

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020717

MEDICAL REVIEW(S)

**DIVISION OF NEUROPHARMACOLOGICAL DRUG
PRODUCTS
CLINICAL REVIEW OF NDA**

Brand Name: Provigil

Generic Name: modafinil

Indication: narcolepsy

NDA Classification: 1S

NDA Number: 20-717

Original Receipt Date: December 30, 1996

Clinical Reviewer: Bob A. Rappaport, M.D.

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SECTION 1.0**MATERIALS UTILIZED IN REVIEW****Table 1. Materials Utilized in Review**

Volume	Submission Date	Material
Item 2; 1.1A-1.1B	12/30/96	Summary and proposed labeling
Item 8; 1 - 79	12/30/96	Clinical data
Item 8; 3	12/30/96	Integrated summary of efficacy
Item 8; 3	12/30/96	Integrated summary of safety
by fax only	9/9/97	Response to request for additional information

SECTION 2.0 BACKGROUND**SECTION 2.1 INDICATION:**

The proposed indication for modafinil (Provigil) is:

"PROVIGIL is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy." [from "Annotated Labeling", Item 2, Vol. 1.1.A, p. 00021]

SECTION 2.2 RELATED IND'S AND NDA'S:

There are no related NDA's. The only related IND's are: [REDACTED]

SECTION 2.3 ADMINISTRATIVE HISTORY:

Cephalon, Inc. licensed modafinil in 1993 from [REDACTED] for development in the U.S. and other territories. Modafinil received orphan drug designation [REDACTED] for excessive daytime sleepiness associated with narcolepsy in 1993. Cephalon conducted its clinical pharmacology trials, safety trials and pivotal efficacy trials under IND [REDACTED]

SECTION 2.4 **PROPOSED DIRECTIONS FOR USE:****Table 2. Dosage and Administration**

Patient Population	Initial Dose (mg/d)	Dose Adjustment Schedule
Adult (17-65 yrs)	200	If response is not observed within 1 to 3 weeks, daily dose may be increased to a maximum of 400 mg.
Liver Disease	100	Same dose adjustment as for adult. Maximum daily dose 400 mg.

[based on sponsor's Table 2.1.3 "Dosage and Administration", Item 2, Vol. 1.1A, p. 00062]

In addition, the sponsor has included the following paragraph to follow the above table in the product labeling:

"No study has been specifically designed to evaluate the metabolism, safety, or efficacy of modafinil in geriatric or pediatric patients with narcolepsy. Experience in a limited number of patients (15) who were greater than 65 years of age in US Phase 1, 2, and 3 clinical trials showed a comparable incidence of adverse experiences compared to other age groups. Foreign studies in geriatric subject populations showed that doses of 150 to 400 mg per day were well tolerated and that patients 67 to 85 years of age metabolized modafinil more slowly than younger subjects; the data suggest that the initial dose in geriatric patients should be approximately half that of the adult initial dose (100 mg) and that a dose adjustment schedule should be similar to the adult schedule (a maximum of 400 mg) based on individual patient needs...

"Modafinil was well tolerated in patients with hepatic insufficiency. Plasma levels of modafinil, however, were increased roughly 2-fold, and plasma levels of the inactive metabolite were decreased; the data suggest a decrease in the initial modafinil dose by half (100 mg) and that a dose adjustment schedule would be similar to the adult schedule (a maximum of 400 mg) based on individual patient needs." [Item 2, Vol. 1.1A, p. 00062]

SECTION 2.5 **FOREIGN MARKETING:**

Marketing authorization in France was granted in 1992, although the product was not commercially available there until 1994 when it received pricing and reimbursement authorization. Initially, modafinil could only be obtained through a prescription from a public hospital neurologist and dispensing hospital pharmacies. The prescribing requirements were relaxed by the French Health Ministry in November 1995 in accordance with the schedule for exceptional drugs of restricted prescription. This requires that the prescription be restricted to specialists and physicians working in departments of neurology and public or private sleep

centers, with dispensing by retail pharmacists. General practitioners may renew prescriptions, provided that the specialist carries out a clinical assessment every year, and that a specialized evaluation (polysomnography followed by a Multiple Sleep Latency Test) is performed every five years.

Lafon filed a Multistate Application in October 1994 to: Belgium, Denmark, Greece, Ireland, Italy, Netherlands, Portugal, Spain, and the United Kingdom. Objections were raised by the member states and in October of 1996, responses were submitted to the CPMP for evaluation. At the time of submission of this NDA, approval was pending in 13/14 European countries, France being the only European state where the drug has been approved.

The [REDACTED] licensee, [REDACTED] submitted its [REDACTED] marketing application in May 1993. The application was rejected due to a lack of sufficient data to assess efficacy. It was supplemented and resubmitted in August 1996, with approval pending.

There have been no instances where approval has been refused due to issues regarding safety of the drug. Since the 1994 commercial availability of modafinil in [REDACTED] has not issued any warning letters to the prescribing physicians.

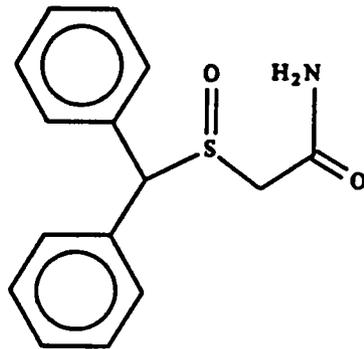
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SECTION 3.0 CHEMISTRY

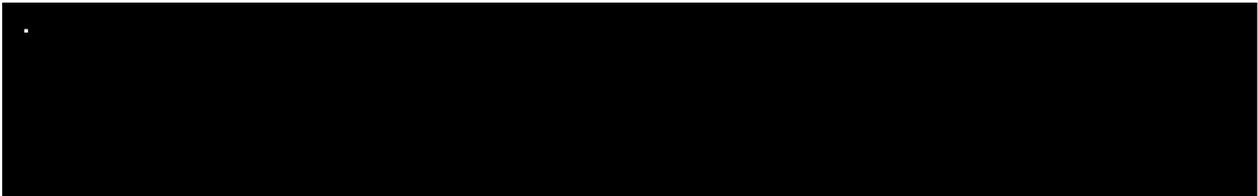
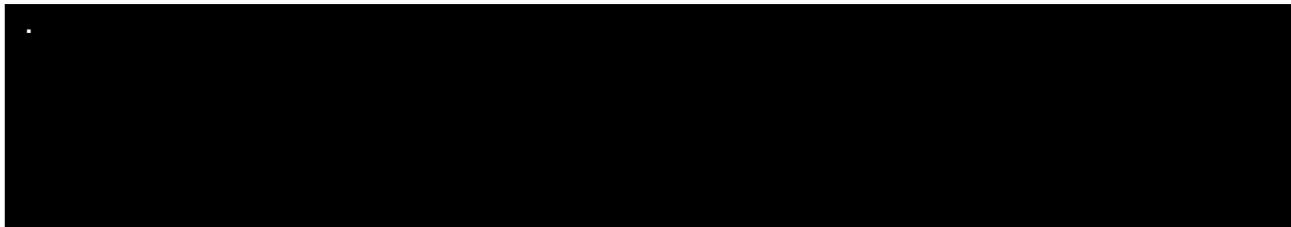
Compound Name: modafinil

Chemical Names: 2-[(Diphenylmethyl)sulfinyl]acetamide
2-(Benzhydrylsulfinyl)acetamide

The structural formula for modafinil is:

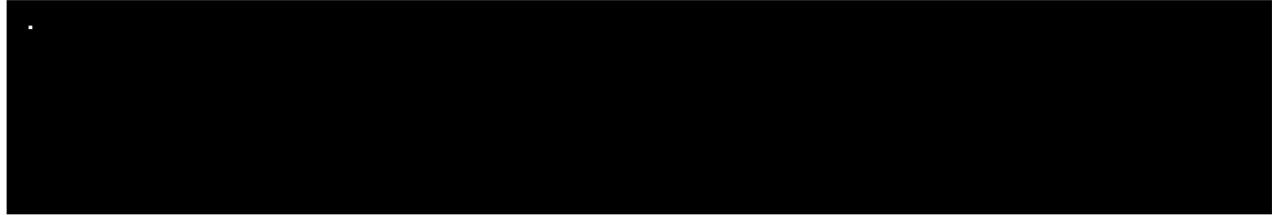


The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.36. Modafinil appears as a white to off-white crystalline powder that is practically insoluble in water and cyclohexane. It is sparingly to slightly soluble in methanol and acetone...



Modafinil is formulated as a tablet containing 100 mg or 200 mg of the active modafinil drug





Dr. Martha Heimann, the chemistry reviewer for this NDA, reports that one of the manufacturing sites has failed inspection and a second has not yet been inspected. The exact nature of the problems at the first site are not yet clear. Both sites are in Europe.

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SECTION 4.0 ANIMAL PHARMACOLOGY/TOXICOLOGY

The sponsor has summarized the pharm/tox data for modafinil in Section 2.5 of Item 2, Vol. 1.1A of the NDA. The following is a condensation of that summary.

Primary activity studies in the rat and in narcoleptic dogs demonstrated that modafinil maintains and/or promotes wakefulness in a dose-dependent manner. The pharmacological mechanism of action of modafinil has not been fully defined. Nonclinical studies have shown that modafinil is pharmacologically distinct from amphetamine, methylphenidate, and other psychomotor stimulants.

Mouse and rat oral or intraperitoneal LD50 dose levels correspond to approximately 130 to 260 fold higher levels than the projected maximum human therapeutic dose (400 mg/70 kg). The minimal lethal oral dose in dogs (300 mg/kg) represents an approximately 50 fold higher dose.

Consistent observations across species at the high dose levels were body weight loss and increased liver weights. Also seen were microscopic evidence of hepatocellular hypertrophy and alterations in red cell parameters such as decreased erythrocyte counts, packed red cell volumes and hemoglobin levels, and increased reticulocyte counts and indications of erythropoiesis. *In vitro* assessment of hemolytic potential and evaluation of erythrocyte fragility did not indicate that modafinil has a direct effect on erythrocytes.

The no effect levels (NOEL) observed in the rat ranged from 100 mg/kg/day in the 4 week study to approximately 20 mg/kg/day in the 26 week study. In the dog, the NOEL was less than 20 mg/kg/day. These doses are at least 3 fold higher than the highest proposed therapeutic dose in humans, approximately 6 mg/kg or 400 mg to a 70 kg individual. The NOEL in the 52 week study in the rat and in the mouse and rat carcinogenicity studies was 6 mg/kg/day, comparable to the proposed maximum human therapeutic dose.

The sponsor reports that lifetime carcinogenicity studies in mouse and rat found no evidence of treatment related difference in the incidence, type, or distribution of neoplastic lesions in either species. However, Dr. Aisar Atrakchi, the pharmacology/toxicology reviewer for this NDA has concluded, (with concurrence from the Center CAC-Exec), that the mouse carcinogenicity study did not reach an MTD. [REDACTED]

No genotoxic or teratogenic potential, or reproductive or developmental toxicity were observed in standard animal models.

The preclinical pharmacokinetic studies of modafinil in mice, rats, dogs, and rabbits have shown that its metabolism is stereospecific and involves cytochrome P450. Enzyme induction was observed in mice and dogs after daily doses at the highest levels used. Metabolism followed by excretion in the urine was found to be the predominant clearance pathway.

SECTION 5.0 DESCRIPTION OF CLINICAL DATA SOURCES

SECTION 5.1 STUDY TYPE AND DESIGN/PATIENT ENUMERATION:

The following table is based on the sponsor's Table 2.8-1, "Overview of Modafinil Clinical Studies and Exposure" [Item 2, Vol. 1.1A, p. 00267].

Table 3. Summary of All Studies Submitted to this NDA

Study Type	Cephalon-sponsored	Foreign, Non-Cephalon
	Number of Studies Modafinil-treated/Total treated	Number of Studies Modafinil-treated/Total treated
Clinical Pharmacology	12 232/271	27 334/363
Controlled and Uncontrolled	21 529/558	52 533/539
Indications other than narcolepsy	not applicable	49 837/1237
Total	14 761/829	81 1704/2139
Combined Total	955 2465/2968	

- 1 The 2 controlled studies have population pharmacology components and uncontrolled (open label 40 week continuation and 48 week extension) treatment periods. The controlled double blind studies include 369 patients treated with modafinil (558 total); the uncontrolled treatment periods are ongoing; safety data through June 15, 1996 are included in the data base. An additional study (1 patient, idiopathic hypersomnia) was conducted under IND [REDACTED]
- 2 The completed foreign, non-Cephalon sponsored studies in patients with narcolepsy are comprised of 2 controlled and 3 uncontrolled studies. An additional 5 studies (2 controlled, 3 uncontrolled) are ongoing and are not included in the data base. These studies include narcolepsy and idiopathic hypersomnia patients.
- 3 The NDA includes information from the total of 149 studies: 95 studies are included in the integrated data base(s) (14 Cephalon sponsored and 81 foreign, non-Cephalon sponsored); there is also documented information from an additional 9 foreign, non-Cephalon sponsored studies that are ongoing (2 controlled, 3 uncontrolled, 4 other) and 45 , non-Cephalon sponsored studies that do not have available CRF's (20 clinical pharmacology, 1 uncontrolled, 24 other) and are, therefore, non included in the integrated data base(s).

SECTION 5.2 DEMOGRAPHICS:

See Sections 7.2.1.4 and 7.2.2.4 of this review.

SECTION 5.3 EXTENT OF EXPOSURE:

See Section 8.3.1 of this review.

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SECTION 6.0 SUMMARY OF HUMAN PHARMACOKINETICS

Based on seventeen Phase 1 (9 Cephalon; [REDACTED]), two Phase 2 (1 Cephalon; [REDACTED]); and two Phase 3 (both Cephalon) studies, the sponsor has summarized the human pharmacokinetics and bioavailability data as follows:

"Modafinil was well absorbed after oral administration. Peak modafinil plasma concentration occurred at 1-4 hr. The elimination half-life was between 9 and 14 hr after a single oral dose of 200 or 400 mg. Both modafinil and modafinil acid exhibited linear pharmacokinetics over a dose range of 50-499 mg. The oral bioavailability of a 200 mg tablet relative to a micronized aqueous suspension was close to 100%. The apparent volume of distribution (V/F) of modafinil (approximately 60 L or 0.8-0.9 L/kg) was larger than the volume of total body water (0.6 L/kg). Females (35%) appeared to excrete less modafinil acid in urine than males (51%). The clearance of modafinil in males decreased slightly (approximately 10-20%) as the age increased. Stereospecific pharmacokinetics of modafinil enantiomers have been demonstrated. The *d*-modafinil enantiomer was eliminated faster (100-140 mL/min) than the *l*-modafinil enantiomer (35-50 mL/min). Modafinil was extensively metabolized after oral dosing by deamidation, oxidation, and aromatic ring hydroxylation. The total oral clearance of modafinil after a single dose was approximately 60 mL/min. Less than 10% of the modafinil dose was excreted in urine as the parent drug. Modafinil acid was the major urinary metabolic [sic] which accounted for 50-60% of the dose in males and 30-40% in females. Urinary excretion of modafinil sulfone was negligible. The remaining portion of the dose excreted in the urine appeared as the products of side-chain cleavage at the sulfur atom. The renal clearance of modafinil only accounts for 5-6% of the plasma clearance, indicating that modafinil is primarily eliminated by liver metabolism. Following a single dose of side-chain labeled ¹⁴C-modafinil, (mean ± SD) 79.6 ± 5.9% and 1.0 ± 0.3% of the dose was recovered in urine and feces, respectively, over a period of 11 days.

"After multiple once daily 200, 400, and 600 mg doses of modafinil, apparent steady-state plasma levels were reached after 2-4 days of dosing. The elimination half-life following the last dose of the multiple dose regimen was 13-18 hr.

"Modafinil was moderately bound to plasma proteins (61-65%), essentially to albumin. In the presence of warfarin, diazepam or propranolol, modafinil did not change the binding characteristics of these three drugs of [sic] therapeutic concentrations, suggesting little or no interaction with these three drugs based on the absence of protein binding displacement with modafinil *in vitro*. Modafinil plasma protein binding was not affected by modafinil acid.

"Food delays the absorption of modafinil (T_{max} : 3.21 versus 2.05 hr) in Study MOD-022. However, the AUC and elimination $t_{1/2}$ are not different between fasted and fed conditions. A continuation of the analysis showed that there were no statistical differences in any of the pharmacokinetic parameters (C_{max} , T_{max} , $AUC_{0-\infty}$, CL/F, V/F and $t_{1/2}$) for either *l*-modafinil or *d*-modafinil between fasted and fed conditions.

"In a study involving patients with renal impairment, the elimination of modafinil acid was reduced after a single dose of 200 mg. Only 25% of the modafinil dose was excreted in urine as

modafinil acid in patients with renal insufficiency. In contrast, 45% of the modafinil dose was excreted as modafinil acid in the urine of healthy subjects.

"In a multiple-dose study (200 mg/day) for eight days in patients with liver cirrhosis, the patients exhibited high modafinil AUC and extended $t_{1/2}$, suggesting that the major elimination route of modafinil was liver.

"In a single-dose pharmacokinetic interaction study with modafinil and methylphenidate, no clinically important alterations in the pharmacokinetic profile of modafinil or methylphenidate were noted. A delay in the oral absorption of modafinil was observed (T_{max} of 2.9 versus 1.9 hr). Similarly, in a single-dose pharmacokinetic interaction study with modafinil and a single dose of clomipramine, no clinically important alterations in the pharmacokinetic profile of modafinil or clomipramine were noted." [Item 2, Vol. 1.1A, pp. 00208-00209]

Study MOD-020 was an open label, multiple dose, pharmacokinetic study in elderly male and female volunteers. Subjects received 300 mg modafinil per day for seven days. Plasma levels were determined on Days 1 and 7. The maximum plasma concentrations after the first dose were much higher than those from a previous study in with healthy young volunteers. Plasma levels of modafinil obtained from Day 7 were higher than those of Day 1, which, the sponsor notes, suggests that accumulation might occur after seven days of daily dosing of 300 mg modafinil in elderly subjects.

Protocol P1424 was a double blind, randomized, placebo controlled, multiple dose, pharmacokinetic study in healthy male volunteers. The results of this study were suggestive of enzyme induction at doses of 400 mg/d and above.

The pharmacokinetic portions of the two pivotal Phase 3 efficacy trials, C1538a/301/NA/US (C301) and C1538a/302/NA/US (C302), were designed to evaluate the steady state plasma trough levels of modafinil and two well characterized metabolites, modafinil acid and modafinil sulfone. In Study C301, after daily doses of 200 mg modafinil, plasma trough levels of modafinil and the two metabolites reached steady state by Week 3 and remained unchanged through Week 9. However, after daily doses of 400 mg of modafinil, the plasma trough levels of modafinil at Week 9 were significantly lower (approximately 20 %) than those of Week 3. The two metabolites did not show this difference. Also of note in Study C301, the plasma trough levels of modafinil sulfone were negatively correlated with age, suggesting the metabolism of modafinil to modafinil sulfone might be slower in older patients. In addition, plasma levels of modafinil sulfone from female patients in the 400 mg group were higher than those of male patients at Weeks 3 and 6.

In Study C302, stable plasma trough levels of modafinil and the two metabolites were again noted after daily doses of 200 mg modafinil. Also, after daily doses of modafinil 400 mg, the plasma trough levels of modafinil decreased approximately 18% at Week 6 and 26% at Week 9 compared to Week 3. The metabolites, again, did not show this difference. The plasma trough and discharge levels of modafinil and the two metabolites were not affected by age or gender. Plasma levels were significantly higher for females only at Week 3 at the time of clinic discharge.

SECTION 7.0 EFFICACY FINDINGS**SECTION 7.1 OVERVIEW OF CLINICAL STUDIES:**

Two adequate and well controlled clinical trials have been submitted to this NDA in support of the sponsor's claim for efficacy of modafinil in the treatment of narcolepsy. The first of these is C1538A/301/NA/US (C301). This was a randomized, placebo controlled, parallel group, double blind, multicenter trial in which patients were treated with one of two fixed doses of modafinil or placebo. The second controlled study, C1538a/302/NA/US (C302), was a randomized, placebo controlled, parallel group, double blind, multicenter trial in which patients were treated with one of two fixed doses of modafinil or placebo. This trial was followed by a two week discontinuation segment to study withdrawal effects. The primary efficacy variables for both Studies C301 and C302 were 1) the average sleep latency at Endpoint on the Maintenance of Wakefulness Test, and 2) support for #1 by the Clinical Global Impression of Change Scale.

In addition, the sponsor has submitted six other studies as supportive product efficacy, and numerous studies (as outlined in Sections: 5.1 and 7.2.4 of this review) in support of product safety.

SECTION 7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY:**SECTION 7.2.1 STUDY C1538A/301/NA/US****Section 7.2.1.1 Protocol Synopsis:**

Title: A Nine-Week Placebo-Controlled, Double-Blind, Randomized, Parallel-Group Study of the Safety and Efficacy of Two Fixed Doses (200 mg, 400 mg) of Oral Modafinil in Patients with Narcolepsy Followed by a 40 Week, Open-Label, Flexible-Dose Continuation Study

Objectives: "The purpose of the double-blind phase of this study is to compare the safety and efficacy of two fixed doses of modafinil and placebo in the treatment of patients with narcolepsy..."

"The purpose of the open label phase of this study is to collect additional information regarding the safety and tolerance of modafinil during extended exposure."

[Item 8, Vol. 11, p. 04723]

Study Design:

The double blind phase is a multicenter, parallel group, placebo controlled, fixed dose study of modafinil in patients with narcolepsy. The open label phase is a 40 week, flexible dose study. The double blind phase will begin with a screening period followed by randomization to either

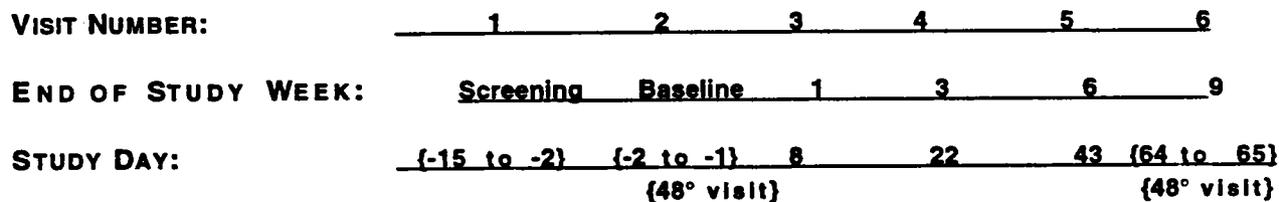
placebo or one of two dosage levels of modafinil for a period of nine weeks. The protocol calls for three groups of 95 patients each to be randomly assigned to one of the three treatment arms. Approximately 15 patients are to be randomized at each of the twenty sites during a six month enrollment period. Eligible patients will receive a specified number of tablets to be taken daily for nine consecutive weeks in one of the following three treatment groups:

Group I	placebo
Group II	modafinil, 200 mg/day
Group III	modafinil, 400 mg/day

Patients will take a single, daily, oral dose of study medication consisting of four tablets (4 x 100 mg or 2 x 100 mg + 2 x placebo or 4 x placebo) in the morning (approximately 30 to 45 minutes after a morning meal) for nine consecutive weeks.

Patients eligible for the double blind phase will be male or female outpatients, 18 to 65 years of age, inclusive. Females must be either surgically sterile, two years postmenopausal, or, if of child bearing potential, using an acceptable birth control method. Patients must have a current diagnosis of narcolepsy. Nocturnal polysomnography and a Multiple Sleep Latency Test (MSLT) will be done at the Screen Visit unless they have been performed within the five years prior to screening. The diagnosis of narcolepsy must include the following characteristics: recurrent daytime naps or lapses into sleep that have occurred almost daily for at least three months, and a history of loss of postural muscle tone in association with intense emotion, i.e. cataplexy. Associated features may include: sleep paralysis, hypnagogic hallucinations, automatic behaviors, and nocturnal sleep disruption. The MSLT must document a mean sleep latency of ≤ 8 minutes. Eligible patients must demonstrate an absence of any medical or psychiatric disorders that could account for the excessive daytime sleepiness. Patients requiring routine use of antiepileptic medication will be excluded.

Figure 1. Study Schemata



At the Baseline Visit, in addition to examination and laboratory studies, the patient will complete: an Epworth Sleepiness Scale; "Steer Clear" Performance Test training session; two nocturnal polysomnography recordings within 48 hours, one followed by a MSLT and the other followed by a Maintenance of Wakefulness Test (MWT); one "Steer Clear" Performance Test (SCPT); Patient's Daily Sleep Log; Baseline Signs and Symptoms; Quality of Life in Narcolepsy (QOLIN) patient inventory; and, Clinical Global Impression of Severity (CGI-S).

On-Study Visits (end of Weeks 1, 3 and 6 following the Baseline Visit) will include, in addition to vital signs and laboratory studies: HLA typing at Week 1; a nocturnal polysomnography recording; a MWT; a SCPT; the Clinical Global Impression of Change (CGI-C) Scale; the Epworth Sleepiness Scale; the Patient's Daily Sleep Log; and, adverse experience and concomitant drug review.

The Termination Visit will include, in addition to physical examination and laboratory studies: two nocturnal polysomnography recordings within 48 hours, one followed by a MSLT and the other by a MWT; one SCPT; the CGI-C; the Epworth Sleepiness Scale; the Patient's Daily Sleep Log; the QOLIN inventory; and adverse experience and concomitant drug review.

Patients entering the open label phase must have completed the double blind phase or at least two efficacy evaluations post Baseline of the double blind phase and terminated for reasons other than noncompliance or a study drug related adverse experience.

Qualifying patients will begin the open label phase taking 200 mg/day of modafinil for one week. The dosage may then be adjusted at the investigator's discretion, but no daily dose may be increased by less than 100 mg or more than 200 mg every week. The minimum daily dose will be 200 mg and the maximum daily dose will be 400 mg.

Section 7.2.1.2 Statistical Analysis:

There will be two primary efficacy variables: 1) excessive daytime sleepiness measured as time awake on the MWT; and, 2) whether a reduction in excessive daytime sleepiness on the MWT is supported by the CGI-C, as assessed by an independent clinician.

The original protocol calls for the following statistical analysis of the primary efficacy endpoints:

"Change scores from baseline will be compared between treatment groups for variables having baseline evaluations. For the CGI-C, the actual score will be analyzed since no baseline value is assessed. Endpoint analyses will be performed to include data from all evaluated patients. Data by protocol evaluation periods including completers (Week 9 data) will also be analyzed.

"Parametric analyses adjusting for investigator effect will be performed if the assumptions of normality are met. Parametric analyses will be performed as supportive evidence of treatment by investigator homogeneity. Two-tailed tests will be used to test study hypotheses. Mantel-Haenszel tests, having investigator as the strata, will also be performed for the CGI-C." [Item 8, Vol. 11, p. 04767]

Secondary efficacy variables are:

1) "To determine independently for each of two doses of modafinil, whether that dose (200 mg/day, 400 mg/day) compared to treatment with placebo produces beneficial effects measured by the MWT and the CGI-C. The effects established in testing the primary hypothesis may be attributable to both doses of modafinil or only to one treatment dose."

- 2) "To determine whether modafinil/placebo differences in awake time and global clinical change are reflected in the tendency to initiate sleep [Multiple Sleep Latency Test, clinical version]; impaired vigilance ['Steer Clear' Performance Test]; and patient assessed general level of daytime sleepiness [Epworth Sleepiness Scale]."
- 3) "To determine whether modafinil/placebo differences in awake time and global clinical change are reflected in the patient's daily record of the severity and frequency of patient reported narcoleptic symptoms, the Patient's Daily Sleep Log."
- 4) "To determine the effects of modafinil concerning patient health status and ability to perform daily activities, through evaluation of a Quality of Life in Narcolepsy Patient Inventory."

[the four items above from: Item 8, Vol. 11, p. 04740]

The original protocol also states: "Statistically significant results are not required of secondary hypotheses C, D, E and F [1, 2, 3 and 4 above]. Failure to support secondary hypotheses will not invalidate the results of the study." [Item 8, Vol. 11, p. 04740]

Section 7.2.1.3 Protocol Amendments:

Amendment 1:

This amendment was dated 1/19/95. It consists of a change in the Inclusion Criteria which provides that the diagnosis of narcolepsy is based on the criteria established by the American Sleep Disorders Association, published in "The International Classification of Sleep Disorders" in 1990. Based on this document the patient must meet one of two minimal diagnostic criteria:

Criteria A: recurrent daytime naps or lapses into sleep occurring almost daily for at least three months; plus sudden bilateral loss of postural muscle tone in association with intense emotion.

Criteria B: a complaint of excessive sleepiness or sudden muscle weakness; plus associated features such as sleep paralysis, hypnagogic hallucinations, automatic behaviors, and disrupted major sleep episode; plus polysomnography demonstrating either 1) sleep latency less than 10 minutes, or 2) REM sleep latency less than 20 minutes, and 3) an MSLT that demonstrates a mean sleep latency less than 5 minutes, and 4) two or more sleep onset REM periods; plus absence of any medical or psychiatric disorder that could account for the symptoms.

Eligible patients diagnosed under Criteria A must have a MSLT with a mean sleep latency of ≤ 8 minutes. Eligible patients diagnosed under Criteria B must have a MSLT with a mean sleep latency of ≤ 5 minutes. Eligible patients must have two sleep onset REM periods documented within the MSLT.

Further modifications called for in this amendment are simply to maintain consistency with the changes noted above.

Amendment 2:

This amendment was dated 3/3/95. It consists of the following features:

- 1) Clarification in Inclusion Criteria that open label phase begins two weeks or more after completion of the double blind phase.
- 2) Exclusion criteria have been expanded to include prior responses to stimulant medication such as chest pain, ischemic ECG changes or clinically significant cardiac arrhythmia; also excludes clinically significant manifestations of mitral valve prolapse.
- 3) Clarification of the drug supply in the Study Drug section.
- 4) A change in clinical monitor.
- 5) Provides a hierarchical structure to the statistical analyses with the following statement:

"The primary hypothesis will determine if treatment with modafinil (combined 200 mg/day and 400 mg/day treatment group) compared to placebo, can modify the excessive daytime sleepiness (EDS) of narcolepsy in patients receiving medication \leq 9 weeks (double-blind segment) as reflected in the Maintenance of Wakefulness Test (MWT) and the Clinical Global Impression of Change (CGI-c) assessed by an independent clinician. Both hypotheses must be statistically significant ($p \leq 0.05$, two-tailed) in the 9 week endpoint analysis to support the primary objective of the study. A secondary hypothesis will determine independently for each of two doses of modafinil, whether that dose compared with placebo produces beneficial effects measured by the MWT and CGI-c which may be attributable to both doses of modafinil. If the primary hypothesis is not significant, the pairwise comparisons with placebo of dose level will utilize the Dunnett test procedure to adjust the level of significance.

"Endpoint analysis will be the primary analysis, performed to include data from all evaluated patients during the double-blind segment of protocol. Data by protocol evaluation periods including completers (Week 9 data) also will be analyzed to determine treatment differences based upon specific durations of treatment. Persistence of effect will be examined using patient trends through Weeks 3, 6, and 9 evaluations on the MWT." [Item 8, Vol. 11, p. 04706]

- 6) Addition of a third phase to the protocol which represents an additional 48 week extended open label period.

Amendment 3:

This amendment was dated 7/25/95. It consists of two features:

- 1) To allow patients to take concomitant medications for the treatment of cataplexy during

the open label phase of the study.

2) To remove the requirement for the completion of the Baseline Signs and Symptoms Checklist at the Baseline Visit of the double blind phase. This was replaced by physical examination, medical history and adverse events obtained at baseline.

Amendment 4:

This amendment was dated 11/14/95. It consists of three features:

- 1) Changes one of the clinical monitors.
- 2) Allows for the use of commercial 200 mg tablets during the extended open label phase of the study.
- 3) Revises the statistical analysis plan as follows:

The primary hypothesis will be that treatment with modafinil at 400 mg/day for nine weeks will result in a statistically significant (5% level of significance, two sided test) increase in sleep latency compared to placebo and a statistically significant improvement in the CGI-C score. The analysis population will include all randomized patients who receive study medication and have at least one post-baseline measurement. The primary analysis endpoint will be the last double blind measurement for each patient. Measures of sleep latency will be analyzed using a generalized ANCOVA model including effects for treatment group, study site, baseline sleep latency and other covariates. These other covariates will be any that show baseline variability which significantly correlates with sleep latency at endpoint and any that show clinically significant variation between treatment groups at baseline. A stepwise selection procedure will be used to identify these covariates with the statistical criteria for inclusion in the model being $p < 0.10$.

The CGI-C score will be analyzed with an ordinal logistic regression model including effects for treatment, study site, baseline severity and other covariates. The selection criteria for the other covariates will be the same as for the MWT.

The following variables will be analyzed as secondary measures of efficacy:

- 1) MWT
 - a) sleep latency (average, time of day, profile)
 - b) sleep latency (categorization of patients remaining awake 20 minute {complete success} for 0, 1, 2, 3 or 4 tests)
 - c) sleep latency to 10 seconds (average, time of day, profile)
 - d) latency to REM sleep (average, time of day, profile)
 - e) total sleep time (average, time of day, profile)
- 2) MSLT
 - a) sleep latency (average, time of day, profile)
 - b) sleep latency (categorization of patients remaining awake for the entire 20

- minutes (complete success) for 0, 1, 2, 3 or 4 tests)
 - c) sleep latency to 16 seconds (average, time of day, profile)
 - d) latency to REM sleep (average, time of day, profile)
 - e) Stage II latency (average, time of day, profile)
 - f) Stage III latency (categorization of patients responding "NO" for 0, 1, 2, 3 or 4 tests)
- 3) Nocturnal Polysomnography
- a) time variables (time in bed, time awake after sleep onset, total REM sleep, sleep latency, REM latency,
 - b) duration variables (sleep Stages I, II, III, IV)
 - c) counts (numbers of awakenings, awakenings > 2 min., arousals, periodic leg movements in sleep [PLMS], PLMS with arousals, PLMS with awakening, respiratory disturbance index)
- 4) Epworth Sleepiness Score (ESS)
- total ESS score (0-24) from eight questions
- 5) SCPT
- number of obstacles hit in the 30 minute test period
- 6) QOLIN
- a) qualitative questions scored on an ordinal scale in a uniform assignment (0, 1, 2...etc.)
 - b) Visual Analog Scale (VAS); count and/or percent of total of the chosen oval to be used for each patient
- 7) Patient Daily Sleep Log
- a) patient response to time questions (number of minutes, hours) and count questions (number of times, episodes) summarized
 - b) patient response to qualitative questions scored on an ordinal scale of 0 to 4 (much worse to much better) and summarized

Analysis of treatment efficacy will be performed after 3, 6 and 9 weeks of double blind treatment except for the QOLIN results for which efficacy at 9 weeks will be compared to baseline and the Patient Daily Sleep Log for which the average profiles of response over time in the double blind phase will be compared among treatment groups. The patient population for the secondary efficacy analyses will be the same as that for the primary analyses.

Continuous secondary efficacy variable will be analyzed with a generalized ANCOVA model. Categorical responses will be analyzed with a logistic regression model. Both models will include effects for treatment group, study site and other covariates. These other covariates will be selected on the same basis used in the primary efficacy variable analysis.

*For the primary efficacy analyses of MWT and CGI-C, the primary comparison of interest is modafinil 400 mg versus placebo. Each comparison will be a two-sided test at the 5% level of significance.

"For secondary analyses, dose response will be tested by partitioning the treatment sum of squares into single degree of freedom tests for linear and quadratic trend. Pairwise comparisons among treatment groups will be performed with variance estimated from the model mean square error (MSE) without adjustment. All tests are two-sided tests at the 5% level of significance.

"Demographic characteristics and medical history will be compared among treatment groups for comparability at randomization into the double blind phase. For each parameter, baseline will refer to the last measurement prior to study treatment.

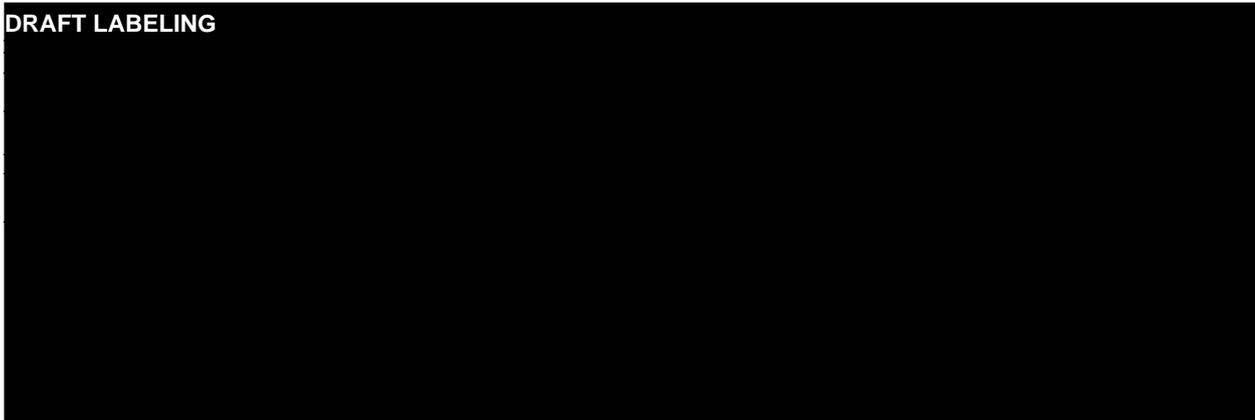
"Continuous variables will be analyzed with an analysis of variance model (ANOVA), including treatment (dose) and study center effects. Categorical variables will be analyzed with the Mantel-Haenszel with investigator as stratum." [Item 8, Vol. 11, p. 04682-3]

Amendment 5:

This amendment was dated 2/5/96 . It, once again, revises the Statistical Analysis section of the protocol as follows:

1. changes the analysis of the primary efficacy endpoint CGI-C score to an ordinal logit model.
2. changes some of the actual measurements to be analyzed in the secondary efficacy parameters
3. adds the following statement in the Treatment Comparisons statement:

DRAFT LABELING



Amendment 6:

This amendment was dated 7/23/96 . It allows for a continuation of the open label maintenance phase until modafinil becomes commercially available or until the sponsor terminates the protocol.

Section 7.2.1.4 Conduct of Study:**Patient Distribution/Disposition:**

Of the 285 patients randomized, 283 (99%) received study medication and were considered to be evaluable for the safety analyses. Two patients from Site 14 were not considered to be evaluable for either safety or efficacy analyses. Patient 1418 was randomized to the placebo group and was dispensed study medication. However, this patient was discontinued soon after due to a history of illicit drug use and a positive urine drug screen. The patient did not report medication use, but when it was returned there were twelve tablets missing. The database does not include study medication or AE data (other than a note stating that the patient did not have any AE's) for this patient. Patient 1421 was randomized to the placebo group and did receive study medication. However, the patient was discontinued when the investigator determined that the baseline MSLT did not show two sleep onset REM periods. The patient returned all study medication. No safety or efficacy data are included for these patients.

Of the 285 patients, 273 (96%) were considered to be evaluable for the efficacy analyses. Patients were excluded from the efficacy evaluable population if they did not have at least one post-baseline evaluation for both the MWT and the CGI-C. The following table summarizes the patients who were excluded and their respective missing evaluation(s):

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Table 4. Patients Excluded from Efficacy Evaluable Population

Patient Number	Treatment Group	Missing Evaluation
0403 ^a	Modafinil 400 mg	CGI-C and MWT
0409 ^b	Modafinil 400 mg	CGI-C
0603 ^c	Modafinil 400 mg	CGI-C and MWT
0612 ^b	Modafinil 400 mg	CGI-C and MWT
1018 ^b	Modafinil 400 mg	MWT
1204 ^b	Modafinil 400 mg	CGI-C and MWT
1207 ^b	Modafinil 400 mg	CGI-C and MWT
1403 ^c	Modafinil 400 mg	CGI-C and MWT
1418 ^d	Placebo	CGI-C and MWT
1421 ^d	Placebo	CGI-C and MWT
1912 ^b	Modafinil 400 mg	MWT
2101 ^b	Modafinil 400 mg	CGI-C and MWT
^a Patient withdrew consent and was discontinued ^b Patient discontinued due to AE ^c Patient discontinued due to protocol violation ^d Patient did not use study medication and was excluded from both Safety and Efficacy Evaluable Populations		

[based on sponsor's Table 6A, Item 8, Vol. 8., p. 03047]

n.b. Patient 0507 was randomized to modafinil 400 mg but was mistakenly given the medication kit for Patient 0512 (not enrolled) which was placebo. Patient 0507 is, nevertheless, included in the modafinil 400 mg treatment group for all analyses.

Fourteen patients (15%) in the modafinil 400 mg group discontinued the study compared to 3 patients (3%) in the modafinil 200 mg group and 5 patients (5%) in the placebo treatment group. Eleven of the 14 patients who discontinued from the modafinil 400 mg group did so because of AE's. None of the patients in the placebo group and one patient in the modafinil 200 mg group discontinued for AE's. The following table summarizes patient disposition:

Table 5. Patient Disposition

	Modafinil 400 mg	Modafinil 200 mg	Placebo
Total Patients Randomized	95	96	94
Patients Evaluable for Safety	95(100%)	96(100%)	92(98%)
Patients Evaluable for Efficacy	86(91%)	95(99%)	92(98%)
Completed Double Blind Phase	81(85%)	93(97%)	87(93%)
Early Discontinuations:	14(15%)	3(3%)	5(5%)
Adverse Clinical Experiences	11(12%)	1(1%)	0
Protocol Violation	1(1%)	1(1%)	0
Patient Withdrew Consent	2(2%)	0	0
Patient Noncompliance	0	0	1(1%)
Lost to Follow-up	0	0	1(1%)
Lack of Study Medication Efficacy	0	1(1%)	3(3%)

[based on sponsor's Table 6B, Item 8, Vol. 8, p. 03048]

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Protocol violations are summarized for individual patients in the table below. Protocol violations also occurred in the assignment of patients at three sites. The investigators at Sites 01, 03 and 12 assigned some patient numbers out of sequence.

Table 6. Patient Specific Protocol Violations

Protocol Violation	Treatment	Patient Numbers
Entry Criteria:		
MSLT at Baseline > 8 min	Modafinil 400 mg	0106, 2116, 1120, 2202, 2214
	Modafinil 200 mg	1104, 1502, 2118, 1206, 1115, 2210
	Placebo	1008
Patient was > 65 years old	Modafinil 400 mg	1423, 1207
	Modafinil 200 mg	0906, 1216
	Placebo	1205
Primary Efficacy Assessment at Week 9		
CGI-C not done during Week 9 visit	Modafinil 200 mg	2110, 0613
All patients listed are included in safety and efficacy analyses.		

[based on sponsor's Table 6C, Item 8, Vol. 8, p. 03049]

n.b. During the study the blind for Patient 1403 was broken by the investigator because of concerns that the patient had taken another stimulant. This patient did not experience an AE and is excluded from the efficacy evaluable population for missing post-baseline evaluations of CGI-C and MWT.

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Demographics:

The following table summarizes the demographic characteristics of the three treatment groups:

Table 7. Demographics - Safety Evaluable Population

	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo
Age (years)	n	95	96	92
	mean	44	40	42
	s.d.	14	14	12
	median	47	42	43
	range	19-67	18-67	18-68
Women	%	55	54	54
Race:				
Caucasian	n (%)	77 (81%)	70 (73%)	73 (79%)
African-American	n (%)	16 (17%)	23 (24%)	17 (18%)
Hispanic	n (%)	1 (1%)	2 (2%)	0
Other	n (%)	1 (1%)	1 (1%)	2 (2%)
Weight (lb)	n	94	95	91
	mean	189	195	186
	s.d.	44	43	45
	median	188	192	180
Height (in)	n	93	91	90
	mean	67	67	67
	s.d.	4	4	4
	median	66	67	68

[based on sponsor's Table 6E, Item 8, Vol. 8, p. 03052]

Greater than half of the patients in each treatment arm reported light to moderate use of caffeine. Most of the patients denied tobacco use. Approximately half of the patients in each treatment group reported light to moderate alcohol use.

Patients in the three treatment groups were comparable with respect to all demographic and background characteristics with all p values ≥ 0.050 .

All three treatment groups were similar at baseline with respect to the mean number of years since initial diagnosis of narcolepsy and the mean number of years since disease onset, as indicated in the following table:

Table 8. Baseline Narcolepsy History -Safety Evaluable Population

Characteristic	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo
Total # Patients	n	95	95	92
Years Since Initial Diagnosis	n	94	94	92
	mean	9.7	8.8	7.3
	s.d.	11.5	9.5	9.6
	median	5	5	3
	minimum	0	0	0
	maximum	46	44	40
Years Since Onset	n	93	93	91
	mean	23.2	21.0	22.0
	s.d.	15.4	14.6	12.2
	median	19	18	20
	minimum	2	1	2
	maximum	62	64	50

[based on sponsor's Table 2.1.0, Item 8, Vol. 9, p. 03205]

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All three treatment groups had similar severities of illness at baseline, as measured by the CGI-S; these findings are summarized in the following table:

Table 9. CGI-S at Baseline - Efficacy* Evaluable Population

	Modafinil 400 mg	Modafinil 200 mg	Placebo
Total number patients	86	95	92
no signs illness	0	0	1 (1%)
borderline ill	1 (1%)	2 (2%)	2 (2%)
slightly ill	10 (12%)	14 (15%)	10 (11%)
moderately ill	37 (43%)	38 (40%)	47 (51%)
markedly ill	32 (37%)	31 (33%)	28 (30%)
extremely ill	6 (7%)	10 (11%)	4 (4%)

[based on sponsor's Table 6F, Item 8, Vol. 8, p. 03054; * Table 6F titled "Safety Evaluable Population; however, telecon with P. Nemeth, Cephalon, Inc., 6/3/97 confirmed that this is error]

There were differences among treatment groups at some levels of severity for related narcolepsy symptoms. However, these differences were small.

The three treatment groups were similar with respect to prior overall medication use and prior medication use for the treatment of narcolepsy and related disorders; these findings are summarized in the following table:

Table 10. Prior Medications - Safety Evaluable Population

	Modafinil 400 mg	Modafinil 200 mg	Placebo
Total number of patients	95	96	92
Number of patients taking prior medications	89 (94%)	87 (91%)	87 (95%)
Number of patients taking narcolepsy medications	71 (75%)	71 (74%)	70 (76%)

[based on sponsor's Table 6G, Item 8, Vol. 8, p. 03056]

Concomitant medications included drugs that were stopped weeks before the administration of study drug. The three treatment groups were similar with respect to concomitant medication use; these findings are summarized in the following table:

Table 11. Concomitant Medications with CNS Activity - Safety Evaluable Population

	Modafinil 400 mg	Modafinil 200 mg	Placebo
Total number of pts.	95	96	92
Any concomitant meds	85 (89%)	80 (83%)	82 (89%)
EDS meds ^a	5 (5%)	4 (4%)	3 (3%)
Cataplexy meds ^b	5 (5%)	0	0
Other drugs with stimulant effect:			
pseudoephedrine ^c	5 (5%)	4 (4%)	3 (3%)
Drugs with sedative effect:			
antihistamines ^d	14 (15%)	13 (14%)	17 (18%)
diazepam	0	0	1 (1%)
^a dexamphetamine, caffeine, pemoline, methylphenidate ^b imipramine, desipramine, protriptyline ^c either alone or as component of combination drug ^d astemizole, brompheniramine, chlorpheniramine, diphenhydramine, loratadine, terfenadine, triprolidine			

[based on sponsor's Table 6H, Item 8, Vol. 8, p. 03057]

Section 7.2.1.5 Sponsor's Efficacy Results:

Treatment-by-site Interaction:

The sponsor found a significant (interaction considered significant at the $\alpha = 0.100$ level) treatment-by-site interaction effect ($p = 0.062$) for the MWT Average Sleep Latency. They included this interaction in all statistical analyses of continuous variables for the MWT. This treatment-by-site interaction was due to interaction between the active treatments (200 mg and 400 mg) among sites. For the majority of sites (12/18), the mean sleep latencies were

higher in both modafinil treatment groups compared to placebo group. Among these twelve sites, four had a higher mean sleep latency in the 200 mg compared to the 400 mg group. Of the remaining six sites, five showed a higher mean sleep latency in one of the modafinil groups compared to placebo group. The remaining site showed a slightly higher mean sleep latency in the placebo compared to either of the active treatment groups. The sample size at this site was quite small. The median sleep latencies were higher in both active treatment groups compared to placebo.

Primary Efficacy Variables:

MWT Average Sleep Latency:

Patients in the modafinil 400 mg treatment group were able to stay awake for a significantly longer time at endpoint on the MWT compared to patients in the placebo treatment group. The following table summarizes the results of this analysis:

Table 12. MWT Average Sleep Latency at Endpoint - Efficacy Evaluable Population

Evaluation	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo	p-value Placebo vs. Modafinil 400 mg
Total # pts.	n	86	95	92	
MWT Average Sleep Latency (min)*	mean	8.90	8.18	5.07	< 0.001
	s.d.	6.26	6.16	4.65	

* mean of four tests taken at each visit

[based on sponsor's Table 7A, Item 8, Vol. 8, p. 03059]

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CGI-C:

A greater proportion of patients in the Modafinil 400 mg treatment group had clinical improvement in symptoms based on the CGI-C when compared to patients in the placebo group. These results are summarized in the following table:

Table 13. CGI-C at Endpoint - Efficacy Evaluable Population

CGI-C Result	Modafinil 400 mg	Modafinil 200 mg	Placebo	p-value Placebo vs. Modafinil 400 mg
n	86	95	92	
very much improved	8 (9%)	7 (7%)	4 (4%)	< 0.001
much improved	35 (41%)	25 (26%)	8 (9%)	
minimally improved	19 (22%)	29 (31%)	22 (24%)	
no change	20 (23%)	27 (28%)	43 (47%)	
minimally worse	3 (3%)	5 (5%)	11 (12%)	
much worse	1 (1%)	2 (2%)	3 (3%)	
very much worse	0	0	1 (1%)	

[based on sponsor's Table 7A, Item 8, Vol. 8, p. 03059]

Secondary Efficacy Variables:

Maintenance of Wakefulness Test:

Patients in the modafinil 400 mg and 200 mg treatment groups were able to stay awake significantly longer as measured by all parameters of the MWT when compared to patients in the placebo treatment group.

SLEEP LATENCY:

Patients in both active treatment groups exhibited statistically significantly higher Average Sleep Latency values compared to patients in the placebo group at Weeks 3, 6 and 9, and at Endpoint. All p-values were < 0.001. Modafinil 400 mg vs. modafinil 200 mg was not significant for MWT average sleep latency at any timepoint. All p-values were > 0.400. Treatment group comparisons were also not significant at baseline, with all p-values > 0.300.

This data is summarized in the following table:

Table 14. MWT Average Sleep Latency (min.) by Visit - Efficacy Evaluable Population

Visit	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo
Baseline	n	86	95	92
	mean ± s.d.	6.63 ± 5.16	5.84 ± 5.02	5.79 ± 4.67
Week 3	n	85	95	92
	mean ± s.d.	9.21 ± 5.73	8.15 ± 6.16	5.58 ± 4.52
Week 6	n	82	93	88
	mean ± s.d.	8.99 ± 5.78	8.44 ± 6.38	5.44 ± 4.98
Week 9	n	82	94	87
	mean ± s.d.	8.93 ± 6.18	8.05 ± 6.07	5.15 ± 4.73
Endpoint	n	86	95	92
	mean ± s.d.	8.90 ± 6.26	8.18 ± 6.16	5.07 ± 4.65

[based on sponsor's Table 7B, Item 8, Vol. 8, p. 03061]

In their analysis of individual tests on the MWT (four tests per MWT) at Endpoint, the sponsor found that the modafinil 400 mg treatment group was significantly better than placebo for Tests 2, 3 and 4 (all p-values < 0.001) and that modafinil 200 mg was significantly better than placebo at all test periods (all p-values < 0.050), as was the combined modafinil dose group (all p-values < 0.050). No significant difference was found between the active treatment groups for any individual test.

In comparing the number of patients staying awake for 0 to 4 tests at Endpoint, the sponsor found that the modafinil 400 mg group, the modafinil 200 mg group and the combined treatment groups each exhibited significantly more patients staying awake than patients in the placebo group (all p-values < 0.050).

SLEEP LATENCY TO SLEEP LASTING ≥ 10 SECONDS

The sponsor reports that the results of this analysis were similar to the findings for Average Sleep Latency. Review of the sponsor's Tables 8.1.0 through 8.1.9 (Item 8, Vol. 9, p. 03249-03268) confirms this conclusion.