo treatment group were similar, with 67% (142 patients) less than 12 years of age, 71% (152 patients) boys, and 76% (161 patients) white. The median average daily dose of modafinil was 337.3 mg for the modafinil-treated patients.

In all Phase 1, 2, and 3 studies in children and adolescents with ADHD combined, a total of 933 patients received modafinil. The mean age of modafinil-treated patients was 9.8

years (72%, 674 patients <12 years of age), 72% (676 patients) were boys, and 76% (712 patients) were white. The median average daily dose of modafinil was 308.9 mg for the modafinil-treated patients.

7.2.2.1 Evaluation of Adverse Events

(a) Overview of Adverse Events

In the Phase 3 placebo-controlled studies (studies 309, 310, and 311) in children and adolescents with ADHD, 78% (328 of 420) of patients who received modafinil and 63% (135 of 213) of patients who received placebo reported at least 1 adverse event during double-blind treatment. Treatment-related events were reported by 55% (229 of 420) of patients who received modafinil and 29% (62 of 213) of patients who received placebo. For all studies combined (ie, Phases 1, 2, and 3), 86% (798 of 933) of patients who received modafinil reported at least 1 adverse event, and 63% (590 patients) reported at least 1 treatment-related adverse event. An overview of adverse events in the Phase 3 placebo-controlled studies and in all studies combined is presented in Table 5.

In the Phase 3 placebo-controlled studies, serious adverse events were reported for less than 1% (4 of 420) of patients in the modafinil treatment group and none of the patients in the placebo treatment group. Adverse events leading to discontinuation from study were reported for 5% (23 of 420) of patients in the modafinil treatment group and 3% (7 of 213) of patients in the placebo treatment group. For all studies combined, 2% (18 of 933) of the patients reported serious adverse events and 9% (83 of 933) of the patients withdrew due to adverse events.

Table 5: Overview of Adverse Events in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

	Number (%) of patients		
	Phase 3 double-blind studies		All studies
Category	Modafinil (N=420)	Placebo (N=213)	Modafinil (N=933)
Any adverse event	328 (78)	135 (63)	798 (86)
Treatment-related adverse events	229 (55)	62 (29)	590 (63)
Serious adverse events	4 (<1)	0	18 (2)
Withdrawals due to adverse events	23 (5)	7 (3)	83 (9)
Deaths	0	0	0

(b) Incidence of Adverse Events

In the Phase 3 placebo-controlled studies, adverse events with an incidence of at least 5% that occurred more frequently with modafinil treatment than with placebo treatment included insomnia, headache, anorexia (primarily reported as decreased appetite), abdominal pain, fever, and nervousness (Table 6).

Table 6: Adverse Events Occurring in at Least 5% of Patients in the All Modafinil Treatment Group and More Frequently Than in the Placebo Treatment Group by Adverse Event Type in Phase 3 Placebo-Controlled Studies (Safety Analysis Set)

	Number (%) of patients[a]	
Adverse event	**Modafinil (N=420)**	**Placebo (N=213)**
Number of patients with at least 1 adverse event	**328 (78)**	**135 (63)**
Insomnia	115 (27)	8 (4)
Headache	82 (20)	27 (13)
Anorexia	67 (16)	6 (3)
Abdominal pain	40 (10)	17 (8)
Fever	21 (5)	7 (3)
Nervousness	19 (5)	9 (4)

[a] Patients may have reported more than 1 adverse event type.

Few of the adverse events that occurred in at least 5% of modafinil-treated patients and more frequently than in placebo-treated patients in these 3 placebo-controlled studies were of severe intensity or led to withdrawal of the patient from the study (Table 7).

Table 7: Summary of Numbers of Patients With Adverse Events Occurring in at Least 5% of Patients in the All Modafinil Treatment Group and More Frequently Than in the Placebo Treatment Group in Phase 3 Placebo-Controlled Studies (Safety Analysis Set)

	Number (%) of patients (all modafinil) (N=420)		
Adverse event	**Incidence**	**Severe intensity**	**Led to withdrawal**
Insomnia	115 (27)	9 (2)	5 (1)
Headache	82 (20)	3 (<1)	2 (<1)
Anorexia	67 (16)	1 (<1)	2 (<1)
Abdominal pain	40 (10)	0	3 (<1)
Fever	21 (5)	0	1 (<1)
Nervousness	19 (5)	0	1 (<1)

The majority of patients who reported adverse events in these 3 studies had events that were mild to moderate in severity (304 [93%] of 328 modafinil-treated patients; 131 [97%] of 135 placebo-treated patients). The only severe adverse event that occurred in more than 1% of all patients who received modafinil was insomnia (2% [9 of 420 patients] modafinil; <1% [1 of 213 patients] placebo).

The time to onset of adverse events was examined by summarizing the incidence of adverse events by time on treatment. Approximately 75% (245 of 328 patients) of modafinil-treated patients who reported adverse events had these events within the first 2 weeks of treatment. The first 2 to 3 weeks of treatment was the period of dose titration in these studies, ie, up to 22 days of dose titration in studies 309 and 311, and 7 to 9 days of titration in study 310.

For all studies combined (Phases 1, 2, and 3), the overall incidence of adverse events for modafinil-treated patients was 86% (798 of 933 patients) (Table 8). The most frequent adverse events were insomnia (30%), headache (25%), infection (19%), anorexia (18%), abdominal pain (14%), accidental injury (12%), cough increased (12%), and rhinitis (11%). Most (90% [720 of 798 patients]) modafinil-treated patients who reported adverse events had events that were mild or moderate in severity. Severe insomnia was reported by 2% (16 of 933) of all patients who received modafinil; all other severe adverse events occurred in less than 1% of patients who received modafinil.

Table 8: Adverse Events Occurring in More Than 5% of Patients Adverse Event Type in All Studies (Safety Analysis Set)

	Number (%) of patients[a]
Body system **Adverse event**	**Modafinil (N=933)**
No. of patients with at least 1 adverse event	**798 (86)**
Insomnia	278 (30)
Headache	236 (25)
Infection	177 (19)
Anorexia	166 (18)
Abdominal pain	133 (14)
Cough increased	110 (12)
Accidental injury	108 (12)
Rhinitis	105 (11)
Pharyngitis	86 (9)
Vomiting	80 (9)
Fever	79 (8)
Nausea	61 (7)
Nervousness	61 (7)
Rash	53 (6)

[a] Patients may have reported more than 1 adverse event type.

(c) Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect

- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition

Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study were not considered serious adverse events.

In the Phase 3 placebo-controlled studies, a total of 8 serious adverse events were reported for 4 (<1%) of 420 patients who received modafinil (Table 9). No serious adverse events were reported for placebo-treated patients.

In all studies combined, serious adverse events were reported for 18 (2%) of 933 patients who received modafinil (Table 9). Two patients reported 3 serious adverse events (erythema multiforme [EM] and Stevens-Johnson syndrome [SJS]) for 1 patient in study 311, and maculopapular rash for 1 patient in study 207). Complete information on these patients is provided in section 7.3.1.

Serious adverse events reported by more than 1 patient each included accidental injury, gastroenteritis, dehydration, and asthma. Seven of the patients who reported serious adverse events were withdrawn from the study. Somnolence was reported for 1 patient that occurred 5 days after the completion of the study.

Table 9: Serious Adverse Events by Patient in All Studies

Patient number[a]	Modafinil dosage (mg/day)	Age (y)/ Sex	Serious adverse event, COSTART preferred term (verbatim)	Study day		Severity	Investigator assessment of relationship to study drug
				Start	Stop		
315	100	11/F	Maculopapular rash (morbiliform rash)[d]	15	22	Moderate	Probably
001105	340	6/M	Somnolence (drowsiness)[b]	27	28	Severe	Not related
013201 (024001)	255	15/M	Accidental injury (closed head injury)	129	153	Moderate	Not related
014016 (014210)	340	6/F	Personality disorder (abnormal behavior)[d,e]	93	189	Severe	Not related
019012 (019338)	340	9/M	Stomach ulcer (gastric ulcers)	18	24	Severe	Not related
021191	340	9/M	Asthma (acute asthma attack)[c,d]	8	8	Severe	Unlikely
024010 (024701)	425	14/F	Accidental injury (laceration left buttock)	108	cont	Severe	Not related
034187	340	6/M	Flu syndrome (influenza)[c]	15	18	Moderate	Not related
			Dehydration[c]	15	18	Mild	Not related
037029 (037135)	340	6/M	Periodontal abscess (dental abscess)	336	341	Severe	Unlikely
			Cellulitis (preseptal cellulitis)	336	341	Severe	Unlikely
042309	425	8/M	Peptic ulcer (stress ulcer)[c,d]	40	41	Severe	Unlikely
			Hypertonia (spasm)[c,d]	40	41	Severe	Unlikely
			Duodenitis[c,d]	40	41	Severe	Unlikely
048017 (048178)	425	9/M	Pneumonia	48	51	Severe	Not related
058006 (058158)	425	6/M	Dehydration	147	148	Severe	Not related
061012 (061341)	425	10/F	Gastroenteritis	66	67	Mild	Not related
062338	340	7/M	Erythema multiforme[c,d]	16	Cont	Severe	Possible
			Stevens-Johnson syndrome[c,d]	23	30	Mild	Possible
065008 (065265)	340	7/M	Asthma (asthma exacerbation)	24	28	Severe	Not related
11002	200/100	8/M	Psychosis (psychotic disorder, aggravated)[d]	19	25	Severe	Not related
19008	Unknown	11/M	Accidental injury (second degree and third degree burns, right leg)[d]	12	Cont	Severe	Not related
27005	200/200	11/M	Gastroenteritis (viral gastroenteritis)	14	18	Severe	Not related
			Vomiting	15	17	Moderate	Not related
			Dehydration	16	18	Moderate	Not related

[a] Patient number in parentheses is the patient number in the double-blind study.
[b] The serious adverse event occurred 5 days after the patient's last dose of modafinil.
[c] Serious adverse event occurred in a Phase 3, placebo-controlled study.
[d] Adverse event also led to withdrawal of the patient from the study.
[e] The patient stopped taking modafinil for unknown reasons 2 days before the serious adverse event occurred.
COSTART=Coding Symbols for a Thesaurus of Adverse Reaction Terms; y=year; M=male; F=female; Cont=continuing.

(d) Adverse Events Leading to Withdrawal

In the Phase 3 placebo-controlled studies, 23 (5%) of 420 patients who received modafinil and 7 (3%) of 213 of patients who received placebo had adverse events that resulted in discontinuation from study (Table 10). In the modafinil treatment group, the most common adverse event leading to discontinuation from study was insomnia (5 [1%] of 420 patients).

Table 10: Adverse Events Leading to Withdrawal in the Phase 3 Placebo-Controlled Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Safety Analysis Set)

	Number (%) of patients	
	All adverse events leading to withdrawal	
Body system **Adverse event**	**Modafinil (N=420)**	**Placebo (N=213)**
Number of patients with at least 1 adverse event leading to withdrawal	**23 (5)**	**7 (3)**
Body as a whole		
Abdominal pain	3 (<1)	0
Headache	2 (<1)	0
Fever	1 (<1)	0
Malaise	1 (<1)	0
Cardiovascular		
Tachycardia	2 (<1)	1 (<1)
Digestive		
Anorexia	2 (<1)	0
Duodenitis	1 (<1)	0
Peptic ulcer	1 (<1)	0
Hemic and lymphatic		
Leukopenia	1 (<1)	1 (<1)
Nervous		
Insomnia	5 (1)	1 (<1)
Emotional lability	3 (<1)	1 (<1)
Agitation	2 (<1)	0
Hypertonia	2 (<1)	0
Somnolence	2 (<1)	0
Anxiety	1 (<1)	1 (<1)
Dystonia	1 (<1)	0
Hallucinations	1 (<1)	0
Nervousness	1 (<1)	2 (<1)
Suicidality	1 (<1)	0
Thinking abnormal	1 (<1)	0
Hostility	0	2 (<1)
Hyperkinesia	0	1 (<1)
Respiratory		
Asthma	1 (<1)	0
Cough increased	1 (<1)	0
Dyspnea	1 (<1)	0
Skin and appendages		
Erythema multiforme/Stevens-Johnson syndrome[a]	1 (<1)	0

[a] Erythema multiforme and Stevens-Johnson syndrome were reported for the same patient.

In all studies combined, 83 (9%) of 933 patients who received modafinil had adverse events leading to withdrawal (Table 11). As in the Phase 3 placebo-controlled studies, the most common adverse event leading to withdrawal in all studies combined was insomnia (22 [2%] of 933 patients).

Table 11: Adverse Events Leading to Withdrawal in All Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Safety Analysis Set)

	Number (%) of patients
Body system **Adverse event**	**Modafinil** **(N=933)**
Number of patients with at least 1 adverse event leading to withdrawal	**83 (9)**
Body as a whole	
Abdominal pain	5 (<1)
Headache	5 (<1)
Fever	4 (<1)
Asthenia	2 (<1)
Face edema	1 (<1)
Malaise	1 (<1)
Accidental injury	1 (<1)
Infection	1 (<1)
Cardiovascular	
Tachycardia	2 (<1)
Digestive	
Anorexia	12 (1)
Nausea	4 (<1)
Gamma glutamyl transpeptidase increased	2 (<1)
Vomiting	2 (<1)
Duodenitis	1 (<1)
Gastrointestinal disorder	1 (<1)
Liver function tests abnormal	1 (<1)
Peptic ulcer	1 (<1)
Hemic and lymphatic	
Leukopenia	5 (<1)
Metabolic and nutritional	
Weight loss	4 (<1)
Hypercholesteremia	1 (<1)
SGPT increased	1 (<1)
Weight gain	1 (<1)
Musculoskeletal	
Twitching	2 (<1)

(continued)

Table 11: **Adverse Events Leading to Withdrawal in All Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Safety Analysis Set) (Continued)**

Body system Adverse event	Number (%) of patients All modafinil (N=933)
Nervous	
Insomnia	22 (2)
Emotional lability	8 (<1)
Nervousness	5 (<1)
Agitation	4 (<1)
Personality disorder	3 (<1)
Depression	2 (<1)
Dystonia	2 (<1)
Hostility	2 (<1)
Hyperkinesia	2 (<1)
Hypertonia	2 (<1)
Somnolence	3 (<1)
Thinking abnormal	2 (<1)
Anxiety	1 (<1)
Hallucinations	1 (<1)
Suicidality	1 (<1)
Tremor	1 (<1)
Paresthesia	1 (<1)
Psychosis	1 (<1)
Respiratory	
Asthma	2 (<1)
Cough increased	1 (<1)
Dyspnea	1 (<1)
Skin and appendages	
Rash	5 (<1)
Urticaria	2 (<1)
Erythema multiforme/Stevens-Johnson syndrome[a]	1 (<1)
Maculopapular rash	1 (<1)
Pruritus	1 (<1)
Vesiculobullous rash	1 (<1)
Special senses	
Amblyopia	1 (<1)
Taste perversion	1 (<1)

[a] Erythema multiforme and Stevens-Johnson syndrome were reported for the same patient.

(e) Evaluation of Adverse Events

Modafinil was generally well tolerated by children and adolescents with ADHD in Cephalon-sponsored Phase 1, 2, and 3 clinical studies. The most frequently reported adverse events were common to drugs that affect the central nervous system, but seldom were they severe and few led to discontinuation of treatment. Cardiovascular adverse events were rare. Overall, few serious adverse events were reported, and reasons for withdrawal from the study were varied, with no discernible trends. Some of the reported

adverse events (ie, skin reactions and psychiatric events) are evaluated further (see sections 7.3.1and 7.3.2).

7.2.2.2 Clinical Laboratory Evaluations

(a) Serum Chemistry

In the Phase 3 double-blind studies, mean and median changes from baseline to endpoint (ie, last observation) were minimal in both the modafinil and placebo treatment groups for most serum chemistry parameters. The only notable differences between the modafinil and placebo treatment groups were observed for alkaline phosphatase and gamma-glutamyl transpeptidase (GGT) (Table 12). For alkaline phosphatase, mean increases from baseline were observed in both treatment groups; however, the increase in the modafinil group (16.8 U/L) was approximately twice that observed in the placebo group (7.6 U/L). For GGT, a mean increase from baseline (6.3 U/L) was observed in the modafinil group compared to a mean decrease (–0.1 U/L) in the placebo group. The effects of modafinil on alkaline phosphatase and GGT appeared to be more pronounced in the higher dosage groups (340 and 425 mg/day) than among patients receiving ≤255 mg/day.

Table 12: Mean Changes From Baseline to Endpoint in Gamma-Glutamyl Transpeptidase and Alkaline Phosphatase in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder in Phase 3 Placebo-Controlled Studies (Safety Analysis Set)

		Modafinil (N=420)		Placebo (N=213)	
Serum chemistry variable	Statistic	Baseline	Change from baseline to endpoint	Baseline	Change from baseline to endpoint
Alkaline phosphatase (U/L)	n	419	382	213	197
	Mean	261.1	16.8	270.0	7.6
	SD	88.32	42.27	100.18	44.60
	Median	253.0	15.0	256.0	5.0
	Min, max	55.0, 697.0	–224.0, 206.0	58.0, 865.0	–155.0, 154.0
Gamma-glutamyl transpeptidase (U/L)	n	419	382	213	197
	Mean	13.3	6.3	13.5	–0.1
	SD	4.71	6.01	4.51	2.94
	Median	12.0	6.0	12.0	0.0
	Min, max	5.0, 40.0	–8.0, 49.0	7.0, 35.0	–9.0, 23.0

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

Clinically significant abnormalities in serum chemistry values during treatment were infrequent in the Phase 3 placebo-controlled studies. No patient had a clinically significant value for more than 1 of the following parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), or GGT.

In all studies combined, mean and median changes from baseline to endpoint (ie, last observation) were minimal for most serum chemistry parameters in patients who received modafinil. The mean increase in alkaline phosphatase (Table 13) was similar to that seen

in patients who received placebo in the placebo-controlled studies, and the mean increase in GGT was similar to that seen in patients who received modafinil in the placebo-controlled studies.

Table 13: Mean Changes From Baseline to Endpoint in Gamma-Glutamyl Transpeptidase and Alkaline Phosphatase in All Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Safety Analysis Set)

		Modafinil (N=933)	
Serum chemistry variable	**Statistic**	**Baseline**	**Change from baseline to endpoint**
Alkaline phosphatase (U/L)	n	906	810
	Mean	266.7	5.8
	SD	91.35	65.88
	Median	256.0	8.0
	Min, max	55.0, 865.0	–403.0, 482.0
Gamma-glutamyl transpeptidase (U/L)	n	857	792
	Mean	13.5	5.8
	SD	5.06	6.79
	Median	12.0	5.0
	Min, max	5.0, 83.0	–11.0, 63.0

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

Clinically significant abnormalities in serum chemistry values during treatment were infrequent in all studies combined. Across all studies, less than 1% of the patients who received modafinil had clinically significant abnormal values for AST, ALT, alkaline phosphatase, or GGT. Only 3 patients had clinically significant abnormal values for more than 1 of the following parameters: ALT, AST, and GGT. During treatment in an open-label extension, 2 patients had clinically significant abnormal values for both ALT and AST, and 1 patient had clinically significant abnormal values for both ALT and GGT. These patients had no significant medical history and their values for these parameters were within the normal range at baseline and at the end of double-blind treatment. One patient had clinically significant elevations in ALT and AST that were reported as adverse events and considered severe by the investigator. The patient's ALT and AST values returned to the normal ranges after modafinil treatment was stopped due to other adverse events (fever, vomiting, urticaria, and facial edema). A second patient had clinically significant elevations in ALT and AST that were reported as mild adverse events and returned to the normal ranges while the patient continued to take modafinil. One patient had clinically significant elevations in ALT and GGT that were reported by the investigator as mild adverse events. The patient's ALT value decreased below the clinically significant level and the GGT value returned to the normal range while the patient continued treatment with modafinil; however, the patient was subsequently withdrawn from the study due to these adverse events.

(b) Hematology

In the Phase 3 placebo-controlled studies, clinically significant low ANC values ($\leq 1 \times 10^9$/L) were seen for 7 (2%) of 420 patients in the modafinil treatment group and for 5 (2%) of 213 patients in the placebo treatment group, while clinically significant low WBC values ($\leq 3 \times 10^9$/L) were seen for 8 (2%) modafinil-treated patients and 3 (1%) placebo-treated patients (Table 14). These data show that transient decreases in ANCs and WBC counts occur in children and that there appears to be no causal link to treatment with modafinil. There were no other trends in mean changes from baseline to endpoint in hematology parameters

Table 14: Clinically Significant Abnormal Absolute Neutrophil Counts and White Blood Cell Counts Values by Treatment Group in Phase 3 Placebo-Controlled Studies (Safety Analysis Set)

		Number (%) of patients	
		Phase 3 double-blind studies	
Hematology Variable	**Criteria**	**Modafinil (N=420)**	**Placebo (N=213)**
White blood cell count	$\leq 3.0 \times 10^9$/L	8 (2)	3 (1)
Absolute neutrophil count	$\leq 1.0 \times 10^9$/L	7 (2)	5 (2)

In all studies combined, clinically significant low ANC values were seen for 32 (3%) of 933 patients, and clinically significant low WBC values were seen for 41 (4%) of 933 patients (Table 15).

Table 15: Clinically Significant Abnormal Absolute Neutrophil Counts and White Blood Cell Counts Values in All Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

		Number (%) of patients
		All studies combined
Hematology Variable	**Criteria**	**Modafinil (N=933)**
White blood cell count	$\leq 3.0 \times 10^9$/L	41(4)
Absolute neutrophil count	$\leq 1.0 \times 10^9$/L	32 (3)

7.2.3 Clinical Studies With Modafinil in Other Children and Adolescents and Ongoing Studies

Cephalon's clinical program for the evaluation of modafinil includes 4 clinical studies in children and adolescents with excessive sleepiness associated with narcolepsy or OSAHS. Three of these studies are completed and 1 is ongoing. In addition, 2 open-label studies in children and adolescents with ADHD are ongoing.

Cephalon has conducted a clinical program of modafinil treatment in children and adolescents with excessive sleepiness associated with narcolepsy or OSAHS. A total of

270 patients received treatment with modafinil in these studies. In all studies combined, the mean age was 12.2 years, 57% (155) of patients were boys, and 66% (179) were white.

The safety profile for modafinil demonstrated in this clinical program was consistent with that seen in the ADHD program and no additional safety concerns were apparent.

In these studies, 75% of modafinil-treated patients had at least 1 adverse event and 47% had at least 1 treatment-related adverse event. A total of 18 (7%) modafinil-treated patients had at least 1 adverse event that was reported as severe. The most frequently reported (at least 10% of patients overall) adverse events were headache (24%), anorexia (12%), and infection, abdominal pain, and insomnia (11% each).

Serious adverse events were reported for 3 patients. Patient withdrawal from these studies due to adverse events was 4% overall (3% of patients with narcolepsy and 4% of patients with OSAHS). Adverse events leading to discontinuation in more than 2 patients each were hyperkinesia, nausea, vomiting, and hostility. All other adverse events leading to discontinuation occurred in 1 patient each.

No trends of clinical importance were identified in clinical laboratory parameters.

7.3 Special Safety Evaluations

The approvable letter from the FDA for the sNDA asked for information relating to the occurrence of serious types of skin rash and specific psychiatric adverse events. Because of cardiovascular adverse events associated with other drugs used to treat patients with ADHD, a more in depth review of cardiovascular effects has been undertaken. Lastly, as there is general concern about potential adverse effects on growth in children using ADHD drugs, the effect of modafinil treatment on growth has been assessed. This section provides an evaluation of the modafinil-use data for these specific areas of interest.

7.3.1 Clinically Important Skin Adverse Events

7.3.1.1 Introduction

Adverse reactions to medications are frequently manifested as skin rashes. In most cases these reactions are mild and self-limiting. However, more severe reactions, including EM, SJS, and toxic epidermal necrolysis (TEN), may be associated with significant morbidity and, occasionally mortality. It is recognized that the diagnosis, classification, and causal relationship of cutaneous reactions in association with either drug administration or infectious agents is often difficult in both clinical and research settings. The majority of severe cutaneous adverse reactions (SCARs) related to drug occur early in the course of treatment and risk factors may include both dosage and inherent patient factors.

In the section below, cases of clinically important skin adverse experiences reported in the clinical program in children and adolescents with ADHD are discussed. Other

potentially significant skin rashes and hypersensitivity reactions are reviewed with analyses of non-urticarial rash-related adverse events (hereafter referred to as non-urticarial rash) reported in studies in children and adolescents with ADHD, as well as in all studies in children and adolescents and in the adult clinical program. Review of hypersensitivity reactions reported in the ADHD program in children and adolescents are presented. Finally, modafinil postmarketing pharmacovigilance data related to SCARs are reviewed.

7.3.1.2 Cases of Clinically Important Rash in the ADHD Studies in Children and Adolescents

(a) Overview

In the clinical program in children and adolescents with ADHD (Phase 1 – Phase 3b studies, N= 1236), a total of 3 clinically important rashes were reported in patients treated with modafinil, all of which resolved without sequelae and none of which required medical intervention or hospitalization for treatment. In order to evaluate these cases further, Cephalon convened a panel of 3 pediatric dermatologists. The members of the expert panel worked independently of one another and reviewed available case information for each of the 3 cases. Each panel member was asked to provide a specific assessment of the accuracy of the recorded case diagnosis and the potential etiology or etiologies. It should be noted that for this review neither photographs nor skin biopsies were available.

Because no other clinically important rashes were seen in any other pediatric (total patients, N=1622) or adult (total patients, N=4090) study, the above-mentioned cases were the only cases from clinical studies reviewed by the expert panel. These 3 clinically important cases are summarized in Table 16.

Table 16: Clinically Important Rashes in Studies With Modafinil in Children and Adolescents

Patient number Study number	Age (y)/ sex	Adverse event (verbatim)	Number of days on treatment	Modafinil dosage (mg/day)	Duration of event (days)	Intervention/ Outcome
062338 (C1538d/311/AD/US)	7/M	EM/SJS	16	340	15	Discontinued/ resolved
18004 (C1538/213/AD/US)	8/M	EM	23	300	36	Discontinued/ resolved
315 (C1538a/207/AD/US)	11/F	Morbilliform rash	3	200	13	Discontinued/ resolved

SJS= Stevens-Johnson syndrome; EM=erythema multiforme; M=male; F=female.

(b) Case Reviews

Presented below are individual summaries of the 3 clinically important rashes, including summaries of the expert panel review.

Case 1: Patient 062338 (EM/SJS)

Patient 062338 was a 7-year-old Asian boy with ADHD enrolled in study 311. His dosage of modafinil was titrated to 340 mg/day on study day 15. Fifteen days after starting modafinil treatment, the patient developed a fever, slight rash, and a sore throat initially diagnosed as Streptococcal pharyngitis and treated with amoxicillin (only 1 dose taken). A Rapid Strep Test was negative and the pediatrician felt that the papular lesions in the patient's pharynx were more typical of a Coxsackie B infection. The rash worsened and was retrospectively (once the rash had largely resolved) diagnosed by a dermatologist as EM by history and most likely SJS. According to the child's mother, the patient developed a generalized, pruritic rash with extensive skin peeling and mild to moderate blistering and mucosal involvement (lips and urethral meatus). The rash involved the palms and soles of feet but there was no eye involvement. Modafinil was discontinued and the event resolved over 4 weeks with use of a topical steroid. In the investigator's opinion, the EM was probably secondary to the viral infection, possibly secondary to modafinil treatment, and remotely possibly related to amoxicillin, and the SJS was probably related to the viral infection. The patient did not receive study drug from study days 18 through 30 and then received 1 dose (last dose) of study drug on study day 31 (mother's decisions without consulting the investigator). The outcome of the rechallenge is not known. Radioallergosorbent test (RAST) performed 1½ years after the event showed negative results for modafinil and penicillin G.

This case appears to represent a report of a severe cutaneous adverse reaction by history. However, it was also confounded by the antecedent presence of a suspected viral pharyngitis and concomitant administration of a single dose of amoxicillin. The rash was described as pruritic, whereas a painful rash is more typical for SJS. A biopsy was not performed and the lesions were not medically examined during the acute phase. The patient did not require hospitalization and the event resolved without sequelae.

Expert Panel Review: Two panel members rated the diagnosis of EM/SJS as definitely correct and 1 rated the diagnosis as probably correct. One panel member considered the attribution most likely a viral etiology and 2 panel members considered it probably drug related.

Case 2: Patient 18004 (rash on cheeks, blisters on lips; reported as EM post database lock)

Patient 18004 was an 8-year-old white boy with ADHD enrolled in the study C1538/213/AD/US (hereafter referred to as study 213). He began treatment with modafinil as 200 mg in the morning and 100 mg in the afternoon. On day 23, the patient developed a mild fever and a moderate rash on his cheeks, followed 3 days later by blisters on his lips. He was treated with cephalexin and acetaminophen with codeine, but was withdrawn from the study the next day due to a possible drug reaction. He was seen

by a specialist who noted vesicles and erosions of the skin and thick yellow crusts on the lips. It was also noted that there were no convincing target lesions, nothing on the palms, and no lesions on the eyes, nose, genitals or mouth, other than a few on the gingiva. A culture for herpes simplex virus was negative. Symptoms were considered atypical for SJS, and a diagnosis of EM was made. Thirteen days after event onset and 8 days after modafinil treatment was discontinued, the rash and blisters resolved without treatment and with no residual effects.

Although, this case appears to represent a report of a severe cutaneous adverse reaction (EM by definition), there were no target lesions and only 1 mucosal membrane was involved (lips). The event was not serious in nature and resolved without treatment. A skin biopsy was not performed.

Expert Panel Review: All 3 panel members felt that the diagnosis of EM was unlikely to be correct. This was considered to be a case of probable herpetic gingivostomatitis by 1 panel member, a case of drug-related SJS by a second panel member, and was attributed to either a viral etiology or SJS by the third panel member.

Case 3: Patient 315 (morbilliform rash)

Patient 315 was an 11-year-old white girl with ADHD in study C1538a/207/AD/US. She was randomized to receive 200 mg/day of modafinil in a simulated (laboratory) school study. At the week-1 visit, which occurred on day 4, the patient reported fever (101°F), abdominal pain, and diarrhea; these symptoms, although considered by the investigator to be mild in severity, persisted for 9 more days. The symptoms were considered possibly related to a viral/bacterial infection, since similar symptoms were observed in other study classmates. On day 14 she was seen in the emergency room for generalized pruritic urticaria (on face and chest) believed to be contact dermatitis. The patient was treated with diphenhydramine hydrochloride and released. The rash worsened on day 15, and the patient was hospitalized for diagnostic purposes to rule out SJS. Study drug treatment was discontinued (day 15) and the blind was broken. The patient was examined by a dermatologist who established that the condition was not SJS, but rather a moderate morbilliform rash. No target lesions or mucosal blisters or erosions were observed. The patient was treated with hydroxyzine embonate, and the rash resolved in 7 days. The investigator assessed that the morbilliform rash was probably related to modafinil treatment.

This case does not appear to represent a report of a severe cutaneous adverse reaction, since the rash was only moderate in severity and did not involve target lesions or mucosal membranes. A local dermatologist who examined the patient at the time specifically excluded SJS as a diagnosis.

Expert Panel Review: All 3 panel members rated the diagnosis of morbilliform rash as probably correct. Panel members speculated as to both viral and contact dermatitis etiologies, with a viral etiology considered most likely by 2 of 3 panel members (the third panel member concurred with the diagnosis of morbilliform rash but did not speculate as to etiology, other than suggesting the possible diagnosis of a contact dermatitis).

(c) Conclusions

Different levels of diagnostic and etiologic uncertainty exist for the 3 cases of interest.

For the event of morbilliform rash (case 3), the diagnosis of the local dermatologist, who ruled out SJS, was considered to be accurate by all panel members and no concern was raised by the panel in regard to this case.

For the remaining 2 cases, a possible drug-induced SJS condition could not be excluded by at least 1 panel member. In the case of SJS spectrum disorder (case 1), all 3 panel members considered the recorded diagnosis as probably or definitely correct, although the suspected etiology differed amongst the panel members. For the case recorded as EM (case 2), opinions varied from SJS to herpetic gingivostomatitis. Neither of these cases was confirmed by biopsy and neither of these patients was hospitalized for treatment of rash. Treatment was limited to discontinuation of study drug (EM/SJS [case 1], EM [case 2]) and topical steroidal cream (EM/SJS [case 1]). Recovery was complete in both instances. For each of these cases, a viral etiology was proposed as likely or plausible by at least 1 panel member.

Events for all 3 patients resolved without sequelae, and no patient required medical intervention or hospitalization for management of the condition.

7.3.1.3 Other Potentially Significant Skin Rashes and Hypersensitivity Reactions in Children and Adolescents With ADHD

In addition to the evaluation of the 3 clinically important cases of skin rash described above, Cephalon conducted a comprehensive review of all adverse events reported in clinical studies with modafinil in children and adolescents with ADHD. The purpose of this review was to identify any other possible case of skin rash or hypersensitivity reaction that would require further evaluation. Using a “broad net” case-finding approach, Cephalon medical staff have reviewed the adverse events database for all investigator verbatim terms and Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) preferred terms of potential interest, and classified these into 1 of 9 categories potentially indicative of a skin or mucus membrane reaction (Table 17). The 3 cases discussed in above in section 7.3.1.2 are classified in Table 17 under the preferred terms as initially coded using COSTART from the verbatim terms in the case report forms.

Table 17: Adverse Events Potentially Associated With Skin Rash and/or Hypersensitivity Reaction by Classification and Preferred Term During Double-Blind and Open-Label Treatment in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

	Number (%) of patients		
	During double-blind treatment		During open-label treatment
Classification Preferred term	**Modafinil (N=664)**	**Placebo (N=308)**	**Modafinil (N=799)**
Rash EM/SJS/TEN	**1 (<1)**	**0**	**0**
EM/ SJS[a]	1 (<1)	0	0
Herpetic and vesiculobullous conditions	**3 (<1)**	**2 (<1)**	**11 (1)**
Herpes simplex	1 (<1)	1 (<1)	3 (<1)
Herpes zoster	1 (<1)	1 (<1)	6 (<1)
Vesiculobullous rash[b]	1 (<1)	0	2 (<1)
Mucous membrane involvement	**19 (3)**	**2 (<1)**	**25 (3)**
Dry mouth	11 (2)	1 (<1)	8 (<1)
Conjunctivitis	5 (<1)	2 (<1)	11 (1)
Mouth ulceration	2 (<1)	0	1 (<1)
Dysuria	1 (<1)	0	1 (<1)
Gingivitis	1 (<1)	0	2 (<1)
Ulcerative stomatitis	1 (<1)	0	2 (<1)
Aphthous stomatitis	0	0	1 (<1)
Rash and rash-related	**35 (5)**	**12 (4)**	**47 (6)**
Rash[b]	27 (4)	7 (2)	29 (4)
Vasodilatation	3 (<1)	0	0
Maculopapular rash[c]	2 (<1)	2 (<1)	1 (<1)
Photosensitivity reaction	2 (<1)	0	5 (<1)
Contact dermatitis	1 (<1)	1 (<1)	4 (<1)
Pustular rash	1 (<1)	0	4 (<1)
Infection bacterial	0	1 (<1)	0
Viral infection	0	1 (<1)	1 (<1)
Ear disorder	0	0	2 (<1)
Miliaria	0	0	1 (<1)
Pharyngitis	0	0	1 (<1)
Tongue disorder	0	0	1 (<1)
Anaphylaxis-related	**12 (2)**	**1 (<1)**	**48 (6)**
Asthma	6 (<1)	1 (<1)	19 (2)
Bronchitis	3 (<1)	0	22 (3)
Urticaria[c]	3 (<1)	0	6 (<1)
Face edema	1 (<1)	0	3 (<1)
Anaphylactoid reaction	0	0	1 (<1)

Footnotes and abbreviations appear at the end of the table. (continued)

Table 17: Adverse Events Potentially Associated With Skin Rash and/or Hypersensitivity Reaction by Classification and Preferred Term During Double-Blind and Open-Label Treatment in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Continued)

	Number (%) of patients		
	During double-blind treatment		During open-label treatment
Classification Preferred term	**Modafinil (N=664)**	**Placebo (N=308)**	**Modafinil (N=799)**
Dermatitis, eczema, and related condition	**6 (<1)**	**1 (<1)**	**17 (2)**
Contact dermatitis	2 (<1)	0	8 (<1)
Eczema	2 (<1)	0	5 (<1)
Fungal dermatitis	2 (<1)	1 (<1)	4 (<1)
Pruritus	**6 (<1)**	**0**	**9 (1)**
Pruritus[c]	6 (<1)	0	9 (1)
All other preferred terms in skin and appendages body system	**5 (<1)**	**3 (<1)**	**17 (2)**
Sweating	2 (<1)	0	1 (<1)
Dry skin	1 (<1)	1 (<1)	3 (<1)
Skin benign neoplasm	1 (<1)	0	4 (<1)
Skin discoloration	1 (<1)	0	1 (<1)
Alopecia	0	1 (<1)	2 (<1)
Skin hypertrophy	0	1 (<1)	0
Acne	0	0	3 (<1)
Nail disorder	0	0	2 (<1)
Hair disorder	0	0	1 (<1)
Allergic reactions	**10 (2)**	**3 (<1)**	**35 (4)**
Allergic reaction	10 (2)	3 (<1)	35 (4)

[a] Preferred terms reported for case 1 (EM/ SJS).
[b] Preferred terms reported for case 2 (vesiculobullous rash, rash; reported as EM post database lock).
[c] Preferred terms reported for case 3 (maculopapular rash, urticaria, pruritus).
SJS=Stevens-Johnson Syndrome; EM=erythema multiforme; TEN=toxic epidermal necrolysis.
NOTE: Patients could be counted in more than 1 category.

Using this broad search of the adverse events database and on the basis of treatment discontinuation associated with the adverse event, 8 potential cases of interest (in addition to the 3 cases described above) were identified in all ADHD studies in children and adolescents (N=933). These were patients who discontinued treatment with modafinil due to an adverse event of rash or hypersensitivity (Table 18).

Table 18: Patients Who Withdrew From the Study Due to Adverse Events Potentially Associated With Skin Rash and/or Hypersensitivity Reaction

Study number (Patient number)	Age (y)/ sex	Adverse event (verbatim)	Day of onset[a]	Modafinil dosage (mg/day)[b]	Duration of event (days)	Outcome
207 (206)	7/M	asthma	41	100	5	Resolved
207 (411)	10/M	itchy rash on forehead and scalp	22	100	15	Resolved
213 (18001)	6/M	rash	9	300	15	Resolved
213 (08012)	9/M	rash	12	200/100[c]	4	Resolved
213 (24004)	8/F	rash	14	100/200[d]	4	Resolved
310 (021191)	9/M	acute asthma attack	8	340	<1	Resolved
312 (029015/029169)[e]	7/M	rash	34	340	6	Resolved
312 (056003/056180)[e]	9/M	general body hives, swollen eyes	13	340	11	Resolved

[a] Relative to first day of treatment.
[b] Dosage at day of onset.
[c] Patient was randomized to 200 mg in the morning and 100 mg in the afternoon.
[d] Patient was randomized to 100 mg in the morning and 200 mg in the afternoon
[e] Patient number in double-blind study/patient number in open-label study.

Six of the above patients had rash leading to withdrawal from the study. These cases were reviewed and additional information was evaluated. On the basis of source documents and other available information, it was established that these cases were urticarial rash, rash, itchy rash on forehead and scalp, and fifth disease. Of the other 2 patients with rash, 1 had a mild pruritic macular rash that recurred on rechallenge and the other had a severe rash that was not further described. Additional information about patient 021191 indicates that the patient had dyspnea, wheezing, and erythematous face (with temporary respiratory arrest) and the asthma attack was considered serious. None of the other cases was considered serious or required intensive intervention and all resolved without sequelae.

As a result of the above-described case search and review of cases, it was concluded that other than the 3 cases described in section 7.3.1.2, no additional cases of a potential SCAR were reported in the ADHD clinical program in children and adolescents.

7.3.1.4 Non-urticarial Rash

In spite of existing scientific controversy in respect to relationship between risk for SCARs and incidence of non-urticarial rash, the analysis of non-urticarial rash reports in clinical studies with modafinil was considered important for comprehensive evaluation of the risks associated with serious skin reactions. To that end, Cephalon has undertaken an additional review of all verbatim terms and preferred terms in the modafinil clinical studies database of adverse events seeking to identify cases of non-urticarial rash of a potentially drug-induced nature. Two external consulting dermatologists reviewed all verbatim terms and preferred terms and agreed on a case definition for "non-urticarial

rash of a potentially drug-induced nature." The category of adverse events of non-urticarial rash included all verbatim terms within the following preferred terms:

- erythema multiforme
- Stevens-Johnson syndrome
- maculopapular rash
- photosensitivity reaction
- exfoliative dermatitis
- lichenoid dermatitis
- rash (with the exception of verbatim terms of heat rash, scabies, Staph dermatitis, and folliculitis)
- vesiculobullous rash (with the exception of verbatim terms of herpetic rash)

Additional verbatim terms not coding to these preferred terms were the following, classified as "other":

- allergic skin reaction
- allergic reaction in neck
- fifth disease
- viral rash
- itching of rash
- redness and itching around eye
- dry skin with breakouts

On the basis of this methodology, the incidence of non-urticarial rash was calculated across different clinical programs and studies (Table 19).

Table 19: Non-urticarial Rash by Program, Study Type and Treatment

			Number (%) of patients with non-urticarial rash		
Type of study	**Treatment**	**Number of patients**	**All**	**Severe**	**Withdrew [a]**
Pediatric ADHD DB	Modafinil	664	32 (5)	4 (<1)	7 (1)
	Placebo	308	10 (3)	0	0
Pediatric DB	Modafinil	856	35 (4)	5 (<1)	7 (<1)
	Placebo	388	11 (3)	0	0
Adult DB	Modafinil	2337	34 (1)	0	5 (<1)
	Placebo	1217	15 (1)	0	1 (<1)
Pediatric DB and OL	Modafinil	1622	88 (5)	8 (<1)	9 (<1)
Adult DB and OL	Modafinil	4090	88 (2)	1 (<1)	10 (<1)

[a] Includes the 3 cases described in section 7.3.1.2.
ADHD=attention-deficit/hyperactivity disorder; DB=double-blind randomized clinical study; OL=open-label.

In the placebo-controlled clinical studies in children and adolescents with ADHD, the overall incidence of non-urticarial rash was 5% (32 of 664 patients) in the modafinil treatment group and 3% (10 of 308 patients) in the placebo treatment group. A similar small increase in the modafinil group when compared with the placebo treatment group was observed for all placebo-controlled studies in children and adolescents, regardless of indication (4% vs 3% for modafinil and placebo groups, respectively). In contrast, no treatment differences in the incidence of non-urticarial rash were observed in the placebo-controlled studies in adults (1% in both the modafinil and placebo groups). The higher incidence of non-urticarial rash seen in children compared to that seen in adults may be due to a higher incidence of skin-related conditions in the pediatric population in general, as reflected by the higher incidence of rash in the children and adolescents treated with placebo compared to adults treated with placebo. The slightly higher incidence of non-urticarial rash seen in all studies (5%) compared to the double-blind studies (adult and pediatric) (4%) is likely due to the longer observation periods associated with the open-label extension studies.

Additional review of non-urticarial rash in relation to various patient and treatment parameters is presented in Table 20. Data from the placebo-controlled clinical studies in children and adolescents with ADHD were used in this review. The following comparisons were noted:

- There were no differences between the treatment groups (modafinil vs placebo) for mean age and mean weight.
- There was a higher proportion of boys in the placebo treatment group than in the modafinil treatment group and a higher proportion of white patients in the modafinil treatment group than in the placebo treatment group.
- Mean, modal, and median doses of modafinil closely clustered near the mid-range for daily dose.
- There was no meaningful difference in the mean times to onset between the modafinil and placebo treatment groups.

Table 20: Patient Demographics and Treatment Parameters in Patients Experiencing Non-urticarial Rash in Placebo-Controlled Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

Variable	Modafinil (N=664)	Placebo (N=308)
Patients with non-urticarial rash	**32 (5)**	**10 (3)**
Age (years)		
Mean	8.9	8.9
Min, max	6, 15	6, 13
Weight (kg)		
Mean	35	35
Range	22-68	24-51
Sex, n (%)		
Boys	19 (59)	9 (90)
Girls	13 (41)	1 (10)
Race n (%)		
White	26 (81)	6 (60)
Black	2 (6)	1 (10)
Dose (mg)		
Median	300	—
Mode	255	—
Mean	283	—
Min, max	100, 425	—
Duration of exposure (days)		
Mean	42	39
Min, max	13, 68	21, 63

To further explore the association between modafinil dose and occurrence of non-urticarial rash, a matched control dataset was constructed using the data from the 4 placebo-controlled parallel-group studies in children and adolescents with ADHD (studies 213, 309, 310, and 311). The only remaining placebo-controlled study in this patient population (study 207) was not included in this analysis because of its crossover design. A matched cohort was generated by creating 3 risk sets and matching each of the identified 39 cases of non-urticarial rash with 3 other cases who did not develop such rash. The matching was conducted on the basis of the following:

- study protocol
- weight stratum (<30 kg or ≥30 kg)
- time on study at least as long as the time of onset of the non-urticarial rash event

For example, a case of non-urticarial rash occurring at 1 week would be matched to 3 randomly selected controls that were in the study for at least 1 week, in the same study and from the same weight stratum.

An analysis was conducted using this dataset. Conditional logistic regression models were used to assess the effect of several measures of dose, one at a time. The dose measures included the following:

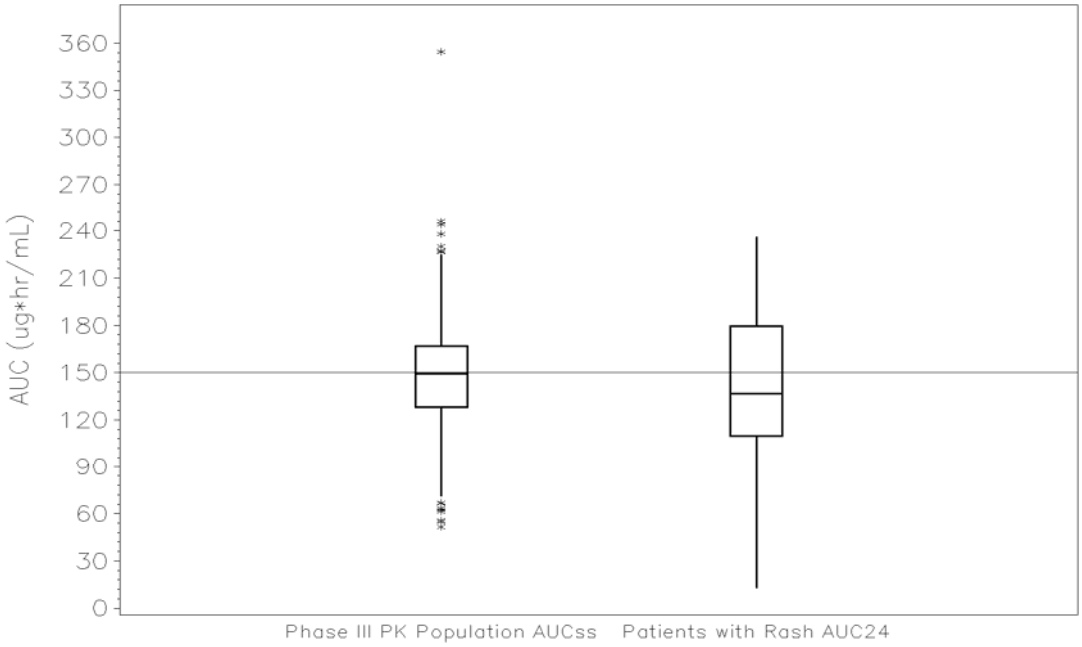
- dose (mg) at onset of the event
- dose mg/kg at the onset of event
- cumulative mg
- cumulative mg/kg
- max dose in mg in the 1 week prior
- max dose in mg/kg in the 1 week prior
- max dose in mg in the 2 weeks prior
- max dose in mg/kg in the 2 weeks prior
- average dose in mg
- average dose in mg/kg
- average dose in mg over the 2 weeks prior
- average dose in mg/kg over the 2 weeks prior

The analyses were repeated treating the dose measures as continuous and as categorical variables defined by the quartiles of the distribution. None of the analyses showed evidence of a statistically significant relationship between any measure of dose and the incidence of non-urticarial rash. The confidence intervals for all odds ratios overlapped 1.

An additional analysis to assess the relationship between modafinil systemic exposure and incidence of non-urticarial rash was conducted. Systemic exposure (assessed by area under the curve [AUC] and peak plasma concentration [Cmax]) was calculated using the Bayesian approach to reconstruct individual profiles for patients with measured plasma concentrations.

Figure 8 provides a graphic illustration of the distribution of the modafinil AUC_{-24} (on the day of the event) for patients experiencing non-urticarial rash. Also presented is the calculated distribution of AUC at steady state (AUCss) (at the endpoint visit or early termination) for patients from the 3 Phase 3 placebo-controlled studies (studies 309, 310, and 311) included in the matched control data set.

Figure 8: Distributions of Bayesian-Based Estimates of Modafinil AUC_{24} for Patients With Non-urticarial Rash (at the Event Onset Date) and Modafinil AUC_{ss} for All Modafinil-Treated Patients in the Phase 3 Placebo-Controlled Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (at the Endpoint Visit or Early Termination)



AUCss=area under the plasma concentration time curve to steady state; AUC_{24}=area under the plasma concentration time curve from zero to 24 hours.

Consistent with the dose-relationship analyses, there was no indication of an association between modafinil systemic exposure and the incidence of non-urticarial rash.

On average, higher concentrations of 1 modafinil metabolite, modafinil sulfone, are observed in children and adolescents compared to adults. In order to explore whether this difference could play a role in the higher incidence of non-urticarial rash in children/adolescents, the concentrations of modafinil sulfone in plasma of children and adolescents with ADHD who reported rash were examined relative to those in the other patients. A review of these data produced no evidence of such a correlation since the incidence of rash did not increase with increasing concentrations of the sulfone metabolite. In addition, none of the 3 patients with serious cases of rash had high levels of modafinil sulfone; the concentrations in all 3 were well within the adult norm (ie, <10 μg/mL).

7.3.1.5 Skin Adverse Events Indicative of Hypersensitivity Reactions

In addition to non-urticarial rash, data from the placebo-controlled ADHD studies in children and adolescents were also reviewed for adverse events indicative of possible hypersensitivity reactions. These included review of adverse events coded as urticaria, angioedema and anaphylaxis.

Urticaria was reported in 3 (<1%) of 664 patients in the modafinil group and no patients in the placebo group. There were no reports of angioedema or anaphylaxis. Two of the 3 urticaria cases were considered mild and unlikely or not related to modafinil treatment and did not result in treatment discontinuation. The third event was considered moderate and probably related to modafinil treatment. For the third case, the event occurred on treatment day 15 and resulted in discontinuation of study drug. On the basis of these small numbers, a causal relationship to modafinil treatment cannot be established.

There was 1 case of a severe anaphylactoid reaction in the open-label studies, which was attributed to a bee sting.

7.3.1.6 Postmarketing Reports of SCARs

A total of 5 spontaneous reports of EM, SJS, or TEN have been identified in Cephalon's worldwide postmarketing database for modafinil, with an estimated exposure of 673,000 patient-treatment years as of 31 August 2005. Postmarketing reporting rates for SCARs expressed as a function of estimated number of patients treated is presented in Table 21.

In children and adolescents, it is estimated that the overall exposure in individuals aged less than 18 years approximate 27,000 patient-treatment years. With this exposure, no postmarketing cases of EM, SJS, or TEN have been reported in patients less than 18 years of age.

Table 21: SCARs Reporting Rates Based on Estimated Number of Patients Treated by Year

	Year						
	1999	2000	2001	2002	2003	2004	2005
SCAR Reports (n)	0	0	0	1	2	0	2
Patients treated (IMS estimate) (n)	44,067	132,422	244,014	297,881	384,140	652,282	734,736
Reporting rate per 100,000 patients	0	0	0	0.336	0.521	0	0.272

The 5 patients with postmarketing reports of SCARs are described in Table 22.

Table 22: Postmarketing Reports of Serious Skin Adverse Events

Report number	Age (y)/ sex	Adverse event (verbatim)	Number of days on treatment	Modafinil dosage (mg/day)	Duration of event (days)	Intervention/ outcome	Comments
US011480	68/ female	SJS	14	200	~13	Discontinued/ resolved	Concomitant medications included fosinopril sodium, raloxifene hydrochloride, ezetimibe, and dextroamphetamine sulfate; all have been associated with skin reactions.
US016653	42/ female	TEN/SJS	14	100	Unknown	Discontinued/ unknown	Concomitant medications included risperidone and escitalopram oxalate (both known to be associated with SJS-spectrum disorders). Rash onset in this case was reported to occur after approximately 2 weeks of modafinil treatment; while risperidone and escitalopram treatment duration were approximately 11 weeks.
US016623	28/ female	EM/SJS	16[a]	50 to 100	Unknown	Discontinued/ unknown	Direct report to FDA (FOI listing): insufficient information. Concurrent systemic lupus with skin and joint manifestations x 3 years
US016624	27 /female	SJS	1	200	Unknown	Discontinued/ unknown	Direct report to FDA (FOI listing): insufficient information. Event occurred on same day as drug initiation.
US016625	54/ unknown	TEN/SJS	Unknown	Unknown	Unknown	Unknown/ unknown	Direct report to FDA (FOI listing): insufficient information. This fatal case was associated with a subarachnoid hemorrhage, postoperative complications and sepsis. Including modafinil, a total of 16 concomitant medications were identified, including phenytoin and phenobarbital, both known to be associated with SJS-spectrum disorders.

[a] Drug discontinued on day 12.

SJS=Stevens-Johnson Syndrome; EM=erythema multiforme; TEN=toxic epidermal necrolysis; FOI=Freedom of Information.

As it was done for the cases of interest in clinical studies, the expert dermatology panel has also reviewed independently the above 5 postmarketing cases using same methodology described earlier. Although skin biopsy results were reported for 4 cases, no photographs of skin lesions were available for review.

The following are the panel opinions by case:

- SJS (US011480): Probably correct (3)
- SJS/TEN (US016653): Definitely correct (3)
- EM/SJS (US016623): Probably correct (1), possibly correct (2)
- SJS (US016624): Possibly correct (2), unlikely correct (1)
- TEN/SJS (US016625): Possibly correct (2), unlikely correct (1)

As a part of the continuous evaluation of postmarketing safety reports, a proportional reporting analysis has been conducted using the FDA's legacy Spontaneous Reporting System and the current Adverse Event Reporting System (AERS) Freedom of Information (FOI) databases as of 31 March 2005. A total of 5 "signaling runs" were conducted for reports of EM, SJS, TEN, SJS or TEN, and EM or SJS or TEN. Of these 5 signaling runs, only 1 met Evans criteria for signaling significance (SJS run) and was considered a low-strength signal. The remaining signaling runs did not yield results meeting the Evans criteria for signaling significance.

On the basis of the SCARs pharmacovigilance reports received by Cephalon and subsequent evaluation, Cephalon introduced necessary labeling changes for modafinil in December 2004 to reflect concerns related to serious skin reactions. Specifically, dermatologic reactions (rare reports of serious skin reactions including suspected cases of both EM and SJS) were added to the Adverse Reactions, Postmarketing Reports section of the product labeling.

7.3.1.7 Conclusions

A comprehensive review of non-urticarial rash and hypersensitivity reactions in clinical studies with modafinil has been conducted. A small increase in incidence of rash in children and adolescents was observed in the modafinil treatment group compared to the placebo treatment group. The observed increase was not dependent on dose or exposure. Adult clinical data did not reveal any imbalance in respect to frequency of rash between modafinil- and placebo-treated patients.

Two cases in the clinical studies were consistent with possible diagnosis of SJS. Although possible confounding factors have been implicated and alternative etiologies suggested, possible association with modafinil treatment could not be excluded. In both cases, however, the event did not require hospitalization and was resolved following discontinuation of treatment.

In light of the level of diagnostic and etiological uncertainties, the serious nature of the adverse events reported warrant communication of the potential risk through appropriate labeling.

7.3.2 Psychiatric Adverse Events

7.3.2.1 Background

In September 2005, the FDA requested a review of psychiatric adverse events, categorized as psychosis/mania, suicidal ideation, aggression and violent behavior, or other serious psychiatric adverse events, be conducted for all approved ADHD drugs and for those drugs pending approval. To comply with this request, psychiatric adverse events reported in clinical studies with modafinil treatment in children and adolescents with ADHD were manually reviewed and categorized into these areas of interest. Verbatim terms assigned by the study investigators and additional information available in individual patient narratives were used for this review. In addition, a search of the verbatim and preferred terms in the database was conducted for any substrings that may include or reflect the events of interest. The psychiatric events identified and classified through this process were summarized by category. In addition, a search of the verbatim and preferred terms in the adverse event database for all children and adolescents with narcolepsy or OSAHS who were treated with modafinil in any clinical study was conducted. The results of this manual review of the data from patients in modafinil clinical studies are presented below.

7.3.2.2 Clinical Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

In the double-blind clinical studies conducted in children and adolescents with ADHD (see Table 4), psychiatric adverse events categorized as psychosis/mania, suicidal ideation, or aggression and violent behavior were reported for a total of 20 patients (15 [2.3%] modafinil-treated and 5 [1.6%] placebo-treated patients) (Table 23). During open-label treatment, psychiatric adverse events categorized as psychosis/mania, suicidal ideation, or aggression were reported for 18 (2.3%) of 799 patients. In addition, during these studies, miscellaneous nonserious psychiatric adverse events were reported for 204 (31%) modafinil-treated patients and 36 (12%) placebo-treated patients in the double-blind studies and 231 (29%) of patients in the open-label studies. No serious events categorized in the group of serious miscellaneous psychiatric adverse events were reported in the double-blind or open-label treatment periods. The frequency of the event aggression and violent behavior was similar across all treatment groups and is not discussed further.

Table 23: Psychiatric Adverse Events Occurring During the Double-Blind and Open-Label Treatment Periods in All Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

	Number (%) of patients		
	During double-blind treatment		During open-label treatment[a]
Category	**Modafinil (N=664)**	**Placebo (N=308)**	**Modafinil (N=799)**
Patients with at least 1 psychiatric adverse event categorized as psychosis/mania, suicidal ideation, aggression and violent behavior	**15 (2.3)**	**5 (1.6)**	**18 (2.3)**
Psychosis/mania	2 (0.3)	0	3 (0.4)
Suicidal ideation	4 (0.6)	0	1 (0.1)
Aggression and violent behavior	9 (1.4)	5 (1.6)	14 (1.8)
Serious miscellaneous psychiatric adverse events	0	0	0

[a] Includes only patients receiving open-label modafinil treatment and cases with onset during open-label treatment.
NOTE: Patients are counted only once in each preferred term category.

Individual patient adverse events categorized as psychosis/mania and suicidal ideation are presented by patient in Table 24.

Table 24: Children and Adolescents With Attention-Deficit/Hyperactivity Disorder With Adverse Events Categorized as Psychosis/Mania or Suicidal Ideation

Category Study_Patient number	Age (y)/ Sex	Adverse event (verbatim)	Number of days on treatment	Modafinil dosage (mg/day)	Duration of event (days)	Intervention/outcome	History
Psychosis/mania							
213_15010	6/boy	Hallucinations	6	300	1	None/continued in study	No remarkable history
310_040629	8/boy	Hallucinations	11	425	5	None/withdrawn from study	Oppositional defiant disorder
213_11002	8/boy	Psychotic disorder, aggravated	19	300	7	Hospitalized, treated with risperidone and nortriptyline; withdrawn from study	Hallucinations, suicide attempt, psychotic disorder, possible fetal alcohol syndrome
312_059271	7/boy	Ideas of referential control	59	340	Ongoing	None/continued in study	Oppositional defiant disorder, conduct disorder
207_410	8/boy	Formication	18	300	2	None/withdrawn from study	No remarkable history
Suicidal ideation							
207_405	7/boy	Suicidal statement	22	200	1	None/continued in study	No remarkable history
207_411	10/boy	Suicidal statement	8	200	1	None/continued in study	No remarkable history
310_040179	8/girl	Suicide threat	8	340	2	None/withdrawn from study	Oppositional defiant disorder
311_053317	8/boy	Voiced vague suicidal statement	13	255	1	None/continued in study	No remarkable history
		Vague suicidal statement	21	255	1	None/continued in study	
312_014016	6/girl	Abnormal behavior	93[a]	340	97	Hospitalization, depressive disorder and oppositional defiant disorder diagnosed and prescribed amphetamine/dextroamphetamine, desmopressin, aripiprazole, and trazodone/withdrawn from study	Patient had history of running away, mood swings, setting fires, occasionally trying to hurt self, and family history of depression and maternal suicide attempts

[a] Patient stopped taking study drug on day 91.

7.3.2.3 Clinical Studies in Children and Adolescents With Narcolepsy or Obstructive Sleep Apnea/Hypopnea Syndrome

In the placebo-controlled clinical studies conducted in children and adolescents with excessive sleepiness associated with narcolepsy or OSAHS (see Table 4), psychiatric adverse events categorized as aggression and violent behavior were reported for 2 girls treated with modafinil (400 mg/day) and for no placebo-treated patients (see Table 25). An adverse event of subjective increase in behavior outbursts (temper tantrums) was reported for one 8-year-old girl and an adverse event of anger was reported for one 13-year-old girl. No psychiatric adverse events, categorized as psychosis/mania or suicidal ideation, were reported during the double-blind treatment period.

During open-label treatment, psychiatric adverse events were reported for 11 (4%) patients, categorized as psychosis/mania for 1 patient and aggression for 10 patients (Table 25). There were no reports of suicidal ideation or of serious miscellaneous psychiatric adverse events the from open-label studies. A 17-year-old girl with no reported history of hallucinations experienced hallucinations during open-label treatment on 2 occasions (study days 21 and 33). Each event resolved the same day without residual effect and the patient continued in the study. She was taking 400 mg/day of modafinil. A total of 10 (4%) patients (6 with narcolepsy and 4 with OSAHS) treated with modafinil had nonserious psychiatric adverse events coded by COSTART as hostility. None of these patients had a reported prior medical history of hostility. Of the 8 patients continuing in the study, 3 had events of hostility that continued and 5 patients had events that resolved with no residual effect without a dose interruption or change in study drug dose. Two patients were withdrawn from study due to adverse events coded to hostility (1 severe and 1 moderate) and the dosage for 1 patient was decreased.

Table 25: Psychiatric Adverse Events Occurring During the Double-Blind and Open-Label Treatment Periods in All Studies in Children and Adolescents With Narcolepsy or Obstructive Sleep Apnea/Hypopnea Syndrome

	Number (%) of patients		
	During double-blind treatment		During open-label treatment[b]
Category	**Modafinil (N=144)**	**Placebo (N=52)**	**Modafinil (N=266)**
Patients with at least 1 psychiatric adverse event categorized as psychosis/mania, suicidal ideation, aggression and violent behavior	**2 (1)**	**0**	**11 (4)**
Psychosis/mania	0	0	1 (<1)
Suicidal ideation	0	0	0
Aggression and violent behavior[a]	2 (1)	0	10 (4)
Serious miscellaneous psychiatric adverse events	0	0	0

[a] One patient had adverse events categorized as aggression and violent behavior during both double-blind and open-label treatment with modafinil.
[b] Includes only patients during open-label modafinil treatment and cases with onset in open-label.

Additional events, coded by COSTART as hallucinations, which occurred in 1 patient during treatment with modafinil during double-blind treatment and in a second patient during both double-blind and open-label treatment with modafinil, were considered a symptom of the pre-existing sleep disorder and are not tabulated below. Both patients had a history of hypnagogic hallucinations.

7.3.2.4 Ongoing Studies in Children and Adolescents

Two patients in ongoing studies with modafinil treatment in children and adolescents (see Table 4) had serious adverse events of suicidality. In addition, suicidal ideation was reported as a symptom of a serious adverse event of depression in 1 patient in an ongoing study (Table 26).

Table 26: Children and Adolescents in Ongoing Studies (Studies 312, 3029, and 3044) With Adverse Events Categorized as Psychosis/Mania or Suicidal Ideation

Category Study_Patient number	Age (y)/ Sex	Adverse event (verbatim)	Number of days on treatment	Modafinil dosage, mg/day	Duration of event (days)	Intervention/outcome	History
Psychosis/mania							
No events	—	—	—	—	—	—	—
Suicidal ideation							
312_003102	15/girl	Situational depression	Unknown	425	Ongoing	None/continuing in study	Unknown
312_016001	15/girl	Suicidal ideation	219	425	8	Hospitalization, treated with escitalopram, oxcarbazepine, and modafinil/withdrawn from study	Depressive disorder, NOS
3029_026701	10/girl	Suicidal gesture	75	400	1	None/continuing in study	Unknown

NOTE: Only demographic and adverse event data obtained for patients at this time.

7.3.2.5 Summary of Psychiatric Adverse Events Occurring in Children and Adolescents in Clinical Studies

The review of the double-blind studies in children and adolescents with ADHD indicates that psychiatric adverse events classified in the category signs and/or symptoms of psychosis or mania were reported in 2 (0.3%) 664 modafinil-treated patients and no placebo-treated patients, while adverse events classified in the category of suicidal ideation and behavior occurred in 4 (0.6%) of modafinil-treated patients and no placebo-treated patients. The events classified in the categories of aggression and violent behavior were reported in 9 (1%) modafinil-treated patients and 5 (2%) of 308 placebo-treated patients. There were no reported cases of serious adverse events within the category of miscellaneous or other psychiatric adverse events. Among modafinil-treated patients, 204 (31%) patients experienced nonserious miscellaneous or other psychiatric events as compared to 36 (12%) placebo-treated patients. The observed higher rate in the modafinil treatment group is largely explained by a higher incidence of insomnia (preferred term), which was present in 142 (21%) modafinil-treated patients compared to 10 (3%) placebo-treated patients.

During open-label modafinil treatment, a total of 799 children and adolescents with ADHD were exposed to long-term modafinil treatment for an average of 169 days and a total exposure of 401 patient-treatment years. During open-label treatment, 2 (0.3%) additional adverse events classified under signs and/or symptoms of psychosis or mania and 14 (2%) additional adverse events classified as aggression and violent behavior were reported. No additional events classified under suicidal ideation and behavior or serious adverse events classified as miscellaneous or other psychiatric events were reported during open-label treatment.

A review of the data from children and adolescents with narcolepsy or OSAHS, demonstrated that the most common psychiatric adverse event of interest reported was categorized as aggression and violent behavior. In the double-blind studies, aggression and violent behavior were infrequent and was reported in 2 (1%) of 144 modafinil-treated patients and in no placebo-treated patients. Both events occurred in girls receiving 400 mg of modafinil daily. There were no reported events classified under psychosis/mania, suicidal ideation, or serious adverse events within the category of miscellaneous or other psychiatric adverse events.

During open-label treatment, a total of 266 children and adolescents with narcolepsy or OSAHS were exposed to modafinil treatment. One (<1%) additional adverse event classified under signs and/or symptoms of psychosis/mania and 10 (4%) additional adverse events classified as aggression and violent behavior were reported during open-label treatment. No additional events classified under suicidal ideation and behavior or serious adverse events classified as miscellaneous or other psychiatric events were reported during open-label treatment.

Psychiatric comorbidities are common in children with ADHD (Biederman et al 1991) with or without an apparent association with pharmacologic treatment. In 1999, approximately 20% to 25% of all students in grades 9 through 12 reported suicidal

ideation and attempts in the United States (National Center for Health Statistics 2000). The above-presented data from clinical studies with modafinil in children and adolescents with ADHD is not inconsistent with the literature and does not suggest significant overall increase in incidence of psychiatric adverse events during treatment with modafinil. However, the adverse events categorized as signs and/or symptoms of psychosis or mania and/or suicidal ideation and behavior were reported only in the modafinil-treated patients. In approximately half of these patients, a comorbid psychiatric disorder was also reported. Likewise, an association with hyperactivity, aggressive behavior, and nocturnal hypoxemia is recognized in pediatric OSAHS populations and improves when sleep hypoxemia is corrected (Owens et al 1998); however, these adverse events were seen only in the modafinil treatment group.

Considering the relatively small number of cases in both development programs, no clear association with age, sex, dose, duration of exposure, and presence/absence of precipitating psychosocial factors could be established. However, it should be noted that in all but 1 of the reported cases of suicidal ideation, aggressive, or psychotic symptoms in the ADHD program, patients were less than 12 years of age.

7.3.2.6 Postmarketing Surveillance

(a) Postmarketing Reports of Psychiatric Adverse Events in Children and Adolescents

Searches were performed using the psychiatric events of interest specifically included in the FDA letter (dated 14 September 2005) and as additional substrings (generated by Cephalon Global Product Safety Department) that may include or reflect the events of interest. The search strategy included identifying spontaneous (health professional and consumer reports) and biomedical literature cases, received between 1 January 2000 and 30 June 2005, using both the MedDRA 8.0 preferred terms and the verbatim terms that pertained to the following categories: signs and/or symptoms of psychosis/mania, suicidal ideation and behavior, aggression and violent behavior, and miscellaneous serious psychiatric events.

A total of 80 individual ADR reports associated with modafinil were received for pediatric patients (<18 years of age) during the time interval of this review. Of these 80 reports, 7 were relevant to the events of interest as follows (4 psychosis/mania, 1 suicidality, 2 aggression/violence, 0 miscellaneous serious psychiatric events) (Table 27).

Of the 4 reports relevant to psychosis or mania, 1 report (case US014704) appears to represent hypnagogic or hypnopompic hallucinations, which are commonly seen in narcolepsy and do not represent a psychotic state. Another case (case US010820) is confounded by an underlying epileptic disorder; focal epilepsy is known to cause visual hallucinations in some patients and epilepsy in general has been associated with an increased risk of psychiatric disorders.

The 1 report of suicidality (suicide attempt) is confounded by both the underlying disorder (depression) and the abrupt discontinuation of duloxetine hydrochloride 1 to 2 weeks before the event (abrupt withdrawal of SSRIs has been associated with dysphoric

mood and suicidality). Moreover, this patient was not taking modafinil prior to the attempt. Accordingly, while modafinil treatment likely contributed to the signs and symptoms of the multidrug overdose, it did not contribute to the suicidal ideation. Modafinil therapy was instituted, after recovery, without further suicidality reported.

Two reports relevant to aggression/violent behavior were retrieved. Both were nonserious in nature and resolved on discontinuation of treatment with modafinil. One case (case US010401) was confounded by a history of bipolar disorder with psychotic features, and in the second case (case US012406) there was a history of sensitivity to other traditional CNS stimulants.

Of the 7 cases with psychiatric events in children and adolescents, only the multidrug suicide attempt and 2 cases with signs and symptoms of psychosis/mania were reported as serious. The other 4 cases were reported as nonserious.

Table 27: Postmarketing Reports of Psychiatric Adverse Events

Category Report number	Age (y)/ Sex	Adverse event (verbatim)	Number of days on treatment	Modafinil dosage (mg/day)	Intervention/ outcome	History
Psychosis/mania						
US010820	11/boy	Visual and auditory hallucinations	<10 days	25 to 100[a]	Discontinuation/ resolved	Epilepsy treated with valproic acid
US008182	~6/boy	Visual hallucination	1	100	Discontinuation/ resolved	Experienced tics while taking amphetamines and methylphenidate hydrochloride
US013271	17/boy	Flight of ideas, sexual excitation, and increased irritability[b]	Unknown	400	Discontinuation/ resolved	Symptoms attributed to possible lowering of mania threshold by starting and stopping psychostimulant therapy in previous 3 years
US014704	6/girl	Awakening at night crying and screaming about bugs biting	Unknown	10	Discontinuation/ resolved	Another episode occurred while taking an over-the-counter cold product containing pseudoephedrine and several episodes in the past under different circumstances.
Suicidal ideation						
US015049	14/girl	Attempted multidrug overdose	Unknown	1000[c]	Supportive/ continued with no recurrence	Discontinued duloxetine hydrochloride treatment 1 to 2 weeks prior
Aggression/violent behavior						
US010401	13/boy	Agitation, easily angered, felt terrible	Unknown	100	None/continuing	Bipolar disorder with psychotic features: concomitant treatment divalproex sodium, topiramate, and risperidone
US012406	13/girl	Anger, jittery feeling, achiness, loss of appetite	Unknown	200	Discontinuation/ decreased dosage	Sensitivity to other stimulants

[a] Modafinil treatment was interrupted, retitrated, interrupted again, then restarted.
[b] At restart of modafinil, insomnia, logorrhea, tachycardia, psychomotor agitation, and visual/auditory hallucinations with persecution mania occurred.
[c] First dose of modafinil was part of the multidrug overdose; after recovery, modafinil treatment was started at 200 mg/day.

(b) Product Labeling Changes Due to Postmarketing Reports of Psychiatric Adverse Events

On the basis of spontaneous reports of symptoms of mania and/or psychosis, the product labeling for modafinil was modified in October 2002 to include "symptoms of mania" and "symptoms of psychosis" in the section on Postmarketing Reports in the Adverse Reactions section. This addition to the labeling was made on the basis of 24 cases with reported symptoms of psychosis (2 cases in children 6 and 16 years of age) and 7 cases with reported symptoms of mania (1 case in a child 16 years of age).

7.3.2.7 Overall Summary of Psychiatric Adverse Events Evaluation

The results of this review show that the overall incidence for psychiatric events of interest is low. However, there is an imbalance of suicidal ideation and psychotic events in patients in the modafinil treatment group compared to patients in the placebo treatment group. Most of the events were short in duration, did not require treatment, and resolved while modafinil treatment continued. Due to the observed imbalance between the treatment groups, appropriate information should be included with the modafinil labeling.

7.3.3 Cardiovascular Evaluation

7.3.3.1 Overview

A thorough evaluation of cardiovascular data (pulse, blood pressure, and electrocardiography) collected in clinical studies of modafinil in children and adolescents has been undertaken because the occurrence of cardiovascular side effects would be a significant concern. In addition, a recent FDA Drug Safety and Risk Management Advisory Committee meeting was held to address such concerns; the committee suggested further studies that could be undertaken to assess cardiovascular effects of ADHD medications. With its basis in data from adults participating in modafinil clinical trials, the modafinil product labeling contains a precaution regarding the emergence of various cardiac symptoms (including chest pain and ECG changes) in patients with specific underlying cardiac disorders. The results of an overall evaluation of cardiovascular data for modafinil, which are presented below, show that treatment with modafinil was not associated with any untoward cardiovascular effects in children.

A series of in vivo nonclinical safety studies was conducted as part of the research and development of modafinil (see section 7.2.1). Overall, no safety concerns were identified in regard to adverse cardiovascular effects of modafinil in animal models.

Cardiovascular data included in this evaluation are presented from an individual Phase 1 study in children and adolescents with ADHD (24 modafinil-treated patients), the 3 double-blind, placebo-controlled Phase 3 studies in children and adolescents with ADHD (420 modafinil- and 213 placebo-treated patients), and from all (combined) Phase 1, 2, and 3 studies undertaken in ADHD, including the open-label extensions (933 modafinil-treated patients). Also presented are cardiovascular data from the clinical program in children and adolescents with excessive sleepiness associated with narcolepsy or OSAHS (270 modafinil-treated patients). It is important to note that only 1 child who

participated in a modafinil clinical study was treated with antihypertensive medication (ADHD study 312). Finally, cardiovascular-related adverse events identified in children from the postmarketing database (105 pediatric patients, all cases reported as of 31 December 2005) were reviewed and evaluated, and are presented in section 7.3.3.3.

7.3.3.2 Clinical Studies

(a) Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

In a single- and multiple-dose bioavailability study in children and adolescents with ADHD (study C1538d/113/BA/US), pulse, blood pressure, and ECG assessments included measurements throughout a 24-hour period after modafinil administration on study day 22, after multiple doses of 340 or 425 mg/kg. This included evaluations at the time of modafinil C_{max}.

In this study, which did not have a placebo control group, a gradual increase in mean pulse was observed, with a peak at approximately 6 hours postdose and a return to an approximate mean baseline value by 24 hours postdose. The highest mean pulse rate observed was 93 bpm (baseline ~78 bpm). Mean changes in systolic and diastolic blood pressure over the 24-hour observation period were small and no consistent pattern was evident. Mean changes from baseline in ECG interval measurements were small, with no clinically relevant changes observed. No patient had a QTc interval greater than 500 msec.

In the Phase 3 placebo-controlled studies in children and adolescents with ADHD (studies 309, 310, 311 [modafinil N=420, placebo N=213]), no differences in mean changes in vital signs measurements, for pulse and systolic and diastolic blood pressure, were observed between the modafinil and placebo treatment groups (Table 28).

Table 28: Vital Signs Values and Changes From Baseline to Endpoint by Treatment Group in Phase 3 Placebo-Controlled Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Safety Analysis Set)

		Phase 3 placebo-controlled studies			
		Modafinil (N=420)		Placebo (N=213)	
Vital signs variable	Statistic	Baseline	Change from baseline	Baseline	Change from baseline
Pulse (bpm)	n	420	416	213	212
	Mean	81.1	1.5	82.2	1.1
	SD	10.62	10.88	10.74	11.24
	Median	80.0	1.0	81.0	0.0
	Min, max	56.0, 110.0	–41.0, 36.0	53.0, 115.0	–28.0, 42.0
Sitting systolic BP (mm Hg)	n	420	416	213	212
	Mean	105.5	−1.2	104.9	−0.9
	SD	10.09	9.19	10.19	9.99
	Median	104.0	–1.0	102.0	0.0
	Min, max	80.0, 134.0	–31.0, 22.0	80.0, 133.0	–31.0, 35.0
Sitting diastolic BP (mm Hg)	n	420	416	213	212
	Mean	65.0	−0.6	65.2	-0.3
	SD	7.28	7.71	7.42	8.59
	Median	64.0	0.0	64.0	0.0
	Min, max	46.0, 82.0	–28.0, 22.0	46.0, 82.0	–24.0, 46.0

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

Changes in individual vital signs values were evaluated against a predefined set of criteria for clinical significance, with clinically significant changes (both increases and decreases) in pulse and systolic and diastolic blood pressure occurring infrequently (Table 29).

Table 29: Clinically Significant Abnormal Vital Signs Measurements by Treatment Group in Phase 3 Placebo-Controlled Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Safety Analysis Set)

		Number (%) of patients	
		Phase 3 double-blind, placebo-controlled studies	
Variable	Criteria	Modafinil (N=420)	Placebo (N=213)
Pulse	≥120 bpm and increase ≥15 bpm	6 (1)	2 (<1)
	≤50 bpm and decrease ≥15 bpm	1 (<1)	0
Sitting systolic BP	≥130 mm Hg and increase ≥20 mm Hg	9 (2)	1 (<1)
	≤80 mm Hg and decrease ≥20 mm Hg	5 (1)	2 (<1)
Sitting diastolic BP	≥85 mm Hg and increase ≥15 mm Hg	5 (1)	1 (<1)
	≤50 mm Hg and decrease ≥15 mm Hg	19 (5)	9 (4)

bpm=beats per minute; BP=blood pressure.

In these studies, data from those patients who had at least 1 clinically significant pulse or blood pressure value were evaluated to assess whether these changes occurred frequently or were isolated findings. Among the patients with clinically significant increases in vital signs measurements, few had more than 1 clinically significant value for pulse and/or blood pressure during treatment (Table 30).

Table 30: Clinically Significant Increases in Vital Signs Measurements by Treatment Group in Phase 3 Placebo-Controlled Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Patients With More Than 1 Significant Value) (Safety Analysis Set)

		Number (%) of patients	
		Phase 3 double-blind, placebo-controlled studies	
Variable	**Criteria**	**Modafinil (N=420)**	**Placebo (N=213)**
Pulse	≥120 bpm and increase ≥15 bpm	1 (<1)	0
Sitting systolic BP	≥130 mm Hg and increase ≥20 mm Hg	2 (<1)	0
Sitting diastolic BP	≥85 mm Hg and increase ≥15 mm Hg	1 (<1)	0

bpm=beats per minute; BP=blood pressure.

In Phase 3 placebo-controlled studies in children and adolescents with ADHD (modafinil N=420, placebo N=213), there were no clinically meaningful differences between the modafinil treatment group and the placebo treatment group with respect to ECG interval durations when assessed as changes from baseline to endpoint. Changes were as follows: QTc interval (Fridericia) for modafinil 0-msec change and for placebo +1.5-msec change; QTc interval (Neuropharm) for modafinil +0.4-msec change and for placebo +1.1-msec change. The distribution of maximum changes from baseline and maximum values during treatment in corrected QT interval were similar for modafinil-treated patients and placebo-treated patients regardless of the correction formula used (ie, Bazett, Fridericia, or Neuropharm [calculation defined by the FDA Division of Neuropharmacological Drug Products]) (Table 31).

Table 31: Maximum Absolute Value and Change From Baseline in QTc Interval by Treatment Group in Phase 3 Placebo-Controlled Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Safety Analysis Set)

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

[a] Based on calculation defined by the FDA Division of Neuropharmacological Drug Products.
QTc=QT interval corrected for heart rate.

In the evaluation of cardiovascular data for these studies, cardiovascular adverse events, including serious adverse events and those leading to withdrawal, were reviewed. Tachycardia occurred in 5 (1%) of 420 modafinil-treated patients and 1 (0.5%) of 213 placebo-treated patients. Vasodilatation occurred in 2 (0.5%) modafinil-treated patients. Cardiovascular disorder, hypertension, palpitation, sinus bradycardia, and syncope occurred in 1 (0.2%) modafinil-treated patient each. These adverse events were not reported for any placebo-treated patients. Atrial septal defect, electrocardiogram abnormal, and QT interval prolonged were reported for 1 (0.5%) of placebo-treated patients. No serious cardiovascular adverse events were reported in either treatment

group. Two (0.5%) modafinil-treated patients and 1 (0.5%) placebo-treated patient withdrew from study due to tachycardia. For the 2 modafinil-treated patients, posttreatment pulse ranged from 90-96 bpm and 80-82 bpm. Posttreatment pulse for the placebo-treated patient was 78 bpm.

For a more complete evaluation of vital signs data, data from a Phase 2 placebo-controlled study (study 213) was pooled with those data from the Phase 3 placebo-controlled studies (studies 309, 310, and 311). Overall, this included 617 modafinil-treated patients and 264 placebo-treated patients. Changes in individual vital signs values were evaluated against a predefined set of criteria for clinical significance, with clinically significant changes in pulse and systolic and diastolic blood pressure occurring infrequently (Table 32).

Table 32: Clinically Significant Abnormal Vital Signs Measurements by Treatment Group in Phase 2 and 3 Placebo-Controlled Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Safety Analysis Set)

		Number (%) of patients	
		Phase 2 and 3 double-blind, placebo-controlled studies	
Variable	Criteria	Modafinil (N=617)	Placebo (N=264)
Pulse	≥120 bpm and increase ≥15 bpm	17 (3)	2 (<1)
	≤50 bpm and decrease ≥15 bpm	12 (2)	1 (<1)
Sitting systolic BP	≥130 mm Hg and increase ≥20 mm Hg	9 (1)	12 (<1)
	≤80 mm Hg and decrease ≥20 mm Hg	6 (<1)	2 (<1)
Sitting diastolic BP	≥85 mm Hg and increase ≥15 mm Hg	5 (<1)	1 (<1)
	≤50 mm Hg and decrease ≥15 mm Hg	29 (5)	10 (4)

bpm=beats per minute; BP=blood pressure.

In these studies, data from those patients who had at least 1 clinically significant pulse or blood pressure value were evaluated to assess whether these changes occurred frequently or were isolated findings. Among the patients with clinically significant increases in vital signs measurements, few had more than 1 clinically significant value for pulse and/or blood pressure during treatment (Table 33).

Table 33: Clinically Significant Increases in Vital Signs Measurements by Treatment Group in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder in Phase 2 and 3 Placebo-Controlled Studies (Patients With More Than 1 Significant Value) (Safety Analysis Set)

		Number (%) of patients	
		Phase 2 and 3 placebo-controlled studies	
Variable	Criteria	Modafinil (N=617)	Placebo (N=264)
Pulse	≥120 bpm and increase ≥15 bpm	1 (<1)	0
Sitting systolic BP	≥130 mm Hg and increase ≥20 mm Hg	2 (<1)	0
Sitting diastolic BP	≥85 mm Hg and increase ≥15 mm Hg	1 (<1)	0

bpm=beats per minute; BP=blood pressure.

For these ADHD studies with a placebo control group (studies 213, 309, 310, and 311 [modafinil N=617, placebo N=264]), mean (±SEM) changes from baseline for pulse (Figure 9) and systolic and diastolic (Figure 10) blood pressure are graphically displayed.

Figure 9: Mean (SEM) Changes in Pulse From Baseline to Endpoint by Treatment Group in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder in Phase 2 and 3 Placebo-Controlled Studies (Safety Analysis Set)

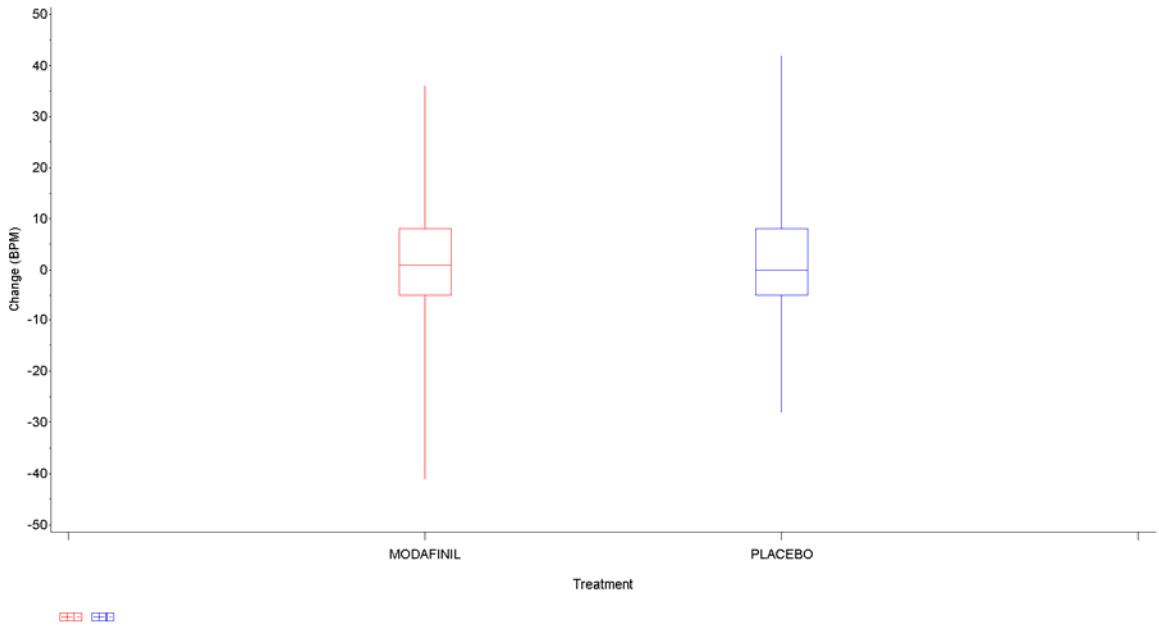
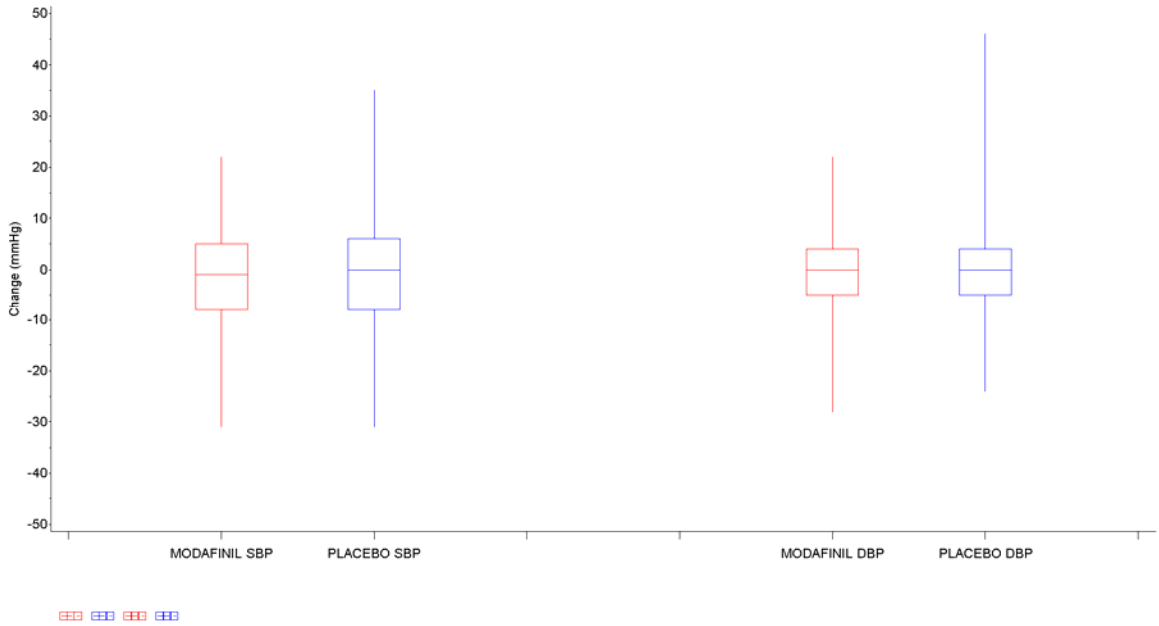


Figure 10: Mean (SEM) Changes in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) From Baseline to Endpoint by Treatment Group in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder in Phase 2 and 3 Placebo-Controlled Studies (Safety Analysis Set)



In all Phase 1, 2, and 3 studies of children and adolescents with ADHD, which included 933 modafinil-treated patients, mean changes from baseline were minimal in vital signs measurements, including pulse and systolic and diastolic blood pressure, for modafinil-treated patients (Table 34).

Table 34: Vital Signs Values and Changes From Baseline to Endpoint in All Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Safety Analysis Set)

		All studies	
		Modafinil (N=933)	
Vital signs variable	**Statistic**	**Baseline**	**Change from baseline[a]**
Pulse (bpm)	n	924	876
	Mean	82.1	1.6
	SD	10.83	12.02
	Median	81.0	1.5
	Min, max	56.0, 119.0	–39.0, 40.0
Sitting systolic BP (mm Hg)	n	925	876
	Mean	105.2	0.1
	SD	10.11	10.07
	Median	104.0	0.0
	Min, max	78.0, 134.0	-49.0, 34.0
Sitting diastolic BP (mm Hg)	n	925	876
	Mean	64.5	0.0
	SD	7.71	8.68
	Median	64.0	0.0
	Min, max	41.0, 86.0	-32.0, 31.0

[a] Baseline is the last observation prior to the first dose of study drug, with the baseline value for patients in the open-label extension study being their baseline value from the double-blind study.
Min=minimum; max=maximum; SD=standard deviation; BP=blood pressure; bpm=beats per minute.

Clinically significant changes (both increases and decreases) in pulse and systolic and diastolic blood pressure occurred infrequently among patients treated with modafinil (Table 35).

Table 35: Clinically Significant Abnormal Vital Signs Measurements in All Studies in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (Safety Analysis Set)

		Number (%) of patients
		All studies
Variable	**Criteria**	**Modafinil (N=933)**
Pulse	≥120 bpm and increase ≥15 bpm	28 (3)
	≤50 bpm and decrease ≥15 bpm	2 (<1)
Sitting systolic BP	≥130 mm Hg and increase ≥20 mm Hg	30 (3)
	≤80 mm Hg and decrease ≥20 mm Hg	18 (2)
Sitting diastolic BP	≥85 mm Hg and increase ≥15 mm Hg	30 (3)
	≤50 mm Hg and decrease ≥15 mm Hg	88 (9)

bpm=beats per minute; BP=blood pressure.

In all Phase 1, 2, and 3 studies of children and adolescents with ADHD, which included 933 modafinil-treated patients, no modafinil-treated patients had increases from baseline

of more than 60 msec or individual maximum values greater than 450 msec in QTc interval (Fridericia).

In the evaluation of cardiovascular data for these studies, cardiovascular adverse events, including serious adverse events and those leading to withdrawal, were reviewed. Among patients treated with modafinil, cardiovascular adverse events including syncope, tachycardia, vasodilatation, electrocardiogram abnormal, hypertension, AV block first degree, bradycardia, cardiovascular disorder, palpitation, and sinus bradycardia occurred in as few as 1 (0.1%) to 10 (1%) patients. No serious cardiovascular adverse events were reported. Two modafinil-treated patients withdrew from study due to tachycardia during double-blind treatment (as reported above).

(b) Other Studies With Modafinil in Children and Adolescents

Additional cardiovascular data are available from other studies conducted in children and adolescents, ie, studies in narcolepsy (modafinil N=123, placebo N=42) and OSAHS (modafinil N=19, placebo N=7) that included 270 patients treated with modafinil in double-blind and open-label studies. Patients in these studies were treated for up to 6 months.

In the 2 placebo-controlled studies in children and adolescents with excessive sleepiness (narcolepsy study C1538/3027/NA/MN, hereafter referred to as study 3027; and OSAHS study C1538/3028/AP/MN, hereafter referred to as study 3028), 142 patients were treated with modafinil and 49 patients were treated with placebo.

In these studies, no differences in mean changes in vital signs measurements, for pulse and systolic and diastolic blood pressure, were observed between the modafinil and placebo treatment groups (Table 36).

Table 36: Mean Values and Changes From Baseline to Endpoint in Vital Signs Measurements by Treatment Group in the Placebo-Controlled Narcolepsy and OSAHS Studies (Safety Analysis Set)

		Modafinil (N=142)			Placebo (N=49)		
Vital signs variable	**Statistic**	**Baseline**	**Endpoint**	**Change**	**Baseline**	**Endpoint**	**Change**
Pulse (bpm)	n	142	139	139	49	48	48
	Mean	80.2	78.9	–1.4	79.0	76.8	–2.5
	SD	12.83	12.25	13.72	12.61	13.95	12.03
	Median	80	78.0	–2.0	77	75.5	–3.5
	Min, max	57, 139	47, 112	–44, 39	61, 112	54, 110	–30, 25
Systolic blood pressure (mm Hg)	n	142	139	139	49	48	48
	Mean	112.9	112.2	–0.6	112.1	113.2	0.5
	SD	12.78	12.01	10.65	10.47	12.69	13.82
	Median	112	112.0	–1.0	113	112.5	0
	Min, max	87, 164	80, 159	–34, 30	87, 132	84, 140	–32, 41
Diastolic blood pressure (mm Hg)	n	142	139	139	49	48	48
	Mean	68.2	68.5	0.3	66.4	68.3	1.8
	SD	9.37	9.60	9.42	8.55	8.34	10.23
	Median	68.5	68.0	0	65	67.5	0
	Min, max	46, 110	50, 111	–26, 30	41, 86	53, 86	–24, 28

bpm=beats per minute; SD=standard deviation; min=minimum; max=maximum.

Clinically significant changes (both increases and decreases) in pulse and systolic and diastolic blood pressure occurred infrequently (Table 37).

Table 37: Clinically Significant Abnormal Vital Signs Measurements in the Placebo-Controlled Narcolepsy and OSAHS Studies (Safety Analysis Set)

		Number (%) of patients[a]	
		Phase 3 double-blind, placebo-controlled studies	
Variable	**Criteria**	**Modafinil (N=142)**	**Placebo (N=49)**
Pulse	≥120 bpm and increase ≥15 bpm	2 (1)	0
	≤50 bpm and decrease ≥15 bpm	2 (1)	0
Systolic BP	≥130 mm Hg and increase ≥20 mm Hg	6 (4)	3 (6)
	≤80 mm Hg and decrease ≥20 mm Hg	0	1 (2)
Diastolic BP	≥85 mm Hg and increase ≥15 mm Hg	5 (4)	2 (4)
	≤50 mm Hg and decrease ≥15 mm Hg	2 (1)	1 (2)

[a] Patients may have ad more than 1 clinically significant abnormality.
bpm=beats per minute; BP=blood pressure.

In these studies, data from those patients who had at least 1 clinically significant pulse or blood pressure value were evaluated to assess whether these changes occurred frequently or were isolated findings. Among the patients with clinically significant increases in vital signs measurements, few had more than 1 clinically significant value for pulse and/or blood pressure during treatment (Table 38).

Table 38: Clinically Significant Increases in Vital Signs Measurements by Treatment Group in the Placebo-Controlled Narcolepsy and OSAHS Studies (Patients With More Than 1 Significant Value) (Safety Analysis Set)

		Number (%) of patients	
		Phase 3 placebo-controlled studies	
Variable	Criteria	Modafinil (N=142)	Placebo (N=49)
Pulse	≥120 bpm and increase ≥15 bpm	0	0
Sitting systolic BP	≥130 mm Hg and increase ≥20 mm Hg	0	0
Sitting diastolic BP	≥85 mm Hg and increase ≥15 mm Hg	1 (<1)	0

bpm=beats per minute; BP=blood pressure.

In all studies in children with narcolepsy or OSAHS who participated in both a double-blind and open-label study (studies 3027, 3028, C1538/3029/ES/MN, and C1538/3034/ES/3034 [270 modafinil-treated patients]), no clinically meaningful changes in vital signs measurements, for pulse and seated systolic and diastolic blood pressure, were observed (Table 39).

Table 39: Mean Values and Changes From Baseline to Endpoint in Vital Signs Measurements by Diagnosis in All Studies Combined in Children and Adolescents With Narcolepsy or Obstructive Sleep Apnea/ Hypopnea Syndrome (Safety Analysis Set)

Vital signs	Time point Statistic	Modafinil		
		Narcolepsy (N=202)	OSAHS (N=68)	Total (N=270)
Pulse (bpm)	Baseline			
	n	202	68	270
	Mean	78.7	79.4	78.9
	SD	12.50	13.11	12.63
	Median	78.0	78.0	78.0
	Min, max	55.0, 112.0	60.0, 139.0	55.0, 139.0
	Change from baseline			
	n	199	68	267
	Mean	–0.2	1.5	0.2
	SD	12.86	12.76	12.84
	Median	0.0	0.0	0.0
	Min, max	–34.0, 38.0	–26.0, 49.0	–34.0, 49.0
Systolic blood pressure (mm Hg)	Baseline			
	n	202	68	270
	Mean	111.4	114.6	112.2
	SD	12.00	14.37	12.69
	Median	111.0	113.0	112.0
	Min, max	80.0, 164.0	85.0, 155.0	80.0, 164.0
	Change from baseline			
	n	199	68	267
	Mean	–1.6	–4.6	–2.3
	SD	11.23	12.82	11.71
	Median	–1.0	–5.0	–2.0
	Min, max	–42.0, 39.0	–30.0, 36.0	–42.0, 39.0
Diastolic blood pressure (mm Hg)	Baseline			
	n	202	68	270
	Mean	67.5	68.1	67.6
	SD	8.83	8.59	8.76
	Median	68.0	69.5	68.0
	Min, max	41.0, 110.0	52.0, 89.0	41.0, 110.0
	Change from baseline			
	n	199	68	267
	Mean	–0.8	–2.7	–1.3
	SD	10.62	9.29	10.31
	Median	0.0	–3.0	–1.0
	Min, max	–54.0, 30.0	–20.0, 21.0	–54.0, 30.0

min=minimum; max=maximum; SD=standard deviation; bpm=beats per minute; OSAHS=obstructive sleep apnea/hypopnea syndrome.

Clinically significant changes (both increases and decreases) in pulse and systolic and diastolic blood pressure occurred infrequently among patients treated with modafinil (Table 40).

Table 40: Clinically Significant Abnormal Vital Signs Measurements by Diagnosis in All Studies Combined in Children and Adolescents With Narcolepsy or Obstructive Sleep Apnea/Hypopnea Syndrome (Safety Analysis Set)

		Number (%) of patients		
Vital Sign	**Criteria**	**Narcolepsy (N=202)**	**OSAHS (N=68)**	**Total (N=270)**
Pulse	≥120 bpm and increase ≥15 bpm	2 (<1)	2 (3)	4 (1)
	≤50 bpm and decrease ≥15 bpm	2 (<1)	1 (1)	3 (1)
Systolic BP	≥130 mm Hg and increase ≥20 mm Hg	11 (5)	2 (3)	13 (5)
	≤80 mm Hg and decrease ≥20 mm Hg	2 (<1)	2 (3)	4 (1)
Diastolic BP	≥85 mm Hg and increase ≥15 mm Hg	12 (6)	6 (9)	18 (7)
	≤50 mm Hg and decrease ≥15 mm Hg	8 (4)	4 (6)	12 (4)

bpm=beats per minute; BP=blood pressure; OSAHS=obstructive sleep apnea/hypopnea syndrome.

In all studies in children with narcolepsy or OSAHS who participated in both a double-blind and open-label study, no clinically meaningful changes were seen in any ECG parameters during the study. For QTc interval (Fredericia), mean changes from baseline for modafinil-treated patients with narcolepsy or OSAHS were +0.3 and +0.8 msec, respectively.

In the evaluation of cardiovascular data for these studies, cardiovascular adverse events, including serious adverse events and those leading to withdraw, were reviewed. Among patients treated with modafinil, tachycardia and syncope occurred in 4 and 3 patients (1% of 270), respectively, and arrhythmia, palpitation, and vasodilatation occurred in less than 1% (1 of 270) of patients. No serious cardiovascular adverse events were reported, nor did any patient withdraw from study due to a cardiovascular adverse event.

7.3.3.3 Postmarketing Surveillance

A search of the postmarketing data for modafinil was conducted to locate all reports of adverse drug reactions in patients who were less than 18 years old, with 105 unique cases identified. This database includes cumulative data up to 31 December 2005 pertaining to the following areas:

- fatal adverse events
- reports of sudden death
- cardiac adverse events
- vascular adverse events including hypertension and increased blood pressure , and cerebrovascular ischemia, infarct, and hemorrhage

Using the above search criteria, the following 8 cases were identified:

- sudden death—1
- cardiac adverse events and vascular adverse events (hypertension and related)—7 (includes 1 case with cardiac and vascular event [hypertension])
- vascular adverse events (cerebrovascular disorders and related)—0

Of these 8 cases, 1 was fatal (and therefore serious), 2 were serious and not fatal, and 5 were not serious (Table 41).

Table 41: Postmarketing Reports of Cardiovascular Adverse Events

Case number	Age (y)/ Sex	Adverse event (verbatim)	Time on treatment	Modafinil dosage	Intervention/outcome	History
US007296[a]	17/boy	Cardiac arrest during physical activity	9 months	100 mg/day	Unknown/death	Steinert's disease[b]
CEPH-1538-99-0029[a]	16/boy	Unspecified tachycardia, unspecified hypertension, adverse CNS symptoms	NA	9 gm[c]	Hospitalization/resolved	Unknown
US015049[a]	14/girl	Unspecified tachycardia, vomiting	NA	1000 mg[d]	Hospitalized/resolved	Depression. Therapy with duloxetine hydrochloride had been discontinued 2 weeks earlier. (Modafinil treatment continued.)
CEPH-1538-99-5207	17/girl	Palpitations	2 hours postdose	100 mg/day	Discontinued treatment with loratadine/pseudoephedrine sulfate/resolved	Unknown
US013863	15/boy	Cardiac erethism[e]	1st days	200 mg/day	None/resolved	Unknown (Modafinil treatment continued.)
US014489	14/girl	Palpitations, flushing, paresthesias	Unknown	200 mg/day	Reduced modafinil to 100 mg/day/resolving	Unknown
US009838	17/girl	Chest pain, palpitations while exercising	Prior	600 mg/day	None/continued	Mitral valve prolapse, autonomic dysfunction not otherwise specified. (Modafinil treatment continued.)
NAV	11/boy	Increase in frequency and duration of attacks	Unknown	200 mg/day	Discontinued modafinil/ unknown	Mitral valve prolapse attacks (heart hurting and a feeling of pressure)

[a] Serious adverse event.
[b] A rare progressive myotonic dystrophy characterized by cataracts, hypogonadism, frontal balding, and cardiac arrhythmias).
[c] Also took 800 mg of amitryptiline in a reported suicide attempt.
[d] Also took 60 mg of zolpidem tartrate and an unknown quantity of bupropion hydrochloride in an apparent suicide attempt. Started modafinil therapy after recovery.
[e] Coded as tachycardia.
mo=months; CNS=central nervous system; NA=not applicable; NAV=not available.
NOTE: 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.

Overall, no signals for adverse cardiovascular events have been detected through postmarketing reporting in either children or adults treated with modafinil. Accordingly, no labeling changes have been made. Note that the modafinil product labeling contains a precaution regarding the emergence of various cardiac symptoms (including chest pain and ECG changes) in patients with either (symptomatic) mitral valve prolapse or (concentric) left ventricular hypertrophy. The labeling also describes a single patient with narcolepsy who developed asystole in association with modafinil treatment. No findings of concern in regard to these specific events have been identified in postmarketing surveillance.

The product labeling for adults with excessive sleepiness also contains a statement regarding blood pressure with these relevant facts. Blood pressure monitoring in short-term (<3 months) placebo-controlled trials showed no clinically significant changes in mean systolic and diastolic blood pressure in patients treated with modafinil as compared to those treated with placebo. However, a retrospective analysis of the use of antihypertensive medication in these studies showed that a greater proportion of modafinil-treated patients required new or increased use of antihypertensive medications (2.4%) compared to placebo-treated patients (0.7%). The differential use was slightly larger when only studies in OSAHS were included, with 3.4% of modafinil-treated patients and 1.1% of placebo-patients requiring such alterations in the use of antihypertensive medication. Increased monitoring of blood pressure may be appropriate during modafinil treatment. Overall, no signals in regard to adverse cardiovascular effects were detected from postmarketing surveillance in pediatric patients treated with modafinil.

7.3.3.4 Overall Summary of Cardiovascular Safety Evaluation From Clinical Studies and Postmarketing Surveillance

The evaluation of cardiovascular data included review of data from modafinil clinical studies, both in children and adolescents with ADHD and with excessive sleepiness associated with narcolepsy or OSAHS. The evaluation of clinical study data included vital signs measurements (pulse and blood pressure) and ECG findings. In addition, the postmarketing database was searched for cardiovascular-related adverse events in children. Overall, this included data from 1308 children and adolescents treated with modafinil. No safety issues of particular concern have been raised in regard to cardiovascular side effects associated with modafinil treatment.

In conclusion, minor increases in pulse were observed, but did not appear to be clinically meaningful. These small increases in mean pulse were observed in children and adolescents with ADHD, but not those with narcolepsy or OSAHS. There were no changes in mean systolic or diastolic blood pressure and no effect on QTc interval was evident. No differences were seen between the modafinil and placebo treatment groups in mean changes in pulse or blood pressure. In general the incidence of cardiovascular adverse events was low. Overall, no signals in regard to adverse cardiovascular effects were detected in children and adolescents treated with modafinil and no cardiovascular safety issues were raised.

7.3.4 Growth (Weight and Height)

7.3.4.1 Nonclinical Studies

In support of the proposed clinical indication for modafinil in the treatment of children and adolescents with ADHD, 3 multiple-dose, nonclinical safety studies were conducted in neonatal (10-day-old) and weanling (21-day-old) rats and in prejuvenile (~3 months of age) dogs. In the neonatal rat study in which animals were administered modafinil at dosages ranging from 30 to 240 mg/kg/day for 13 consecutive weeks, crown-to-rump measurements were made weekly for a subgroup of F_1 generation pups, and measurements of bone length (right femur from the proximal end of the femoral head to the distal end of the femur, excluding the patella) were taken on subgroups of F_1 generation rats at necropsy. In the weanling rat study in which the animals were dosed with modafinil at dosages ranging from 50 to 400 mg/kg/day for 6 consecutive weeks and the prejuvenile dog study (study 97-020) in which the puppies were dosed with modafinil at dosages ranging from 20 to 90→75 mg/kg/day (high-dose of 90 mg/kg/day lowered to 75 mg/kg/day in study week 2) for 13 consecutive weeks, either both femurs (rat) or the right femur (dog) were removed at necropsy and measured for bone length (rat and dog) and weight (dog). In all cases, the femurs were cleaned of adherent tissue prior to assessing bone weight and/or bone length.

In all 3 studies, there were no significant effects on skeletal growth (as assessed by measurements on bone weight and/or length) at any dosage. In contrast, the systemic administration of methylphenidate to neonatal rats has shown an acute growth impairment (reduction in femur length relative to control values) followed by a growth-rebound phenomenon within 30 days of the last exposure (Pizzi et al 1986, Pizzi et al 1987). In the neonatal rat study with modafinil, the crown-to-rump lengths were statistically significantly reduced ($p \leq 0.05$ or $p \leq 0.001$) for rat pups in the high-dose (240 mg/kg/day) group at the post partum day-17 measurement (male rats only) and at measurement intervals on post partum days 17 through 45 in female rats. This difference was no longer apparent at post partum days 24 through 115 (male rats) and days 52 through 115 (female rats) measurements. The change in the high-dose group was associated with an initial loss in body weight/decrement in body weight gain during the early phase of the dosing period. An increase in locomotor activity in these animals resulting in potential reduced or inefficient nursing and/or an increased caloric demand at these times were associated with the initial marked reductions in weight and the resultant, transient reductions in the crown-to-rump differences observed. The lower-dosage groups (30 and 120 mg/kg/day) showed no effects at any measurement interval.

7.3.4.2 Clinical Studies Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

In the Phase 3 placebo-controlled studies, patients in the modafinil treatment group had a mean decrease (0.7 kg) in body weight from baseline to endpoint, while patients in the placebo treatment group had a mean increase (1.0 kg) in body weight. For all studies combined, a mean increase (1.2 kg) was seen in body weight from baseline to endpoint of double-blind treatment.

Following 12 months of treatment with modafinil in study 312, clinically significant decreases (>7%) in body weight were observed in 11% of patients, and clinically significant increases (>7%) in body weight were observed in 33% of patients.

There were mean decreases from baseline in body weight at week 2, month 1, month 2, and month 3 of open-label treatment. Thereafter, mean increases in body weight were observed through month 12, and the change from baseline to the month-12 visit was a mean increase of 1.9 kg (Figure 11). (NOTE: In all Phase 3 studies, only 3 (0.05%) patients discontinued study due to an adverse event of weight loss.) Similar effects were observed on BMI (Figure 12) with a mean decrease of 0.3. The mean height in this population was 143.5 cm at baseline. Height increased at a normal rate during the first 12 months of open-label treatment, with an average 6-cm increase for patients completing 12 months of treatment with modafinil (Figure 13).

Figure 11: Mean Body Weight Over Time in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder Who Completed 12 Months of Modafinil Treatment (Study 312)

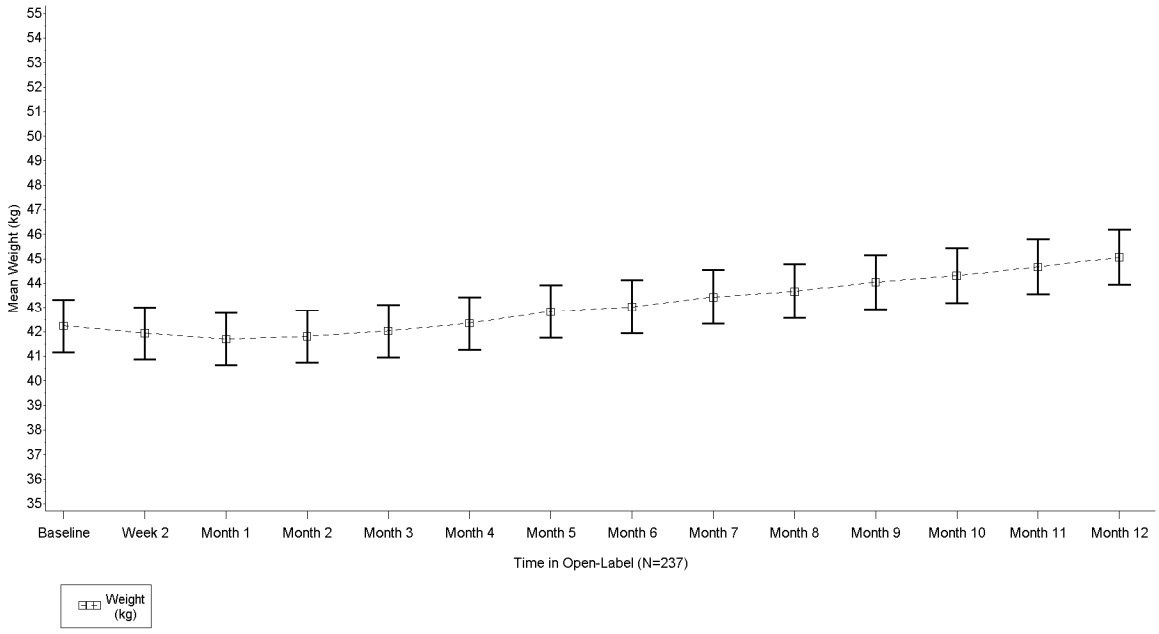


Figure 12: Mean Body Mass Index Over Time in Children and Adolescents in With Attention-Deficit/Hyperactivity Disorder Who Completed 12 Months of Modafinil Treatment (Study 312)

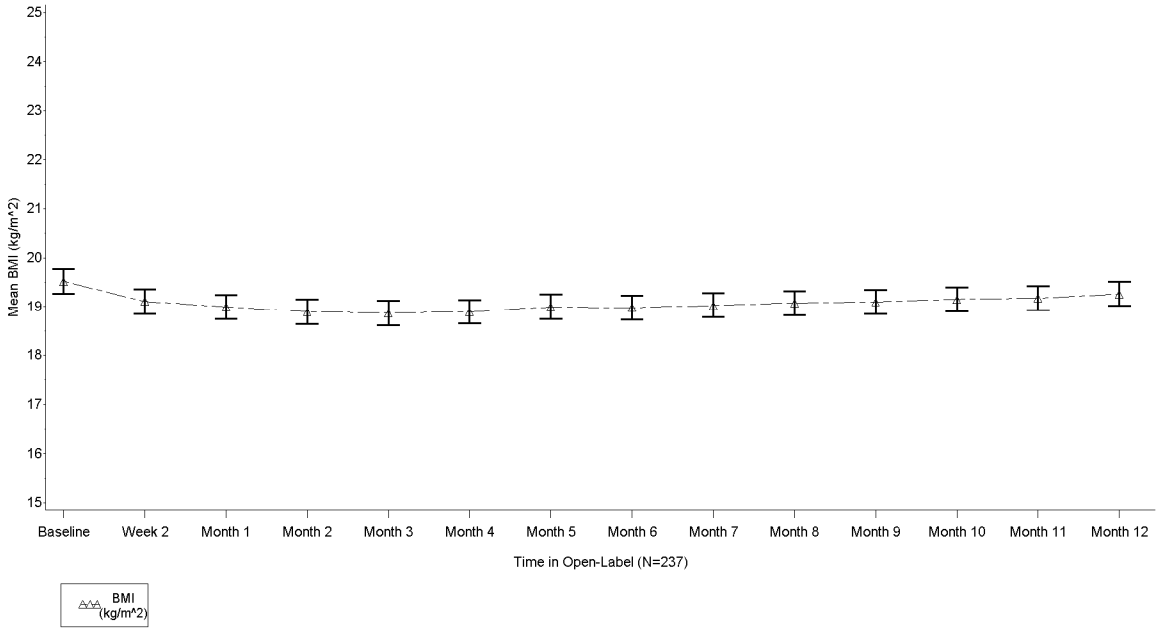
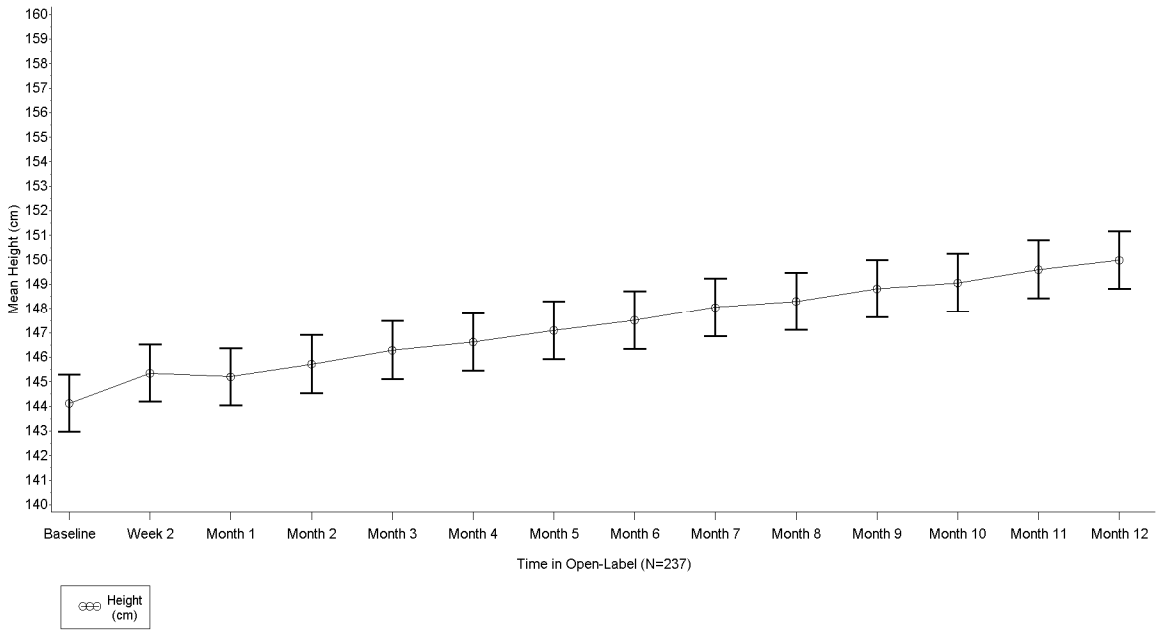


Figure 13: Mean Height Over Time Over Time in Children and Adolescents in With Attention-Deficit/Hyperactivity Disorder Who Completed 12 Months of Modafinil Treatment(Study 312)

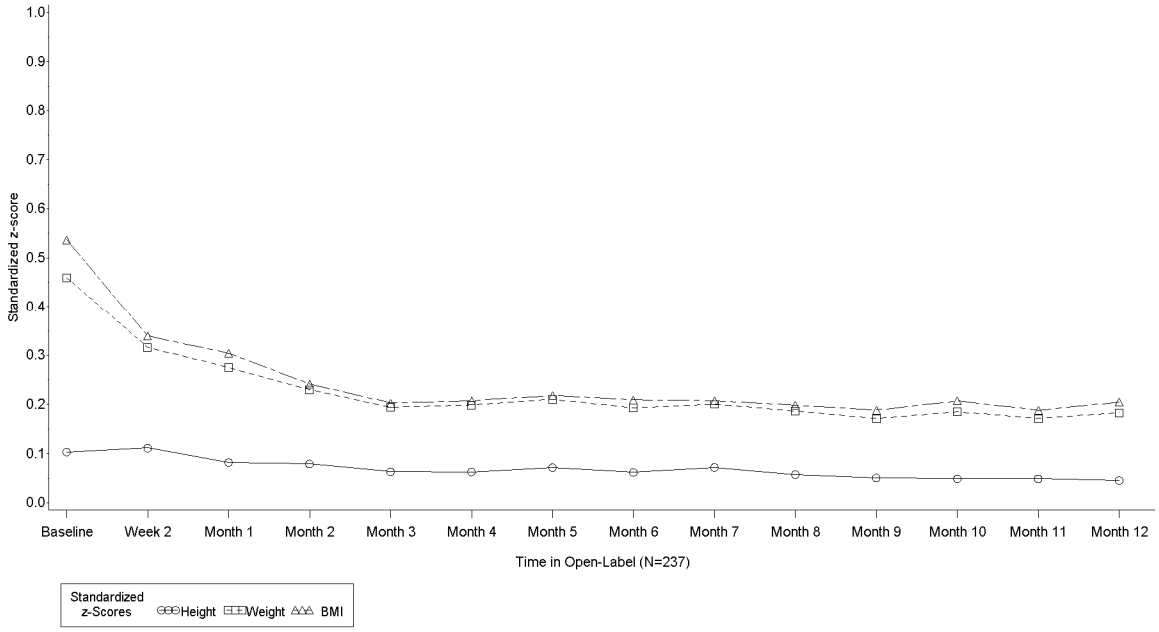


In order to assess normal child development during treatment, the height and weight data collected for the open-label extension study (study 312) were converted to standardized

Z-scores and percentile scores on the basis of each patient's sex and age according to the National Center for Health Statistics. Actual values and changes from baseline at each visit and endpoint were evaluated (Figure 14).

The mean Z-scores for both body weight and BMI at baseline were 0.5, with a mean decrease of 0.3 from months 2 to 12. A mean Z-score of 0.2 (month 12) is still above average. There was little to no change in the Z-score (decrease of 0.06 at endpoint) for height during the first 12 months of open-label modafinil treatment.

Figure 14: Mean Z-Scores for Body Weight, Height, and Body Mass Index Over Time for Children and Adolescents With Attention-Deficit/Hyperactivity Disorder Who Completed 12 Months of Modafinil Treatment (Study 312)



In summary, mild, transient decreases in mean body weight were observed during the first 3 months of open-label treatment with an increase in weight, compared to baseline, from months 4 to 12 in patients completing 1 year of modafinil treatment. There was a slight decrease in the rate of weight gain as assessed by Z-scores (decrease of 0.3); however, patients' weights remained above average. Similar effects were observed on BMI. There was little to no effect on height in patients completing 12 months of open-label treatment.

7.4 Overall Summary of Safety Evaluation

A total of 933 children and adolescents with ADHD have received treatment with modafinil in Cephalon-sponsored Phase 1, 2, and 3 clinical studies with a mean duration of modafinil treatment of 177.1 days. A total of 244 patients have received modafinil for

at least 12 months, and 164 patients have received modafinil for at least 18 months. In addition, a Phase 3b open-label study in 303 children and adolescents with ADHD who have not previously participated in a Cephalon-sponsored study with modafinil is ongoing. Modafinil treatment has also been evaluated in clinical studies in 270 children and adolescents with excessive sleepiness associated with narcolepsy or OSAHS. Across these studies, 171 patients received 3 months or more of modafinil treatment, and 103 patients had at least 6 months exposure to modafinil. Additionally 116 children with other diseases were treated with modafinil.

Treatment with modafinil is generally safe and well tolerated in children and adolescents with ADHD with a low occurrence of serious adverse events and adverse events leading to withdrawal. The most common adverse events (insomnia, anorexia [primarily decreased appetite], and headache) reported in all studies in children and adolescents were those common to drugs that affect the central nervous system. These events were usually mild to moderate in severity and seldom required discontinuation of treatment with the study drug.

Similar to the findings previously seen in adults, progressive mean increases in GGT were observed in children and adolescents with ADHD over time during treatment with modafinil for up to 6 months. Mean increases in alkaline phosphatase appeared highest within the first month of modafinil treatment. However, few values were clinically significantly abnormal or associated with clinical signs or symptoms.

An evaluation of adverse events of special interest (serious skin and rash-related events and psychiatric adverse events) showed 2 cases in children were consistent with a possible diagnosis of Stevens-Johnson Syndrome (SJS) that manifested as skin blistering and/or mucous membrane involvement (although both cases were confounded by alternative infectious/drug etiologies). Neither of these patients was hospitalized. In both cases, the events resolved without sequelae following discontinuation of study drug. No biopsy-confirmed cases of SJS were reported.

A relatively small number of cases of psychiatric adverse events of interest in all modafinil development programs were reported. However, there is an imbalance of suicidal ideation and psychotic events in patients in the modafinil treatment group compared to patients in the placebo treatment group. Most of the events were short in duration, did not require treatment, and resolved while modafinil treatment continued.

Evaluation of cardiovascular adverse events and vital signs measurements showed no cardiovascular safety issues. Minor increases in pulse, which did not appear to be clinically meaningful were observed, and there were no changes in mean systolic or diastolic blood pressure measurements or changes in QTc intervals.

Particular attention was also given to growth rates in children following prolonged treatment with modafinil in the long-term open-label study (study 312). There was little to no effect on growth for patients completing 12 months of open-label treatment.

8 BENEFIT/RISK ASSESSMENT

Modafinil currently has FDA marketing approval as PROVIGIL tablets for the treatment of adults with excessive sleepiness associated with narcolepsy, OSAHS, or SWSD. The recommended adult dosage is 200 mg/day, and dosages up to 400 mg/day have been well tolerated. Cephalon, Inc. is seeking marketing approval for modafinil for the treatment of children and adolescents with ADHD, with a recommended dosage of 340 or 425 mg/day for patients less than 30 or at least 30 kg, respectively.

The diagnosis of ADHD is made by careful collection of patient history. ADHD is characterized by a considerable degree of inattentiveness, distractability, impulsivity, and often, hyperactivity, that are inappropriate for the developmental stage of the child (American Psychiatric Association 1994). The following 3 subtypes of ADHD are currently recognized: predominately inattentive (20%-30% of cases), predominately hyperactive-impulsive (<15% of cases), and a combined subtype (50%-75% of cases). ADHD is the most common neurobehavioral disorder of childhood and among the most prevalent chronic health condition affecting school-aged children. ADHD is estimated to affect 4% to 12% of school-age children (American Academy of Pediatrics 2000). Studies in children with ADHD in which follow-up information was collected in their adolescence and early adulthood indicate that the disorder frequently persists and is associated with significant psychopathology and dysfunction later in life. The adolescent and young adult with ADHD is at risk for school failure, emotional difficulties, poor peer relationships, and trouble with the law (Fischer 1997). Epidemiologic studies have documented high rates of concurrent psychiatric and learning disorders among those with ADHD. Most commonly, comorbidity with ADHD includes oppositional, conduct, mood, and anxiety disorders (Biederman et al 1991). Furthermore, ADHD is associated with poor academic outcome, work difficulty, driving accidents, a 2-fold increase in smoking, and alcohol and drug abuse (Weiss et al 2006).

Medications remain the mainstay of treatment for children and adolescents with ADHD. Recent multicenter studies suggest that management of ADHD with medications is the most important variable in outcome in the context of multimodal treatment. However, even though traditional CNS stimulants are the most commonly used treatments, it has been reported that approximately 40% of children with ADHD do not respond positively to treatment, have unacceptable side effects, or have concurrent depressive or anxiety disorders that stimulant medications may exacerbate (Wilens and Biederman 1992).

With medications currently approved for ADHD, adverse events reported frequently include insomnia, decreased appetite, and weight loss. On review of the literature, 10.6%, 13%, and 27.3% of the patients receiving 18, 36, and 54 mg of methylphenidate, respectively, reported decreased appetite and up to 25% reported problems with sleep (Stein et al 2003). In another study, methylphenidate treatment was also associated with significant increases in poor appetite (23.4%) and sleep difficulties (36.4%) (Klorman et al 1994). In a long-term study of patients adherent to methylphenidate treatment for 5 years, clinically significant decreased appetite persisted for 5 years (Charach et al 2004). In a long-term study of atomoxetine treatment (once daily) in children with ADHD, anorexia and insomnia were reported by 37.1% and 25.7% of patients, respectively, during months 1 through 6 of treatment (McGough et al 2005). In a 3-week

study with extended-release amphetamines in 563 patients with ADHD, significant treatment-emergent adverse events included anorexia, which occurred in 27%, 40%, and 55% of the patients treated with 10, 20, and 30mg, respectively (McKeage and Scott 2003). In a report of the safety database of over 2000 exposures of atomoxetine in children and adolescents with ADHD, patients tended to report decreased appetite at the beginning of treatment, which was associated with weight loss over the first 9 months of treatment (Wernicke and Kratochvil 2002).

Another concern with ADHD medications is the long-term effect on growth. Treatment with CNS stimulants potentially suppressed height and weight gains in children in a dose-related manner and appeared to be more pronounced with dextroamphetamine during the first year of treatment (Safer and Allen 1973). Reductions in weight have been reported with CNS stimulant treatment. In a 21-day short-term study with methylphenidate in 107 children with ADHD, on average patients treated with methylphenidate lost 0.498 kg compared to a weight gain of 0.567 kg in placebo-treated patients (Smithee et al 1988).

Furthermore, products currently used for treating children with ADHD have been associated with skin-related adverse events. Urticaria has been associated with their use as have hypersensitivity, skin rash, urticaria, exfoliate dermatitis, and erythematic multiforme with histopathologic findings of necrotizing vasculitis. Allergic reactions observed include angioneurotic edema, urticaria, and rash.

Concerns were raised about reports of psychiatric adverse events occurring in children treated with medications for ADHD, and FDA requested a comprehensive review of such adverse events for all approved ADHD drugs and for those drugs pending approval. There are warnings for current products for ADHD about psychosis, adverse reactions of psychotic episodes, suicidal ideation, and aggressive behavior or hostility.

Cardiovascular side effects are also of significant concern with any drug used for treating children. The FDA Drug Safety and Risk Management Advisory Committee recently met to discuss ways to handle, and further study, known and recognized cardiovascular adverse reactions in children. Current ADHD therapies cause cardiovascular effects such as increases in pulse and blood pressure along with occasional reports of more serious cardiovascular events. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events. Amphetamines have been observed to cause palpitations and elevation of blood pressure and are contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, and moderate to severe hypertension. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. Methylphenidate has been observed to cause increases in pulse, diastolic and systolic blood pressure, tachycardia, angina, and cardiac arrhythmias.

Of the traditional sympathomimetic CNS stimulants, amphetamines and methylphenidate have FDA approval for the treatment of patients with ADHD. Both amphetamines and methylphenidate can lead to physical or psychological dependence (The Substance Abuse and Mental Health Services Administration, US Department of Health and Human Services). The abuse and diversion risks for amphetamines and methylphenidate are judged to be high and both are listed in Schedule II of the Controlled Substances Act.

Atomoxetine has been approved for adults and children with ADHD. Although it is not a CNS stimulant and is not scheduled, side effects include gastrointestinal effects, insomnia, dizziness, mood swings, adverse growth effects and severe liver injury (recent bolded warning).

There is a need, therefore, for additional pharmacologic treatment options for children and adolescents with ADHD. Modafinil selectively activates the CNS and is chemically and pharmacologically different from traditional sympathomimetic CNS stimulants, and has been shown in clinical trials to be safe and effective in the treatment of children and adolescents with ADHD.

8.1 Benefits of Modafinil Treatment

The clinical studies evaluating the efficacy of modafinil for the treatment of children and adolescents with ADHD have shown modafinil to have significant clinical benefits. The efficacy of modafinil for treatment of children and adolescents with ADHD was reproducibly shown in 3 Phase 3 placebo-controlled studies.

Highly statistically significant ($p<0.0001$) improvements in the total score from the teacher/investigator-rated ADHD-RS-IV (School Version) were seen for patients treated with modafinil compared to those treated with placebo in 3 individual studies. Statistically significant improvements were seen as early as week 1 (in 2 of 3 studies) and maintained throughout the double-blind treatment period. The analysis of the ADHD-RS-IV (School Version) subscale scores of inattention and hyperactivity at endpoint and at each time point during the double-blind treatment period yielded similar results to those seen for the total score with statistically significant improvements ($p<0.01$) demonstrated for those patients treated with modafinil compared to those treated with placebo.

In addition, the parent/investigator-rated ADHD-RS-IV (Home Version) was used to evaluate the continued effectiveness of modafinil on problem behaviors during the evening hours (ie, 6:00-8:00 pm). In each study, the results for the analysis of the ADHD-RS-IV (Home Version) were consistent with those seen for the ADHD-RS-IV (School Version). For patients in the modafinil treatment group, the ADHD-RS-IV (Home Version) total and subscale scores at endpoint showed statistically significant ($p<0.001$) improvement when compared with the placebo treatment group.

Additional efficacy measures supported the findings of the ADHD-RS-IV. The CGI-C was used as a clinician-rated assessment of change over time in the patients' ADHD symptoms during the study, compared with the severity of ADHD rating (CGI-S) at baseline. In each study, there was a statistically significant ($p<0.0001$) increase in the percentage of patients who improved (defined as a CGI-C of much improved or very much improved in ADHD symptoms) in the modafinil treatment group. The CPRS:R-S each provided an ADHD index/score, which indicated statistically significant ($p<0.001$) improvement from baseline for patients in the modafinil treatment group when compared to patients in the placebo treatment group.

Three additional measures to assess other problem behaviors commonly seen in children and adolescents with ADHD were evaluated in the Phase 3 placebo-controlled studies,

the SSRS, CPRS:R-S, and the CHQ. The SSRS was used to evaluate the effect of modafinil on socialization problems, the CPRS:R-S was used to evaluate the effect of modafinil on oppositional and cognitive behavior, and the CHQ was used to assess patient quality of life. When data from the 3 studies are pooled, for patients at the elementary level (grades K through 6), statistically significant improvements ($p<0.05$) were observed at endpoint for the modafinil treatment group compared with the placebo treatment group in the social skills total score, for all of the social skills subscale scores (cooperation, assertion, responsibility, and self-control), for the problem behaviors total score, and for all of the problem behaviors subscale scores (externalizing problems, internalizing problems, and hyperactivity). For patients at the secondary level, no statistically significant differences were observed between the 2 treatment groups. Significant improvements ($p<0.05$) in the CPRS:R-S scores were observed at endpoint in favor of modafinil treatment in oppositional behavior, cognitive problems/inattention, hyperactivity, and ADHD index T-scores. Statistically significant improvements ($p<0.05$) in the CHQ were observed at endpoint for the modafinil treatment group compared with the placebo treatment group for the psychosocial summary score. In addition, statistically significant improvement ($p<0.05$) in favor of modafinil treatment were shown for emotional behavior, behavior, global behavior, mental health, self esteem, parent impact-emotional, parent impact-time, and family activities.

In summary, the results of the Phase 3 placebo-controlled studies clearly and reproducibly demonstrate the clinical benefit of modafinil in the treatment of children and adolescents with ADHD. Highly statistically and clinically significant treatment benefits were observed for those patients treated with modafinil in the primary outcome measure, the ADHD-RS-IV (School Version) as assessed by the school teacher. The effects on this primary measure were strongly supported by statistically significant and clinically relevant treatment benefits in many of the secondary measures including the ADHD-RS-IV (Home Version), as assessed by parents, and CGI-C, as assessed by physicians.

8.2 Potential Risks of Modafinil Treatment

In the Phase 3 placebo-controlled studies in ADHD the most commonly reported adverse events among patients who received modafinil were insomnia, headache, anorexia (primarily reported by study investigators as decreased appetite, and sometimes reported as loss of appetite, and coded to anorexia under COSTART), infection, and abdominal pain. Insomnia was reported for 27% of patients in the modafinil treatment group compared to 4% of patients in the placebo treatment group. Headache was reported by 20% of patients in the modafinil treatment group compared to 13% of patients in the placebo treatment group. Anorexia (decreased appetite) was reported by 16% of patients in the modafinil treatment group compared to 3% of patients in the placebo treatment group. There were no clear dose-related trends with respect to the frequency of specific adverse events.

The insomnia that was observed in the Phase 3 placebo-controlled modafinil studies appeared to occur primarily during the first 2 weeks of treatment. The incidence of insomnia decreased with longer-term exposure to modafinil, ie, from 27% in the first

3 months of treatment to 4% during the second 3 months of treatment. The severity of most adverse events of insomnia was reported as mild or moderate; 9 (2%) of 420 modafinil-treated patients had severe insomnia and 5 (1%) modafinil-treated patients discontinued treatment with modafinil because of insomnia.

Likewise, the anorexia (ie, decreased or loss of appetite) that was observed in the Phase 3 placebo-controlled modafinil studies appeared to occur primarily during the first 2 weeks of treatment. The incidence of this adverse event decreased with longer-term exposure to modafinil, ie, from 16% in the first 3 months of treatment to 2% in the second 3 months of treatment. Severity was reported as mild or moderate; 1 (0.2%) of 420 modafinil-treated patients reported it as severe and 2 (1%) modafinil-treated patients discontinued treatment because of decreased appetite/loss of appetite.

In the Phase 3 placebo-controlled modafinil studies, with a 7- to 9-week treatment period, a mean weight loss of 0.7 kg was observed in the modafinil treatment group compared to a mean weight gain of 1.0 kg in the placebo treatment group. In the 1-year open-label study, clinically significant decreases ($\geq$7%) in body weight were observed in 11% of patients (to date), whereas clinically significant increases ($\geq$7%) in body weight were observed in 33%. Mean decreases from baseline in body weight occurred in the first 3 months of open-label treatment. Thereafter, mean increases in body weight were observed through month 12, and the mean change from baseline to the last visit was an increase of 1.9 kg. This pattern of weight change suggests that weight loss is a relatively short-term phenomenon and may not be a concern with longer-term treatment with modafinil. Further more, changes in body weight, BMI, and height were evaluated on the basis of z-scores (height and weight data converted to z-scores on the basis of each patient's sex and age according to the National Center for Health Statistics). At baseline, the mean z-score for both body weight and BMI was 0.5, with a mean decrease of 0.3 at month 12, still above average. Height increased at a normal rate over 12 months of modafinil treatment. There was little to no change in height Z-scores (baseline 0.5, endpoint –0.06).

In previous clinical studies of modafinil in adults mean values for GGT and alkaline phosphatase and mean changes from baseline were shown to increase with increasing exposure to modafinil. Similar findings for GGT and alkaline phosphatase were observed in children and adolescents. For GGT, a mean increase from baseline (6.3 U/L) was observed in the modafinil group compared to a mean decrease (–0.1 U/L) in the placebo group. For alkaline phosphatase, mean increases from baseline were observed in both treatment groups; however, the increase in the modafinil group (16.8 U/L) was approximately twice that observed in the placebo group (7.6 U/L). Similar to the findings in adults, progressive mean increases in GGT were observed over time during treatment with modafinil for up to 6 months. Mean increases in alkaline phosphatase appeared to peak within the first month of modafinil treatment.

In all the placebo-controlled studies (including Phase 2 and 3 studies), 32 (5%) and 10 (3%) patients receiving modafinil and placebo, respectively, reported non-urticarial rash-related adverse events. Most of these events were reported as mild or moderate, with 4 (<1%) modafinil-treated patients and no placebo-treated patients reporting them as severe. Five modafinil-treated patients and 1 placebo-treated patient withdrew from

study due to non-urticarial rash-related adverse events. Across all studies in children and adolescents, 18 (2%) of 933 modafinil-treated patients had non-urticarial rash-related adverse events. No dose response was evident. Two cases in the clinical studies were consistent with possible diagnosis of SJS. Although possible confounding factors have been implicated and alternative etiologies suggested, possible association with modafinil treatment could not be excluded. In both cases, however, the event did not require hospitalization and was resolved following discontinuation of treatment.

The clinical study data with modafinil have been reviewed specifically for psychiatric adverse events including signs/symptoms of psychosis/mania, suicidal ideation and behavior, and aggression and violent behavior. The findings indicate the overall incidence for the events of interest is low. In regard to suicidal ideation and psychotic events there was an imbalance in the patients treated with modafinil. Most of the events observed were short in duration, did not require treatment, and resolved during continued treatment with modafinil.

In the Phase 3 placebo-controlled studies in children and adolescents minor increases in pulse were observed, but did not appear to be clinically meaningful. There were no changes in mean systolic or diastolic blood pressure and no effect on QTc interval was evident. Overall, no signals in regard to adverse cardiovascular effects were detected in children and adolescents treated with modafinil and no cardiovascular safety issues were raised.

Modafinil is listed in Schedule IV and its potential for abuse is low relative to Schedule II substances. A recently published review of the abuse liability of modafinil showed evidence from nonclinical in vitro and in vivo studies, human laboratory studies, and postmarketing experiences that suggest modafinil has limited potential for large scale abuse (Myrick et al 2004). Chemical and pharmacologic profiles of modafinil are not favorable for abuse. In nonclinical models, modafinil displays minimal addiction potential depending on the animal model utilized and the extent of previous stimulant experience. In several human studies involving both nonsubstance-abusing subjects and those using cocaine, indicate a low potential for abuse. The HAFC Behavioral Research Group, engaged to conduct active surveillance of modafinil abuse and misuse conclude that the abuse liability of modafinil, if it exists, is low. Finally, postmarketing surveillance has shown little to no diversion of drug, little interest on the internet by drug abusers, and has generated only a few clinical reports of potential abuse. However, patients should, however, be evaluated carefully and monitored closely to detect any signs of misuse or abuse, especially those who have a history of drug and/or stimulant abuse.

There were no food-effect, drug-drug interaction, renal or hepatic impairment studies conducted in children or adolescents; however, data for these studies in adults are available. Drug-drug interaction studies showed reductions in C_{max} and AUC for triazolam and for ethinyl estradiol, and the half-life of triazolam decreased from 2.6 to 1.6 hours while that of ethinyl estradiol remained unchanged. In addition, evaluation of adults with hepatic impairment indicates that the dosage of modafinil should be reduced in patients with severe hepatic impairment.

Although modafinil has not been shown to produce functional impairment, any drug affecting the CNS may alter judgment, thinking or motor skills. Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that modafinil therapy will not adversely affect their ability to engage in such activities.

8.3 Benefit/Risk Conclusions

Because current medications for ADHD may not be optimal for up to 40% patients, there is a need for additional safe and effective pharmacologic treatment options for children and adolescents with ADHD. ADHD is a neurobehavioral disorder characterized by developmentally inappropriate inattention, hyperactivity, and impulsivity. Children with ADHD may experience significant functional problems, such as school difficulties, academic underachievement, troublesome interpersonal relationships with family members and peers, and low self esteem.

The clinical benefits of modafinil at dosages up to 425 mg/day have been well established in 3 placebo-controlled Phase 3 clinical studies using multiple measures, both objective and subjective in nature and by multiple observers including the teacher, the parent, and the treating physician. The benefits of modafinil treatment in this patient population include not only a significant reduction in the symptoms of ADHD, and also improvements in the behavioral consequences of this disorder. Modafinil is generally well tolerated in children and adolescents with insomnia and decreased appetite being the predominant side effects of treatment. Other adverse events including skin rash and psychiatric adverse events have been adequately addressed in the proposed prescribing information. On the basis of the data submitted, modafinil treatment is seen as providing safe and effective treatment for children and adolescents with ADHD.

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