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Provigil® (modafinil) Tablets (C-IV)

Supplemental NDA

Briefing Document

For

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

25 September 2003

Sponsor
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LIST OF ABBREVIATIONS AND DEFFINITIONS OF TERMS

AASM	American Academy of Sleep medicine
AHI	apnea-hypopnea index
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ASDA	American Sleep Disorders Association
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CGI-C	Clinical Global Impression of Severity
CGI-S	Clinical Global Impression of Change
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
DBP	diastolic blood pressure
ECG	electrocardiography/electrocardiogram
EDS	excessive daytime sleepiness
ES	excessive sleepiness
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
GGT	gamma-glutamyl-transferase
GABA	gamma aminobutyric acid
HLA	human leukocyte antigen
ICSD	International Classification of Sleep Disorders
KSS	Karolinska Sleepiness Scale
MAO-B	monoamine oxidase type B
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NA	Not applicable
nCPAP	nasal continuous positive airway pressure
NOS	not otherwise specified
NPSG	nocturnal polysomnography
OSAHS	sleep apnea/hypopnea syndrome
PLMD	periodic limb movement disorder
PSG	polysomnography
PVT	Psychomotor Vigilance Task
REM	rapid eye movement
RLS	restless leg syndrome
SAE	serious adverse event
SBP	systolic blood pressure
SCPT	the Steer-Clear Performance Test
SF-36	Short Form Health Survey 36
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamate pyruvate transaminase
SWSD	shift work sleep disorder
t_{max}	time of maximum observed drug concentration
ULN	upper limit of normal
WBC	white blood cell count
WHO	World Health Organisation

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1 NEW INDICATION FOR PROVIGIL: EXCESSIVE SLEEPINESS ASSOCIATED WITH DISORDERS OF SLEEP AND WAKEFULNESS

Background Information

Modafinil was first marketed in France in 1994 for the treatment of narcolepsy, and is currently marketed in over 20 countries. PROVIGIL, the brand name of modafinil in the United States (US), was approved as an orphan drug by the FDA in 1998 to "improve wakefulness in patients with excessive daytime sleepiness (EDS) associated with narcolepsy." The efficacy of PROVIGIL in reducing EDS associated with narcolepsy was established in two 9-week, double-blind, placebo-controlled, multicenter studies conducted in the US in patients with narcolepsy, which served as the basis of approval in the US.

In June 1999, Cephalon met with FDA's Division of Neuropharmacological Drug Products (the Division) to discuss the clinical development program that would be required to expand the indication of PROVIGIL for the treatment of patients with excessive sleepiness associated with other clinical conditions. Specifically, Cephalon proposed that excessive sleepiness (ES) is a debilitating symptom common to many medical disorders, such as obstructive sleep apnea/hypopnea syndrome (OSAHS), Parkinson's disease, and Alzheimer's disease, and that PROVIGIL may be beneficial to any patient with ES. However, at that time, the FDA indicated there was a need for more efficacy data in a "normal" sleep-deprived population and that conditions such as Parkinson's disease and Alzheimer's disease would not be appropriate as the etiology of ES in these patients is not clear. The Division stated they would be interested in efficacy data in OSAHS and other models of sleep-deprived states.

In December 1999, an IND (IND 59,522 Serial 000) was submitted "for use of PROVIGIL in the treatment of excessive daytime sleepiness (EDS) associated with acute and chronic sleep deprivation," and the initial proposed expanded indication for PROVIGIL was "for EDS secondary to sleep deprivation associated with OSAHS." This indication had previously been discussed in the 24 June 1999 meeting with the Division. It was noted in this submission that a broader indication might be pursued for "improvement of wakefulness in patients with EDS associated with acute and chronic sleep deprivation."

In reply to the IND submission, the Division noted that in its view Cephalon's "proposed claim for treatment of EDS in patients with sleep apnea, could be considered a pseudo-specific claim, misleadingly implying that PROVIGIL was specifically effective against EDS in this setting." The Division further noted that "since EDS occurs in multiple clinical settings, they would be willing to grant a general claim for the treatment of EDS if it could be shown that PROVIGIL had an effect on this symptom regardless of the clinical setting in which it occurred."

At a meeting in July 2000, the Division made a new proposal, namely that the expanded indication should be narrowed to "[to improve wakefulness in patients with] ES in sleep disorders due to interference with night time sleep or disordered sleep." In subsequent interactions, this potential indication was referred to as "to improve wakefulness in patients with ES associated with sleep loss in sleep disorders." In the discussion following this proposal, the Division requested data from 3 models meeting these criteria to support this indication and

suggested restless leg syndrome/periodic limb movement disorder (RLS/PLMD) as a potential model in addition to OSAHS. Cephalon discussed with the Division the potential to include ES associated with sleep loss in patients with shift work sleep disorder (SWSD) as the third model. The Division's notes from this meeting stated that "the possibility of using sleep deprived patients due to shift work as a third disease model was discussed and FDA expressed a preference for this type of study in lieu of a study in sleep-deprived healthy subjects, if such a study were appropriately designed to separate out circadian misalignment effects."

In a subsequent letter to the Agency, dated 20 December 2000, Cephalon clarified that patients with SWSD are indeed a highly select population of shift workers with a diagnosed sleep disorder, and that The American Sleep Disorders Association criteria for this disorder have been published since 1987. Cephalon explained in detail that the ES in patients with SWSD is due to both a circadian drive for sleep and chronic sleep disruption.

In that letter, Cephalon also detailed its effort to identify the appropriate third clinical model. Cephalon and its scientific and clinical advisors investigated all potential models and concluded that the 3 models, which represented the broadest group of patients with ES that was at least in part associated with sleep loss in sleep disorders, were residual ES in OSAHS, SWSD, and narcolepsy. At this time Cephalon also proposed the following alternative for the expanded indication for PROVIGIL "to improve wakefulness in patients with excessive sleepiness associated with sleep loss in sleep disorders." In addition, Cephalon proposed the principal and supportive studies that would be sufficient to support the application for this expanded indication. These are the patient populations included in the studies that were submitted in the supplemental New Drug Application for PROVIGIL.

On 2 April 2001, Cephalon and its expert consultants met with the Division to discuss the details of the application to expand the indication for PROVIGIL "to improve wakefulness in patients with excessive sleepiness associated with sleep disorders." This meeting initiated discussion on the appropriateness of SWSD as a model and the desire of the Division to distinguish patients with SWSD from shift workers who are "otherwise normal." This issue was discussed further at a subsequent meeting on 9 August 2001. As a result of these discussions, it was agreed that patients enrolled in the SWSD trial would meet criteria for "substantial pathological sleepiness" and, as such, meet more than the minimal criteria for the SWSD. In addition, the daytime polysomnography (PSG) that would occur as part of screening assessments would confirm objectively that patients were having difficulty with daytime sleep and had no other disorder to account for their sleepiness. In addition, at the 2 April 2001 meeting, agreement was reached between the Division and Cephalon that the narcolepsy data that formed the basis of the approval of the current indication could be resubmitted, with longer-term data, as part of the data supporting the expanded indication.

At the 2 April 2001 meeting and, to a lesser extent, at the 9 August 2001 meeting, there was a good deal of discussion about the appropriateness of the models and what sleep disorders would and would not be included in the potential indication. The Division concluded that it was premature to discuss exact wording of the indication and that because of the precedent-setting nature of the application it would consult with the Advisory Committee to:

a) determine whether the 3 proposed models are adequately representative of sleep disorders to justify a broader label

b) determine the likelihood that the drug effects seen in the models studied would be predictive of the drug effects seen in all sleep disorders

Proceeding under the understanding that an Advisory Committee meeting would be necessary, Cephalon completed the studies and prepared an application containing representative clinical models of ES associated with narcolepsy, residual ES associated with OSAHS, and ES associated with SWSD assuming that these models would be acceptable in pursuit of an expanded indication to improve wakefulness in patients with ES associated with disorders of sleep and wakefulness.

The following points are provided as an overall summary of rationale behind this effort:

- ES is a symptom that occurs in qualitatively similar ways in many clinical settings.
- ES is a consequence of some degree of sleep disruption and/or increased drive for sleep.
- Regardless of the underlying cause, ES can be measured objectively and subjectively using standardized, clinically relevant, well-validated tools.
- Patients with ES associated with disorders of sleep and wakefulness ES can be grouped into 3 diagnostic categories based of the nature of the primary underlying pathophysiology: disorders of sleep-wake dysregulation, disorders of sleep disruption, and disorders of circadian misalignment.
- These disorders can be operationally defined as disorders of sleep and wakefulness.
- Within the disorders of sleep and wakefulness, clinical studies have been conducted, or resubmitted with longer-term data, in clinical models that are representative of each of the 3 categories defined above: disorders of sleep-wake dysregulation (ie, narcolepsy [resubmitted]), disorders of sleep disruption (ie, residual ES in OSAHS), and disorders of circadian misalignment (ie, SWSD).
- Together these 3 models represent the largest group of patients encountered in clinical practice in which pharmacologic management of ES may be necessary and appropriate.

2 REVIEW OF EXCESSIVE SLEEPINESS AND DISORDERS OF SLEEP AND WAKEFULNESS

2.1 Introduction

Excessive sleepiness (ES) is a disabling symptom that is associated with many clinical conditions. This review of ES and disorders of sleep and wakefulness explains the physiology of normal and excessive sleepiness and delineates specific disorders of sleep and wakefulness with the symptom of ES.

Furthermore, the manifestations and consequences of ES are described, as is how these are assessed in clinical practice and in clinical trials using objective and subjective measures. Finally, the treatment of patients with ES associated with disorders of sleep and wakefulness is considered.

2.2 Normal and Excessive Sleepiness

2.2.1 Physiology of Normal sleepiness

Sleepiness is defined as a biologic drive state characterized by a decreased ability to maintain wakefulness or an increased propensity to fall asleep. Sleepiness is a physiologic indication of the need for sleep, analogous to hunger reflecting the need for food (Carskadon and Dement 1982, Thorpy 1992). Like hunger, it is normal for individuals to experience some degree of sleepiness.

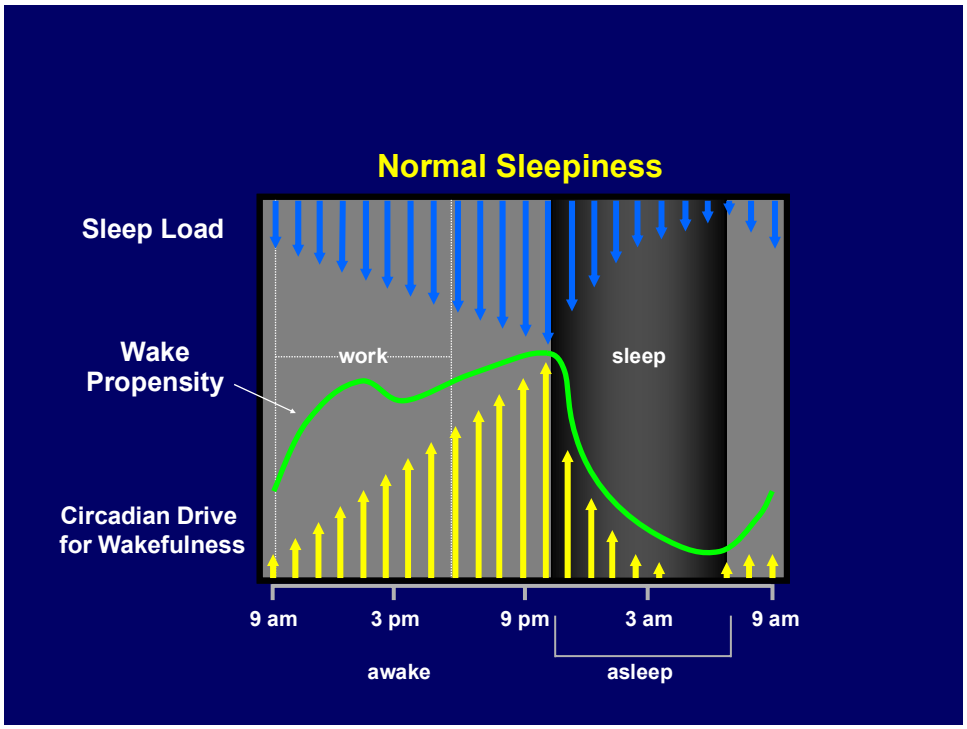
The normal variation in sleepiness is primarily determined by an interaction between 2 processes: (1) the homeostatic sleep drive (ie, sleep load or sleep pressure), which is determined by the amount and continuity of sleep and the time since last sleep, and (2) the circadian drive for wakefulness or sleep, which is determined by the biological time of day (Borbély 1982).

Sleep load/pressure increases nearly linearly as a function of the amount and continuity of sleep as well as the amount of time awake since the last sleep episode. This accumulation of sleep pressure serves to increase sleep propensity and decrease ones ability to maintain wakefulness. In healthy people therefore, homeostatic sleep pressure builds up with increasing time awake and is relieved by sleep.

In humans, a circadian process controlled by the suprachiasmatic nucleus is responsible for generating an alerting signal during the day that opposes the homeostatic sleep pressure so that wakefulness can be sustained throughout the entire waking day. At night a circadian drive for sleep serves to increase sleep propensity and decrease one's ability to maintain wakefulness.

The level of sleepiness or, inversely, wakefulness that a person experiences is therefore the result of a well-defined interaction between the homeostatic and circadian sleep-wake processes. The daily variation in wakefulness can be expressed as the wake propensity rhythm, which is depicted in Figure 1.

Figure 1: Physiologic Determinants of Sleepiness



2.2.2 Excessive Sleepiness

Excessive sleepiness is a symptom that is defined as difficulty in maintaining wakefulness and increased propensity to fall asleep, even in inappropriate circumstances and in situations that interfere with activities of daily living. Depending on the population sample and definition, the prevalence of ES is about 10%.

ES is the result of either sleep disruption or an increased drive for sleep during wakefulness. Sleep disruption can take multiple forms including inability to initiate or sustain consolidated sleep or sleep fragmentation. ES can also occur as a result of an inappropriate increased drive for sleep. This increased drive for sleep can be a result of dysregulation in the sleep-wake mechanisms or as a result of misalignment between a person's sleep-wake patterns and the internal circadian rhythms responsible for promoting sleep and wakefulness.

2.3 Sleep Disorders

The information presented in this section is an attempt to categorize sleep disorders according to (1) the international Classification of Sleep Disorders (ICSD), (2) the ICSD differential diagnosis of ES, and (3) the disorders of sleep and wakefulness.

2.3.1 International Classification of Sleep Disorders (ICSD)

Sleep disruption and/or increased drive for sleep during wakefulness and the subsequent ES can be seen in a variety of sleep disorders. These sleep disorders are classified as part of the International Classification of Sleep Disorders (ICSD). The ICSD was produced by the American Academy of Sleep medicine (AASM) in association with the European Sleep Research Society, the Japanese Society of Sleep Research, and the Latin American Sleep Society.

The ICSD classifies sleep disorders into 4 categories as outlined below.

1. Dyssomnias	A. Intrinsic Sleep Disorders B. Extrinsic Sleep Disorders C. Circadian Rhythm Sleep Disorders
2. Parasomnias	A. Arousal Disorders B. Sleep–Wake Transition Disorders C. Parasomnias Usually Associated with REM Sleep D. Other Parasomnias
3. Sleep Disorders Associated with Mental, Neurologic or Other Medical Disorders	A. Associated with Mental Disorders B. Associated with Neurologic Disorders C. Associated with Other Medical Disorders
4. Proposed Sleep Disorders	

REM = rapid eye movement.

The first category comprises the dyssomnias (ie, the disorders of initiating and maintaining sleep and the disorders of excessive sleepiness, or both). The second category, the parasomnias, comprises the disorders of arousal, partial arousal, or sleep stage transition. These disorders do not cause a primary complaint of insomnia or excessive sleepiness. The third category, sleep disorders associated with mental, neurologic, or other medical disorders, comprises disorders with a prominent sleep complaint that is felt to be secondary to another condition. The fourth category, proposed sleep disorders, includes those disorders for which there is insufficient information available to confirm their acceptance as definitive sleep disorders.

The disorders that are considered primary sleep disorders are contained in the first 2 categories (dyssomnias and parasomnias). The dyssomnias are further subdivided in part into the intrinsic, extrinsic and circadian-rhythm sleep disorders. The distinction into intrinsic and extrinsic sleep disorders divides the major causes of insomnia and excessive sleepiness into those that are induced primarily by factors within the body (intrinsic) and those primarily by factors outside of the body (extrinsic). The full presentation of the ICSD outline can be found in Appendix 1.

2.3.2 ICSD Differential Diagnosis of Excessive Sleepiness

The classification outlined above classifies the sleep disorders mainly for coding purposes; it is not a differential-diagnostic tool. For the purpose of categorizing disorders with ES, it may be useful to classify those disorders based on the presence of this symptom. Outlined below is a differential-diagnostic listing of sleep disorders that have ES as a primary symptom from the ICSD (pages 334-335). Using this organizational classification it is easier to define the primary sleep disorders with associated ES.

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ICSD Differential Diagnosis of Excessive Sleepiness

Primary sleep disorders	*Other**
Associated with Sleep Induced Respiratory Impairment	**Associated with Behavioural/Pyschologic Disorders**
a. Obstructive Sleep Apnea Syndrome b. Central Sleep Apnea Syndrome c. Central Alveolar Hypoventilation Syndrome d. Sleep-Related Neurogenic Tachypnea†	a. Inadequate Sleep Hygiene b. Insufficient Sleep Syndrome c. Limit-Setting Sleep Disorder d. Adjustment Sleep Disorder
Associated with Movement Disorders	**Associated with Mental Disorders**
a. Periodic Limb Movement Disorder b. Restless Legs Syndrome	a. Mood Disorders b. Psychoses c. Alcoholism
Associated with Disorders of the Timing of the Sleep-Wake Pattern	**Associated with Environmental Factors**
a. Long Sleeper† b. Time Zone Change (Jet-Lag) Syndrome c. Shift Work Sleep Disorder d. Delayed Sleep-Phase Syndrome e. Advanced Sleep-Phase Syndrome f. Non-24-Hour Sleep-Wake Syndrome g. Irregular Sleep-Wake Pattern	a. Environmental Sleep Disorder b. Toxin-Induced Sleep Disorder **Associated with Drug Dependency** a. Hypnotic-Dependent Sleep Disorder b. Stimulant-Dependent Sleep Disorder c. Alcohol-Dependent Sleep Disorder **Other Causes of Excessive Sleepiness** a. Menstrual-Associated Sleep Disorder b. Pregnancy Associated Sleep Disorders
Associated with Neurologic Disorders (NOS)	**Associated with Neurologic Disorders (NOS)***
a. Narcolepsy b. Idiopathic Hypersomnia c. Post-Traumatic Hypersomnia d. Recurrent Hypersomnia e. Subwakefulness Syndrome†	f. Fragmentory Myoclonus, g. Parkinsonism, h. Dementia i. Sleeping Sickness j. Sleep-Related Epilepsy

*Not considered primary sleep disorders (excluded).
†Proposed sleep disorder (excluded).
ICSD = International Classification of Sleep Disorders (2001); NOS = not otherwise specified.

In summary, the categories of primary sleep disorders that are associated with ES are those associated with sleep-induced respiratory impairment, movement disorders, the timing of the sleep-wake pattern, and neurologic disorders (items a through e only).

2.4 Excessive Sleepiness Associated With Disorders of Sleep and Wakefulness

2.4.1 Categorization of Disorders of Sleep and Wakefulness

As discussed earlier, the pathophysiology of ES is sleep disruption and increased drive for sleep during wakefulness. It is therefore possible to link the 4 categories of primary sleep disorders with ES to the main underlying pathophysiologic driver of the ES, resulting in 3 categories. These 3 categories are:

(a) **sleep-wake dysregulation** – disorders in which there is a central nervous system (CNS) pathology leading to an increased drive for sleep during the time one needs to be awake. These disorders would include those classified as associated with neurologic disorders (items a through e only) using the ICSD differential diagnosis outlined in section 2.3.2

(b) **sleep disruption** – disorders in which there is disturbed sleep resulting in increased sleep load during the time one needs to be awake. These disorders would include those classified as associated with sleep induced respiratory impairment and movement disorders using the ICSD differential diagnosis outlined in section 2.3.2.

(c) **circadian misalignment** – disorders in which there is a displacement or misalignment of situational appropriate sleep and wakefulness to times that are not in phase with the circadian rhythm leading to both an increased drive for sleep during the time of desired wakefulness, and disturbed sleep during the time of desired sleep. These disorders would include those associated with disorders of the timing of the sleep wake pattern using the ICSD differential diagnosis outlined in section 2.3.2.

It is important to note that, in respect to these disorders of sleep and wakefulness, regardless of which specific disorder is being considered the main driver of the ES, the disorders have evidence of both disturbed sleep and an increased drive for sleep during times of desired wakefulness. It is therefore possible to refer to these disorders collectively as *Disorders of Sleep and Wakefulness*.

Using the categories outlined above, the *Disorders of Sleep and Wakefulness* are definable in terms of those disorders which should be included in the indication being sought and are listed in Table 1.

Table 1: Pathologic Categories of Disorders of Sleep and Wakefulness With Associated Excessive Sleepiness

Disorders of sleep and wakefulness (ICSD)		
Sleep–wake dysregulation	**Sleep disruption**	**Circadian-rhythm misalignment**
Narcolepsy∗	**OSAHS∗**	**SWSD∗**
Idiopathic Hypersomnia	Central Sleep Apnea Syndrome	Advanced Sleep-Phase Syndrome
Recurrent Hypersomnia	Central Alveolar Hypoventilation Syndrome	Delayed Sleep-Phase Syndrome
Post-Traumatic Hypersomnia	Periodic Limb Movement Syndrome	Non-24-hour Sleep-wake Syndrome
	Restless Leg Syndrome	Time Zone Change Syndrome
		Circadian Rhythm Sleep Disorder NOS
		Irregular Sleep Wake Pattern

∗Narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD) are the most commonly encountered disorders in the 3 categories and will be discussed in greater detail below.
ICSD = International Classification of Sleep Disorders.
CNS = central nervous system.
NOS = not otherwise specified.

In deciding the contents of this submission, Cephalon in conjunction with external advisors and after discussions with the Agency considered various representative disorders of sleep and wakefulness that would best suit a clinical program that would ultimately support the new indication. The efforts of this endeavor resulted in the belief that 3 models comprising narcolepsy, OSAHS, and SWSD were the best representation of primary sleep disorders with ES as the primary symptom. The rationale for this was that in clinical practice narcolepsy, OSAHS and SWSD are the most commonly encountered disorders of sleep-wake dysregulation, disorders of sleep disruption, and disorders of circadian-rhythm misalignment, respectively.

Thus, ES, the same symptom but from 3 distinct underlying disorders, is at the center of this broadened indication. Cephalon's clinical program did not focus on a single specific disease or disorder; rather, it focused on a single symptom, ie, ES associated with disorders of sleep and wakefulness. A more in-depth discussion on each category follows.

2.4.2 Excessive Sleepiness Associated With Disorders of Sleep-Wake Dysregulation

In these disorders, ES is primarily caused by some CNS disruption in the internal processes responsible for promoting wakefulness and sleep. The disorders in this category are narcolepsy, idiopathic hypersomnia, recurrent hypersomnia, and posttraumatic hypersomnia. All of these disorders involve some degree of CNS disturbance that leads to the dysregulation of the sleep-wake processes.

Narcolepsy results from a hypocretin (orexin) deficiency in the brain that is characterized by excessive sleepiness that typically is associated with cataplexy and other rapid eye movement (REM) sleep phenomena, such as sleep paralysis and hypnagogic hallucinations. It is the most prevalent of the *Disorders of Sleep-Wake Dysregulation* and is estimated to occur in 0.03% to 0.16% of the general population (ICSD 2001). Narcolepsy most commonly begins in the second

decade of life and excessive sleepiness is usually the first symptom to appear. Accidents due to sleepiness and cataplexy can occur in almost any situation and serious social consequences can result because of ES leading to marital disharmony and loss of employment.

The diagnostic criteria for narcolepsy are given in the International Classification of Sleep Disorders (ICSD 347) and are provided in Appendix 2.

2.4.3 Excessive Sleepiness Associated With Disorders of Sleep Disruption

In these disorders, ES is caused by insufficient duration of sleep or, most commonly, inadequate consolidation of sleep (ie, sleep disruption). Sleep in these patients is characterized by frequent, brief arousals of less than 15 seconds in duration. The disorders in this category are the sleep-related breathing disorders such as obstructive sleep apnea syndrome, central sleep apnea syndrome, central alveolar hypoventilation syndrome; movement disorders such as periodic limb movement syndrome and restless legs syndrome.

The arousing stimulus differs among these disorders and can be identified in some (eg, apneas in OSAHS or leg movements in PLMD), but not in others. Regardless of the etiology, these arousals result in disturbed sleep. This results in a decrease in the more restorative "deep" sleep (ie, stages 3 to 4 non–rapid-eye-movement [NREM] and rapid-eye-movement [REM] sleep) and an increase in the less restorative "light" sleep (ie, stage 1 NREM sleep). Overall, regardless of the underlying etiology, disturbed sleep leads to patients starting each day with an elevated sleep load manifested by the symptom of ES.

Obstructive sleep apnea is the most commonly diagnosed and clinically managed disorder in this category. OSAHS is estimated to affect 2% to 4% of middle-aged adults (Young et al 1993). Men are at greater risk for OSAHS than women; other risk factors include obesity and increasing age (American Sleep Disorders Association 2000). It is characterized by repeated episodes of complete or partial collapse of the upper airway during sleep, with a reduction in blood oxygen saturation (American Sleep Disorders Association 2000). This leads to frequent arousals during sleep and disrupted, inefficient, poor-quality sleep (Guilleminault 1989). The sleep disruption seen in OSAHS (ie, sleep fragmentation/impaired sleep consolidation) is also typical of the other disorders in this category in which ES is a primary complaint.

The diagnostic criteria for OSAHS are given in the International Classification of Sleep Disorders (ICSD 780.53-0) and are provided in Appendix 2.

2.4.4 Excessive Sleepiness Associated With Disorders of Circadian Misalignment

In these disorders, ES is caused by a misalignment between the sleep-wake patterns and the internal processes responsible for promoting sleep and wakefulness. The disorders in this category are shift work sleep disorder, time zone change syndrome, irregular sleep-wake pattern, delayed sleep-phase syndrome, advanced sleep-phase syndrome, and non-24-hour sleep-wake syndrome.

Due primarily to the large number of shift workers and its profound impact on productivity and safety, SWSD is the most commonly encountered disorder in this category. A shift worker is

defined as someone who works outside the standard hours of 0700 to 1800 (Monk and Folkard 1992). Although the true prevalence of SWSD is unknown it is thought to affect 2% to 5% of shift workers (ICSD 2001).

Shift workers experience a major misalignment between the work-rest schedule imposed by their occupation and the circadian rhythm. A proportion of shift workers are not able to adapt to this misalignment and experience ES in relation to work shifts. Although the specific predisposing factors are not known, there are individual differences both in the ability to adapt internal circadian rhythms to different work-rest/light-dark schedules and in the ability to tolerate working and sleeping out of alignment with the internal processes responsible for promoting sleep and wakefulness. Regardless of the predisposing factors, ES associated with SWSD is caused by increased drive for sleep because individuals are attempting to work when the internal sleep-wake processes are promoting sleep and attempting to sleep when the internal sleep-wake processes are promoting wakefulness causing disturbed sleep. In the other disorders within the category of circadian misalignment, the primary cause of ES is the same, ie, misalignment between external sleep-wake patterns and the internal sleep-wake processes.

The diagnostic criteria for SWSD are given in the International Classification of Sleep Disorders (ICSD 307.45-1) and are provided in Appendix 2.

2.4.5 Appropriateness of Models Used in the Clinical Program

The 3 models chosen in this clinical program (ie, narcolepsy, OSAHS, and SWSD) appropriately represent the individual disorders with associated ES within the *Disorders of Sleep and Wakefulness* on the basis of prevalence, severity of ES, and chronicity of ES.

(a) Prevalence of Excessive Sleepiness

As stated previously, the models chosen, narcolepsy, OSAHS, and SWSD, are the most commonly diagnosed and managed disorders within the categories of sleep-wake dysregulation, sleep disruption, and circadian misalignment, respectively, for which the symptom of ES is a primary complaint. Although narcolepsy is by far the most commonly diagnosed disorder of sleep-wake dysregulation, it remains an uncommon disorder with a prevalence of 0.03% to 0.16% of the general population. OSAHS is considerably more common with a prevalence of 2% to 4% of middle-aged adults, and although the true prevalence of SWSD is unknown, it is thought to affect approximately 2% to 5% of shift workers.

(b) Severity of Excessive Sleepiness

The symptom of ES can be rated as mild, moderate, or severe. Mild ES, which may not manifest itself every day, is present only during times of rest or when little attention is required, and produces a minor impairment of social or occupational function. Moderate ES that manifests itself every day is present in very mild physical activities requiring a mild to moderate degree of attention, and produces moderate impairment of social or occupational function. Severe ES, which manifests itself every day, is present during times of physical activity and when moderate levels of attention are required, and produces marked impairment of social or occupational function.

ES associated with *Disorders of Sleep and Wakefulness* can occur with different levels of severity and, as such, disorders with varying levels of severity of ES were included in Cephalon's clinical program. For example, patients with OSAHS treated with nasal continuous positive airway pressure (nCPAP) therapy tend to experience less severe ES than patients with narcolepsy. Although patients with SWSD do not have ES upon awakening they experience moderate to severe ES during their night shift and commute home. It is well documented that patients with narcolepsy are clearly at the extreme with severe ES throughout the entire waking day.

The inclusion of disorders with differing degrees of severity of ES has allowed the assessment of efficacy and safety of PROVIGIL at the current approved dose of 200 mg administered once daily across a spectrum of patients with moderate to severe ES.

(c) Chronicity of Excessive Sleepiness

The chronicity of ES is another important factor. ES associated with the *Disorders of Sleep and Wakefulness* can have different levels of chronicity. The symptom of ES in some disorders, such as recurrent hypersomnia and non-24-hour sleep-wake syndrome, can be quite severe but may occur in relatively short episodes, from several days to several weeks at a time. In other disorders, such as idiopathic hypersomnia, the symptoms of ES can be life-long. The disorders studied, ie, narcolepsy, OSAHS and SWSD, reflect this diversity in chronicity. Although it can be a chronic disorder, SWSD is a disorder that by definition occurs temporally associated with night work and, therefore, requires intermittent drug administration. Narcolepsy, on the other extreme, is a chronic condition that requires life-long pharmacologic management. Therefore, Cephalon's clinical program included disorders required daily and intermittent administration.

2.5 Manifestations and Consequences of Excessive Sleepiness Associated With Disorders of Sleep and Wakefulness

Regardless of the underlying pathophysiology of the ES, the manifestations and consequences of ES are similar and consistent across the disorders of sleep and wakefulness. The manifestations of ES vary with the degree of ES present and include changes in concentration, lapses of attention, and unintentional napping. The most disabling consequences of ES in these disorders are behavioral in nature and fall into 3 categories: undesired sleep episodes, effects on performance, and effects on mood (Greenberg et al 1987, Roth et al 1988, Aldrich 1989, Breslau et al 1996, Simon and Vonkorff 1997, Roth and Ancoli-Israel 1999, Mitler et al 2000, Richardson and Roth 2001). Behavioral consequences can include accidents, decreased work productivity, and depressed mood. These can all contribute to impaired quality of life, health perceptions, and functional status (Broughton et al 1981, Broughton and Broughton 1994, Weaver et al 1997, Marrone et al 1998).

2.6 Excessive Sleepiness, Sleep, and Quality-of-Life Measures

2.6.1 Excessive Sleepiness

Excessive sleepiness can be quantified using objective or subjective measures. The key methods of measuring ES include the following:

- Objective measures
  - —Physiologic measures of sleep tendency, eg, the Maintenance of Wakefulness Test (MWT), the Multiple Sleep Latency Test (MSLT)
  - —Neurobehavioral measures of the impact of ES, eg, the Psychomotor Vigilance Task (PVT), the Steer-Clear Performance Test (SCPT)
- Subjective measures
  - —Clinician-completed measures based on patient interview, eg, Clinical Global Impression of Severity or Change (CGI-S or CGI-C)
  - —Patient-completed measures, eg, Epworth Sleepiness Scale (ESS), Karolinska Sleepiness Scale (KSS), and patient diaries

2.6.1.1 Objective Measures

(a) MSLT/MWT

The standard objective measures of ES are the MSLT and MWT, both of which are measures of the physiologic tendency to fall asleep. Although, as described below, the testing procedures differ, they are considered to be largely interchangeable and measure the same variable, ie, sleep latency. An increased or faster tendency to fall asleep reflects a greater level of sleepiness. The methodology for the MSLT was first described more than 25 years ago. The procedure requires a subject to lie down in a quiet darkened room and not resist falling asleep (Carskadon et al 1986).

The methodology of the MWT resembles that of the MSLT except that the subject is instructed to attempt to stay awake, sitting in a darkened room without taking extraordinary measures such as vigorous mental or physical activity to remain awake (Hartse et al 1982, Mitler et al 1982, Doghramji et al 1997). In general, a mean MSLT latency of less than 10 minutes and a mean MWT latency of less than 15 minutes are considered indicative of ES.

The MSLT and MWT have been validated in a wide variety of clinical conditions known to cause ES. They have been shown to be sensitive to factors that increase sleepiness, such as sleep disruption, sleep loss, and sleep disorders, and have been shown to be responsive to manipulations that reduce ES (Dement et al 1978, Härmä et al 1998, US Modafinil in Narcolepsy Multicenter Study Group 1998). Using the MSLT and the MWT, pathologic levels of ES have been documented in patients with narcolepsy and OSAHS (Mitler et al 1982, George et al 1996, Roth and Roehrs 1996, US Modafinil in Narcolepsy Multicenter Study Group 1998, 2000).

Studies have demonstrated that a subset of night shift workers demonstrates significant sleepiness during their usual work times as assessed by the MSLT and MWT (Åkerstedt 1998).

(b) PVT/SCPT

The impact of ES can be measured by objective neurobehavioral measures such as the PVT and SCPT (Dinges et al 1997, George et al 1997). The tendency to experience microsleeps, evidenced by lapses and increased reaction times during performance tasks such as these is considered relevant to real-world situations.

One of the most frequently used neurobehavioral measures of the impact of sleepiness is the PVT, which measures behavioral alertness (Dinges et al 1997, Jewett et al 1999). During PVT testing, a visual stimulus appears and the subject responds. The ability to sustain attention and respond rapidly becomes unstable when ES is present. The PVT has been extensively validated to be sensitive to measure ES.

Although there are a number of performance parameters that can be extracted from the PVT, the key parameter is number of lapses. Lapses of attention are brief episodes of nonresponsivity, sometimes caused by microsleeps, and are associated with impairment of performance.

The SCPT is a personal computer-based test of performance that evaluates the operator's ability to avoid obstacles. Individual results are reported on the basis of the number and percentage of obstacles that were avoided or hit, the time of each hit, and the frequency that the obstacles appeared (speed). The SCPT has been used in studies in patients with OSAHS and narcolepsy (Findley et al 1995, Cephalon data on file).

2.6.1.2 Subjective Measures

Subjective measures of ES can be divided into assessments completed by clinicians on the basis of patient interviews and those completed by the patients themselves.

(a) CGI

The most commonly used clinician-completed measure is the Clinical Global Impressions (CGI) scale. The CGI scale is a standardized assessment tool that allows the clinician to rate the severity of illness, change in clinical condition over time, and efficacy of treatment on the basis of an interview with a patient (Guy 1976). The CGI scale consists of the Clinical Global Impression of Severity (CGI-S) scale, a measure of the severity of the clinical condition and the CGI-C scale, a measure of the change in condition. The CGI-C scale consists of 7 categories from very much improved to very much worse. This instrument can be also anchored to a specific symptom, such as the patient's report of their level of ES.

(b) ESS/KSS

The patient-completed measures of ES can be divided into 3 categories: (a) self-reports of the level of sleepiness, (b) self-reports of sleep propensity in various daily-life situations, and (c) reports of sleep events (eg, unintentional naps). Measures of the level of sleepiness, such as

the KSS are sensitive to both sleep deprivation and time of day (Hoddes et al 1973, Åkerstedt and Gillberg 1990, Babkoff et al 1991, Johnson et al 1991). The KSS is a 9-point scale that ranges from 1=very alert to 9=very sleepy, great effort to keep awake or fighting sleep. Patients rate the level of sleepiness that occurred within the 5 minutes before the scale is completed (Åkerstedt and Gillberg 1990). The KSS has been commonly used in occupational medicine research.

The ESS, a measure of subjective sleep propensity, is the most commonly administered patient-completed scale for assessing ES in medicinal research and has been validated in many patient populations. Subjects are instructed to rate their chance of dozing off or falling asleep in 8 different situations varying in their soporific nature using an evaluation interval of the previous 4 weeks. An ESS score of 10 or more is considered representative of ES (Roehrs et al 2000). An ESS score is independent of short-term variations in sleepiness due to time of day and inter-day variations (Johns 1994).

2.6.2 Sleep

The polysomnogram (PSG) is the continuous and simultaneous recording of multiple physiologic variables during sleep. A variety of parameters of sleep can be obtained from a PSG recording. On of the most valuable parameters in patients with ES is sleep efficiency, because it is a good indicator of disturbed sleep. Sleep efficiency is the proportion of total sleep time to time in bed (ICSD 2001).

2.6.3 Quality-of-Life Measures and Functional Outcomes

In addition to those measures described above, the impact of ES on health perceptions and functional status can be measured by using non–disease-specific measures such as the Short Form Health Survey 36 (SF-36) or scales more disease- or symptom-specific such as the Functional Outcomes of Sleep Questionnaire (FOSQ).

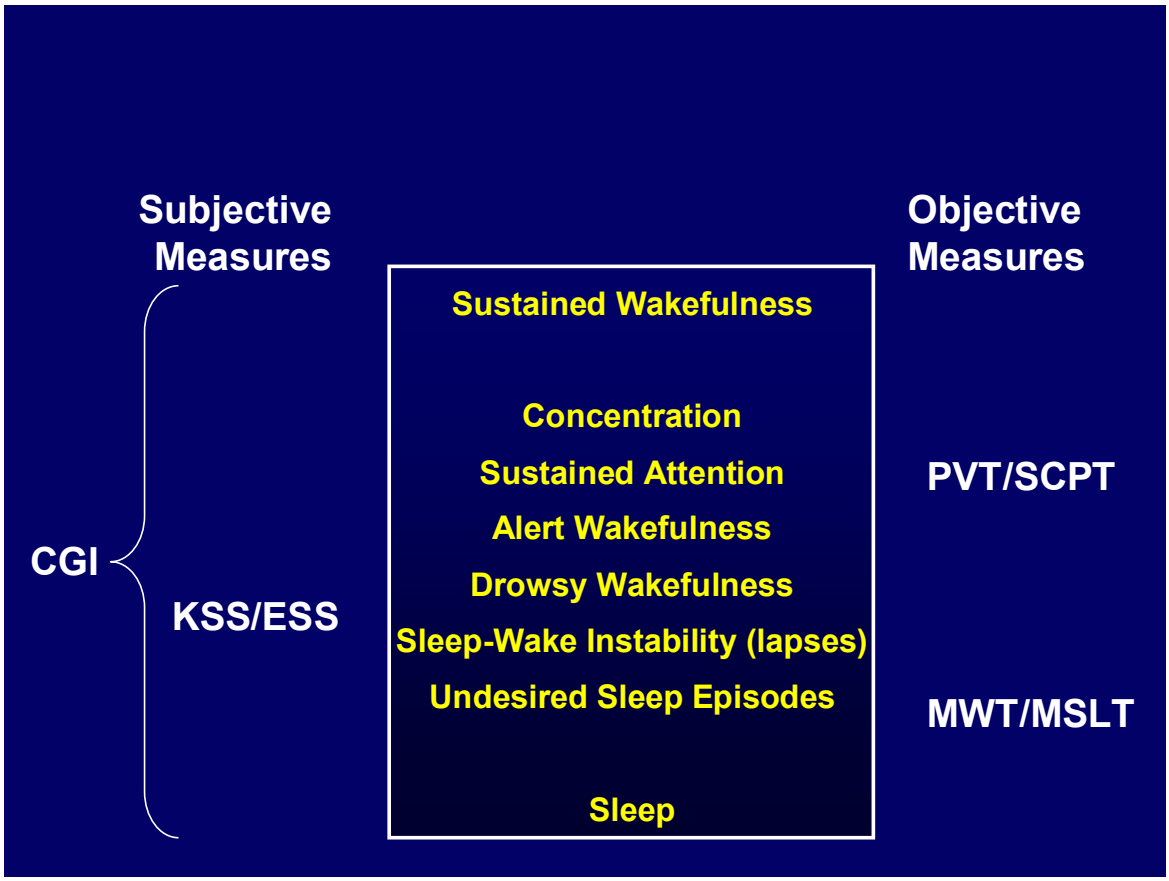
The SF-36 was developed as a generic measure of perceived health status, and has been used across a wide range of clinical settings, providing self-reports of behavioral functioning and perceived psychological well-being.

The FOSQ was specifically designed to assess the impact of disorders of ES on functional outcomes relevant to daily behaviors and quality of life and was developed utilizing patients with OSAHS (Weaver et al 1997).

2.6.4 Overview of Measures of Excessive Sleepiness

Across the disorders of sleep and wakefulness, ES and the impact of ES, can be measured in a variety of ways using both objective and subjective measures. These measurements of ES, or the impact of ES, can be conceptualized as providing information in a way that corresponds to the different manifestations of ES (Figure 2); thus, while these measures are interrelated, they each also provide unique and complementary information. All of the above measures were employed in the assessment of efficacy in Cephalon's clinical program.

Figure 2: Measurements of Excessive Sleepiness



2.7 Excessive Sleepiness Treatment Considerations

In assessing patients with a symptom of ES, appropriate measures should be taken to diagnose and manage, where possible, the underlying pathology and primary cause of the symptom. For example, in patients with OSAHS, nCPAP is considered appropriate primary therapy and should be instigated prior to initiating a pharmacologic therapy to promote wakefulness. In patients with disorders of circadian misalignment attempts may be made to shift the patient's circadian rhythm by using light therapy or chronobiotics (Loube et al 1999, Kryger 2000). Often these treatments, however, do not completely resolve the ES (Seidel et al 1984, Walsh et al 1991, Sforza and Krieger 1992, Bédard et al 1993, Engleman et al 1994, Czeisler and Wright 1999, Turek and Czeisler 1999, Stradling and Davies 2000). Patients with ES despite appropriate treatment of the underlying pathology would therefore be candidates for clinical intervention to manage this symptom

2.8 Overall Summary

In summary, ES is a disabling symptom that is associated with many clinical conditions. The *Disorders of Sleep and Wakefulness* define a subgroup of sleep disorders that are associated with

a primary complaint of ES, both in terms of disorders that should be included in this definition, and, as importantly, in terms of those disorders that should be excluded.

Cephalon believes that narcolepsy, OSAHS, and SWSD are representative models of the *Disorders of Sleep and Wakefulness* with associated ES in terms of prevalence, severity of the symptom of ES, the chronicity of the symptom of ES, and that the data outlined in the sections on efficacy and safety should be translatable to the other disorders of sleep and wakefulness. The manifestations and consequences of ES are consistent across the disorders of sleep and wakefulness, although varying in degree of severity and chronicity. In addition, there are standardized and accepted methods to quantify and measure ES, which are routinely used in clinical research and are sensitive to the effects of therapeutic interventions.

3 PHARMACOLOGY OF MODAFINIL

Modafinil, the active ingredient in PROVIGIL, is a racemic compound. The product is formulated as white, capsule-shaped, uncoated tablets (100 mg and 200 mg).

Mechanism of action

The precise molecular target(s) for modafinil are not yet known, but at pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including adenosine, benzodiazepines, GABA (gamma aminobutyric acid), histamine-3, hypocretin/orexin (an intact hypocretin/orexin system is not required for modafinil-promoted wakefulness), melatonin, norepinephrine, 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 has no activity.

Unlike the wakefulness induced by central nervous system (CNS) stimulants, modafinil-induced wakefulness appears not to be mediated by dopamine. Modafinil is not a direct or indirect dopamine agonist and is inactive in several nonclinical models designed to detect enhanced dopaminergic activity (Akaoka et al 1991, De Sereville et al 1994, Ferraro et al 1997). Modafinil is only a weak inhibitor of the dopamine reuptake site, leading to a small increase in extracellular dopamine but no increase in dopamine release (Mignot et al 1994) (data on file).

Modafinil-induced wakefulness is not antagonized by haloperidol or α-methyl-p-tyrosine, as occurs with stimulants, and there is no effect on the firing rate of dopaminergic neurons in the substantia nigra or of adrenergic neurons in the locus coeruleus with modafinil (Lin et al 1992, Ferraro et al 1997) (data on file).

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). Unlike sympathomimetic agents, modafinil treatment does not cause significant locomotor activity and there is no evidence of rebound hypersomnia compared to that observed with amphetamine treatment (Simon et al 1994, Touret et al 1995, Edgar and Seidel 1997). Modafinil has minimal peripheral autonomic effects, including changes in cardiovascular and hemodynamic parameters (data on file).

Modafinil has been reported to promote wakefulness in rats, cats, dogs, nonhuman primates, and drosophilia. Of note, modafinil has been shown to promote wakefulness in dogs with narcolepsy and dogs with sleep apnea. In addition, modafinil treatment attenuates rest in drosophilia, but does not alter circadian synchronization (Hendricks et al 2001).

Pharmacokinetics

Pharmacokinetic evaluations have shown that the absorption of modafinil is rapid with peak plasma concentrations occurring at 2 to 4 hours after oral administration. The single- and multiple-dose pharmacokinetics of modafinil are similar. Steady-state concentrations of total modafinil are reached after 2 to 4 days of treatment, and the average half-life of modafinil after multiple doses is about 15 hours. The major route of elimination (~90%) is metabolism, primarily by the liver, with subsequent renal elimination of the metabolites. Two metabolites reach appreciable concentrations in plasma, ie, modafinil acid and modafinil sulfone; however, they do not contribute to the wake-promoting activity of modafinil. Food has no effect on overall modafinil bioavailability; however, its absorption (t_{max}) may be delayed by approximately 1 hour if taken with food.

Drug interactions

The results of clinical drug-drug interaction studies suggest that the likelihood of clinically significant pharmacokinetic interactions with modafinil is low, with the exception of substrates for CYP3A4/5 that undergo substantial gastrointestinal pre-systemic elimination. In vitro, modafinil was determined to be an inducer of CYP1A2, CYP2B6, and CYP3A4/5 and a suppressor of CYP2C9 in primary cultures of human hepatocytes. Clinical interaction studies were conducted to determine whether sustained treatment with modafinil at 400 mg/day would cause alterations in the pharmacokinetic parameters for substrates for those enzymes, ie, warfarin (CYP2C9, CYP1A2, and CYP3A4/5) or ethinyl estradiol and triazolam (CYP3A4/5). No effect was shown on the pharmacokinetic parameters for either of the enantiomers of warfarin, but evidence of CYP3A4/5 induction was obtained for ethinyl estradiol and triazolam. However, the enzyme induction appeared to be primarily gastrointestinal rather than hepatic. There also has been a single report (Le Cacheux et al 1997) of an apparent interaction of modafinil with cyclosporine, another CYP3A4/5 substrate. The results suggest that the likelihood of clinically significant interactions is highest for medications that undergo extensive gastrointestinal first-pass metabolic elimination via CYP3A4/5, such as cyclosporine, verapamil, lovastatin, buspirone, and triazolam.

The potential drug interactions of modafinil (200 mg) with methylphenidate (40 mg) and dextroamphetamine (10 mg) were examined in single-dose crossover studies. The only effects observed, ie, approximately 1-hour delays in the t_{max} for modafinil, were not considered to be clinically significant. The effects of methylphenidate 20 mg per day and dextroamphetamine 20 mg per day at steady state on the pharmacokinetics of modafinil 400 mg per day at steady state were also examined, with administration of the stimulant 8 or 7 hours, respectively, after the daily dose of modafinil. No effects on the pharmacokinetic parameters of modafinil were observed. Overall, modafinil appears to have a low potential for pharmacokinetic drug interactions with dextroamphetamine or methylphenidate.

A crossover study of the potential interaction of modafinil at 200 mg per day for 3 days with clomipramine (50 mg) did not produce evidence of an interaction. However, there has been a single report (Grözinger et al 1998) of an interaction in a patient with narcolepsy who was CYP2D6-deficient. This result was consistent with in vitro results indicating that modafinil and its sulfone metabolite are selective, reversible inhibitors of the enzyme CYP2C19, which contributes to the metabolic elimination of clomipramine. The results of a subsequent in vitro study, conducted in human liver microsomal preparations, confirmed that modafinil and modafinil sulfone can decrease the rates of metabolism of diazepam, clomipramine, desmethylclomipramine, and fluoxetine, which are substrates of CYP2C19. However, the effects were generally small and highly variable, suggesting that the incidence of clinically significant interactions will be low.

The potential for interactions via the other enzymes on which effects were observed in vitro cannot be definitively ruled out. Therefore, it is recommended that caution be exerted when modafinil is administered concomitantly with substrates of any of these enzymes, particularly if the substrates are drugs with small therapeutic indices (eg, phenytoin, warfarin).

4 STUDY DESIGNS, PATIENT POPULATIONS, AND EFFICACY AND QUALITY-OF-LIFE RESULTS

4.1 Overview of Studies and Study Designs for the Evaluation of Efficacy

Six double-blind, placebo-controlled, parallel-group studies (furthered described in Table 2) form the basis of the determination of the efficacy of PROVIGIL treatment to improve wakefulness in adults with ES associated with disorders of sleep and wakefulness. The 6 double-blind placebo controlled studies, hereafter referred to as the principal studies, are:

- narcolepsy studies C1538a/**301**/NA/US and C1538a/**302**/NA/US (hereafter referred to as studies 301 and 302)
  NOTE: These studies were the basis of the approval of PROVIGIL in narcolepsy.
- OSAHS studies C1538a/**303**/AP/US-UK and C1538a/**402**/AP/US (hereafter referred to as studies 303 and 402)
- SWSD studies C1538a/**305**/CM/US and C1538a/**306**/CM/US-UK (hereafter referred to as studies 305 and 306)

Table 2: Description of Principal Studies

	Narcolepsy		OSAHS		SWSD	
Description	**Study 301**	**Study 302**	**Study 303**	**Study 402**	**Study 305**	**Study 306**
Double-blind Placebo-controlled Parallel-group	√	√	√	√	√	√
Dosage studied (mg/day)	200, 400	200, 400	200, 400	400	200	200, 300
Visits (screening, (baseline [BL] and week)	1, 3, 6, 9	1, 3, 6, 9	4, 8, 12	1, 4	4, 8, 12	4, 8, 12
Treatment regimen	once daily in the morning		once daily in the morning		intermittently once before night shifts	

OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder.

In all 6 studies, patients had a documented complaint of ES, met standard accepted diagnostic criteria for the respective disorder of sleep and wakefulness being studied, and had no other cause of ES.

Outcome measures used in the studies included:

- objective measures of sleepiness (measures of physiologic sleepiness [MWT/MSLT])
- objective measures of the impact of sleepiness (PVT/SCPT)
- subjective measures of sleepiness (clinician rating [CGI-C] and patient rating [ESS/KSS])
- other measures (quality of life [SF-36] and functional status [FOSQ])

Outcome measures were designated as either primary or secondary (Table 3).

Table 3: Primary and Secondary Outcome Measures by Study

	Narcolepsy		OSAHS		SWSD	
Measures	**Study 301**	**Study 302**	**Study 303**	**Study 402**	**Study 305**	**Study 306**
Efficacy						
MWT	P	P	P	---	---	---
MSLT	S	S	---	S	P	---
CGI-C	P	P	P	S	P	---
ESS/KSS	S	S	S	P	S	---
PVT/SCPT	S	S	S	S	S	---
Other						
FOSQ	---	---	S	S	S	S
SF-36	S	S	S	---	---	S

P = primary; S = secondary; MWT = Maintenance of Wakefulness Test; MSLT = Multiple Sleep Latency Test; CGI-C = Clinical Global Impression of Change; ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale; PVT = Psychomotor Vigilance Task; SCPT = Steer-Clear Performance Test; FOSQ = Functional Outcomes of Sleep Questionnaire; OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder; SF-36 = Short Form Health Survey 36.

Of note, 4 of the 6 principal studies are considered pivotal in nature. These are narcolepsy studies 301 and 302, OSAHS study 303, and SWSD study 305. Each of these 4 studies had dual primary outcome measures (MWT/MSLT and CGI-C), an objective measure and a subjective measure. With regard to the 2 remaining studies, OSAHS study 402 is not considered a pivotal study because of its shorter duration and single primary efficacy measure (ESS), and SWSD study 306 is not considered a pivotal study because it did not include any predetermined efficacy measures. A summary of data from the primary efficacy outcome measures of the 4 pivotal studies follows the individual presentations of efficacy of the 6 individual studies.

In the sections below for the presentation of efficacy and quality-of-life data, first the individual studies are described followed by individual presentations of study population data then individual presentations of efficacy and quality-of-life results (by study) relative to primary measures, secondary measures, and quality-of-life and functional status assessments.

Data from these 6 studies demonstrate that PROVIGIL significantly and consistently improved wakefulness across the disorders of sleep and wakefulness and across objective and subjective measures.

4.2 Narcolepsy—Studies 301 and 302

Narcolepsy studies 301 and 302 (both pivotal)

Narcolepsy studies 301 and 302 are the pivotal Phase 3 studies that formed the basis of PROVIGIL's approved indication, ie, to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy. For that reason, the presentation of results included herein is brief in comparison to that of the OSAHS and SWSD studies.

4.2.1 Narcolepsy Study Design

The evaluation of the efficacy of PROVIGIL for the treatment of adult patients with ES associated with narcolepsy is based on 2 double-blind, placebo-controlled studies (studies 301 and 302).

Studies 301 and 302 were conducted at 18 and 21 US centers, respectively. Patients with narcolepsy were randomized to receive a daily dose of 200 or 400 mg of PROVIGIL, or a placebo, during a 9-week, double-blind, treatment period. For study 301, a 2-week wash-out period followed the double-blind treatment period, and for study 302 a 2-week discontinuation/withdrawal period followed the double-blind treatment period, in which the effects of treatment withdrawal were evaluated. For both studies there were separate 40-week open-label continuation periods and subsequent 48-week open-label extension phases followed by 3 additional open-label continuous 48-week extension phases of each study.

Eligible patients had a current diagnosis of narcolepsy according to criterion A or B as established by the American Sleep Disorders Association (ASDA), as follows:

- criterion A: recurrent daytime naps or lapses into sleep that occurred almost daily for at least 3 months plus sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy)
- criterion B: a complaint of ES or sudden muscle weakness plus associated features: sleep paralysis, hypnagogic hallucinations, automatic behaviors, disrupted major sleep episode; plus polysomnography demonstrating 1 of the following: (a) sleep latency less than 10 minutes; (b) rapid eye movement (REM) sleep latency less than 20 minutes and an MSLT with a mean sleep latency of less than 5 minutes; or (c) 2 or more sleep onset REM periods; and the absence of any medical or psychiatric disorder that could account for the symptoms

For inclusion in the study, eligible patients considered under criterion A (cataplexy) had to have had a mean sleep latency of 8 minutes or less on the MSLT. Eligible patients considered under criterion B (narcolepsy and no cataplexy) had to have had a mean sleep latency of 5 minutes or less on the MSLT. All eligible patients had to have had 2 sleep onset REM periods documented within the MSLT.

The primary efficacy measures in these studies were the MWT and CGI-C. The secondary efficacy measures that were evaluated included the MSLT, ESS, and SCPT; the quality-of-life measure is the SF-36. The MWT, ESS, and SCPT were measured at baseline, week 3, week 6, and week 9 (or final visit). The MWT involved 4 sessions conducted at 2-hour intervals (0800, 1000, 1200, and 1400). The average sleep latency from the 4 sessions was the primary variable of the MWT. CGI-C was measured at week 3, week 6, and week 9 (or final visit) relative to baseline CGI-S. MSLT and SF-36 were measured at baseline and at week 9 (or final visit). The MSLT was performed on the day following the MWT. The MSLT involved 4 naps at approximately 2-hour intervals with sleep latency determined from the average of the 4 tests.

4.2.2 Narcolepsy Data Analysis

The *efficacy evaluable set* included data from all patients who received at least 1 dose of study drug (PROVIGIL or placebo) and had at least 1 postbaseline assessment for both primary efficacy assessments (MWT and CGI-C). The primary time point for analysis was defined as the last postbaseline assessment. All continuous efficacy and quality-of-life variables (average sleep latency from the MWT, total score from the ESS, average sleep latency from the MLST, and 8 individual and 2 composite scores from the SF-36) were analyzed as the change from baseline to the final visit. The change from baseline for each continuous variable was analyzed using an analysis of covariance (ANCOVA) with treatment and center as factors and baseline value as a covariate. Pairwise comparisons between each PROVIGIL treatment group and the placebo group were performed.

The distribution of the 7 CGI-C categories was compared across the 3 treatment groups by a Cochran-Mantel-Haenszel (CMH) chi-square test adjusted for center and modified ridit scores were used to account for the ordered categories of this scale.

4.2.3 Narcolepsy Study Population

4.2.3.1 Patient Disposition

Narcolepsy studies 301 and 302

Together in studies 301 and 302, 350 PROVIGIL-treated patients and 180 placebo-treated patients were considered efficacy evaluable. A summary of patient disposition for the studies is presented in Table 4.

Table 4: **Patient Disposition in Narcolepsy Studies 301 and 302 (Randomized Patients)**

	Treatment group					
	Study 301			Study 302		
Analysis set	PROVIGIL 200 mg/day N (%)	PROVIGIL 400 mg/day N (%)	Placebo N (%)	PROVIGIL 200 mg/day N (%)	PROVIGIL 400 mg/day N (%)	Placebo N (%)
Randomized	96	95	94	90	90	93
Efficacy evaluable	95 (99)	86 (91)	92 (98)	83 (92)	86 (96)	88 (95)
Completed study	93 (97)	81 (85)	87 (93)	77 (86)	84 (93)	82 (88)
Discontinued study	3 (3)	14 (15)	5 (5)	12 (13)	5 (6)	11 (12)
Adverse event	1 (1)	11 (12)	0	6 (7)	1 (1)	3 (3)
Lack of efficacy	1 (1)	0	3 (3)	2 (2)	0	2 (2)
Consent withdrawn	0	2 (2)	0	3 (3)	3 (3)	3 (3)
Protocol violation	1 (1)	1 (1)	0	0	1 (1)	1 (1)
Other	0	0	2 (2)	1 (1)	0	2 (2)

4.2.3.2 Demographic Characteristics

Narcolepsy studies 301 and 302

Patient demographic characteristics were similar for the 3 treatment groups. A summary of patient characteristics including sex, race, age, weight for the 2 studies is presented in Table 5.

Table 5: Demographic Characteristics in Narcolepsy Studies 301 and 302 (Safety Evaluable Set)

		Treatment group					
		Study 301			Study 302		
Characteristic		PROVIGIL 200 mg/day (N=96)	PROVIGIL 400 mg/day (N=95)	Placebo (N=92)	PROVIGIL 200 mg/day (N=89)	PROVIGIL 400 mg/day (N=89)	Placebo (N=93)
Sex, N (%)	Male	44 (46)	43 (45)	42 (46)	37 (42)	44 (49)	43 (46)
	Female	52 (54)	52 (55)	50 (54)	52 (58)	45 (51)	50 (54)
Race, N (%)	White	70 (73)	77 (81)	73 (79)	79 (89)	75 (84)	81 (87)
	Black	23 (24)	16 (17)	17 (18)	9 (10)	6 (7)	9 (10)
	Other	3 (3)	2 (2)	2 (2)	1 (1)	8 (9)	3 (3)
Age (yr)	Mean (SD)	40 (13.5)	44 (13.7)	42 (12.3)	42 (13.1)	42 (13.3)	41 (14.1)
	Min, max	18, 67	19, 67	18, 68	18, 67	18, 66	17, 66
Weight (lb)	Mean (SD)	195 (42.5)	189 (44.3)	186 (45.0)	174 (44.3)	181 (39.1)	179 (38.2)

Min = minimum; max = maximum.

4.2.3.3 Baseline Patient Characteristics

Narcolepsy studies 301 and 302

The 3 treatment groups were comparable with regard to baseline CGI-S ratings, MWT sleep latency, and NPSG sleep efficiency (Table 6). At baseline, more than 80% of all patients studied were at least moderately ill as assessed by the CGI-S, with MWT sleep latency of approximately 6 minutes.

Table 6: Baseline Patient Characteristics in Narcolepsy Studies 301 and 302 (Efficacy Evaluable Set)

Baseline parameter		Treatment group					
		Study 301			Study 302		
		PROVIGIL 200 mg/day (N=95)	PROVIGIL 400 mg/day (N=86)	Placebo (N=92)	PROVIGIL 200 mg/day (N=83)	PROVIGIL 400 mg/day (N=86)	Placebo (N=88)
CGI-S rating, N (%)	Normal	0	0	1 (1)	0	0	0
	Borderline ill	2 (2)	1 (1)	2 (2)	4 (5)	1 (1)	5 (6)
	Mildly ill	14 (15)	10 (12)	10 (11)	18 (22)	11 (13)	12 (14)
	Moderately ill	38 (40)	37 (43)	47 (51)	38 (46)	39 (45)	38 (43)
	Markedly ill	31 (33)	32 (37)	28 (30)	19 23)	30 (35)	26 (30)
	Severely ill	0	0	0	0	0	0
	Extremely ill	10 (11)	6 (7)	4 (4)	4 (5)	5 (6)	7 (8)
Mean (SD) MWT sleep latency in minutes		5.8 (5.02)	6.6 (5.16)	5.8 (4.67)	6.1 (4.86)	5.9 (4.37)	6.0 (4.97)
NPSG sleep efficiency (% of time in bed spent asleep)							
N		95	86	92	83	86	87
Mean (SD)		86 (11.2)	87 (8.7)	88 (8.7)	87 (9.5)	89 (7.7)	85 (14.0)

CGI-S = Clinical Global Impression of Severity
MWT = Maintenance of Wakefulness Test; NPSG = nocturnal polysomnography.

Overall, the patients who participated in narcolepsy studies 301 and 302 had baseline subjective and objective evidence of ES (from CGI-S and MWT assessments) and had baseline disturbed sleep (from NPSG).

4.2.4 Narcolepsy Efficacy and Quality-of-Life Results

4.2.4.1 Primary Efficacy Measures: MWT and CGI-C

MWT sleep latency

In narcolepsy study 301, mean sleep latency from the MWT increased from the baseline assessment to the final visit by 2.3 minutes in both the 200-mg/day and 400-mg/day PROVIGIL groups, while mean sleep latency for the placebo group decreased by 0.7 minutes.

Between-treatment comparisons (each PROVIGIL dose vs placebo) were statistically significant ($p<0.001$).

In narcolepsy study 302, mean sleep latency from the MWT increased from the baseline assessment to the final visit by 2.2 minutes for the 200-mg/day PROVIGIL group and by 2.0 minutes for the 400-mg/day PROVIGIL groups, while mean sleep latency for the placebo group decreased by 0.7 minutes. Between-treatment comparisons (each PROVIGIL dose vs placebo) were statistically significant ($p<0.001$).

MWT sleep latency results for studies 301 and 302 are presented in Table 7.

Table 7: Average Sleep Latency (Minutes) From MWT at the Final Visit in Narcolepsy Studies 301 and 302 (Efficacy Evaluable Set)

	Study 301			Study 302		
Observation	**PROVIGIL 200 mg/day (N=95)**	**PROVIGIL 400 mg/day (N=86)**	**Placebo (N=92)**	**PROVIGIL 200 mg/day (N=83)**	**PROVIGIL 400 mg/day (N=86)**	**Placebo (N=88)**
Baseline						
Mean (SD)	5.8 (5.0)	6.6 (5.2)	5.8 (4.7)	6.1 (4.9)	5.9 (4.4)	6.0 (5.0)
Final visit						
Mean (SD)	8.2 (6.2)	8.9 (6.3)	5.1 (4.7)	8.3 (5.9)	7.9 (5.3)	5.3 (4.5)
Change from baseline						
Mean (SD)	2.3 (4.7)	2.3 (4.9)	-0.7 (4.6)	2.2 (4.5)	2.0 (4.8)	-0.7 (4.2)
p-value[a]	<0.001	<0.001	---	<0.001	<0.001	---

[a] The p-value under each PROVIGIL treatment group column is for the comparison of that treatment group to the placebo treatment group.
MWT = Maintenance of Wakefulness Test.

In both narcolepsy studies, MWT sleep latency was significantly higher for both the 200- and 400-mg/day PROVIGIL groups compared to the placebo group at each time point (weeks 3, 6, and 9 [p=0.001]).

CGI-C ratings

Comparisons of the distribution of CGI-C ratings at the final visit showed statistically significant improvement in clinical condition for patients in both the PROVIGIL 200- and 400-mg/day treatment groups in the 2 narcolepsy studies ($p<0.00)1$ in study 301 and $p<0.003$ in study 302 for both PROVIGIL treatment groups) when compared with patients in the placebo treatment groups. GCI-C rating results for studies 301 and 302 are presented in Table 8.

Table 8: CGI-C Ratings (Number [%] in Each Category) at the Final Visit in Narcolepsy Studies 301 and 302 (Efficacy Evaluable Set)

		Number (%) of patients		
Narcolepsy study	**Response category**	**PROVIGIL 200 mg/day**	**PROVIGIL 400 mg/day**	**Placebo**
Study 301	Total number of subjects	95	86	92
	Very much improved	7 (7)	8 (9)	4 (4)
	Much improved	25 (26)	35 (41)	8 (9)
	Minimally improved	29 (31)	19 (22)	22 (24)
	No change	27 (28)	20 (23)	43 (47)
	Minimally worse	5 (5)	3 (3)	11 (12)
	Much worse	2 (2)	1 (1)	3 (3)
	Very much worse	0	0	1 (1)
	p-value[a]	<0.0001	<0.0001	---
Study 302	Total number of subjects	83	86	88
	Very much improved	7 (8)	5 (6)	0
	Much improved	21 (25)	24 (28)	12 (14)
	Minimally improved	20 (24)	23 (27)	21 (24)
	No change	27 (33)	26 (30)	42 (48)
	Minimally worse	7 (8)	5 (6)	9 (10)
	Much worse	1 (1)	3 (3)	4 (5)
	Very much worse	0	0	0
	p-value[a]	0.0011	0.0028	---

[a] The p-value under each PROVIGIL treatment group column is for the comparison of that treatment group to the placebo treatment group.
CGI-C = Clinical Global Impression of Change.

4.2.4.2 Secondary Efficacy Measures: MSLT, ESS, and SCPT

The positive effect of PROVIGIL treatment in patients with narcolepsy as assessed by the secondary measures of the MSLT, ESS, and SCPT was consistent with that observed with the dual primary measures. The results of secondary measures for studies 301 and 302 are presented in Table 9.

Table 9: Mean (SD) Change From Baseline to the Final Visit in MSLT, ESS, and SCPT Results in Narcolepsy Studies 301 and 302 (Efficacy Evaluable Set)

	Study 301			Study 302		
Variable	PROVIGIL 200 mg/day	PROVIGIL 400 mg/day	Placebo	PROVIGIL 200 mg/day	PROVIGIL 400 mg/day	Placebo
MSLT sleep latency	1.9 (3.18) p=0.0059	1.9 (4.07) p=0.0059	0.5 (2.98)	2.0 (3.65) p=0.2033	2.3 (3.39) p=0.0334	1.3 (2.64)
ESS total score	–3.6 (4.7) p<0.0005	–4.3 (4.8) p<0.0001	–1.4 (3.7)	–4.3 (4.9) p<0.0001	–5.7 (5.0) p<0.0001	–1.7 (3.6)
SCPT % obstacles hit	–1.9 (11.6) ns	–1.5 (11.6) ns	0.8 (7.2)	–2.3 (8.2) p=0.016	–1.7 (6.6) p=0.018	0.6 (11.1)

Note: The p-value under each PROVIGIL treatment group column is for the comparison of that treatment group to placebo treatment.
ns = not statistically significant.
MSLT = Multiple Sleep Latency Test; ESS = Epworth Sleepiness Scale; SCPT = Steer-Clear Performance Test.

4.2.4.3 Quality-of-Life Assessment: SF-36

In narcolepsy study 301, there was no significant effect of PROVIGIL treatment on the change from the baseline assessment in physical composite summary score with either dosage; however, the mental composite summary score was increased significantly for the 400-mg/day PROVIGIL group compared to the placebo group (p=0.03). For the individual domains, significant differences from placebo were observed for vitality (200 mg/day, p=0.04; 400 mg/day, p<0.001), role physical (400 mg/day, p=0.009), and social functioning (400 mg/day, p=0.014).

In narcolepsy study 302, there was no significant effect of PROVIGIL treatment on the change from the baseline assessment in physical composite summary score with either dosage; however, the mental composite summary score was increased significantly for both PROVIGIL groups compared to the placebo group (200 mg/day, p=0.002; 400 mg/day, p=0.001). For the individual domains, significant differences from placebo treatment were observed for vitality (200 mg/day, p=0.003; 400 mg/day, p=0.013), role emotional (200 mg/day, p<0.001; 400 mg/day, p=0.002), physical functioning (200 mg/day, p=0.016), role physical (200 mg/day, p=0.036; 400 mg/day, p=0.008), and social functioning (400 mg/day, p=0.004).

4.2.5 Conclusions on Narcolepsy

The efficacy of PROVIGIL in the treatment of patients with narcolepsy was evaluated in 2 Phase 3 double-blind, placebo-controlled studies (studies 301 and 302) involving a total of 350 efficacy evaluable patients treated with PROVIGIL and 180 treated with placebo for up to 9 weeks (double-blind treatment period). The evaluations of efficacy in each study show that PROVIGIL treatment provides relief from the symptoms of ES associated with narcolepsy.

The results of the analyses of the MWT at the final visit demonstrate a significant increase in sleep latency for PROVIGIL-treated patients compared to placebo-treated patients (p<0.001, both PROVIGIL dosages). This is corroborated by the results of the analyses of CGI-C, which

indicate a significant difference between PROVIGIL and placebo treatment ($p<0.001$, both PROVIGIL dosages) in the distribution of CGI-C scores at the final visit. The results for secondary assessments of efficacy, including the MSLT, ESS, and SCPT were consistent with those for the primary assessments (MWT and CGI-C), with significant improvement in symptoms of sleepiness observed for both dosages of PROVIGIL compared to placebo. The data indicate that efficacy was obtained by week 3 and sustained over the course of the 9-week double-blind treatment period.

4.3 Obstructive Sleep Apnea/Hypopnea Syndrome—Studies 303 and 402

OSAHS studies 303 (pivotal study) and 402

The efficacy of PROVIGIL for the treatment of adult patients with residual ES associated with OSAHS was demonstrated in 2 double-blind, placebo-controlled studies (studies 303 and 402).

4.3.1 Study Design for OSAHS Study 303

Study 303 was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 39 centers by 42 investigators in the US and 4 centers in the UK. Patients with residual ES associated with OSAHS were randomized to receive a daily dose of 200 or 400 mg of PROVIGIL, or a placebo, during a 12-week, double-blind treatment period. The usage and effectiveness of nCPAP therapy was evaluated during a pre-enrollment period that included a screening visit, a 2-night evaluation of nCPAP therapy effectiveness, and a 2-week evaluation of nCPAP therapy compliance. Initially, patients were stratified into 3 subpopulations (nCPAP-compliant, partially nCPAP-compliant, and nonusers of nCPAP therapy) prior to randomization. However, after enrollment for the study began, the protocol was amended to discontinue the nonuser strata from the study. At the time of the amendment, 18 nonusers of nCPAP therapy had been enrolled and were allowed to continue in the study. After completion of the double-blind treatment period, patients were eligible to enter a 12-month open-label treatment extension period.

Eligible patients met the ICSD criteria for OSAHS (ICSD Code 780.53-0), were users of nasal nCPAP therapy, and had residual ES (as indicated by an ESS score greater than or equal to 10 at screening) associated with OSAHS. Patients who met the following criteria were enrolled:

- nCPAP-compliant—nCPAP therapy use was ≥4 hours/night on ≥70% of nights, with documentation of prior adequate nCPAP therapy education and intervention efforts, and for whom nCPAP therapy was effective (had an apnea-hypopnea index [AHI] decrease [<10 and >50%] from historic AHI [ie, while not treated with nCPAP therapy])
- partially nCPAP-compliant—nCPAP therapy use was <4 hours/night on >30% of nights during the 2-week pre-enrollment evaluation period despite documentation of prior adequate nCPAP therapy education and intervention efforts, and for whom nCPAP therapy was effective

The primary efficacy measures in this study were the MWT and CGI-C. The secondary efficacy measures included the ESS and the PVT. The quality of life measures were the SF-36 and FOSQ. All efficacy and quality-of-life measures were assessed at baseline, week 4, week 8, and week 12 (or final visit). At each time point, four 20-minute sessions of the MWT were performed at 2-hour intervals. The first MWT session was to be conducted at least 2 hours after the morning dose of study drug. The PVT sessions were performed prior to each MWT session.

4.3.2 Data Analysis for OSAHS Study 303

The *efficacy evaluable set* included data from all patients who received at least 1 dose of study drug (PROVIGIL or placebo) and had at least 1 postbaseline efficacy evaluation on any measure. Patients who were nonusers of nCPAP therapy were excluded from the efficacy analysis since they were excluded from enrollment in an amendment to the protocol. The primary time point for analysis was defined as the last postbaseline assessment.

All continuous variables (MWT, ESS, PVT, SF-36, and FOSQ) were analyzed as the change from baseline; an ANCOVA with treatment and nCPAP strata (compliant vs partially compliant) as factors and the baseline value as a covariate was utilized. The CGI-C data were analyzed using the CMH (Cochran-Mantel-Haenszel) chi-square test adjusted for nCPAP strata, with modified ridit scores to account for ordered categories of CGI-C.

4.3.3 Study Population for OSAHS Study 303

4.3.3.1 Patient Disposition

In OSAHS study 303, 191 PROVIGIL-treated patients and 100 placebo-treated patients were considered efficacy evaluable (Table 10).

Table 10: Patient Disposition in OSAHS Study 303 (Randomized Patients)

	Number (%) of patients								
	PROVIGIL 200 mg/day			PROVIGIL 400 mg/day			Placebo		
Patient disposition	Compliant	Partially compliant	Nonuser	Compliant	Partially compliant	Nonuser	Compliant	Partially compliant	Nonuser
Randomized	91 (100)	13 (100)	6 (100)	88 (100)	13 (100)	7 (100)	89 (100)	15 (100)	5 (100)
Completed	75 (82)	11 (85)	4 (67)	71 (81)	10 (77)	4 (57)	80 (90)	13 (87)	4 (80)
Withdrawn	16 (18)	2 (15)	2 (33)	17 (19)	3 (23)	3 (43)	9 (10)	2 (13)	1 (20)
Death	0	0	0	0	0	0	0	0	0
Adverse event	8 (9)	2 (15)	0	10 (11)	1 (8)	3 (43)	2 (2)	1 (7)	0
Lack of efficacy	0	0	1 (17)	0	0	0	0	1 (7)	0
Consent withdrawn	1 (1)	0	0	6 (7)	1 (8)	0	1 (1)	0	1 (20)
Protocol violation	1 (1)	0	0	0	0	0	3 (3)	0	0
Noncompliance	3 (3)	0	0	0	0	0	1 (1)	0	0
Lost to follow-up	3 (3)	0	0	0	0	0	0	0	0
Other	0	0	1 (17)	1 (1)	1 (8)	0	2 (2)	0	0
Combined efficacy population		99 (90)			92 (85)			100 (92)	
Combined safety population		109 (99)			106 (98)			108 (99)	

4.3.3.2 Demographic Characteristics

A summary of patient characteristics including sex, race, age, weight, and body mass index (BMI) for study 303 is presented in Table 11.

Table 11: Demographic Characteristics in OSAHS Study 303 (Randomized Patients)

Demographic variable	PROVIGIL 200 mg/day (N=110)	PROVIGIL 400 mg/day (N=108)	Placebo (N=109)
Age, years			
Mean (SD)	47.9 (10.0)	48.5 (8.7)	50.9 (9.4)
Min, max	24.0, 68.0	28.0, 70.0	28.0, 68.0
Sex, n (%)			
Men	95 (86.4)	74 (68.5)	80 (73.4)
Women	15 (13.6)	34 (31.5)	29 (26.6)
Race, n (%)			
Caucasian	97 (88.2)	95 (88.0)	98 (89.9)
Black	7 (6.4)	9 (8.3)	8 (7.3)
Asian	2 (1.8)	1 (0.9)	2 (1.8)
Hispanic	3 (2.7)	2 (1.9)	1 (0.9)
Other	1 (0.9)	1 (0.9)	0
Weight, kg			
Mean (SD)	109.6 (23.3)	109.9 (25.9)	110.5 (24.4)
BMI			
Mean (SD)	35.8 (7.6)	36.0 (7.0)	36.9 (8.4)

OSAHS = obstructive sleep apnea/hypopnea syndrome; BMI = body mass index; min = minimum; max = maximum.

The distribution of patients across treatment groups was similar with regard to race, height, and weight with no statistically significant differences between the combined PROVIGIL treatment group and the placebo treatment group. Although the mean age and the distribution of men and women of patients in the placebo group were statistically significantly different when compared to the PROVIGIL treatment groups, this was not considered clinically significant. The average BMI (approximately 36 kg/m^2) indicates that the patient population in this study consisted of predominantly obese patients, which is a characteristic of patients with OSAHS.

4.3.3.3 Baseline Respiratory Disturbance Index and Oxygen Saturation

At entry into OSAHS study 303, the effectiveness of the patients' nCPAP therapy was demonstrated by relatively low apnea-hypopnea index (AHI) and high oxygen saturation values (Table 12). Historic (ie, without CPAP therapy) AHI values are included for comparative purposes.

Table 12: Historic and Baseline Apnea-Hypopnea Index (AHI) and Baseline Oxygen Saturation for Patients in OSAHS Study 303

Parameter	PROVIGIL 200 mg/day (N=99)	PROVIGIL 400 mg/day (N=92)	Placebo (N=100)
Historic AHI			
Mean (SD)	46.8 (26.52)	46.9 (28.87)	49.6 (31.65)
Baseline AHI			
Mean (SD)	4.2 (5.56)	4.2 (5.58)	5.8 (8.11)
Baseline oxygen saturation			
Mean (SD)	91.0 (3.70)	90.7 (3.46)	90.1 (5.53)

OSAHS = obstructive sleep apnea/hypopnea syndrome

4.3.3.4 Baseline Patient Characteristics

The 3 treatment groups were comparable with regard to baseline CGI-S, MWT sleep latency, and NPSG sleep efficiency (Table 13). At baseline, about 60% of all patients studied were at least moderately ill as assessed by the CGI-S, with mean MWT sleep latency of approximately 13 minutes.

Table 13: Baseline Patient Characteristics in OSAHS Study 303 (Efficacy Evaluable Set)

Baseline parameter		Treatment group: PROVIGIL 200 mg/day (N=99)	PROVIGIL 400 mg/day (N=92)	Placebo (N=100)
CGI-S rating, N (%)	Normal	2 (1.9)	0	2 (1.9)
	Borderline ill	10 (9.5)	7 (7.1)	5 (4.8)
	Mildly ill	24 (22.9)	23 (23.2)	26 (24.8)
	Moderately ill	45 (42.9)	39 (39.4)	47 (44.8)
	Markedly ill	16 (15.2)	14 (14.1)	20 (19.1)
	Severely ill	2 (1.9)	8 (7.1)	0
	Extremely ill	0	0	0
MWT sleep latency (minutes)				
Mean (SD)		13.1 (5.5)	13.6 (5.4)	13.8 (5.7)
NPSG sleep efficiency (% of time in bed spent asleep)				
N		95	89	95
Mean (SD)		86.7 (8.4)	86.0 (11.7)	82.3 (14.9)

CGI-S = Clinical Global Impression of Severity; OSAHS = obstructive sleep apnea/hypopnea syndrome; MWT = Maintenance of Wakefulness Test; NPSG = nocturnal polysomnography.

Overall, the patients who participated in OSAHS study 303 had baseline subjective and objective evidence of ES (from CGI-S and MWT assessments) and had disturbed sleep at baseline (from NPSG).

4.3.4 Efficacy and Quality-of-Life Results for OSAHS Study 303

4.3.4.1 Primary Efficacy Measures: MWT and CGI-C

MWT sleep latency

In OSAHS study 303, mean sleep latency from the MWT increased from the baseline assessment to the final visit by 1.6 and 1.5 minutes for patients in the 200-mg/day and 400-mg/day PROVIGIL treatment groups, respectively, while mean sleep latency for the placebo treatment decreased by 1.1 minutes ($p<0.0001$ for the primary comparison between the combined PROVIGIL and placebo treatment groups). Between-treatment comparisons (each dose of PROVIGIL vs placebo) were also statistically significant ($p<0.0001$). MWT sleep latency results for study 303 are presented in Table 14.

Table 14: Average Sleep Latency (Minutes) From the MWT at the Final Visit for OSAHS Study 303 (Efficacy Evaluable Set)

	Treatment group						
	PROVIGIL 200 mg/day		PROVIGIL 400 mg/day		Placebo		
Time point	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	p-value[a]
Baseline	96	13.1 (5.46)	89	13.6 (5.37)	100	13.8 (5.69)	
Week 12 (or final visit)	90	14.8 (5.30)	88	15.0 (5.29)	95	12.6 (5.83)	
Mean change from baseline to week 12 (or final visit)	88	1.6 (4.82)	86	1.5 (5.00)	95	–1.11 (4.56)	
p-value[a]		0.0001		0.0001		---	<0.0001

[a]The p-value under each PROVIGIL treatment group column is for the comparison of that treatment group to the placebo treatment group. The p-value in the far-right column is the p-value for the comparison of the combined PROVIGIL treatment group to the placebo treatment group.
MWT = Maintenance of Wakefulness Test; OSAHS = obstructive sleep apnea/hypopnea syndrome.

Improvements in mean sleep latency from the MWT were apparent at the first postbaseline observation (week 4), with mean increases of 1.2 and 2.1 minutes for patients in the 200-mg/day and 400-mg/day PROVIGIL treatment groups, respectively, and a mean decrease of 1.9 minutes in the placebo treatment group. The differences in average sleep latency were statistically significant ($p<0.0001$) at weeks 4 and 8 for patients in the combined PROVIGIL treatment group compared to patients in the placebo treatment group.

CGI-C ratings

In OSAHS study 303, comparison of the distribution of CGI-C ratings at the final visit showed statistically significant ($p<0.0001$) improvement in clinical condition for patients in the combined PROVIGIL treatment group compared to patients in the placebo treatment group. Between-treatment comparisons (each dose of PROVIGIL vs placebo) were also statistically significant for both the PROVIGIL 200-mg/day ($p=0.0006$) and 400-mg/day ($p<0.0001$) treatment groups. CGI-C rating results for study 303 are presented in Table 15.

Table 15: CGI-C Ratings (Number [%] in Each Category) at the Final Visit in OSAHS Study 303 (Efficacy Evaluable Set)

Category	Number (%) of patients			
	PROVIGIL 200 mg/day (N=99)	PROVIGIL 400 mg/day (N=92)	Placebo (N=100)	p-value[a]
Very much improved	14 (14)	12 (13)	6 (6)	
Much improved	27 (27)	28 (30)	11 (11)	
Minimally improved	19(19)	23 (25)	20 (20)	
No change	33 (33)	22 (24)	59 (59)	
Minimally worse	4 (4)	5 (5)	2 (2)	
Much worse	2 (2)	2 (2)	2 (2)	
Very much worse	0	0	0	
p-value[a]	0.0006	<0.0001	---	<0.0001

[a]The p-value under each PROVIGIL treatment group column is for the comparison of that treatment group to the placebo treatment group. The p-value in the far-right column is the p-value for the comparison of the combined PROVIGIL treatment group to the placebo treatment group.
CGI-C = Clinical Global Impression-Change; OSAHS = obstructive sleep apnea/hypopnea syndrome.

The comparison of the distributions of CGI-C ratings after 4 and 8 weeks of treatment showed statistically significant improvement in clinical condition for patients in the combined PROVIGIL treatment group compared to patients in the placebo treatment group at these time points (p=0.0003 and p=0.0013, respectively).

4.3.4.2 Secondary Efficacy Measures: ESS and PVT

The positive effect of PROVIGIL treatment in patients with OSAHS as assessed by the secondary measures of the ESS and PVT was consistent with that observed with both primary measures.

ESS total score

In OSAHS study 303, at the final visit, decreases from the baseline assessment in mean total ESS score were 4.5 for both the 200- and 400-mg/day PROVIGIL groups compared to a decrease of 1.8 for the placebo group. Between-treatment comparisons (each dose of PROVIGIL vs placebo) were statistically significant (p<0.0001). ESS results for study 303 are presented in Table 16.

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Table 16: Total Score From ESS at the Final Visit in OSAHS Study 303 (Efficacy Evaluable Set)

Category	Treatment group			
	PROVIGIL 200 mg/day (N=99)	PROVIGIL 400 mg/day (N=92)	Placebo (N=100)	p-value[a]
No. included in analysis	98	92	99	
Baseline				
Mean (SD)	15.7 (3.41)	14.9 (3.34)	14.7 (2.83)	
Final visit				
Mean (SD)	11.2 (4.90)	10.4 (5.37)	12.9 (3.81)	
Change from baseline				
Mean (SD)	–4.5 (4.65)	–4.5 (4.31)	–1.8 (3.54)	
p-value[a]	<0.0001	<0.0001	---	<0.0001

[a]The p-value under each PROVIGIL treatment group column is for the comparison of that treatment group to the placebo treatment group. The p-value in the far-right column is the p-value for the comparison of the combined PROVIGIL treatment group to the placebo treatment group.

OSAHS = obstructive sleep apnea/hypopnea syndrome; ESS = Epworth Sleepiness Scale.

The mean change from baseline ESS scores to all other time points (weeks 4, 8, and 12) showed statistically significant ($p<0.0001$) improvement (decrease in ESS score) for patients in the PROVIGIL treatment group compared with patients in the placebo treatment group.

PVT results

In OSAHS study 303, the mean change from baseline to the final visit for PVT measurements showed a decrease in the number of lapses (reaction times greater than 500 msec) that was statistically significant ($p=0.0006$) for patients in the PROVIGIL treatment group compared with patients in the placebo treatment group. PVT results for study 303 are presented in Table 17.

Table 17: Change from Baseline in PVT Number of Lapses at the Final Visit for OSAHS Study 303 (Efficacy Evaluable Set)

PVT parameter	Treatment group						p-value[a]
	PROVIGIL 200 mg/day		PROVIGIL 400 mg/day		Placebo		
Number of lapses	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	
Baseline	82	5.21 (11.45)	79	2.30 (3.85)	82	3.71 (6.61)	
Week 12 (or final visit)	78	2.30 (7.27)	76	1.38 (2.19)	80	3.54 (5.37)	
Mean change from baseline to week 12 (or final visit)	78	–2.76 (6.46)	76	–0.84 (3.48)	80	–0.24 (4.97)	
p-value[a]		0.0005		0.0131		---	0.0006

[a]The p-value under each PROVIGIL treatment group column is for the comparison of that treatment group to the placebo treatment group. The p-value in the far-right column is the p-value for the comparison of the combined PROVIGIL treatment group to the placebo treatment group.
PVT = Psychomotor Vigilance Task.

4.3.4.3 Quality-of Life Assessments: SF-36 and FOSQ

SF-36 results

At the final visit, for the SF-36, a statistically significant improvement was seen for patients in the combined PROVIGIL treatment group compared with the placebo treatment group for the physical composite summary ($p=0.0065$), general health ($p=0.0229$), and vitality ($p<0.0001$). For other component scores of the SF-36, positive trends were generally observed for the PROVIGIL treatment groups compared to the placebo treatment group; however, statistically significant differences were not observed for the domains of physical functioning, role physical, bodily pain, social functioning, role emotional, or mental heath.

FOSQ results

In OSAHS study 303, the mean change from the baseline assessment to the final visit in the total FOSQ score showed statistically significant ($p=0.001$) improvement for patients in the combined PROVIGIL treatment group compared with patients in the placebo treatment group. Statistically significant improvements were also seen for the individual subscales of activity ($p=0.0242$), general productivity ($p=0.0006$), and vigilance ($p=0.0007$), but not for social outcome or intimate relationships and sexual activity.

4.3.5 Study Design for OSAHS Study 402

Study 402 was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 22 centers in the US. Patients with obstructive sleep apnea appropriately treated with nCPAP therapy, but who had residual sleepiness, were randomized to receive either PROVIGIL or a placebo during a 4-week, double-blind treatment period. Prior to randomization, nCPAP therapy effectiveness was monitored for 2 days (overnight at screening), and the use of nCPAP therapy was monitored during a 21-day assessment period. Patients who were assigned to the

PROVIGIL treatment group received 200 mg/day for 1 week (week 1), followed by 400 mg/day for the remainder of the double-blind treatment period (weeks 2, 3, and 4). A 12-week, open-label treatment extension was offered to patients who completed the 4-week double-blind phase.

Eligible patients met the ICSD criteria for OSAHS (ICSD Code 780.53-0) and had residual ES (as indicated by an ESS score greater than or equal to 10 at screening) associated with OSAHS, despite regular use of nCPAP therapy (defined as 4 or more hours/night, 70% of nights during the 21-day nCPAP assessment period). All patients were required to have a current diagnosis of OSAHS, with an historic respiratory disturbance index (RDI) of 15 or more events/hour prior to or without nCPAP therapy. The effectiveness of nCPAP therapy was confirmed by baseline NPSG, ie, RDI of less than 10 and a greater than 50% reduction in RDI as previously demonstrated.

The primary efficacy measure in this study was the ESS. The secondary efficacy measures included the MSLT, CGI-C, and PVT. The quality-of-life measure was the FOSQ. The ESS, CGI-C, and FOSQ were evaluated at baseline, week 1, and week 4 (or final visit). The MSLT and PVT were performed at baseline and at week 4 (or final visit).

4.3.6 Data Analysis for OSAHS Study 402

The *efficacy evaluable set* included data from all patients who received at least 1 dose of study drug (PROVIGIL or placebo) and had at least 1 postbaseline efficacy evaluation on any measure.

All continuous variables (ESS, MSLT, PVT, and FOSQ) were analyzed as the change from baseline; an ANCOVA with treatment and center as factors and the baseline value as a covariate was utilized for detecting treatment differences. The discrete variable of CGI-C was analyzed using the CMH chi-square test adjusted for center with modified ridit scores to account for ordered categories of CGI-C.

4.3.7 Study Population for OSAHS Study 402

4.3.7.1 Patient Disposition

In OSAHS study 402, 75 PROVIGIL-treated patients and 80 placebo-treated patients were considered efficacy evaluable (Table 18).

Table 18: Patient Disposition in OSAHS Study 402 (Randomized Patients)

Patient disposition	Number (%) of patients	
	PROVIGIL 400 mg/day	Placebo
Randomized	77 (100)	80 (100)
Completed	66 (85.7)	77 (96.3)
Withdrawn	11 (14.3)	3 (3.8)
Adverse event	8 (10.4)	1 (1.3)
Protocol violation	0 (0.0)	1 (1.3)
Noncompliance	2 (2.6)	1 (1.3)
Other	1 (1.3)	0 (0.0)
Efficacy evaluable	75 (97.4)	80 (100)
Safety evaluable	77 (100)	80 (100)

4.3.7.2 Demographic Characteristics

In OSAHS study 402, patient demographic characteristics were similar for the 2 treatment groups. A summary of patient characteristics including sex, race, age, and weight for study 402 is presented in Table 19.

Table 19: Demographic Characteristics in OSAHS Study 402 (Randomized Patients)

Demographic variable	PROVIGIL (N = 77)	Placebo (N = 80)
Age (years)		
Mean (SD)	50.3 (8.5)	50.1 (10.0)
Min, max	(32, 76)	(28, 72)
Sex, n (%)		
Male	61 (79.2)	59 (73.8)
Female	16 (20.8)	21 (26.3)
Race, n (%)		
Caucasian	68 (88.3)	68 (85.0)
Black	6 (7.8)	6 (7.5)
Asian	0 (0.0)	1 (1.3)
Hispanic	2 (2.6)	4 (5.0)
Other	1 (1.3)	1 (1.3)
Weight (kg)		
Mean (SD)	110.0 (22.0)	107.7 (23.5)

Min = minimum; max = maximum.

4.3.7.3 Baseline Patient Characteristics

The 2 treatment groups were comparable with regard to baseline GCI-S, MSLT sleep latency, and NPSG parameters (Table 20). At baseline, about 80% of all patients studied were at least moderately ill as assessed by the CGI-S, with mean MSLT sleep latency of approximately 7 minutes.

The 3 treatment groups were comparable with regards to the NPSG parameter of sleep efficiency (percentage of time in bed spent asleep).

Table 20: Baseline Patient Characteristics in OSAHS Study 402 (Safety Evaluable Set)

Baseline parameter		Treatment group: PROVIGIL 400 mg/day (N=77)	Treatment group: Placebo (N=80)
CGI-S rating, N (%)	Normal	5 (8.8)	4 (6.9)
	Borderline ill	3 (5.3)	2 (3.4)
	Mildly ill	4 (7.0)	5 (8.6)
	Moderately ill	31 (54.0)	38 (66.0)
	Markedly ill	14 (25.0)	9 (16.0)
	Severely ill	0	0
	Extremely ill	0	0
Mean (SD) MSLT sleep latency (minutes)		7.4 (4.8)	7.5 (4.6)
NPSG sleep efficiency (% of time in bed spent asleep)			
N		77	80
Mean (SD)		87.1 (9.5)	87.3 (77.9)

Note: In study 402, the number of patients with CGI-S ratings is less than the number of efficacy evaluable patients because the CGI-C assessment was not part of the original protocol but was added in an amendment after the start of the study.
CGI-S = Clinical Global Impression of Severity; MSLT = Multiple Sleep Latency Test; NPSG = nocturnal polysomnography.

Overall, the patients who participated in OSAHS study 402 had baseline subjective and objective evidence of ES (from CGI-S and MSLT assessments) and had baseline disturbed sleep (from NPSG).

4.3.8 Efficacy and Quality-of-Life Results for OSAHS Study 402

4.3.8.1 Primary Efficacy Measure: ESS

In OSAH study 402, mean ESS total score decreased from the baseline assessment to the final visit by 4.6 for the PROVIGIL group and 2.0 for the placebo group. The comparison was statistically significant ($p<0.0001$). ESS results for study 402 are presented in Table 21.

Table 21: Total Score From ESS at the Final Visit in OSAHS Study 402 (Efficacy Evaluable Set)

Category	Treatment group	
	PROVIGIL 400 mg/day (N=75)	**Placebo (N=80)**
No. included in analysis	75	80
Baseline		
Mean (SD)	14.2 (2.94)	14.4 (3.19)
Final visit		
Mean (SD)	9.6 (4.78)	12.4 (4.50)
Change from baseline		
Mean (SD)	–4.6 (4.33)	–2.0 (3.61)
p-value	<0.0001	---

The mean change from baseline in ESS scores showed a statistically significant improvement at week 1 and week 4 (both, $p<0.01$) for the PROVIGIL treatment group compared to the placebo treatment group.

4.3.8.2 Secondary Efficacy Measures: MSLT, CGI-C, PVT

The positive effect of PROVIGIL treatment in patients with OSAHS as assessed by the secondary measures of the MSLT, CGI-C, and PVT was consistent with that observed with the primary measure.

MSLT sleep latency

In OSAHS study 402, mean sleep latency from the MSLT increased for PROVIGIL-treated patients by approximately 1 minute from the baseline assessment to the final visit compared to a decrease of 0.2 minutes for patients in the placebo treatment group. The comparison was statistically significant ($p=0.0212$). MSLT sleep latency results for study 402 are presented in Table 22.

Table 22: Average Sleep Latency From the MSLT Mean Change From Baseline at the Final Visit for OSAHS Study 402 (Efficacy Evaluable Set)

MSLT variable	Treatment group			
	PROVIGIL 400 mg/day		Placebo	
	N	Mean (SD)	N	Mean (SD)
Average sleep latency (min)				
Baseline	77	7.4 (4.78)	80	7.5 (4.60)
Final visit	67	8.6 (5.07)	77	7.2 (4.40)
Mean change from baseline to final visit	67	1.0 (3.65)	77	–0.2 (4.06)
p-value		0.0212		---

CGI-C ratings

In OSAHS study 402, comparison of the distribution of CGI-C ratings indicated statistically significant differences between the PROVIGIL and placebo treatment groups at the final visit (p=0.0157). CGI-C rating results for study 402 are presented in Table 23.

Table 23: CGI-C Ratings (Number [%] in Each Category) at the Final Visit in OSAHS Study 402 (Efficacy Evaluable Set)

Category	Number (%) of patients	
	PROVIGIL 400 mg/day	Placebo
n	56	58
Very much improved	8 (14)	4 (7)
Much improved	6 (11)	10 (17)
Minimally improved	23 (41)	6 (10)
No change	17 (30)	37 (64)
Minimally worse	2 (4)	1 (2)
Much worse	0	0
Very much worse	0	0
p-value	0.0157	---

Note: In study 402, the number of patients with CGI-C ratings is less than the number of efficacy evaluable patients because the CGI-C assessment was not part of the original protocol but was added in an amendment after the start of the study.
CGI-C=Clinical Global Impression-Change.

PVT results

For OSAHS study 402, a numerical difference in favor of the PROVIGIL-treated group was observed between the 2 treatment groups with respect to number of lapses. However, this change was not statistically significant. PVT results for study 402 are presented in Table 24.

Table 24: Change from Baseline in PVT Results at the Final Visit for OSAHS Study 402 (Efficacy Evaluable Set)

PVT parameter	PROVIGIL 400 mg/day		Placebo		p-value[a]
Number of lapses	**N**	**Mean (SE)**	**N**	**Mean (SE)**	
Baseline	46	4.03 (0.73)	58	2.75 (0.66)	
Week 4/final visit	46	2.66 (0.60)	58	2.63 (0.67)	
Change from baseline	46	–1.38 (0.48)	58	–0.12 (0.61)	0.1102

[a] p-values for between group comparisons were based on a t-test with a pooled standard deviation estimate.
PVT = Psychomotor Vigilance Task.

4.3.8.3 Quality of Life Assessment: FOSQ

In OSAHS study 402, statistically significant differences between the PROVIGIL treatment group and the placebo treatment group were observed for the mean change from baseline assessments to the final visit in total FOSQ score (p=0.0211) and the individual subscales of activity level (p=0.0383) and vigilance (p=0.0102), but not for general productivity, social outcome, or intimate relationships and sexual activity.

4.3.9 Conclusions on OSAHS

The efficacy of PROVIGIL in the treatment of patients with residual ES associated with OSAHS was evaluated in a 12-week double-blind, placebo-controlled study (study 303) involving 191 efficacy evaluable patients treated with PROVIGIL (200 or 400 mg/day) and 100 treated with placebo for up to 12 weeks. A second double-blind, placebo-controlled study (study 402) involved 75 efficacy evaluable patients treated with PROVIGIL (400 mg/day) and 80 treated with placebo for up to 4 weeks. The evaluations of efficacy in each study showed that treatment with PROVIGIL improved wakefulness in patients with residual sleepiness associated with OSAHS who were receiving nCPAP therapy.

In study 303, the analysis of average sleep latency from the MWT at the final visit indicated a significant increase from baseline in sleep latency for PROVIGIL-treated patients compared to placebo-treated patients; the difference was significant for the combined PROVIGIL group and for both the 200- and 400-mg/day PROVIGIL groups (all p<0.0001). Similar results were observed for average sleep latency from the MSLT obtained in study 402, with significant increases in sleep latency for the PROVIGIL group compared to the placebo group at the final visit (p=0.0212).

For the common efficacy measure of CGI-C, the results of study 303 indicate a significant difference between PROVIGIL and placebo treatment in the distribution of CGI-C ratings at the final visit ($p<0.001$) for the combined PROVIGIL group and both PROVIGIL dosages. For study 402, there was also a significant difference between PROVIGIL and placebo treatment in the distribution of CGI-C ratings at the final visit ($p<0.05$). In both studies, the CGI-C results corroborate the sleep latency results.

In study 303, a significant improvement in ESS score with PROVIGIL treatment was observed ($p<0.0001$ for both dosages of PROVIGIL and the combined PROVIGIL group compared to placebo). In study 402, a significant improvement ($p<0.0001$) with PROVIGIL treatment over placebo treatment was also observed in ESS score.

In study 303, a significant decrease ($p=0.0006$) in the number of lapses from the PVT was observed for patients treated with PROVIGIL compared to those treated with placebo. In study 402, a difference (though not significant) between the treatment groups was observed.

4.4 Shift Work Sleep Disorder—Studies 305 and 306

SWSD studies 305 (pivotal study) and 306

The efficacy data in patients with chronic SWSD are derived from study 305. Study 306 was a study of the safety and quality of life of PROVIGIL in patients with ES associated with SWSD.

4.4.1 Study Design for SWSD Study 305

Study 305 was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 28 centers in the US. Patients with ES associated with chronic SWSD were randomized to receive a daily dose of 200 mg of PROVIGIL or a placebo during a 12-week, double-blind treatment period. Efficacy measures were obtained overnight in a laboratory setting (overnight clinic visit), which took place at the study center during nighttime hours (approximately 2000 to 0900 hours) similar to those that the patient routinely worked. The overnight clinic visit occurred on the night immediately following the last night of work for the night shift work period (minimum of 3 consecutive nights). After completion of the double-blind treatment period, patients were allowed to enter a 12-month open-label treatment extension period.

Eligible patients had a CGI-S score of moderately ill as related to sleepiness on work nights (including the commute to and from work). In addition, patients enrolled in SWSD study 305 had a mean sleep latency of 6 minutes or less on the screening MSLT, and a sleep efficiency of 87.5% or less on daytime PSG.

Patients met the ICSD criteria for chronic SWSD (ICSD Code 307.45-1) and worked a minimum of 5 night shifts per month with at least 3 of the nights being consecutive. The night shifts included at least 6 hours between the hours of 2200 and 0800 and were no more than 12 hours in duration. An effort was made to enroll at least 20% of patients who worked 5 to 10 night shifts per month and at least 20% of patients who worked more than 10 night shifts per month. Study drug administration was intermittent, ie, patients took their dose of study drug approximately

30 minutes to 1 hour before the start of each night shift worked, but not on the days (and nights) not at work.

The primary efficacy measures in this study were the MSLT and CGI-C. Mean sleep latency from the MSLT was based on four 20-minute naps performed at 0200, 0400, 0600, and 0800 of overnight in a laboratory setting, with study drug administered at 2200. The CGI-C scale assessed the severity of sleepiness during night shifts (including the commute to and from work), was performed during clinic visits after the overnight clinic visit. The secondary efficacy measures included the KSS, which was performed at hourly intervals (from 2400 to 0800) during each overnight clinic visit, and the PVT, which was performed 1 hour prior to each MSLT nap. The quality-of-life measure was the FOSQ. All efficacy and quality-of-life measures were assessed at baseline and at 3 postbaseline visits (ie, visits 4, 5, and 6), which were to occur approximately every 4 weeks (weeks 4, 8, and 12). These visits were to occur the night after working at least a 3-night shift work period.

4.4.2 Data Analysis for SWSD Study 305

The *efficacy evaluable set* included data from all patients who received at least 1 dose of study drug (PROVIGIL or placebo) and had at least 1 postbaseline observation for at least 1 primary efficacy measure. The primary efficacy variables were the change from baseline in the mean sleep latency from the MSLT performed at the last postbaseline overnight clinic visit, using a last observation carried forward (LOCF) approach, and the CGI-C rating at the last postbaseline visit using the LOCF approach.

All continuous variables (MSLT, KSS, PVT, and FOSQ) were analyzed as the change from baseline using an analysis of variance (ANOVA) with treatment and center as factors. The discrete variable of CGI-C rating was summarized with frequency and percentage for each category and for each treatment group. The CGI-C data were analyzed using a CMH chi-square test adjusted for center with modified ridit scores to account for the ordered categories of the CGI-C. The percentage of patients who experienced some improvement on the CGI-C scale was analyzed using a CMH chi-square test adjusted for site.

4.4.3 Study Population for SWSD Study 305

4.4.3.1 Patient Disposition

In SWSD study 305, 89 PROVIGIL-treated patients and 104 placebo-treated patients were considered efficacy evaluable (Table 25).

Table 25: Patient Disposition in SWSD Study 305 (All Randomized Patients)

	Number (%) of patients	
Patient disposition[a]	**PROVIGIL 200 mg (N=99)**	**Placebo (N=110)**
Randomized	99 (100)	110 (100)
Randomized but not treated	3 (3)	2 (2)
Safety analysis set	96 (97)	108 (98)
Efficacy evaluable	89 (90)	104 (95)
Completed	72 (73)	81 (74)
Withdrawn	27 (27)	29 (26)
Death	0	0
Adverse event	3 (3)	4 (4)
Lack of efficacy	0	0
Consent withdrawn	6 (6)	8 (7)
Protocol violation	1 (1)	1 (<1)
Noncompliance	0	3 (3)
Lost to follow-up	7 (7)	8 (7)
Other[b]	10 (10)	5 (5)

[a]In total, 609 patients were screened for enrollment into the study.
[b]All patients who withdrew for "other" reasons were withdrawn due to a change in night shift work status.

The placebo treatment group had 11 more patients than the PROVIGIL treatment group. This imbalance was mostly due to the stratum of patients who worked 5 through 10 night shifts per month (2 patients in the PROVIGIL treatment group and 11 patients in the placebo treatment group). The distribution of patients across treatment groups who worked more than 10 night shifts per month was 94 patients in the PROVIGIL treatment group and 97 patients in the placebo treatment group. However, the number of patients who worked 5 through 10 night shifts per month was higher in the placebo treatment group. The randomization procedure was designed to balance patients (1:1) within each of the 2 strata defined by the number of night shifts per month and the low number of patients in the stratum of patients who worked 5 through 10 night shifts per month is the most likely cause for the imbalance observed.

4.4.3.2 Demographic Characteristics

Patient demographic characteristics were similar for the 2 treatment groups. A summary of patient characteristics including sex, race, age, and weight for study 305 is presented in Table 26.

Table 26: Demographic Characteristics in SWSD Study 305 (Safety Analysis Set)

Demographic variable	Treatment group	
	PROVIGIL 200 mg (N = 96)	**Placebo (N = 108)**
Age, years		
n	96	108
Mean (SD)	37.5 (9.24)	38.8 (9.06)
Sex, n (%)		
Male	58 (60)	67 (62)
Female	38 (40)	41 (38)
Race, n (%)		
White	62 (65)	75 (69)
Black	25 (26)	27 (25)
Asian	1 (1)	0
Other	8 (8)	6 (6)
Weight, kg		
n	96	108
Mean (SD)	88.5 (18.55)	87.0 (17.53)

4.4.3.3 Baseline Patient Characteristics

The 2 treatment groups were comparable with regard to baseline CGI-S, MSLT sleep latency, daytime PSG, and type of shift worker (Table 27).

Table 27: Baseline Patient Characteristics in SWSD Study 305 (Safety Analysis Set)

Baseline parameter		Treatment group: PROVIGIL 200 mg/day (N=96)	Treatment group: Placebo (N=108)
CGI-S rating, N (%)	Normal	0	0
	Borderline ill	0	0
	Mildly ill	0	0
	Moderately ill	49 (51)	53 (49)
	Markedly ill	29 (30)	34 (31)
	Severely ill	17 (17)	17 (16)
	Extremely ill	2 (2)	4 (4)
Mean (SD) MSLT sleep latency (minutes)		2.07 (1.5)	2.04 (1.8)
PSG sleep efficiency (% of time in bed spent asleep)			
Mean (SD)		73.7 (11.7)	74.1 (12.6)
Type of shift worker			
Permanent (not rotating)		89 (93)	95 (88)
Rotating		7 (7)	13 (12)

CGI-S = Clinical Global Impression of Severity; MSLT = Multiple Sleep Latency Test; PSG = polysomnography.

Overall, the patients who participated in SWSD study 305 had baseline subjective and objective evidence of ES (from CGI-S and MSLT assessments) and had disturbed sleep at baseline (from daytime PSG).

4.4.4 Efficacy and Quality-of-Life Results for SWSD Study 305

4.4.4.1 Primary Efficacy Measures: MSLT and CGI-C

MSLT sleep latency

In SWSD study 305, mean sleep latency from the MSLT increased from the baseline assessment to the final visit by 1.7 minutes for patients in the PROVIGIL treatment group compared to an increase of 0.3 minutes in the placebo treatment group. The comparison was statistically significant (p=0.0022). Sleep latency results for study 305 are presented in Table 28.

Table 28: Average Sleep Latency (Minutes) From the MSLT at the Final Visit in SWSD Study 305 (Efficacy Evaluable Set)

Time point Statistic	PROVIGIL 200 mg (N=89)	Placebo (N=104)	p-value
Baseline			
n	86	96	
Mean (SD)	2.1 (1.53)	2.0 (1.82)	
Final visit			
n	86	96	
Mean (SD)	3.8 (4.32)	2.4 (2.73)	
Change from baseline at the final visit			
n	86	96	
Mean (SD)	1.7 (3.79)	0.3 (2.77)	0.0022

MSLT = Multiple Sleep Latency Test.

CGI-C ratings

In SWSD study 305, comparisons of the distribution of CGI-C ratings at the final visit showed statistically significant ($p<0.0001$) improvement in sleepiness during the night shift (including the commute home) for the PROVIGIL treatment group when compared to the placebo treatment group (Table 29).

Table 29: CGI-C Ratings (Number [%] in Each Category) at the Final Visit in SWSD Study 305 (Efficacy Evaluable Set)

	Number (%) of patients	
Category	PROVIGIL 200 mg (N=89)	Placebo (N=104)
Very much improved	21 (24)	8 (8)
Much improved	28 (31)	13 (13)
Minimally improved	17 (19)	16 (15)
No change	20 (22)	61 (59)
Minimally worse	2 (2)	4 (4)
Much worse	1 (1)	2 (2)
Very much worse	0	0
p-value[a]	<0.0001	---

CGI-C = Clinical Global Impression of Change.

CGI-C ratings at all postbaseline visits (weeks 4, 8, and 12) showed statistically significant ($p<0.0001$ at all time points) improvement in sleepiness during the night shift (including the

commute home) for the PROVIGIL treatment group when compared to the placebo treatment group.

4.4.4.2 Secondary Efficacy Measures: KSS and PVT

The positive effect of PROVIGIL treatment in patients with SWSD as assessed by the secondary measures of the KSS and PVT was consistent with that observed with both primary measures.

KSS results

In SWSD study 305, the mean KSS score decreased from the baseline assessment to the final visit by 1.5 for patients in the PROVIGIL treatment group compared to a decrease of 0.4 for patients in the placebo treatment group (Table 30). The comparison was statistically significant ($p<0.0001$).

Table 30: KSS Score at the Final Visit in SWSD Study 305 (Efficacy Evaluable Set)

	Treatment group	
Category	**PROVIGIL 200 mg/day**	**Placebo**
Baseline		
n	85	95
Mean (SD)	7.3 (1.04)	7.1 (1.20)
Final visit		
n	86	97
Mean (SD)	5.8 (1.45)	6.7 (1.54)
Change from baseline		
n	85	95
Mean (SD)	–1.5 (1.52)	–0.4 (1.50)
p-value	<0.0001	---

KSS = Karolinska Sleepiness Scale; n = number of patients with values at specified interval.

PVT results

In SWSD study 305, the mean change from the baseline assessment to the final visit for the PVT parameter of number of lapses (reaction times greater than 500 msec) showed a decrease that was statistically significant (p=0.0065) for patients in the PROVIGIL treatment group compared with patients in the placebo treatment group. PVT results for study 305 are presented in Table 31.

Table 31: Change From Baseline in PVT Results at the Final Visit in SWSD Study 305 (Efficacy Evaluable Set)

	Treatment group				
	PROVIGIL 200 mg/day (N = 89)		Placebo (N = 104)		
PVT parameter	Baseline	Change from baseline	Baseline	Change from baseline	p-value
Number of lapses					
n	77	77	83	83	
Mean (SD)	22.9 (21.5)	–4.1 (20.14)	22.4 (24.4)	6.1 (20.6)	0.0065

PVT = Psychomotor Vigilance Task.

4.4.4.3 Quality of Life Assessment: FOSQ

FOSQ results

No statistically significant improvements in any of the subscale scores (total score, vigilance, activity level, general productivity, social outcome, or intimate relationships and sexual activity) from the FOSQ were observed for patients in the PROVIGIL treatment group when compared to patients in the placebo treatment group.

4.4.5 Study Design for SWSD Study 306

Study 306 was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 31 centers in the US. Patients with ES associated with chronic SWSD were randomized to receive a daily dose of 200 or 300 mg of PROVIGIL, or a placebo, during a 12-week, double-blind treatment period. This was primarily a safety and tolerability study including evaluation of quality-of-life measures (FOSQ and SF-36). Study visits occurred on the mornings immediately after working the last night of a night shift work period of at least 3 consecutive nights. After completion of the double-blind treatment period, patients were allowed to enter a 12-month open-label treatment extension period.

Eligible patients had a CGI-S score of at least moderately ill as related to sleepiness on work nights (including the commute to and from work). Patients met the ICSD criteria for chronic SWSD (ICSD Code 307.45-1) and worked a minimum of 5 night shifts per month with at least 3 of the nights being consecutive. The night shifts included at least 6 hours between the hours of 2200 and 0800, and were no more than 12 hours in duration. Study drug administration was

intermittent, ie, patients took their dose of study drug approximately 30 minutes to 1 hour before the start of each night shift worked, but not on the days (and nights) not at work.

This was a safety and quality-of-life study for which no primary or secondary efficacy variables were specified. The quality-of-life measures, the FOSQ and SF-36, were evaluated at baseline, week 4, and week 12 (or final visit).

4.4.6 Data Analysis for SWSD Study 306

Quality-of-life (continuous) variables (FOSQ, SF-36) were analyzed as the change from baseline and an analysis of covariance (ANCOVA) with treatment and center as factors and the baseline value as a covariate was utilized for detecting treatment differences.

The change from baseline at week 12 (or final visit) for the 5 individual subscales and the total score from the FOSQ were analyzed using an ANCOVA with treatment and center as factors and baseline value as a covariate. The presence of a treatment by covariate interaction was evaluated using an ANCOVA with treatment, center, baseline, and treatment*baseline as factors.

4.4.7 Study Population for SWSD Study 306

4.4.7.1 Patient Disposition

In SWSD study 306, 176 PROVIGIL-treated patients and 86 placebo-treated patients were considered efficacy evaluable (Table 32).

Table 32: Patient Disposition in SWSD Study 306 (All Randomized Patients)

	Number (%) of patients		
Patient disposition[a]	**PROVIGIL 200 mg/day (N=92)**	**PROVIGIL 300 mg/day (N=93)**	**Placebo (N=93)**
Randomized	92 (100)	93 (100)	93 (100)
Completed	68 (74)	61 (66)	60 (65)
Withdrawn	24 (26)	32 (34)	33 (35)
Death	0	0	0
Adverse event	6 (7)	18 (19)	5 (5)
Lack of efficacy	0	1 (1)	0
Consent withdrawn	3 (3)	3 (3)	6 (6)
Protocol violation	5 (5)	2 (2)	3 (3)
Noncompliance	0	2 (2)	5 (5)
Lost to follow-up	6 (7)	3 (3)	7 (8)
Other	4 (4)	3 (3)	7 (8)
Patients in efficacy evaluable set	86 (93)	90 (97)	86 (92)
Patients in the safety analysis set	87 (95)	90 (97)	86 (92)

[a]In total, 482 patients were screened for enrollment into the study.

4.4.7.2 Demographic Characteristics

In SWSD study 306, patient demographic characteristics were similar for the 3 treatment groups. A summary of patient characteristics including sex, race, age, and weight for study 306 is presented in Table 33.

Table 33: Demographic Characteristics in SWSD Study 306 (Safety Analysis Set)

	Treatment group		
Demographic variable	**PROVIGIL 200 mg/day (N = 87)**	**PROVIGIL 300 mg/day (N = 90)**	**Placebo (N = 86)**
Age, years			
Mean (SD)	40.0 (9.3)	40.2 (9.7)	39.9 (8.9)
Sex, n (%)			
Male	44 (51)	43 (48)	38 (44)
Female	43 (49)	47 (52)	48 (56)
Race, n (%)			
White	67 (77)	67 (74)	57 (66)
Black	14 (16)	15 (17)	19 (22)
Asian	1 (1)	1 (1)	0
Pacific Islander	0	0	1 (1)
Other	5 (6)	(8)	9 (10)
Weight, kg			
Mean (SD)	90.9 (19.6)	88.2 (24.6)	88.3 (21.1)

4.4.7.3 Baseline Patient Characteristics

The 3 treatment groups were comparable with regard to baseline CGI-S (Table 34).

Table 34: Baseline Patient Characteristics in SWSD Study 306 (Safety Analysis Set)

Baseline parameter		Treatment group PROVIGIL 200 mg/day (N=87)	PROVIGIL 300 mg/day (N=90)	Placebo (N=86)
CGI-S rating, N (%)	Normal	0	0	0
	Borderline ill	0	0	0
	Mildly ill	0	0	0
	Moderately ill	64 (74)	59 (66)	65 (76)
	Markedly ill	13 (15)	19 (21)	17 (20)
	Severely ill	10 (11)	12 (13)	4 (5)
	Extremely ill	0	0	0

CGI-S = Clinical Global Impression of Severity

Overall, the patients who participated in SWSD study 306 had subjective evidence of ES at baseline (from CGI-S).

4.4.8 Quality of Life Assessments for SWSD Study: SF-36 and FOSQ

SF-36 results

In SWSD study 306, improvement from the baseline assessment to the final visit for the mental composite summary score from the SF-36 was statistically significant for the patients in the PROVIGIL 300-mg/day treatment group (mean change 3.20, p=0.0113) and the PROVIGIL 200-mg/day treatment group (mean change 3.66, p=0.015) in comparison to the placebo group (mean change 0.68).

Statistically significant improvements at the final visit were also seen for individual domains for patients in both PROVIGIL treatment groups when compared with patients in the placebo treatment group: vitality (PROVIGIL-300 mg/day [p<0.0001] and PROVIGIL-200 mg/day [p=0.0003] groups versus the placebo group), and role emotional (PROVIGIL-300 mg/day group versus placebo group [p=0.0444]). There was no evidence of consistent trends in improvement in the physical component and the other domains of bodily pain, general health, mental health, physical functioning, role physical, and social functioning.

FOSQ results

In SWSD study 306, improvement was observed in total FOSQ score at all time points for patients in the PROVIGIL-treated groups compared with the placebo-treated group. Improvement from baseline to week 12 (or final visit) in the total score was statistically significantly higher (p=0.0126) for the patients in the PROVIGIL-300 mg/day group (mean change from baseline 2.26) compared with patients in the placebo-treated group (mean change from baseline 1.58). Although not statistically significant, the p-values for the change from baseline for the PROVIGIL-200 mg/day treatment group showed a trend toward significance. Statistically significant improvements at week 12 (or final visit) were also seen for the following

individual domains: activity level (PROVIGIL-300 mg/day and PROVIGIL-200 mg/day groups versus placebo group), and vigilance and general productivity (PROVIGIL-300 mg/day group versus placebo group). Although improvements were seen in the PROVIGIL treatment groups for the domains of social outcome and intimate relationships and sexual activity in comparison to placebo**,** at the final visit these changes did not reach statistical significance.

4.4.9 Conclusions on SWSD

The efficacy of PROVIGIL in the treatment of patients with ES associated with chronic SWSD was evaluated in double-blind, placebo-controlled study 305 involving 89 efficacy evaluable patients treated with PROVIGIL (200 mg/day) and 104 treated with placebo for up to 12 weeks of double-blind treatment. The evaluations of efficacy in SWSD study 305 show that intermittent administration with PROVIGIL provides improvement in measures of excessive sleepiness in patients with chronic SWSD.

In SWSD study 305, the results of the CGI-C corroborate the results of the MSLT, ie, both primary efficacy measures indicated significant improvement for patients receiving PROVIGIL compared to those receiving placebo. The analysis of average sleep latency from the MSLT at the final visit indicated a significant increase from baseline in sleep latency for PROVIGIL-treated patients compared to placebo-treated patients ($p=0.0022$). A significant difference between the PROVIGIL and placebo treatment groups was also observed for the distribution of CGI-C ratings at the final visit ($p<0.0001$). A significant improvement in mean KSS score was observed for the PROVIGIL treatment group compared to the placebo treatment group at the final visit ($p<0.0001$). Significant decreases in the number of lapses compared to baseline from the PVT were observed at the final visit for patients treated with PROVIGIL compared to those treated with placebo.

In addition to patients in SWSD study 305, the effect of PROVIGIL on quality-of-life measures in patients with chronic SWSD was evaluated double-blind, placebo-controlled study 306 involving 176 efficacy evaluable patients treated with PROVIGIL (200 or 300 mg/day) and 86 treated with placebo for up to 12 weeks of double-blind treatment. The results of quality-of-life assessments obtained suggest that PROVIGIL may also improve some aspects of patient well-being. However, the results from the quality-of-life measures were inconsistent between the 2 studies. Those for study 305 showed no significant differences between the PROVIGIL and placebo treatment groups for total FOSQ score or individual subscale scores. However, in study 306, significant improvement for the PROVIGIL 300-mg/day dosage group compared to the placebo group was observed for total FOSQ score and 3 of the 5 subscale scores, and significant improvement relative to placebo treatment was observed for both the 200- and 300-mg/day dosages for the mental composite score and vitality domain of the SF-36.

4.5 Brief Overview of Supportive Efficacy Studies

As mentioned above, the presentation of data from the 6 principal studies is the focus of the efficacy evaluation of PROVIGIL treatment, but there is supportive evidence for the efficacy of PROVGIL from 14 other studies.

Supportive evidence of the efficacy of PROVIGIL for the treatment of patients with excessive sleepiness associated with narcolepsy is provided by the results of 3 studies conducted by Cephalon in the US and UK (study C1538a/406/NA/US, study C1538a/401/NA/US, and a named patient program), and 8 studies conducted outside the US (MOD-024, MOD-025, MOD94003, MOD-026, MOD-027, MOD-028, E1027 and E1028). In these studies, which included 1234 patients with narcolepsy, PROVIGIL was administered from 1 to 4 times daily at dosages ranging from 50 to 1000 mg/day. Study durations ranged from 2 - 40 weeks to 2 - 8 years. The efficacy of PROVIGIL was demonstrated using objective measures of sleep latency, as well as subjective measures of sleepiness and quality of life. Observed in studies utilizing objective assessments were improvements in wakefulness as measured by the MWT, and decreases in the numbers of sleep episodes/attacks, diurnal yawns, and episodes of somnolence/sleepiness. There was also improvement with regard to subjective measures of clinical condition and quality of life.

Additional studies of efficacy in residual ES in patients with sleep apnea include 1 Cephalon-sponsored study (C1538a/407/AP/UK) conducted in the UK and 2 studies sponsored by other licensees (E1030, MOD-02), in which 91 patients were enrolled from 1 day to 6 weeks. The results of these placebo-controlled, crossover studies indicate positive trends for PROVIGIL treatment (300 to 400 mg/day) on objective and subjective measures in patients with excessive sleepiness associated with OSAHS. These measures include the MWT, MSLT, ESS, apnea index, and vigilance testing.

4.6 Summary of Results of Primary Efficacy Measures in the Four Pivotal Studies—Narcolepsy Studies 301 and 302, OSAHS Study 303, and SWSD Study 305

4.6.1 Overview of Efficacy Evaluation in the Four Pivotal Studies

Across the 4 pivotal studies (narcolepsy studies 301 and 302, OSAHS study 303, and SWSD study 305), 630 patients were treated with PROVIGIL and underwent efficacy evaluations (ie, efficacy evaluable patients), with an additional 384 placebo-treated patients evaluated for comparative purposes (total 1014).

4.6.2 Patient Populations in the Four Pivotal Studies

The patient populations in the narcolepsy and SWSD studies were similar with respect to demographic characteristics (ie, age, sex, race, and body weight). Compared with these populations, the patient population in the OSAHS studies was slightly older and there were more men than women. This finding is consistent with the characteristics of patients with OSAHS in general.

The patient populations studied had varying degrees of ES at study entry, ie, patients with OSAHS tended to have less severe ES that those with narcolepsy or SWSD. At the baseline evaluations, however, all populations had objective evidence of ES as assessed by the MWT/MSLT, and all had evidence of significant illness as assessed by the CGI-S. All had evidence of disturbed sleep.

4.6.3 Primary Efficacy Analyses for the Four Pivotal Studies: MWT/MSLT and CGI-C at the Final Visit

With regard to the primary objective outcome measures in the 4 pivotal studies, for patients treated with PROVIGIL at either 200 or 400 mg/day, statistically significant improvements, as compared to placebo treatment, were observed in mean sleep latency as measured by the MWT in the narcolepsy and OSAHS studies, and by the MSLT in the SWSD studies (Table 35).

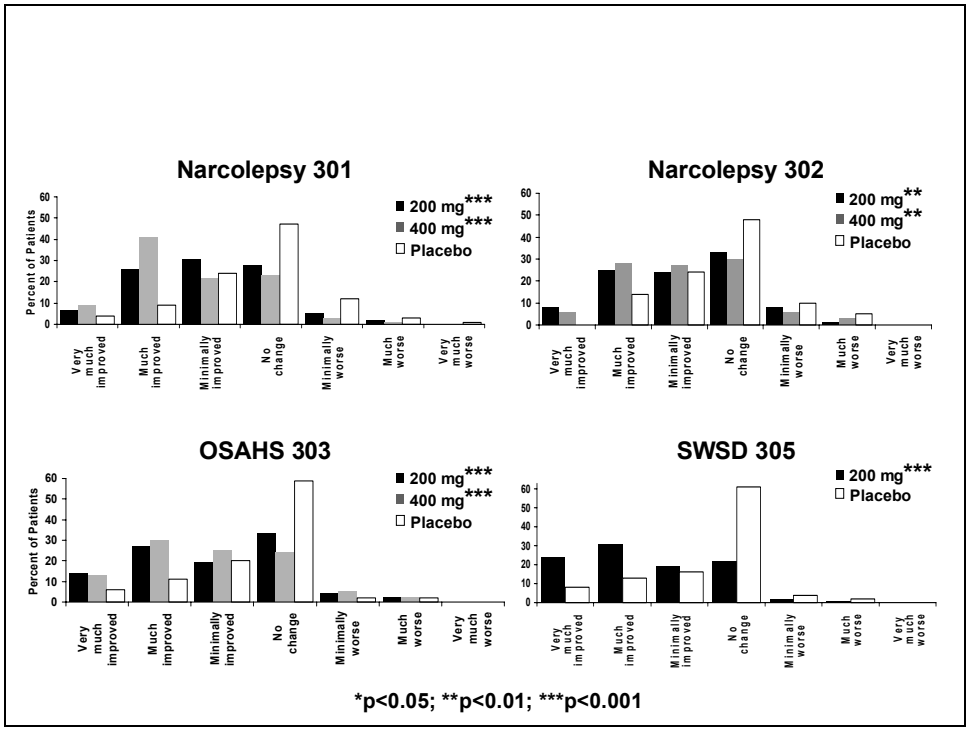
Table 35: Mean (SD) Change From Baseline in Mean Sleep Latency (Minutes)

			Treatment group		
Disorder	**Study no.**	**Measure**	**200 mg/day**	**400 mg/day**	**Placebo**
Narcolepsy	301	MWT	2.3 (4.7)***	2.3 (4.9)***	–0.7 (4.6)
	302	MWT	2.2 (4.5)**	2.0 (4.8)**	–0.7 (4.2)
OSAHS	303	MWT	1.6 (4.8)***	1.5 (5.0)***	–1.1 (4.6)
SWSD	305	MSLT	1.7 (3.8)***	---	0.3 ± 2.8

OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder;
MWT = Maintenance of Wakefulness Test; MSLT = Multiple Sleep Latency Test.
*p<0.05; **p<0.01; ***p<0.001.

With regard to the primary subjective outcome measure in the 4 pivotal studies, for patients treated with PROVIGIL at either 200 or 400 mg/day, statistically significant improvements compared to placebo-treated patients were observed in clinical condition as assessed by the difference in distribution of CGI-C ratings (Figure 3).

Figure 3: CGI-C at the Final Visit in Studies 301, 302, 303, and 305



CGI-C = Clinical Global Impression of Change; OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder.

The results of the analyses of both the primary objective and subjective outcome measures demonstrate the efficacy or PROVIGIL treatment over placebo treatment. The clinical significance of the 1.5- to 2.3-minute change seen on laboratory-based measures (ie, MWT and MSLT) is corroborated by the statistically significant ($p<0.05$) improvements seen in clinical condition, as assessed by the clinician-based measure CGI-C.

4.6.4 Analysis of MWT/MSLT and CGI-C Over Time in the Four Pivotal Studies

For patients treated with PROVIGIL at either 200 or 400 mg/day, improvements in mean sleep latency (Figure 4) and clinical condition (ie, CGI-C) (Figure 5) were observed beginning with the first postbaseline visit and sustained throughout the double-blind treatment periods of all 4 pivotal studies. All improvements were statistically significant, in favor of PROVIGIL treatment over placebo treatment, with the exception, in the SWSD study, of the sleep latency value of sleep latency for the 200-mg/day PROVIGIL treatment group at week 8.

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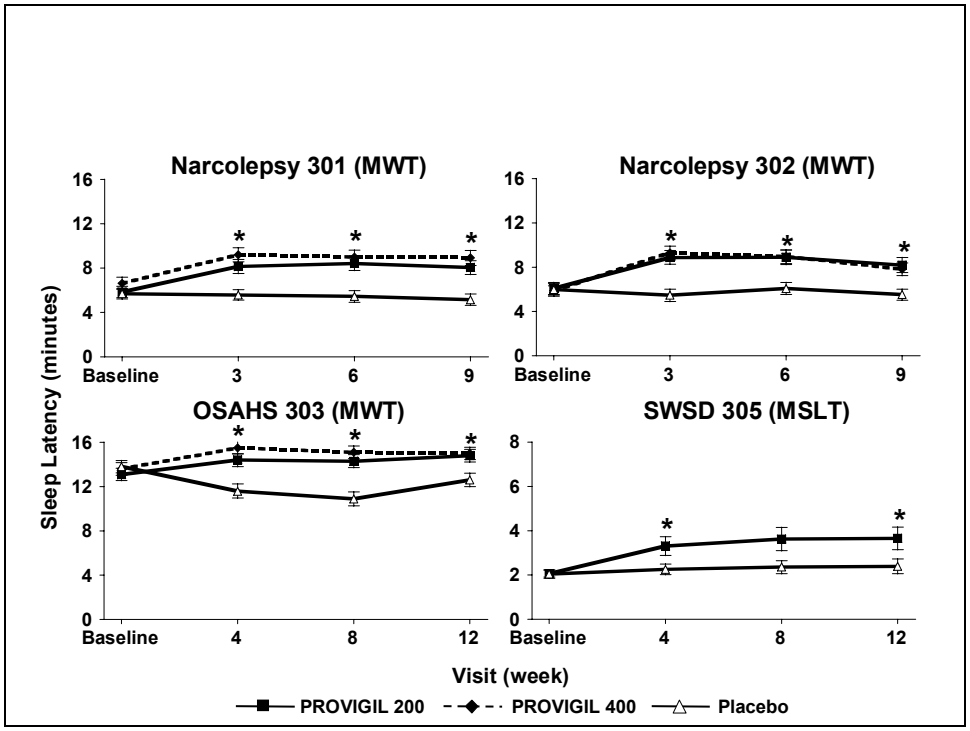
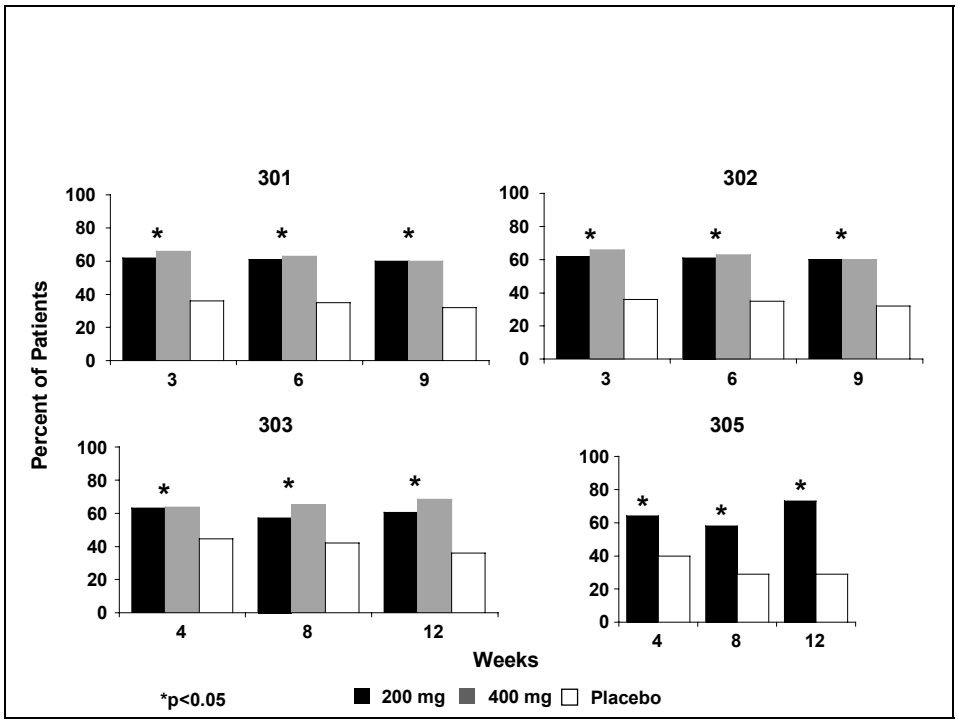
Figure 4: MWT/MSLT Sleep Latency by Visit in Studies 301, 302, 303, and 305



MWT = Maintenance of Wakefulness Test; MSLT = Multiple Sleep Latency Test.
*p<0.05 (between-treatment comparisons [each PROVIGIL dose vs placebo]).

Figure 5: CGI-C Ratings by Visit for Patients Whose Conditions Improved in Studies 301, 302, 303, and 305



CGI-C – Clinical Global Impression of Change (patients who improved at least minimally).

4.7 Consistency of PROVIGIL Effects Across Disorders of Sleep and Wakefulness in the Principal Studies—Narcolepsy Studies 301 and 302, OSAHS Studies 303 and 402, and SWSD Study 305

For continuous efficacy variables assessed in the principal studies (narcolepsy studies 301 and 302, OSAHS studies 303 and 402, and SWSD study 305 [study 306 did not contribute efficacy data for SWSD]), including MSLT, MWT, ESS, and KSS, effect sizes for the change from baseline assessment to the final visit were calculated within sleep disorder model to facilitate evaluation of the consistency of effect of PROVIGIL across the patient populations. Effect size was calculated as follows: (change from baseline in PROVIGIL group minus change from baseline in placebo group)/common estimate of standard deviation.

Individual studies demonstrated positive efficacy effects with PROVIGIL treatment over placebo treatment, which allowed for effect-size analyses to be done on combined data from the pairs of narcolepsy and OSAHS studies.

The results of these analyses indicate that the positive effects of PROVIGIL treatment on wakefulness are consistent across disorders of sleep and wakefulness (Table 36). For the variables from measures of MSLT, MWT, and ESS/KSS, the effect sizes were consistent for the

3 study populations. In addition, the percentage of patients with some improvement from baseline as assessed by CGI-C was consistent across all 3 populations.

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Table 36: Estimates of Effect Size for the Change From Baseline to the Final Visit for Continuous Efficacy Variables in Studies 301, 302, 303, 402, and 305 (Efficacy Evaluable Set)

Disorder	Study	Treatment group	Effect size[a] (95% confidence interval) MSLT	MWT	ESS/KSS[b]	Percentage Improved CGI-C
Narcolepsy	301 and 302 (combined analysis)	200 mg/day	0.32 (0.29, 0.34)	0.64 (0.62, 0.67)	–0.54 (-0.56, -0.51)	61
		400 mg/day	0.37 (0.35, 0.39)	0.61 (0.59, 0.64)	–0.77 (–0.79,–0.74)	66
OSAHS	303 and 402 (combined analysis)	200 mg/day	---	0.56[c] (0.52, 0.61)	–0.65 (–0.68, –0.61)	61
		400 mg/day	0.31 (0.26, 0.37)	0.53[c] (0.49, 0.58)	–0.62 (–0.64, 0.67)	68
SWSD	305	200 mg/day	0.41 (0.37, 0.46)	---	–0.52 (–0.52, –0.51)	74

[a] Effect size calculated as (change from baseline in PROVIGIL group minus change from baseline in placebo group)/common estimate of standard deviation.
[b] KSS assessed in SWSD study 305 only.
[c] MWT was not measured in study 402.
CGI-C = Clinical Global Impression of Change; ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale; MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test; OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder.

4.8 Efficacy Conclusions

The efficacy of PROVIGIL treatment to promote wakefulness in patients with ES associated with disorders of sleep and wakefulness was demonstrated in 6 double-blind, placebo-controlled studies conducted in patient populations representing disorders of sleep and wakefulness, specifically, narcolepsy, OSAHS, and SWSD. The results of these studies support the following conclusions:

- PROVIGIL significantly improved ES across the disorders of sleep and wakefulness as assessed by the dual primary outcome measures of MWT/MSLT and CGI-C in the pivotal studies.
- The efficacy of PROVIGIL shown by the primary outcome measures is supported by the positive results of other outcome measures.
- Consistent and reproducible treatment effects were observed across both objective and subjective measures and across patient populations.
- Treatment effect was demonstrated at the first posttreatment visit and sustained over time.
- The efficacy of PROVIGIL was observed at all dosages studied.

5 SAFETY RESULTS

5.1 Evaluation of Adverse Events

5.1.1 Introduction

A key review of the safety data of PROVIGIL treatment in patients with narcolepsy, OSAHS, and SWSD involved an evaluation of adverse events from the double-blind treatment periods of the 6 principal studies (narcolepsy studies 301 and 302, OSAHS studies 303 and 402, and SWSD studies 305 and 306), where comparisons of safety parameters were made between PROVIGIL and placebo treatment and among the 3 disorders of sleep and wakefulness. These evaluations were made on data from individual studies and from combined data.

The information below addressing adverse events begins with an overview of adverse event categories and types of adverse events for individual studies (across the 6 studies by treatment groups) and for combined data by disorder (narcolepsy, OSAHS, and SWSD by treatment group).

Following the determination of the consistency in adverse event profiles among the studies and the disorders, an additional higher-level review of treatment exposure and adverse events was undertaken where these data were combined for the 6 principal studies by treatment group (PROVIGIL or placebo).

Further review of treatment exposure and adverse event data was done for other PROVIGIL safety data sets.

5.1.2 Principal Studies in Narcolepsy, OSAHS, and SWSD

5.1.2.1 Overview of Adverse Events

A review of the adverse event categories for each of the individual principal studies is presented by treatment group (Table 37) and for these studies combined (Table 38). The parameters reviewed were adverse events, treatment-related adverse events, serious adverse events, adverse events leading to withdrawal, and deaths.

The percentages of PROVIGIL-treated patients who experienced adverse events ranged from 83% to 90% for narcolepsy, 66% to 78% for OSAHS, and 67% to 74% for SWSD. The percentages of PROVIGIL-treated patients who experienced serious adverse events were low overall (at most 3%). The percentages of PROVIGIL-treated patients who experienced adverse events leading to withdrawal ranged from 1% to 12% for narcolepsy, 9% to 13% for OSAHS, and 3% to 21% for SWSD. With the exception of narcolepsy study 302, generally there were more withdrawals due to adverse events from the higher PROVIGIL dose groups. In general, more PROVIGIL-treated patients withdrew due to adverse events than placebo-treated patients.

Table 37: Overview of Adverse Events in Individual Principal Studies (Safety Analysis Set)

Patient population	Number (%) of patients					
Adverse event category	Study 301			Study 302		
Narcolepsy	PROVIGIL 200 mg	PROVIGIL 400 mg	Placebo	PROVIGIL 200 mg	PROVIGIL 400 mg	Placebo
Number of patients	96	95	92	89	89	93
Adverse events (AEs)	86 (90)	82 (86)	76 (83)	74 (83)	79 (89)	76 (82)
Treatment-related AEs	11 (11)	20 (21)	5 (5)	5 (6)	10 (11)	3 (3)
Serious adverse events	0	3 (3)	2 (2)	3 (3)	3 (3)	3 (3)
AEs leading to withdrawal	1 (1)	11 (12)	0	6 (7)	1 (1)	3 (3)
Deaths	0	0	0	0	0	0
	Study 303			Study 402		
OSAHS	PROVIGIL 200 mg	PROVIGIL 400 mg	Placebo	PROVIGIL 400 mg		Placebo
Number of patients	109	106	108	77		80
Adverse events (AES)	85 (78)	81 (76)	70 (65)	51 (66)		39 (49)
Treatment-related (AEs)	55 (52)	45 (41)	22 (20)	34 (44)		20 (25)
Serious adverse events	2 (2)	2 (2)	0	1 (1)		0
AEs leading to withdrawal	10 (9)	14 (13)	3 (3)	8 (10)		1 (1)
Deaths	0	0	0	0		0
	Study 305			Study 306		
SWSD	PROVIGIL 200 mg		Placebo	PROVIGIL 200 mg	PROVIGIL 300 mg	Placebo
Number of patients	96		108	87	90	86
Adverse events (AEs)	64 (67)		68 (63)	59 (68)	67 (74)	50 (58)
Treatment-related AEs	37 (39)		25 (23)	26 (30)	40 (44)	15 17)
Serious adverse events	0		1 (<1)	2 (2)	1 (1)	2 (2)
AEs leading to withdrawal	3 (3)		4 (4)	5 (6)	19 (21)	4 (5)
Deaths	0		0	0	0	0

OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder.

Table 38: Overview of Adverse Events in the Principal Studies by Disorder of Sleep and Wakefulness (Safety Analysis Set)

	Number (%) of patients					
	Narcolepsy Studies 301 and 302		OSAHS Studies 303 and 402		SWSD Studies 305 and 306	
Adverse event category	**PROVIGIL**	**Placebo**	**PROVIGIL**	**Placebo**	**PROVIGIL**	**Placebo**
Number of patients	369	185	292	188	273	194
Adverse events (AEs)	321 (87)	152 (82)	217 (74)	109 (58)	190 (70)	118 (61)
Treatment-related AEs	46 (12)	8 (4)	134 (46)	42 (22)	103 (38)	40 (21)
Serious adverse events	9 (2)	5 (3)	5 (2)	0	3 (1)	3 (2)
AEs leading to withdrawal	19 (5)	3 (2)	32 (11)	4 (2)	27 (10)	8 (4)
Deaths	0	0	0	0	0	0

OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder.

5.1.2.2 Types of Adverse Events

A review was undertaken of adverse event types for the individual principal studies by treatment group (Table 39) and for these studies combined (Table 40). In this review, the focus was placed on adverse events that occurred frequently among PROVIGIL-treated patients (≥5%) and more frequently than in placebo-treated patients. Overall, an essentially consistent safety profile was observed across studies, disorders, and treatment groups.

The adverse event profile with PROVIGIL treatment is consistently composed primarily of 2 categories, those adverse events related to the CNS and those related to the digestive system. The most common adverse events observed with PROVIGIL treatment across all the studies are headache, nausea, and nervousness.

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Table 39: Adverse Events Occurring in ≥5% of PROVIGIL-Treated Patients and at a Greater Percentage Than in Placebo-Treated Patients in Individual Principal Studies (Safety Analysis Set)

Patient population	Number (%) of patients					
Adverse event	Study 301			Study 302		
Narcolepsy	PROVIGIL 200 mg (N=96)	PROVIGIL 400 mg (N=95)	Placebo (N=92)	PROVIGIL 200 mg (N=89)	PROVIGIL 400 mg (N=89)	Placebo (N=93)
Number of patients with at least 1 adverse event	86 (90)	82 (86)	76 (83)	74 (83)	79 (89)	76 (82)
Headache	50 (52)	48 (51)	33 (36)	37 (42)	48 (54)	41 (44)
Nausea	12 (13)	12 (13)	5 (5)	12 (13)	11 (12)	2 (2)
Infection	13 (14)	14 (15)	18 (20)	10 (11)	14 (16)	11 (12)
Rhinitis	10 (10)	14 (15)	11 (12)	10 (11)	8 (9)	3 (3)
Nervousness	9 (9)	9 (9)	5 (5)	8 (9)	4 (4)	7 (8)
Dry mouth	8 (8)	4 (4)	0	0	7 (8)	1 (1)
Back pain	8 (8)	8 (8)	3 (3)	9 (10)	10 (11)	13 (14)
Dyspepsia	8 (8)	2 (2)	8 (9)	8 (9)	8 (9)	6 (6)
Diarrhea	7 (7)	7 (7)	4 (4)	7 (8)	9 (10)	4 (4)
Anorexia	6 (6)	3 (3)	1 (1)	2 (2)	6 (7)	1 (1)
Flu syndrome	5 (5)	3 (3)	4 (4)	3 (3)	2 (2)	3 (3)
Anxiety	3 (3)	2 (2)	0	2 (2)	6 (7)	1 (1)
Dizziness	4 (4)	2 (2)	3 (3)	5 (6)	6 (7)	4 (4)
Pharyngitis	4 (4)	7 (7)	3 (3)	4 (4)	8 (9)	2 (2)
Pain abdomen	4 (4)	4 (4)	2 (2)	3 (3)	5 (6)	5 (5)
Depression	3 (3)	6 (6)	5 (5)	3 (3)	2 (2)	0
Cataplexy	3 (3)	7 (7)	1 (1)	1 (1)	1 (1)	3 (3)
Insomnia	2 (2)	7 (7)	1 (1)	1 (1)	1 (1)	1 (1)
Fever	2 (2)	2 (2)	4 (4)	1 (1)	5 (6)	2 (2)
Cough increased	2 (2)	3 (3)	4 (4)	2 (2)	5 (6)	2 (2)
Eosinophilia	2 (2)	1 (1)	0	5 (6)	0	0
Rash	1 (1)	7 (7)	4 (4)	3 (3)	0	3 (3)
Lung disorder	0	3 (3)	2 (2)	4 (4)	6 (7)	1 (1)
	Study 303			Study 402		
OSAHS	PROVIGIL 200 mg (N=109)	PROVIGIL 400 mg (N=106)	Placebo (N=108)	PROVIGIL 400 mg (N=77)		Placebo (N=80)
Number of patients with at least 1 adverse event	85 (78)	81 (76)	70 (65)	51 (66)		39 (49)
Headache	24 (22)	31 (29)	13 (12)	18 (23)		9 (11)
Nausea	12 (11)	12 (11)	2 (2)	5 (6)		3 (4)
Diarrhea	8 (7)	7 (7)	8 (7)	2 (3)		2 (3)
Insomnia	7 (6)	5 (5)	1 (1)	4 (5)		1 (1)
Anxiety	7 (6)	11 (10)	2 (2)	5 (6)		1 (1)
Nervousness	6 (6)	6 (6)	2 (2)	9 (12)		2 (3)
Dizziness	6 (6)	7 (7)	3 (3)	5 (6)		3 (4)
Rhinitis	6 (6)	6 (6)	8 (7)	6 (8)		2 (3)
Hypertension	5 (5)	8 (8)	2 (2)	1 (1)		1 (1)
Anorexia	1 (1)	5 (5)	1 (1)	2 (3)		2 (3)
Somnolence	1 (1)	5 (5)	0	0		0

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Table 39: Adverse Events Occurring in ≥5% of PROVIGIL-Treated Patients and at a Greater Percentage Than in Placebo-Treated Patients in Individual Principal Studies (Safety Analysis Set) (Continued)

	Study 305		Study 306		
SWSD	PROVIGIL 200 mg (N=96)	Placebo (N=108)	PROVIGIL 200 mg (N=87)	PROVIGIL 300 mg (N=90)	Placebo (N=86)
Number of patients with at least 1 adverse event	64 (67)	68 (63)	59 (68)	67 (74)	50 (58)
Headache	25 (26)	21 (19)	15 (17)	23 (26)	16 (19)
Nausea	9 (9)	3 (3)	5 (6)	17 (19)	4 (5)
Nervousness	6 (6)	1 (<1)	3 (3)	9 (10)	2 (2)
Insomnia	6 (6)	0	8 (9)	4 (4)	2 (2)
Infection	6 (6)	11 (10)	4 (5)	2 (2)	3 (3)
Pain abdomen	6 (6)	2 (2)	0	3 (3)	4 (5)
Accidental injury	6 (6)	9 (8)	0	6 (7)	0
Dry mouth	5 (5)	4 (4)	0	4 (4)	4 (5)
Tooth disorder	5 (5)	1 (<1)	2 (2)	1 (1)	0
Diarrhea	3 (3)	4 (4)	3 (3)	7 (8)	4 (5)
Dizziness	2 (2)	3 (3)	0	6 (7)	4 (5)
Anorexia	2 (2)	1 (<1)	3 (3)	5 (6)	0
Sinusitis	3 (3)	1 (<1)	5 (6)	3 (3)	4 (5)
Flu syndrome	2 (2)	4 (4)	7 (8)	5 (6)	1 (1)
Pharyngitis	1 (1)	2 (2)	6 (7)	4 (4)	5 (6)
Hypertension	1 (1)	0	3 (3)	6 (7)	0
Cough increased	0	1 (<1)	4 (5)	1 (1)	1 (1)
Periodontal abscess	0	0	4 (5)	1 (1)	2 (2)

OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder.

Table 40: Adverse Events Occurring in ≥5% of PROVIGIL-Treated Patients and at a Greater Percentage Than in Placebo-Treated Patients in the Principal Studies by Disorder of Sleep and Wakefulness (Safety Analysis Set)

	Number (%) of patients					
	Narcolepsy		OSAHS		SWSD	
Adverse event	All PROVIGIL (N=369)	Placebo (n=185)	All PROVIGIL (N=292)	Placebo (n=188)	All PROVIGIL (N=273)	Placebo (n=194)
Headache	183 (50)	74 (40)	73 (25)	22 (12)	63 (23)	37 (19)
Nausea	47 (13)	7 (4)	29 (10)	5 (3)	31 (11)	7 (4)
Rhinitis	42 (11)	14 (8)	18 (6)	10 (5)	9 (3)	9 (5)
Nervousness	30 (8)	12 (6)	21 (7)	4 (2)	18 (7)	3 (2)
Diarrhea	30 (8)	8 (4)	16 (5)	10 (5)	12 (4)	8 (4)
Pharyngitis	23 (6)	5 (3)	5 (2)	2 (1)	11 (4)	7 (4)
Dry mouth	19 (5)	1 (<1)	9 (3)	3 (2)	9 (3)	5 (3)
Anorexia	17 (5)	2 (1)	8 (3)	3 (2)	10 (4)	1 (<1)
Dizziness	17 (5)	7 (4)	18 (6)	6 (3)	8 (3)	7 (4)
Flu syndrome	13 (4)	7 (4)	10 (3)	5 (3)	14 (5)	5 (3)
Anxiety	13 (4)	1 (<1)	23 (8)	3 (2)	8 (3)	1 (<1)
Insomnia	11 (3)	2 (1)	16 (5)	2 (1)	18 (7)	2 (1)
Hypertension	6 (2)	0	14 (5)	3 (2)	10 (4)	0

OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder.

5.1.3 Rationale for Combining Adverse Event Data From the Principal Studies

Because of the consistent adverse event profile, including categories and types of adverse events, that was observed in the 6 individual principal studies and across the disorders of narcolepsy, OSAHS, and SWSD, it was determined that it was appropriate to integrate adverse event data from the principal studies by all PROVIGIL-treated and all placebo-treated patients. The primary evaluation of safety (and the remainder of the safety presentations) is therefore made on the integrated data from 2 studies each in narcolepsy, OSAHS, and SWSD. For specific disorders, however, targeted safety reviews were additionally conducted as described in section 5.3.2.

5.1.4 Principal Studies in Narcolepsy, OSAHS, and SWSD—Data Combined

5.1.4.1 Treatment Exposure in the Principal Studies

For the principal studies combined the majority of PROVIGIL-treated patients (83%) were treated for a month or more, with few patients (5%) treated for 3 months or more) (Table 41). Overall treatment exposure is a reflection of the duration of the double-blind treatment periods.

Table 41: Treatment Exposure in Combined Principal Studies (Safety Analysis Set)

	Number (%) of patients	
Months of exposure	**PROVIGIL (N=934)**	**Placebo (N=567)**
≥ 1	773 (82.76)	435 (76.72)
≥ 3	45 (4.82)	24 (4.23)
≥ 6	1 (0.11)	0

5.1.4.2 Overview of Adverse Events

Overall, in the integrated data sets from the principal studies (double-blind treatment periods), 78% of PROVIGIL-treated patients and 67% of placebo-treated patients experienced adverse events (Table 42). The percentage of PROVIGIL-treated patients (30%) with treatment-related adverse events was about twice that of placebo-treated patients (16%). The frequency of serious adverse events was low (PROVIGIL 2%, placebo 1%), as was the frequency of withdrawals due to adverse events (PROVIGIL 8%, placebo 3%).

Table 42: Overview of Adverse Events in the Combined Principal Studies (Safety Analysis Set)

	Number (%) of patients	
Adverse event category	**PROVIGIL**	**Placebo**
Number of patients	934	567
Adverse events (AEs)	728 (78)	379 (67)
Treated-related AEs	283 (30)	90 (16)
Serious adverse events	17 (2)	8 (1)
AEs leading to withdrawal	78 (8)	15 (3)
Deaths	0	0

5.1.4.3 Types of Adverse Events

The most common adverse events among patients who received PROVIGIL were headache (34%), nausea (11%), and nervousness (7%) (Table 43). In addition to these, adverse events that occurred in at least 5% of PROVIGIL-treated patients and more frequently with PROVIGIL treatment than with placebo treatment were rhinitis, diarrhea, back pain, insomnia, dyspepsia, anxiety, and dizziness. Most of the adverse events were mild or moderate in severity (91%).

Table 43: Adverse Events Occurring in ≥5% of PROVIGIL-Treated Patients and at a Greater Percentage Than in Placebo-Treated Patients in the Combined Principal Studies (Safety Analysis Set)

	Number (%) of patients	
Adverse event	**PROVIGIL (N=934)**	**Placebo (N=567)**
Headache	319 (34)	133 (23)
Nausea	107 (11)	19 (3)
Nervousness	69 (7)	19 (3)
Rhinitis	69 (7)	33 (6)
Diarrhea	58 (6)	26 (5)
Back pain	52 (6)	26 (5)
Insomnia	45 (5)	6 (1)
Dyspepsia	44 (5)	21 (4)
Anxiety	44 (5)	5 (<1)
Dizziness	43 (5)	20 (4)

In the integrated data sets for the principal studies, 18 serious adverse events were reported for 17 (2%) of 934 patients who received PROVIGIL and 9 were reported for 8 (1%) of 567 patients who received placebo (Table 44). Only 1 serious adverse event, chest pain, was reported by more than 1 patient in the principal studies (1 occurrence each in PROVIGIL-treated patients in narcolepsy study 302, OSAHS study 402, and SWSD study 306). For the 17 patients with serious adverse events in the PROVIGIL treatment group, 7 events were considered treatment-related: chest pain (1 of 3 reported), palpitation and ventricular extrasystoles in 1 patient, and liver function tests abnormal, leukopenia, dyspnea, and hypoventilation, reported as treatment-related for 1 patient each. There were no deaths reported in any of the principal studies.

Table 44: Serious Adverse Events in the Combined Principal Studies (Safety Analysis Set)

	Number (%) of patients			
	All serious adverse events (SAEs)		Treatment-related SAEs	
Adverse event	All PROVIGIL (N=934)	Placebo (N=567)	All PROVIGIL (N=934)	Placebo (N=567)
No. of patients with at least 1 SAE	17 (2)	8 (1)	6 (<1)	0
Chest pain	3 (<1)	0	1 (<1)	0
Accidental overdose	1 (<1)	0	0	0
Cellulitis	1 (<1)	0	0	0
Hernia	1 (<1)	0	0	0
Palpitation	1 (<1)	0	1 (<1)	0
Ventricular extrasystoles	1 (<1)	0	1 (<1)	0
Liver function tests abnormal	1 (<1)	0	1 (<1)	0
Vomiting	1 (<1)	0	0	0
Leukopenia	1 (<1)	0	1 (<1)	0
Osteomyelitis	1 (<1)	0	0	0
Depersonalization	1 (<1)	0	0	0
Dyspnea	1 (<1)	0	1 (<1)	0
Hypoventilation	1 (<1)	0	1 (<1)	0
Pneumonia	1 (<1)	0	0	0
Skin carcinoma	1 (<1)	0	0	0
Unintended pregnancy[a]	1 (<1)	1 (<1)	0	0
Abdominal pain	0	2 (<1)	0	0
Accidental injury	0	3 (<1)	0	0
Infection	0	1 (<1)	0	0
Cholecystitis	0	1 (<1)	0	0
Urogenital neoplasia	0	1 (<1)	0	0

[a]Pregnancies were not uniformly reported as serious adverse events.
SAE = serious adverse event.

The overall percentage of patients who withdrew from any of the principal studies due to adverse events is relatively low. Adverse events leading to withdrawal from study were reported for 74 (8%) of 934 patients who received PROVIGIL and 15 (3%) of 567 patients who received placebo (Table 45). The most frequent reasons for withdrawal were consistent with the overall adverse event profile of PROVIGIL.

Table 45: Most Common (≥5 Patients) Adverse Events Leading to Withdrawal in PROVIGIL-Treated Patients in Combined Principal Studies (Safety Analysis Set)

Adverse events leading to withdrawal	Number (%) of patients	
	PROVIGIL (N=934)	Placebo (n=567)
No. of patients who withdrew due to adverse events	74 (8)	15 (3)
Headache	16 (2)	3 (<1)
Nausea	9 (<1)	0
Anxiety	9 (<1)	0
Dizziness	9 (<1)	1 (<1)
Insomnia	9 (<1)	1 (<1)
Chest pain	8 (<1)	3 (<1)
Nervousness	7 (<1)	0

5.1.5 Other Adverse Event Data Sets Analyzed

5.1.5.1 Overview of Other Adverse Event Data Sets

Presented above is an evaluation of adverse event data for PROVIGIL treatment in patients with disorders of sleep and wakefulness made on the basis of the 6 principal studies, 2 each in patients with narcolepsy (studies 301 and 302), OSAHS (studies 303 and 402), and SWSD (studies 305 and 306).

Another review of the adverse event data that was undertaken involved all studies done specifically in disorders of sleep and wakefulness (ie, all narcolepsy, OSAHS, and SWSD studies combined, including open-label extension periods of the principal studies and other supportive controlled and uncontrolled studies.). This database is referred to as "all narcolepsy, OSAHS, and SWSD studies." In total, this data set includes data from 10 narcolepsy studies, 3 OSAHS studies, and 2 SWSD studies.

A further review of adverse event data from adults in studies with PROVIGIL was undertaken in any phase of clinical research and in any indication. This database, referred to as "all studies"[1] includes 95 studies submitted in the original NDA (14 studies conducted in the United States [US] and the United Kingdom [UK] and 81 studies conducted in Europe) and an additional 39 studies submitted with the supplemental application (23 studies conducted in the US and UK and 16 studies conducted in Europe). Among the 95 studies originally submitted, there were

[1] Among the studies that were part of the original ISS database (NDA 20-717) were 81 studies of PROVIGIL. Among the subjects/patients who were enrolled in these studies, some participated in 2 or more studies. In the summary of drug exposure for all studies in all indications presented in this document, only the number of unique, identifiable subjects/patients from the 81 studies are included in the denominator. However, in the summaries of adverse events presented for all studies in all indications, the denominator includes all subject exposures, ie, the number of unique subjects (n=3546) plus 198 additional subject-exposures (total of 3744 subject exposures).

pharmacokinetic and pharmacodynamic studies in healthy subjects, and controlled and uncontrolled studies in patients with narcolepsy, OSAHS, and SWSD. There were also a number of controlled and uncontrolled studies in patients with disorders other than narcolepsy, OSAHS, and SWSD.

5.1.5.2 Treatment Exposure in All Studies in Narcolepsy, OSAHS, and SWSD

In all narcolepsy, OSAHS, and SWSD studies, for patients treated with PROVIGIL, there were 1286 patients with narcolepsy, 485 patients with OSAHS, and 375 patients with SWSD (Table 46). For these studies combined (including open-label extension periods of double-blind studies), the mean duration of exposure to PROVIGIL was 349 days (a total of 2083 patient-years), with more than 740 patients exposed to PROVIGIL for a year or more.

Table 46: Treatment Exposure in All Studies in Narcolepsy, OSAHS, and SWSD (Safety Analysis Set)

	Number (%) of subjects/patients			
Months of exposure	**All narcolepsy, OSAHS, and SWSD studies (n=2146)**	**All narcolepsy studies (N=1286)**	**All OSAHS studies (N=485)**	**All SWSD studies (N=375)**
≥ 1	1778 (83)	1058 (82)	405 (84)	315 (84)
≥ 3	1348 (63)	778 (61)	333 (69)	237 (63)
≥ 6	1031 (48)	612 (48)	218 (45)	201 (54)
≥ 9	872 (41)	540 (42)	194 (40)	138 (37)
≥ 12	741 (35)	485 (38)	166 (34)	90 (24)

OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder.

NOTE: At the time of the submission of this briefing document, the open-label treatment period of SWSD study 305 is ongoing. It is anticipated that patient participation in this study will end in October. At that time, it is estimated that safety data will be available from approximately 165 patients with SWSD exposed to PROVIGIL for 12 months.

5.1.5.3 Treatment Exposure in All PROVIGIL Studies

Across all studies in all indications (in adults), there were 3598 unique subjects/patients who received PROVIGIL. The mean duration of exposure to PROVIGIL was 220 days (a total of 2200 patient-years), with 738 patients exposed to PROVIGIL for a year or more and 309 patients exposed for over 2 years.

Table 47: Treatment Exposure in All Studies (Safety Analysis Set)

	Number (%) of subjects/patients
Months of exposure	All studies (N=3598)
≥ 1	2183 (61)
≥ 3	1422 (40)
≥ 6	1069 (30)
≥ 9	860 (24)
≥ 12	738 (21)
≥ 24	309 (9)

5.1.5.4 Overview of Adverse Events Across the Three Data Sets (Principal Studies, All Studies in Narcolepsy, OSAHS, and SWSD, and All Studies)

The percentages of PROVIGIL-treated patients who experienced adverse events were comparable among the 3 safety data sets for the principal studies (78%); all narcolepsy, OSAHS, and SWSD studies (68%); and all studies (64%). The percentage of patients who experienced serious adverse events was low overall (2% to 5%). The percentage of patients who experienced adverse events leading to withdrawal for the 3 data sets ranged from 8% to 10% (Table 48).

Table 48: Overview of Adverse Events in the Principal Studies, in All Studies in Narcolepsy, OSAHS, and SWSD, and in All Studies (Safety Analysis Set)

	Number (%) of patients			
	Principal studies		All Narcolepsy, OSAHS, and SWSD studies	All studies
Adverse event category	PROVIGIL	Placebo	PROVIGIL	PROVIGIL
Number of patients	934	567	2146	3796
Adverse events (AEs)	728 (78)	379 (67)	1470 (68)	2434 (64)
Treatment-related AEs	283 (30)	90 (16)	845 (39)	1578 (42)
Serious adverse events	17 (2)	8 (1)	99 (5)	132 (3)
AEs leading to withdrawal	78 (8)	15 (3)	211 (10)	345 (9)
Deaths	0	0	2 (<1)	13 (<1)

Of interest is the rate of serious adverse events for PROVIGIL-treated patients per 100 patient-treatment-years in all narcolepsy, OSAHS, and SWSD studies, which is 4.8, lower than that for placebo-treated patients in the principal studies, which is 9.6.

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None of the 13 deaths that were reported for patients who participated in clinical studies was related to PROVIGIL treatment. Two deaths (1 accidental injury, 1 cardiomyopathy) are from the data set for all narcolepsy, OSAHS, and SWSD studies. The causes of death were reported as:

- accident
- cardiomyopathy
- progression of amyotropic lateral sclerosis (ALS)
- heart failure, renal function abnormal
- syncope and dyspnea
- myocardial infarction
- progression of alcoholic cirrhosis
- suicide (patient with history of attempts)
- postoperative complications in a patient with Alzheimer's disease
- lymphoproliferative disorder in a patient with Parkinson's disease
- cancer progression (3 patients)

5.1.5.5 Adverse Events in the Principal Studies, in All Studies in Narcolepsy, OSAHS, and SWSD, and in All Studies

Consistent with the adverse event data from the principal studies data set, the most common adverse events reported in the data set for all narcolepsy, OSAHS, and SWSD studies and the data set for all studies were headache (28% and 23%, respectively), nausea (10% and 9%, respectively), and nervousness (9% and 10%, respectively) (Table 49).

Table 49: Adverse Events Occurring in ≥5% of PROVIGIL-Treated Patients and at a Greater Percentage Than in Placebo-Treated Patients in the Principal Studies, in All Studies in Narcolepsy, OSAHS, and SWSD, and in All Studies (Safety Analysis Set)

	Number (% of patients)			
	Principal studies		All narcolepsy, OSAHS, and SWSD studies	All studies
Adverse event	PROVIGIL (N=934)	Placebo (N=567)	PROVIGIL (N=2146)	PROVIGIL (N=3796)
Headache	319 (34)	133 (23)	601 (28)	881 (23)
Nausea	107 (11)	19 (3)	219 (10)	342 (9)
Nervousness	69 (7)	19 (3)	195 (9)	371 (10)
Rhinitis	69 (7)	33 (6)	188 (9)	220 (6)
Diarrhea	58 (6)	26 (5)	123 (6)	160 (4)
Back pain	52 (6)	26 (5)	134 (6)	150 (4)
Insomnia	45 (5)	6 (1)	150 (7)	348 (9)
Dyspepsia	44 (5)	21 (4)	132 (6)	163 (4)
Anxiety	44 (5)	5 (<1)	124 (6)	248 (7)
Dizziness	43 (5)	20 (4)	108 (5)	158 (4)

5.1.6 Adverse Events in the Principal Studies by Dose

The overall incidence of adverse events was similar for the 3 PROVIGIL dosage groups (Table 50). There were no clear dose-related trends with respect to the frequency of specific adverse events except for headache, for which the incidence was higher among patients receiving 400 mg/day of PROVIGIL (40%) compared to those receiving 200 mg/day (32%).

Table 50: Adverse Events Occurring in ≥5% of PROVIGIL-Treated Patients in the Principal Studies by Dose (Safety Analysis Set)

	Number (%) of patients			
Adverse event	**PROVIGIL 200 mg/day (N=477)**	**PROVIGIL 300 mg/day (N=90)**	**PROVIGIL 400 mg/day (N=367)**	**Placebo (N=567)**
No. of patients with at least 1 adverse event	368 (77)	67 (74)	289 (79)	373 (66)
Headache	151 (32)	23 (26)	145 (40)	133 (23)
Infection	53 (11)	2 (2)	42 (11)	68 (12)
Nausea	50 (10)	17 (19)	40 (11)	19 (3)
Nervousness	32 (7)	9 (10)	28 (8)	19 (3)
Rhinitis	32 (7)	3 (3)	34 (9)	33 (6)
Diarrhea	27 (6)	7 (8)	24 (7)	26 (5)
Pain	29 (6)	5 (6)	11 (3)	33 (6)
Back pain	25 (5)	4 (4)	23 (6)	26 (5)
Flu syndrome	22 (5)	5 (6)	10 (3)	17 (3)
Dyspepsia	25 (5)	4 (4)	15 (4)	21 (4)
Insomnia	24 (5)	4 (4)	17 (5)	6 (1)
Dizziness	17 (4)	6 (7)	20 (5)	20 (4)
Pharyngitis	18 (4)	4 (4)	17 (5)	14 (2)
Accidental injury	16 (3)	6 (7)	8 (2)	30 (5)
Hypertension	12 (3)	6 (7)	12 (3)	3 (<1)
Dry mouth	16 (3)	4 (4)	17 (5)	9 (2)
Anorexia	14 (3)	5 (6)	16 (4)	6 (1)
Anxiety	16 (3)	4 (4)	24 (7)	5 (<1)

NOTE: Narcolepsy studies 301 and 302, OSAHS studies 303 and 402, and SWSD studies 305 and 306 utilized PROVIGIL doses of 200 and/or 400 mg/day. Only SWSD study 306 utilized a PROVIGIL dose of 300 mg/day. OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder.

5.1.7 Adverse Events in the Principal Studies Over Time

In the 6 principal studies, the majority (68%) of adverse events occurred in the first month of treatment, and the most of these adverse events occurred in the first week of treatment (Table 51).

Table 51: Cumulative Incidence of Adverse Events (Adverse Events Occurring in ≥5% of Patients in Any Treatment Group) by Time on Treatment in the Principal Studies (Safety Analysis Set)

	First week of treatment		First month of treatment		0 to 3 months of treatment	
Adverse event	**PROVIGIL (N=934)**	**Placebo (N=567)**	**PROVIGIL (N=934)**	**Placebo (N=567)**	**PROVIGIL (N=934)**	**Placebo (N=567)**
No. of patients with at least 1 adverse event	451 (48)	166 (29)	632 (68)	288 (51)	718 (77)	367 (65)
Headache	188 (20)	50 (9)	271 (29)	104 (18)	318 (34)	132 (23)
Nausea	67 (7)	12 (2)	90 (10)	17 (3)	107 (11)	19 (3)
Nervousness	49 (5)	8 (1)	62 (7)	13 (2)	69 (7)	19 (3)
Insomnia	33 (4)	5 (<1)	42 (4)	6 (1)	45 (5)	6 (1)
Diarrhea	25 (3)	12 (2)	43 (5)	17 (3)	58 (6)	24 (4)
Dry mouth	29 (3)	7 (1)	35 (4)	9 (2)	37 (4)	9 (2)
Anxiety	25 (3)	3 (<1)	42 (4)	5 (<1)	44 (5)	5 (<1)
Dizziness	25 (3)	9 (2)	37 (4)	19 (3)	43 (5)	20 (4)
Back pain	19 (2)	5 (<1)	31 (3)	16 (3)	52 (6)	26 (5)
Dyspepsia	16 (2)	11 (2)	28 (3)	17 (3)	43 (5)	21 (4)
Anorexia	23 (2)	5 (<1)	31 (3)	6 (1)	35 (4)	6 (1)
Rhinitis	18 (2)	5 (<1)	47 (5)	15 (3)	69 (7)	32 (6)

With prolonged exposure to PROVIGIL treatment (up to 24 months), the overall incidence of adverse events and of the most frequently occurring adverse events were highest within the first 3 months of treatment with the exception of infection, which occurred at a consistent rate across the treatment intervals (Table 52).

Table 52: Incidence of Selected Adverse Events Occurring in ≥5% of PROVIGIL-Treated Patients by Onset Interval in All Narcolepsy, OSAHS, and SWSD Studies (Safety Analysis Set)

Adverse event	Number (%) of patients			
	Onset interval (months)			
	0 to ≤3 (N=2146)	>3 to ≤6 (N=1336)	>6 to ≤12 (N=1024)	>12 to ≤24 (N=753)
No. of patients with at least 1 adverse event	1366 (64)	504 (38)	409 (40)	305 (41)
Headache	534 (25)	119 (9)	81 (8)	71 (9)
Nausea	182 (8)	29 (2)	7 (<1)	9 (1)
Nervousness	162 (8)	28 (2)	6 (<1)	13 (2)
Infection	157 (7)	80 (6)	86 (8)	71 (9)
Insomnia	125 (6)	6 (<1)	9 (<1)	11 (1)
Anxiety	97 (5)	15 (1)	11 (1)	4 (<1)
Diarrhea	96 (4)	15 (1)	14 (1)	11 (1)
Hypertension	47 (2)	8 (<1)	9 (<1)	12 (2)

OSAHS = obstructive sleep apnea/hypopnea syndrome.

5.1.8 Adverse Events in the Principal Studies and in the Current PROVIGIL Labeling

Overall, the adverse event profile observed in the 6 principal studies in the 3 disorders of sleep and wakefulness is no different from that of the current PROVIGIL labeling for patients with EDS associated with narcolepsy (Table 53).

Table 53: Adverse Events Occurring in ≥5% of PROVIGIL-Treated Patients Data From the Principal Studies Compared With Current PROVIGIL Labeling

Adverse event	Number (%) of patients			
	Principal studies		Current PROVIGIL labeling	
	PROVIGIL (N=934)	Placebo (N=567)	PROVIGIL (N=369)	Placebo (N=185)
Headache	319 (34)	133 (23)	183 (50)	74 (40)
Nausea	107 (11)	19 (3)	47 (13)	7 (4)
Nervousness	69 (7)	19 (3)	30 (8)	12 (6)
Rhinitis	69 (7)	33 (6)	42 (11)	14 (8)
Diarrhea	58 (6)	26 (5)	30 (8)	8 (4)
Back pain	52 (6)	26 (5)	35 (9)	16 (9)
Insomnia	45 (5)	6 (1)	11 (3)	2 (1)
Dyspepsia	44 (5)	21 (4)	26 (7)	14 (8)
Anxiety	44 (5)	5 (<1)	13 (4)	1 (1)
Dizziness	43 (5)	20 (4)	17 (5)	7 (4)

5.2 Clinical Laboratory Evaluations

Laboratory data was evaluated for mean changes, shifts (eg, from normal to high and normal to low) and for clinically significant values, based on criteria from the Agency (Division of Neuropharmacological Drug Products memorandum dated 1985 [see Table 55 and Table 56 for criteria]). There were no overall trends in clinical laboratory evaluations that indicated a clinically meaningful effect of PROVIGIL.

Mean changes from baseline to the last observation for hematologic and serum chemistry parameters were minimal in both the PROVIGIL and placebo treatment groups in the 6 principal studies at the final visit. Mean values for alkaline phosphatase and gamma-glutamyl-transferase (GGT) and mean changes from baseline showed small increases with increasing duration of exposure to PROVIGIL (all narcolepsy, OSAHS, and SWSD studies database) (Table 54). However, these increases were not accompanied by mean increases in SGOT, SGPT, or total bilirubin.

Table 54: Mean (SD) and Mean Change from Baseline by Time Interval for Alkaline Phosphatase and GGT (All Studies in Narcolepsy, OSAHS, and SWSD) (Safety Analysis Set)

	Time interval (months) of PROVIGIL treatment			
Variable	**0 to ≤3**	**>3 to ≤6**	**>6 to ≤12**	**>12 to ≤24**
Alkaline phosphatase (U/L)				
N	1476	854	688	472
Baseline	80.9 (24.44)	79.7 (23.23)	78.8 (21.69)	78.0 (22.11)
Last value	84.1 (25.92)	85.1 (24.56)	85.1 (23.25)	86.9 (25.03)
Change from baseline	3.2 (11.95)	5.4 (11.79)	6.3 (12.89)	8.9 (14.63)
GGT (U/L)				
N	685	496	431	306
Baseline	29.4 (27.80)	28.2 (24.14)	27.9 (23.26)	27.2 (22.88)
Last value	35.3 (33.56)	38.0 (38.06)	39.1 (38.85)	39.6 (34.49)
Change from baseline	5.9 (18.86)	9.8 (26.49)	11.3 (25.93)	12.4 (18.25)

GGT = gamma-glutamyl-transferase; N = number of patients with both baseline and postbaseline observation values; OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder.

The numbers of patients with shifts from normal in alkaline phosphatase values were not notable. Shifts in GGT values from normal (at baseline) to high were observed more frequently for patients receiving PROVIGIL (5%, 22 of 447 patients) than for those receiving placebo (1%, 3 of 283 patients) in the 6 principal studies; however, few (5, <1%) of the PROVIGIL-treated patients had GGT values that met the criteria for a clinically significant abnormality. Overall, clinically significant abnormalities in serum chemistry values were infrequent (<1%) for all variables (Table 55).

Table 55: Clinically Significant Abnormal Chemistry Values (Principal Studies and All Narcolepsy, OSAHS, and SWSD Studies) (Safety Analysis Set)

		Number (%) of patients		
		Principal studies		All narcolepsy, OSAHS, and SWSD studies
Serum chemistry variable	Criteria	PROVIGIL (N=934)	Placebo (N=567)	PROVIGIL (N=1989)
BUN (mmol/L)	≥10.71	7 (<1)	5 (<1)	19 (<1)
Creatinine (μmol/L)	≥177	0	2 (<1)	2 (<1)
Uric acid (μmol/L)	≥506 (F)	7 (<1)	5 (<1)	16 (<1)
	≥625 (M)	0	0	2 (<1)
SGOT (U/L)	≥3 x UNL	2 (<1)	5 (<1)	11 (<1)
SGPT (U/L)	≥3 x UNL	5 (<1)	3 (<1)	14 (<1)
GGT (U/L)	≥3 x UNL	5 (<1)	2 (<1)	19 (<1)
Total bilirubin (μmol/L)	≥34.2	0	4 (<1)	2 (<1)

BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; OSAHS = obstructive sleep apnea/hypopnea syndrome; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate pyruvate transaminase; SWSD = shift work sleep disorder; UNL = upper limit of normal (range).

Mean changes in hematology values were minimal. Clinically significant abnormalities in hematology values were also infrequent (Table 56).

Table 56: Clinically Significant Abnormal Hematology Values (Principal Studies and All Narcolepsy, OSAHS, and SWSD Studies) (Safety Analysis Set)

		Number (%) of patients		
		Principal studies		All narcolepsy, OSAHS, and SWSD studies
Hematology variable	Criteria	PROVIGIL (N=934)	Placebo (N=567)	PROVIGIL (N=1989)
WBC (x 10^9/L)	≤3.0	8 (<1)	3 (<1)	17 (<1)
	≥20	0	0	0
Hemoglobin (g/L)	≤115 (M)	3 (<1)	2 (<1)	4 (<1)
	≤95 (F)	0	0	2 (<1)
Hematocrit (L/L)	<0.37 (M)	5 (<1)	1 (<1)	13 (<1)
	<0.32 (F)	5 (<1)	1 (<1)	13 (<1)
ANC (x 10^9/L)	≤1.0	5 (<1)	3 (<1)	9 (<1)
Eosinophils (%)	≥10.0	19 (2)	10 (2)	36 (2)
Platelets (x 10^9/L)	≤75	0	1 (<1)	0
	≥700	0	1 (<1)	2 (<1)

ANC = absolute neutrophil count; OSAHS = obstructive sleep apnea/hypopnea syndrome; SWSD = shift work sleep disorder; WBC = white blood cell count.

5.3 Vital Signs

5.3.1 Evaluation of Vital Signs in Patients With Narcolepsy, OSAHS, or SWSD

Mean changes in vital signs values were minimal and there were no marked differences between the PROVIGIL treatment group and the placebo treatment group or among the 3 patient populations (narcolepsy, OSAHS, and SWSD) (Table 57).

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Table 57: Changes From Baseline in Vital Signs Values (Principal Studies and All Narcolepsy, OSAHS, and SWSD Studies) (Safety Analysis Set)

		Principal studies				All narcolepsy, OSAHS, and SWSD studies	
		PROVIGIL (N=934)		Placebo (N=567)		PROVIGIL (N=1613)	
Vital sign variable	Statistic	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
Heart rate (bpm)	N	902	902	551	551	1537	1537
	Mean (SD)	73.2 9 (10.74)	0.1 (11.14)	71.7 (10.08)	–0.1 (10.06)	73.0 (10.48)	1.6 (11.51)
Systolic blood pressure (mmHg)	N	902	902	551	551	1567	1567
	Mean (SD)	123.9 (14.53)	–0.3 (13.19)	124.2 (13.92)	–1.3 (12.83)	123.3 (14.44)	1.6 (13.41)
Diastolic blood pressure (mmHg)	N	902	902	551	551	1567	1567
	Mean (SD)	77.8 (9.71)	–0.4 (9.11)	78.3 (9.34)	–1.0 (9.03)	77.6 (9.58)	0.9 (9.66)

bpm = beats per minute; N = number of patients with both baseline and postbaseline observation values; OSAHS = obstructive sleep apnea/hypopnea syndrome; rpm = respirations per minute; SWSD = shift work sleep disorder.

Vital signs measurements, including body weight, were evaluated for clinically significant changes as determined by the Agency (Division of Neuropharmacological Drug Products memorandum dated 1985 [see Table 58 for criteria]). Except for increases and decreases in body weight, clinically significant abnormalities in vital signs were infrequent (Table 58). In the 6 principal studies, clinically significant decreases in body weight were more frequent in the PROVIGIL treatment group (3%) than in the placebo treatment group (1%). This trend was most pronounced in the OSAHS studies (7% PROVIGIL; 1% placebo).

Table 58: Clinically Significant Abnormal Vital Signs Values (Principal Studies and All Narcolepsy, OSAHS, and SWSD Studies) (Safety Analysis Set)

		Number (%) of patients		
		Principal studies		All narcolepsy, OSAHS, and SWSD studies
Variable	Criteria	PROVIGIL (N=934)	Placebo (N=567)	PROVIGIL (N=1613)
Heart rate (bpm)	≥120 and increase ≥15	1 (<1)	1 (<1)	3 (<1)
	≤50 and decrease ≥15	4 (<1)	6 (1)	21 (1)
Systolic BP (mmHg)	≥180 and increase ≥20	1 (<1)	0	13 (<1)
	≤90 and decrease ≥20	9 (<1)	3 (<1)	24 (2)
Diastolic BP (mmHg)	≥105 and increase ≥15	9 (<1)	0	34 (2)
	≤50 and decrease ≥15	7 (<1)	3 (<1)	19 (1)
Weight (kg)	Increase ≥7	10 (1)	5 (<1)	152 (9)
	Decrease ≥7	28 (3)	7 (1)	184 (11)

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

5.3.2 Evaluation of Blood Pressure and Heart Rate in Patients With OSAHS

It has been reported in the literature that having OSAHS is an independent risk factor for the development of hypertension and cardiovascular disease; therefore, further analyses of heart rate and systolic and diastolic blood pressures were undertaken specifically in patients with OSAHS.

Specifically, in the OSAHS principal studies, there was no clinically relevant difference in mean systolic or diastolic blood pressure or heart rate (Table 59).

Table 59: Evaluation of Blood Pressure and Heart Rate in Patients with OSAHS (OSAHS Studies 303 and 402)

	Treatment group		
Parameter	PROVIGIL 200 mg (N=109)	PROVIGIL 400 mg (N=183)	Placebo
Systolic BP (mmHg)			
Baseline mean (SD)	127.7 (13.2)	126.4 (12.4)	129.5 (12.3)
Mean (SD) change	–1.4 (15.1)	0.3 (11.8)	–2.1 (12.8)
Diastolic BP (mmHg)			
Baseline mean (SD)	80.4 (8.3)	79.7 (7.9)	80.4 (8.3)
Mean (SD) change)	–2.0 (10.1)	0.2 (8.7)	–1.6 (8.7)
Heart rate (bpm)			
Baseline mean (SD)	71.3 (10.5)	73.0 (9.9)	71.1 (9.9)
Mean (SD) change	–0.8 (10.0)	0.3 (10.6)	0.2 (10.1)

Mean change = mean change from baseline to the final visit.
OSAHS = obstructive sleep apnea/hypopnea syndrome.

In addition, an evaluation of high systolic and diastolic blood pressure values based on the World Health Organisation (WHO) definition of hypertension (SBP ≥140 mmHg and DPB ≥90 mmHg) was made utilizing data from the 2 principal (studies 303 and 402), and a placebo-controlled crossover study (study 407).

The results of this evaluation show that there is no evidence of any clinically meaningful differences between the PROVIGIL and placebo treatment groups (Table 60).

Table 60: Patients With High Blood Pressure Values (WHO Criteria) at the Final Visit by Treatment Group for Patients With OSAHS (OSAHS Studies 303, 402, and 407)

Parameter	Criteria	Number (%) of patients			
		PROVIGIL 200 mg/day (N=109)	PROVIGIL 400 mg/day (N=214)	PROVIGIL combined (N=323)	Placebo (N=218)
SBP (mmHg)	140 to 159 (inclusive)	14 (13)	36 (18)	50 (16)	37 (17)
	160 to 179 (inclusive)	2 (2)	3 (1)	5 (2)	3 (1)
	≥140 and ≥10% change from baseline	7 (7)	15 (7)	22 (7)	15 (7)
DBP (mmHg)	90 to 99 (inclusive)	7 (7)	29 (14)	36 (12)	25 (12)
	100 to 110 (inclusive)	1 (<1)	5 (2)	6 (2)	1 (<1)
	≥90 and ≥10% change from baseline	3 (3)	15 (7)	18 (6)	9 (4)

OSAHS = obstructive sleep apnea/hypopnea syndrome; SBP = systolic blood pressure; DBP = diastolic blood pressure; WHO = World Health Organization.

5.4 Electrocardiography

There was no difference in the incidence of newly diagnosed electrocardiography (ECG) findings reported for patients receiving PROVIGIL (17% [162 of 934 patients]) and those receiving placebo (18% [102 of 567 patients]) in the 6 principal studies.

ECG intervals including QTC interval were evaluated in the 6 principal studies at baseline and the final visit. No trends were seen in changes in mean interval lengths and no clinically relevant outlier values were observed.

5.5 Overall Summary of Safety Evaluations

The primary evaluation of the safety of PROVIGIL treatment in patients with excessive sleepiness associated with disorders of sleep and wakefulness was made on the basis of the 6 principal studies that contributed data to the evaluation of efficacy above. A total of 934 patients received PROVIGIL treatment in these studies (477 patients at 200 mg/day, 90 patients at 300 mg/day, and 367 patients at 400 mg/day), and 567 patients received placebo treatment. Of the 934 patients who received PROVIGIL, 369 patients had excessive sleepiness associated with narcolepsy, 292 patients had excessive sleepiness associated with OSAHS, and 273 patients had excessive sleepiness associated with SWSD.

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Supportive safety data are obtained from open-label treatment extensions of these double-blind studies and additional controlled and uncontrolled studies in adult patients with narcolepsy or OSAHS (all narcolepsy, OSAHS, and SWSD studies). Across all narcolepsy, OSAHS, and SWSD studies combined, a total of 2146 patients received PROVIGIL treatment. The mean duration of exposure to PROVIGIL in these studies was 349 days (2083 patient-years). Over 700 patients were treated with PROVIGIL for a year or more and more than 300 patients for more than 2 years.

In adult patients with excessive sleepiness associated with disorders of sleep and wakefulness, the type and incidence of adverse events reported were consistent with the known safety profile of PROVIGIL as represented in the current product labeling. The type and incidence of adverse events observed for all narcolepsy, OSAHS, and SWSD studies combined, and for all studies in all indications, were similar to that observed in the principal studies.

In the principal studies, the type and incidence of adverse events was similar among the 3 study populations (narcolepsy, OSAHS, and SWSD), except for headache, which was observed more frequently in patients with narcolepsy. The overall incidence of adverse events was similar for the 3 PROVIGIL dosage groups (200, 300, and 400 mg/day). There were no clear dose-related trends with respect to the frequency of specific adverse events except for headache. The majority of adverse events were mild to moderate in severity and occurred within the first month of treatment. The incidence of adverse events, and headache in particular, was higher for women compared to men in both the PROVIGIL and placebo treatment groups. There were no apparent differences in the adverse event profile of PROVIGIL based on race (white vs nonwhite), age (≤65 years vs >65 years), or body mass index (≤32 vs >32).

In the principal studies, 8% of patients who received PROVIGIL treatment and 3% of patients who received placebo treatment had adverse events leading to withdrawal from study. In the PROVIGIL treatment group, the most common adverse events leading to withdrawal were headache (16 patients, 2%), nausea, anxiety, dizziness, and insomnia (9 patients each, <1%), chest pain (8 patients, <1%), and nervousness (7 patients, <1%). The incidence of serious adverse events was 2% for patients treated with PROVIGIL and 1% for patients treated with a placebo. Six (<1%) patients in the PROVIGIL treatment group had serious adverse events that were considered related to treatment.

In all narcolepsy, OSAHS, and SWSD studies combined, withdrawal due to adverse events was reported for 10% of patients and serious adverse events were reported for 5% of patients. Across all narcolepsy, OSAHS, and SWSD studies combined, there were 2 patient deaths in an open-label extension of one of the principal placebo-controlled narcolepsy studies, both of which were considered unrelated to study drug.

There were no overall trends in clinical laboratory evaluations of patients receiving PROVIGIL treatment in either the principal studies or all narcolepsy, OSAHS, and SWSD studies combined that indicate a clinically significant effect of PROVIGIL.

In the principal studies, mean changes from baseline to the last observation for serum chemistry parameters were minimal in both the PROVIGIL and placebo treatment groups. The only difference between the treatment groups was a greater mean increase from baseline in alkaline

phosphatase and GGT in the PROVIGIL treatment group compared to the placebo treatment group. In all narcolepsy, OSAHS, and SWSD studies combined, including long-term open-label extension periods of double-blind studies, mean values for alkaline phosphatase and GGT and mean changes from baseline showed small increases with increasing duration of exposure to PROVIGIL. In both groups of studies, increases in alkaline phosphatase and GGT were not accompanied by increases in SGOT, SGPT, or total bilirubin. In the principal studies, the distribution of shifts relative to the normal range for serum chemistry variables was similar in the PROVIGIL and placebo treatment groups, with the exception of GGT, for which there was a somewhat higher incidence of patients with values above the normal range both at baseline and the final visit (ie, high to high) for PROVIGIL (6%, 27 of 447 patients) compared to placebo (3%, 8 of 283 patients), and of patients whose values shifted from within the normal range at baseline to above the normal range at the final visit (ie, normal to high), for which the incidence was 5% (22 of 447 patients) for PROVIGIL and 1% (3 of 283 patients) for placebo. Five (<1%) patients who received PROVIGIL in the principal studies had GGT values that met the criteria for clinically significant abnormality. Clinically significant abnormalities in serum chemistry values were infrequent (<1% for all variables) in both the principal studies combined and all narcolepsy, OSAHS, and SWSD studies combined.

In the principal studies, mean changes from baseline to the last observation for hematology parameters were minimal in both the PROVIGIL and placebo treatment groups, and the distribution of shifts relative to the normal range was similar for the 2 treatment groups. Clinically significant abnormalities in hematology values were infrequent both in the principal studies and all narcolepsy, OSAHS, and SWSD studies combined.

There was no evidence of clinically significant effects of PROVIGIL on vital signs in the principal studies or for all narcolepsy, OSAHS, and SWSD studies combined. In response to a request made by the Division of Neuropharmacological Drug Products of the FDA at a pre-submission meeting with Cephalon on 9 August 2002, additional evaluations of the effect of PROVIGIL treatment on blood pressure and heart rate in patients with excessive sleepiness, and specifically in patients with OSAHS were performed. The results of these additional analyses demonstrate that chronic administration of PROVIGIL at 200 to 400 mg/day is not associated with clinically relevant changes in blood pressure (SBP or DBP) or HR in patients with excessive sleepiness associated with OSAHS. No consistent effects or patterns of change in BP or HR were seen in patients with OSAHS, whether or not the patients had evidence for a diagnosis of hypertension and/or had elevated BP or HR at baseline.

Though there has been no evidence from postmarketing surveillance to suggest that PROVIGIL treatment contributes to an alteration of ECG intervals, a review of the available (electronic) ECG interval data was undertaken in response to a specific request made by the Division of Neuropharmacological Drug Products (9 August 2002). In a review of data from over 90 healthy subjects treated with PROVIGIL who had ECG data recorded during the time of the expected PROVIGIL C_{max}, no evidence was found that PROVIGIL led to clinically relevant changes in ECG intervals. In particular, there was no evidence of prolonged ventricular repolarization, as measured by the QTc interval. PROVIGIL doses 2 to 4 times higher than those used in efficacy studies in patient populations had no effect on QTc intervals in healthy subjects when ECGs were done during the time of the expected PROVIGIL C_{max}. Similarly, in patients with SWSD,

there was also no evidence that chronic treatment with PROVIGIL led to clinically relevant changes in ECG intervals.

5.6 Safety Conclusions

The safety of PROVIGIL has been evaluated in more than 4000 healthy subjects/patients enrolled in clinical studies. Across all studies conducted in patients with narcolepsy, OSAHS, or SWSD, nearly 700 patients have received PROVIGIL for more than 1 year and more than 300 patients have received PROVIGIL for more than 2 years. The results of these studies support the following conclusions for this patient population:

- PROVIGIL treatment is well tolerated.
- PROVIGIL's safety profile is similar among the 3 disorders of sleep and wakefulness (narcolepsy, OSAHS, and SWSD).
- PROVIGIL's safety profile for the broader indication under consideration is consistent with its known profile, with no new trends emerging.

6 SPECIAL CONSIDERATIONS

6.1 Effect on Nighttime/Daytime Sleep

Situationally appropriate sleep (ie, nighttime sleep for patients with narcolepsy or OSAHS, daytime for patients with SWSD) was evaluated during the double-blind treatment periods in the principal studies in narcolepsy (studies 301 and 302), OSAHS (studies 303 and 402), and SWSD (study 305) using polysomnography (PSG). Results of PSG indicate that treatment with PROVIGIL did not have an adverse effect on the sleep of these patients. Assessments of sleep efficiency (percentage of time in bed spent asleep), arousal index (number of arousals per hour of sleep), and time spent awake after sleep onset showed no clinically important difference between the PROVIGIL and placebo treatment groups in any of the patient populations. There was also no evidence, on the basis of these data, that PROVIGIL treatment alters the underlying disturbed sleep.

Furthermore, in SWSD study 305 (Table 61) and study 306 (Table 62), patient-reported (from sleep logs) sleep efficiency during the days following the nights worked showed that treatment with PROVIGIL did not adversely affect daytime sleep in this patient population.

Table 61: Patient-Reported Sleep Efficiency (%) From Daytime Sleep Logs in SWSD Study 305

	PROVIGIL 200 mg			Placebo		
Statistic	**Pretreatment**	**On-treatment**	**Change on treatment**	**Pretreatment**	**On-treatment**	**Change on treatment**
n	78	78	78	84	84	84
Mean (SD)	80.3 (19.92)	87.5 (14.39)	7.3 (18.55)	78.0 (20.67)	87.5 (14.12)	9.5 (18.32)
Median	85.5	91.5	2.5	84.9	90.4	5.4
Min, max	2.7, 100.0	17.4, 99.8	–34.7, 87.2	4.6, 100.0	13.9, 100.0	–26.3, 73.0

Note: Data are for sleep efficiency during days following the night shift worked.
SWSD = shift work sleep disorder; min = minimum; max = maximum.

Table 62: Patient-Reported Sleep Efficiency (%) From Daytime Sleep Logs in SWSD Study 306

	PROVIGIL 200 mg/day			PROVIGIL 300 mg/day			Placebo		
Statistic	Pre-treatment	On-treatment	Change on treatment	Pre-treatment	On-treatment	Change on treatment	Pre-treatment	On-treatment	Change on treatment
n	34	73	34	33	69	33	32	63	31
Mean (SD)	85.07 (11.50)	92.35 (5.99)	5.53 (10.30)	87.04 (9.72)	88.13 (12.53)	3.41 (8.16)	89.13 (8.53)	90.29 (7.66)	3.97 (8.71)
Median	88.21	93.17	2.15	88.72	91.71	3.98	89.47	91.84	2.31
Min, max	48.7, 100.0	70.8, 100.0	-6.4, 41.3	51.1, 100.0	28.6, 100.0	-12.6, 30.9	67.3, 100.0	68.9, 100.0	-8.9, 30.9

Note: Data are for sleep efficiency during days following the night shift worked.
SWSD = shift work sleep disorder; min = minimum; max = maximum.

6.2 Effect on Nasal Continuous Positive Airway Pressure Usage in Patients With OSAHS

In the 2 OSAHS studies 303 and 402, which included 811 patients, the effect of treatment with PROVIGIL on the usage of nCPAP therapy was evaluated during both the double-blind and open-label treatment periods. No notable changes in nCPAP therapy usage were observed either within or between treatment groups from baseline assessments to the end of the treatment period (ie, for either the double-blind or open-label treatment periods).

In OSAHS study 303, nCPAP usage for the 327 patients (218 treated with PROVIGIL and 109 treated with a placebo) remained constant during the double-blind treatment period for patients in all 3 treatment groups. The mean pre-treatment nightly nCPAP therapy usage was 5.99 and 5.95 hours for the 200- and 400-mg/day PROVIGIL treatment groups, respectively, and 5.89 hours for the placebo treatment group. At the end of treatment, values were 5.90, 6.01, and 5.86 hours, respectively. During the open-label extension period, the average nightly use of nCPAP therapy for all patients at the time of entry was 5.88 hours, and the average nCPAP use after 12 months of treatment was 5.40 hours. The mean change in nCPAP usage during the open-label extension period was -0.57 hours, which is above the mean duration of usage reported in the literature.

Furthermore, in study 303, which was the larger of the 2 OSAHS studies, assessment of the change from baseline assessments to the final visit in RDI and oxygen saturation showed that PROVIGIL treatment had no adverse effect on the effectiveness of the patients' nCPAP therapy (Table 63).

Table 63: Mean Change From Baseline Assessments to the Final Visit in Apnea-Hypopnea Index (AHI) and Oxygen Saturation for Patients in OSAHS Study 303

Parameter Mean (SD)	PROVIGIL 200 mg/day (N=99)	PROVIGIL 400 mg/day (N=92)	Placebo (N=100)
AHI			
Baseline	4.2 (5.56)	4.2 (5.58)	5.8 (8.11)
Final visit	5.2 (11.46)	4.3 (7.86)	7.0 (10.03)
Change from baseline	0.7 (11.73)	0.2 (4.78)	1.1 (9.54)
Lowest oxygen saturation			
Baseline	91.0 (3.70)	90.7 (3.46)	90.1 (5.53)
Final visit	89.6 (8.01)	89.6 (8.61)	89.4 (7.22)
Change from baseline	–1.3 (7.90)	–1.3 (8.23)	–0.8 (6.57)

AHI = apnea-hypopnea index.

In OSAHS study 402, nCPAP usage was evaluated for 157 patients (77 treated with PROVIGIL and 80 treated with a placebo). The mean pretreatment nightly nCPAP therapy use in the PROVIGIL-treated group and the placebo-treated group was 6.35 and 6.20 hours, respectively. Similar values were observed at posttreatment, with mean nightly nCPAP therapy use of 6.15 hours and 6.18 hours in the PROVIGIL-treated group and the placebo-treated groups,

respectively. During the open-label extension period, the average nightly usage of nCPAP therapy at the time of entry was 6.28 hours, and the average nCPAP usage at the end of the treatment period was 5.94 hours (mean change of 0.34 hours).

6.3 Effect on Circadian Phase in Patients With SWSD

In order to assess the effect of PROVIGIL treatment on circadian phase, in SWSD study 305, saliva samples from participating patients were collected and melatonin concentrations analyzed. The main variable for the melatonin analysis was DLMO (dim light melatonin onset), defined as the time point when salivary melatonin levels rise to and are sustained above 3 pg/ml in saliva. If the calculation of DLMO was not possible, DLMOff (dim light melatonin offset), defined as the time point when salivary melatonin levels decreased to 3 pg/ml, was calculated for that patient. Melatonin midpoint was derived by adding 6 hours to DLMO or subtracting 6 hours from DLMOff.

The mean change from baseline to the last postbaseline visit in the DLMO was 1.0 hours for patients in the PROVIGIL treatment group versus –0.1 hour for patients in the placebo treatment group. However, the 95% confidence interval for the difference between the mean change from baseline was –0.324 to 2.536 indicating a minimal difference in DLMO phase change between treatment groups. There were also no significant differences for change based on DLMOff or melatonin midpoint between treatment groups.

The results of this analysis suggest that treatment with 200 mg of PROVIGIL in patients with ES associated with SWSD does not affect circadian adaptation to shift work schedules. These findings support the conclusion that the ability of PROVIGIL to treat symptoms of ES in patients with SWSD is a result of improvement in wakefulness, similar to that demonstrated in other models of sleep and wakefulness and not due to differentially affecting circadian adaptation.

The finding that some patients had DLMOffs, but not DLMOs, suggests that there was a small population of patients that showed some degree of circadian adaptation before treatment with PROVIGIL or placebo. However, whether or not a patient showed circadian adaptation before treatment with the study drug, treatment with PROVIGIL did not lead to a meaningful change in circadian phase from baseline or compared to placebo.

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7 BENEFIT/RISK ASSESSMENT

Excessive sleepiness associated with disorders of sleep and wakefulness can be disabling. The ES experienced by patients with these disorders affects their quality of life and their ability to participate in desired waking activities (e.g., work or school), and may represent a safety risk, not only for the patient but for society in general. For these patients, improving wakefulness (or decreasing ES) is important to allow adequate functioning at home, in the workplace, and while commuting to and from work.

PROVIGIL treatment improves wakefulness equally in patients with ES associated with disorders of sleep and wakefulness, regardless of the underlying disorder. The clinical benefits of PROVIGIL have been established in multiple clinical studies using multiple measures, both objective and subjective in nature. Across all disorders and within a disorder, there were statistically significant improvements with PROVIGIL treatment in mean sleep latency as measured by either MWT or MSLT and these improvements were maintained over the course of treatment. Statistically significant improvements in subjectively reported sleepiness were seen in all studies, and PROVIGIL-treated patients showed significant improvement on the basis of clinical impression (CGI-C). PROVIGIL treatment also improves the behavioral consequences of ES. The results of the PVT and SCPT demonstrate the positive effect of PROVIGIL treatment on sustained alertness and vigilance. The results of the studies also support the conclusion that PROVIGIL can have a clinically meaningful impact on some aspects of quality of life for these patients.

Across all disorders of sleep and wakefulness studied, PROVIGIL was generally well tolerated, and the adverse events seen have been generally innocuous. The most common adverse events reported in clinical studies were headache, nervousness, nausea, and insomnia. Most of these adverse events were mild to moderate in severity and occurred within the first month of PROVIGIL treatment. PROVIGIL appears to be well tolerated with long-term use, with no new patterns of adverse events observed. PROVIGIL tablets have been marketed in the US since 1999, with approximately 140,000 patient-treatment years of exposure. The safety profile observed with PROVIGIL in postmarketing surveillance is similar to that seen in clinical studies, and the safety profile as it applies to the broader population under consideration appears to be no different than the safety profile as outlined in the current PROVIGIL labeling.

On the basis of extensive clinical research, the benefits of PROVIGIL treatment clearly exceed its risks. Furthermore, PROVIGIL treatment is seen as fulfilling an unmet need for improving wakefulness in patients with ES associated with disorders of sleep and wakefulness.

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APPENDIX 1
INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS
CLASSIFICATION OUTLINE

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INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS
Classification Outline

1. DYSSOMNIAS	
A. Intrinsic Sleep Disorders	
1. Psychophysiologic Insomnia	307.42-0
2. Sleep State Misperception	307.49-1
3. Idiopathic Insomnia	780.52-7
4. Narcolepsy	347
5. Recurrent Hypersomnia	780.54-2
6. Idiopathic Hypersomnia	780.54-7
7. Post-traumatic Hypersomnia	780.54-8
8. Obstructive Sleep Apnea Syndrome	780.53-0
9. Central Sleep Apnea Syndrome	780.51-0
10. Central Alveolar Hypoventilation Syndrome	780.51-1
11. Periodic Limb Movement Disorder	780.52-4
12. Restless Legs Syndrome	780.52-5
13. Intrinsic Sleep Disorder NOS	780.52-9
B. Extrinsic Sleep Disorders	
1. Inadequate Sleep Hygiene	307.41-1
2. Environmental Sleep Disorder	780.52-6
3. Altitude Insomnia	289.0
4. Adjustment Sleep Disorder	307.41-0
5. Insufficient Sleep Disorder	307.49-4
6. Limit-setting Sleep Disorder	307.42-4
7. Sleep-onset Association Disorder	307.42-5
8. Food Allergy Insomnia	780.52-2
9. Nocturnal Eating (Drinking) Syndrome	780.52-8
10. Hypnotic-Dependent Sleep Disorder	780.52-0
11. Stimulant-Dependant Sleep Disorder	780.52-1
12. Alcohol-Dependent Sleep Disorder	780.52-3
13. Toxin-Induced Sleep Disorder	780.54-6
14. Extrinsic Sleep Disorder NOS	780.52-9
C. Circadian-Rhythm Sleep Disorders	
1. Time Zone Change (Jet Lag) Syndrome	307.45-0
2. Shift Work Sleep Disorder	307.45-1
3. Irregular Sleep-Wake Pattern	307.45-3
4. Delayed Sleep-Phase Syndrome	780.55-0
5. Advanced Sleep-Phase Syndrome	780.55-1
6. Non-24-Hour Sleep-Wake Disorder	780.55-2
7. Circadian Rhythm sleep Disorder	780.55-9

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2. PARASOMNIAS	
A. Arousal Disorders	
1. Confusional Arousals	307.46-2
2. Sleepwalking	307.46-0
3. Sleep Terrors	307.46-1
B. Sleep-Wake Transition Disorders	
1. Rhythmic movement Disorder	307.3
2. Sleep Starts	307.47-2
3. Sleep Talking	307.47-3
4. Nocturnal Leg Cramps	729.82
C. Parasomnias Usually Associated with REM Sleep	
1. Nightmares	307.47-0
2. Sleep Paralysis	780.56-2
3. Impaired Sleep-Related Penile Erections	780.56-3
4. Sleep-Related Painful Erections	780.56-4
5. REM Sleep-Related Sinus Arrest	780.56-8
6. REM Sleep Behavior Disorder	780.59-0
D. Other Parasomnias	
1. Sleep Bruxism	306.8
2. Sleep Enuresis	788.36-0
3. Sleep-Related Abnormal Swallowing Syndrome	780.56-6
4. Nocturnal Paroxysmal Dystonia	780.59-1
5. Sudden Unexplained Nocturnal Death Syndrome	780.59-3
6. Primary Snoring	786.09-1
7. Infant Sleep Apnea	770.80
8. Congenital Central Hypoventilation Syndrome	770.81
9. Sudden Infant Death Syndrome	798.0
10. Benign Neonatal Sleep Myoclonus	780.59-5
11. Other Parasomnia NOS	780.59-9
3. SLEEP DISORDERS ASSOCIATED WITH MENTAL, NEUROLOGIC, OR OTHER MEDICAL DISORDERS	
A. Associated with Mental Disorders	290-319
1. Psychoses	290-299
2. Mood Disorders	296-301,311
3. Anxiety Disorders	300,308,309
4. Panic Disorders	300
5. Alcoholism	303,305
B. Associated with Neurologic Disorders	
1. Cerebral Degenerative Disorders	320-389
2. Dementia	330-337
3. Parkinsonism	331
4. Fatal Familial Insomnia	332

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5. Sleep-Related Epilepsy	337.9
6. Electrical Status Epilepticus of Sleep	345.8
7. Sleep-Related Headaches	346
C. Associated with Other Medical Disorders	
1. Sleeping Sickness	086
2. Nocturnal Cardiac Ischemia	411-414
3. Chronic Obstructive Pulmonary Disease	490-496
4. Sleep-Related Asthma	
5. Sleep-Related Gastroesophageal Reflux	
6. Peptic Ulcer Disease	
7. Fibromyalgia	
4. PROPOSED SLEEP DISORDERS	
1. Short Sleeper	307.49-0
2. Long Sleeper	307.49-2
3. Subwakefulness Syndrome	307.47-1
4. Fragmentary Myoclonus	780.59-7
5. Sleep Hyperhidrosis	780.8
6. Menstrual-Associated Sleep Disorder	780.54-3
7. Pregnancy-Associated Sleep Disorder	780.59-6
8. Terrifying Hypnagogic Hallucinations	307.47-4
9. Sleep-Related Neurogenic Tachypnea	780.53-2
10. Sleep-Related Laryngospasm	780.59-4
11. Sleep Choking Syndrome	307.42-1

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APPENDIX 2
INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS DIAGNOSTIC CRITERIA

Diagnostic Criteria

Diagnostic Criteria: Narcolepsy (347)

A. A patient has a compliant of excessive sleepiness or sudden muscle weakness.

B. Recurrent daytime naps or lapses into sleep occur almost daily for at least 3 months.

C. Sudden bilateral loss of postural muscle tone occurs in association with intense emotion (cataplexy).

D. Associated features include

1. Sleep paralysis
2. Hypnagogic hallucinations
3. Automatic behaviors
4. Disrupted major sleep episode

E. Polysomnograpy demonstrates 1 or more of the following:

1. Sleep latency less than 10 minutes
2. REM sleep latency less than 20 minutes and
3. An MSLT that demonstrates a mean sleep latency of less than 5 minutes

   and
4. Two or more sleep-onset REM periods

F. HLA typing demonstrates DQB1*0602 or DR2 positivity.

G. No medical or mental disorder accounts for symptoms.

H. Other sleep disorders (eg, periodic limb movement disorder or central sleep apnea syndrome) may be present but are not the primary cause of the symptoms.

Minimum Criteria: B plus C, or A plus D plus E plus G.

Diagnostic Criteria: Obstructive Sleep Apnea/Hypopnea Syndrome (780.53-0)

A. The patient has a complaint of excessive sleepiness or insomnia. Occasionally, the patient may be unaware of clinical features that are observed by others.

B. Frequent episodes of obstructed breathing occur during sleep.

C. Associated features include:

1. Loud snoring
2. Morning headaches
3. A dry mouth upon awakening
4. Chest retraction during sleep in young children

D. Polysomnographic monitoring demonstrates:

1. More than 5 obstructive apneas, greater than 10 seconds in duration, per hour of sleep and 1 or more of the following:
   a. Frequent arousals from sleep associated with apneas
   b. Bradytachycardia
   c. Arterial oxygen desaturation in association with apneic episodes
2. MSLT may or may not demonstrate a mean sleep latency of less than 10 minutes.

E. The symptoms can be associated with other medical disorders (eg, tonsilar enlargement).

F. Other sleep disorders can be present (eg, periodic limb movement disorder or narcolepsy

Note: State and code obstructive sleep apnea syndrome on axis A and causative disorders on axis C (eg, tonsilar enlargement).

Minimum Criteria: A plus B plus C.

Diagnostic Criteria: Shift Work Sleep Disorder (307.45-1)

A. The patient has a primary complaint of insomnia or excessive sleepiness.

B. The primary complaint is temporally associated with a work period (usually night work) that occurs during the habitual sleep phase.

C. Polysomnography and the MSLT demonstrate loss of a normal sleep-wake pattern (ie, disturbed chronobiologic rhythmicity).

D. No medical or mental disorder accounts for the symptoms.

E. The symptoms do not meet criteria for any other sleep disorder producing insomnia or excessive sleepiness (eg, time-zone change [jet lag] syndrome).

Minimum Criteria: A plus B.