

**REM SLEEP LATENCY**

The sponsor reports that the results of this analysis were similar to the findings for Average Sleep Latency for the modafinil 400 mg treatment group compared to placebo at Endpoint. However, the modafinil 200 mg group did not differ significantly from placebo. Review of the sponsor's Tables 8.2.0 through 8.2.9 (Item 8, Vol. 9, p. 03269-03288) confirms this conclusion.

**TOTAL SLEEP TIME**

The sponsor reports that on average, patients in the modafinil 400 mg treatment group exhibited lower Total Sleep Time (8.04 min.) than patients in the modafinil 200 mg treatment group (8.31 min.) or the placebo treatment group (9.74 min.) at Endpoint. However, the analyses were only statistically significant for the active treatment groups vs. placebo. The results for scheduled visits were similar to those seen at Endpoint. Review of the sponsor's Tables 8.3.0 through 8.3.9 (Item 8, Vol. 9, p. 03289-03308) confirms these findings.

**PATIENT SUBJECTIVE EVALUATION OF SLEEP LATENCY**

Patients were asked to estimate how long they were able to stay awake at the end of each test period. The sponsor reports that both treatment arms and the combined treatment groups values were all significantly greater than the placebo group values on Tests 2, 3, 4, and on average (p-values <0.010) at Endpoint; and that no significant difference was found between the two active treatment groups at Endpoint. They also state that similar comparisons were made for each scheduled study visit, but do not summarize the results of these evaluations. Review of the sponsor's Tables 8.4.0 through 8.4.9 (Item 8, Vol. 9, p. 03309-03328) confirms these findings for the Endpoint evaluations and documents significant drug effect at the other study visits with the following exceptions: 1) modafinil 200 mg compared to the placebo group for Test 3, Week 6 (11.7 min. vs. 9.01 min., respectively; p = 0.066), 2) combined active treatment groups compared to placebo group for Test 4, Week 6 (11.79 min./12.18 min. [400 mg/200 mg] vs. 9.01, respectively; p = 0.057) and, 3) modafinil 400 mg compared to placebo group for Test 4, Week 6 (11.79 min. vs. 9.01 min., respectively; p = 0.237).

The sponsor also reports that their analysis comparing the number of tests for which patients subjectively evaluated themselves as having stayed awake during the entire test revealed that the modafinil 400 mg, 200 mg and combined treatment groups all exhibited significantly more patients reporting staying awake at Endpoint than patients in the placebo group (all p-values < 0.050). They also note that similar comparisons were made for all other scheduled visits, but do not summarize those results. However, review of the sponsor's Table 8.4.10 (Item 8, Vol. 9, p. 03329-03331) documents a significant treatment effect in the 200 mg group vs. placebo group only for Week 3 (p = 0.008); the p-values for Weeks 6, 9 and Endpoint are 0.083, 0.159 and 0.063, respectively, for this treatment group comparison.

**CGI-C:**

Patients in both active treatment groups had significantly greater improvement than patients in the placebo group at each visit. These results are summarized in the following table:

**Table 15. Patients Improved in CGI-C - Efficacy Evaluable Population**

Visit	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo
Week 3	n (%)	66 (78%)	62 (65%)	36 (39%)
	p-value*	< 0.001	0.005	
Week 6	n (%)	63 (77%)	61 (65%)	34 (38%)
	p-value*	< 0.001	0.003	
Week 9	n (%)	60 (73%)	60 (64%)	32 (37%)
	p-value*	< 0.001	0.001	
Endpoint	n (%)	62 (72%)	61 (64%)	33 (36%)
	p-value*	< 0.001	< 0.001	

\* Modafinil 400 mg or 200 mg compared to placebo

[based on sponsor's Table 7E, Item 8, Vol. 8, p. 03067]

Patients in the modafinil 400 mg treatment group had significantly greater improvement than the patients in the modafinil 200 mg treatment group only at Weeks 3 and 6 (p-values = 0.004 and 0.049, respectively). No treatment group comparisons were significant for the CGI severity scores at baseline (all p-values > 0.200).

**MSLT:****SLEEP LATENCY (16 SEC)**

Patients in the modafinil 400 mg treatment group exhibited a longer average Sleep Latency (16 sec), i.e. to the first 16 seconds of continuous sleep, time (5.15 min.) than patients in the modafinil 200 mg (4.70 min.) or placebo (3.29 min.) treatment groups at Endpoint. The sponsor's analyses found statistically significant treatment effects for the 400 mg, 200 mg and combined active treatment groups when each is compared to the placebo group (p = 0.006, 0.006 and 0.001, respectively). They also note statistically significant increases from Baseline in the active treatment groups of 1.86 min. in the 200 mg group and 1.85 min. in the 400 mg group (p-values both <0.001). No significant differences were found between the two active treatment arms. These results are confirmed by review of the sponsor's Tables 9.0.0 and 9.0.1 (Item 8, Vol. 9, p. 03332-03333).

The sponsor reports that the 400 mg, 200 mg and combined active treatment group Sleep Latency (16 sec) times were all significantly increased compared to the placebo group results for Tests 2, 3, 4, and the four test average (all p-values < 0.050). Review of the sponsor's Tables 9.0.0 through 9.0.9 (Item 8, Vol. 9, p. 03332-03341) confirms these findings, with the exception that the modafinil 400 mg to placebo comparison for Week 9, Test 4 resulted in a p-value of 0.053.

The sponsor reports that there were no significant differences between treatment groups for the Number of Patients Staying Awake for 0 to 4 Tests at Week 9 or Endpoint with all p-values > 0.050. This is confirmed by review of the sponsor's Table 9.0.10 (Item 8, Vol. 9, p. 03342-03343).

#### REM SLEEP LATENCY

There were no significant differences between treatment groups in Rem Sleep Latency at Week 9 or Endpoint. All three treatment groups (including placebo) exhibited significant increases in mean Rem Sleep Latency time from the Baseline results (all p-values < 0.050). When the individual Tests were analyzed, the 400 mg, 200 mg and combined active treatment groups were significantly better than placebo only for Test 2 (p = 0.002) at Week 9 and Endpoint. There were no significant differences between the active treatment groups for any individual test or on average. These findings are confirmed by review of the sponsor's Tables 9.1.0 through 9.1.9 (Item 8, Vol. 9, p. 03344-03353).

#### FIRST CONTINUED SLEEP LATENCY

The sponsor reports that these results are similar to those for the Sleep Latency (16 sec). That is confirmed by review of the sponsor's Tables 9.2.0 through 9.2.9 (Item 8, Vol. 9, p. 03354-03363).

#### STAGE 2 AND STAGE 3 SLEEP LATENCY

The sponsor reports that there were no significant differences between treatment groups for any test period or on average (all p-values > 0.100) at Week 9 or Endpoint. This conclusion is confirmed by review of the sponsor's Tables 9.3.0 through 9.3.9 (Item 8, Vol. 9, p. 03364-03374).

Data was also collected regarding Stage III sleep. Similar results were reportedly seen in each treatment group. Twenty percent or less of patients did not achieve Stage III sleep during one or more tests. No significant differences were found in any treatment group comparisons (all p-values > 0.100) at Week 9 or Endpoint. These results are confirmed by review of the sponsor's Table 9.4.0 (Item 8, Vol. 9, p. 03374-03375).

#### PATIENT SUBJECTIVE EVALUATION OF SLEEP LATENCY

The sponsor reports that the two active treatment arms showed significant (p-values < 0.001) mean Patient Subjective Evaluation of Sleep Latency value increases from baseline at Endpoint. The 400 mg treatment group and combined active treatment groups were significantly better

than placebo for Test 3 only ( $p \leq 0.006$ ) at Endpoint. No significant difference was found between the 200 mg group and the placebo group or between the two active medication groups for any individual test or on average (all  $p$ -values  $> 0.050$ ). These results are confirmed by review of the sponsor's Tables 9.5.0 through 9.5.10 (Item 8, Vol. 9, p 3376-03387); with the additional observation from this review that there were no significant differences between any treatment groups in the observed values for the Patient Subjective Evaluation of Sleep Latency at Week 9 or Endpoint.

**ESS:**

ESS scores from patients in the modafinil 400 mg and 200 mg treatment groups were significantly lower than scores from patients in the placebo group. This indicates less likelihood of falling asleep or dozing during the listed activities. These results are summarized in the following table:

**Table 16. Observed Values for ESS Score by Visit - Efficacy Evaluable Population**

Visit	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo
Baseline	n	85	93	90
	mean $\pm$ s.d.	17.1 $\pm$ 4.2	17.9 $\pm$ 3.8	18.3 $\pm$ 3.3
Week 3	n	83	94	92
	mean $\pm$ s.d.	12.6 $\pm$ 5.6 <sup>ab</sup>	14.0 $\pm$ 5.4 <sup>ab</sup>	16.8 $\pm$ 4.7 <sup>b</sup>
Week 6	n	80	92	86
	mean $\pm$ s.d.	12.6 $\pm$ 5.6 <sup>ab</sup>	13.9 $\pm$ 6.0 <sup>ab</sup>	16.8 $\pm$ 4.8 <sup>b</sup>
Week 9	n	81	92	86
	mean $\pm$ s.d.	13.0 $\pm$ 5.7 <sup>ab</sup>	14.4 $\pm$ 5.7 <sup>ab</sup>	17.1 $\pm$ 5.0 <sup>b</sup>
Endpoint	n	86	95	92
	mean $\pm$ s.d.	12.8 $\pm$ 5.8 <sup>ab</sup>	14.3 $\pm$ 5.7 <sup>ab</sup>	17.0 $\pm$ 4.9 <sup>b</sup>
<sup>a</sup> significantly different from placebo ( $p < 0.001$ ) <sup>b</sup> significantly different from baseline ( $p < 0.001$ )				

[based on sponsor's Table 7G, Item 8, Vol. 8, p. 03073]

Comparisons between treatment groups showed modafinil 400 mg, modafinil 200 mg and modafinil combined treatment group ESS scores were all significantly lower than placebo for all scheduled visits and Endpoint (all  $p$ -values  $< 0.001$ ). No significant difference was found between the two active treatment groups for any scheduled visit or at Endpoint. These findings are confirmed by review of the sponsor's Table 10.0.0 (Item 8, Vol. 8., p. 03388-03389).

**SCPT:**

On average the patients in the modafinil 400 mg treatment group hit a smaller percentage of obstacles at Endpoint (5.9%) than either the modafinil 200 mg treatment group (7.5%) or the placebo treatment group (7.9%). However, none of the pairwise comparisons indicated significance between any of the treatment groups (all p-values > 0.100). At Weeks 3 and 6 each modafinil treatment group showed a significantly lower percentage than the placebo treatment group (all p-values < 0.050). Improvement from baseline was significant for modafinil 400 mg at Week 6 (p = 0.020) and for modafinil 200 mg at Weeks 3 and 6 (both p-values < 0.010). These findings are confirmed by review of the sponsor's Table 7H (Item 8, Vol. 8, p. 03076) and Tables 11.1.0 and 11.1.1 (Item 8, Vol. 8, p. 03396-03399).

**Nocturnal Polysomnography Results:**

There was a reduction from Baseline to Endpoint in periodic leg movements of sleep for the modafinil 400 mg treatment group only. The number of periodic leg movements accompanied by arousals were similarly reduced for this group. Differences from baseline and between treatment groups for other parameters were not significant.

**Patient Sleep Logs:**

The sponsor reports that, on average, patients in the modafinil 400 mg and 200 mg treatment groups reported, at Endpoint, fewer minutes of sleep during the day, fewer episodes of unwanted sleep during the day and fewer episodes of desire for sleep during the day. The actively treated patients also reported more cataplectic attacks per day than did placebo treated patients at Endpoint. However, this was also true at Baseline. The incidence of daily reported cataplectic attacks decreased during the study for both modafinil treated groups but not for the placebo group; similar results were observed at Weeks 3, 6 and 9. The ratings of the ability to resist sleep and of general alertness were similar among all three treatment groups throughout the study.

Reportedly, there were no negative effects of modafinil treatment on nightly sleep. The active treatment groups reported fewer awakenings, fewer episodes of hypnagogic hallucinations and fewer episodes of sleep paralysis.

The sponsor did not report the results of any statistical analyses of this data.

**QOLIN:**

Higher numbers of patients in the two active treatment groups, compared to patients in the placebo group, responded positively to questions regarding "feelings about life as a whole", "quality of life during the past week", "general health", "social functioning", "productivity", "bodily pain", and "driving capability."

However, the sponsor did not report the results of any statistical analyses of this data.

**Section 7.2.1.6 Reviewer's Efficacy Discussion:**

For this study the sponsor chose two primary efficacy variables, average sleep latency at Endpoint on the MWT and improvement of the CGI-C score. Both variables compared modafinil 400 mg to placebo. By their analyses, modafinil 400 mg was proven effective for the treatment of excessive daytime sleepiness in the narcoleptic patient, with  $p < 0.001$  for each variable.

There were numerous secondary efficacy variables. Sleep latency and REM latency results on the MWT supported the efficacy of modafinil over placebo, but did not support a difference between the two modafinil doses, 200 mg and 400 mg. The Total Sleep Time documented increases in improvement in ability to stay awake in a dose-dependent manner. However, the analyses were again only statistically significant for the active groups versus placebo. Subjective evaluation by patients and CGI-C confirmed the above findings.

MSLT sleep latencies also noted improvement in sleep latency (lengthening) in both dose groups and the combined dose groups compared to placebo; and no significant difference between the two active treatment arms. The MSLT REM latencies were not as supportive, and there were no significant differences between the active groups at any point. Modafinil did not appear to affect Stage II or III sleep latency. Subjective patient evaluations of sleep latency on the MSLT did not indicate consistent improvement with either the combined active treatment groups compared to placebo, either individual dose of modafinil compared to placebo, or between the active treatment groups.

Scores on the ESS again showed significant improvement with either the combined treatment group versus placebo or the individual dose groups versus placebo. No significant difference was found between the two active treatment groups. SCPT results noted a trend towards improvement with treatment, but no significant pairwise comparisons were observed. Patient Sleep Log results and QOLIN results did appear to find trends towards improvement with either dose compared to placebo, but the results are difficult to interpret.

Discussion with Dr. David Hoberman, statistical reviewer for this NDA, confirmed the sponsor's conclusions regarding the statistical analyses of the primary efficacy variable data.

**APPEARS THIS WAY ON ORIGINAL**

## SECTION 7.2.2 STUDY C1538a/302/NA/US:

**Section 7.2.2.1 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 2-Week Discontinuation Segment, Followed by a 40 Week, Open-Label, Flexible-Dose Continuation Study.

**Objectives:** "The purpose of the double-blind treatment segment (segment I) 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 Segment II (the 2 week double-blind discontinuation segment) is to determine the effect of abrupt, double-blind discontinuation of modafinil on subsequent selected efficacy and safety assessments. The purpose of the open label segment of this study is to collect additional information regarding the safety and persistence of effect of modafinil during extended exposure. Efficacy and safety data are collected for hypothesis generation."

[Item 8, Vol. 18, p. 07549]

**Study Design:**

The double blind segment I portion of this study is a multicenter, randomized, parallel group, placebo controlled, fixed dose study of modafinil in patients with narcolepsy. Segment II is a double blind discontinuation phase which will follow the treatment phase. 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. The number of patients entering Segment II will be determined by the number of patients completing Segment I. 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

Both Group II and III patients will be dosed 100 mg/day of modafinil for the first week of Segment I.

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Table 17. Dosing Schedule

Weeks 1 through 9	Number of Tablets	Modafinil Dose
Group I: placebo	4 x placebo	0 mg/day
Group II a and b: 200 mg modafinil	Week 1: 1 x 100 mg modafinil + 3 x placebo	100 mg/day
	Week 2-9: 2 x 100 mg modafinil + 2 x placebo	200 mg/day
Group III a and b: 400 mg modafinil	Week 1: 1 x 100 mg modafinil + 3 x placebo	100 mg/day
	Week 2-9: 4 x 100 mg modafinil*	400 mg/day
Weeks 9 through 11	Number of Tablets	Modafinil Dose
Group I	4 x placebo	0 mg/day
Group II a (80%)	4 x placebo	0 mg/day
Group II b (20%)	2 x 100 mg modafinil + 2 x placebo	200 mg/day
Group II a (80%)	4 x placebo	0 mg/day
Group II b (20%)	4 x 100 mg modafinil	400 mg/day
* Group III a and b patients will be titrated to 200 mg Day 8, 400 mg Day 9		

[based on sponsor's Dosing Schedule Tables, Item 8, Vol. 18, p. 07570]

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  $\leq 8$  minutes and two sleep onset REM periods. 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. All drugs or substances with psychotropic effects are prohibited during the study, although deviation from this criterion may be approved by the study medical monitor.

Figure 2. Study Schemata - Segment I/Segment II

	<u>Segment I</u>						<u>Segment II</u>	
VISIT NUMBER:	1	2	3	4	5	6	7	8
END OF STUDY WEEK:	Screening	Baseline	1	3	6	9	10	11
STUDY DAY:	{-15 to -2}	{-2 to -1}	8	22	43	{64 to 65}	71	78
		{48° visit}				{48° visit}		

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 during Segment I (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.

Discontinuation evaluations for Segment II at end of Weeks 10 and 11 will include: physical exam, clinical laboratory tests, vital signs, 12-lead ECG, recording of concomitant medications and AE's. At end of Week 11 patients will also complete: MWT, ESS, SCPT, Patient Daily Sleep Log, and, as baseline data for the Open Label Phase, urine drug screen, modafinil plasma level, QOLIN patient inventory, and CGI-S.

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 will be increased to 400 mg/day for Days 8 through 14. The investigator will then choose the optimal dosage (200 mg or 400 mg) and the patient should remain on that dosage until completion of the study. The minimum daily dosage is 200 mg and the maximum daily dosage is 400 mg. Dosing may be adjusted to maximize clinical benefit and minimize AE's.

#### **Section 7.2.2.2 Statistical Analysis:**

There will be two primary efficacy variables, the MWT and the CGI-C in the double blind segment. The primary hypothesis will determine if treatment with modafinil (the combined 200 mg/day and 400 mg/day treatment groups), when compared to placebo, can modify the EDS of narcolepsy in patients receiving medication for  $\leq 9$  weeks, as reflected by the MWT and the CGI-C assessed by an independent clinician. Endpoint analysis will be the primary analysis, performed to include data from all patients with post-baseline evaluations, and Endpoint defined as the last patient evaluation post-baseline. Both the MWT and the CGI-C analyses must result in statistically significant efficacy being shown for study drug ( $p \leq 0.05$ , two-tailed) in order to support the primary objective of the study. Segment I and Segment II data will be analyzed separately. A secondary hypothesis will determine independently, for each of the two modafinil doses, whether or not those doses produce 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 of dose level will utilize the Dunnett test procedure to adjust the level of significance.

"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. 18, p. 07596]

Secondary efficacy variables will include the MSLT, SCPT, ESS, Patient's Daily Sleep Log, and QOLIN patient inventory. Changes from baseline will be compared between treatment groups when applicable.

For Segment II, within group statistical comparisons of Baseline and Week 9 MWT results with MWT results obtained at the end of the discontinuation segment will be conducted. Persistence of effect will also be examined during the open label portion of the study.

#### **Section 7.2.2.3 Protocol Amendments:**

##### Amendment 1:

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

- 1) 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.

2) 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  $\leq 8$  minutes. Eligible patients diagnosed under Criteria B must have a MSLT with a mean sleep latency of  $\leq 5$  minutes. Eligible patients must have two sleep onset REM periods documented within the MSLT.

3) Allows for the collection of additional modafinil plasma samples to facilitate population pharmacokinetic analyses.

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

5) Clarification of the drug supply in the Study Drug section.

6) A change in clinical monitor.

#### Amendment 2:

This amendment was dated 8/2/95. It consists of two features:

1) Allows patients to take concomitant medications used for the treatment of cataplexy during the open label phase of the study.

2) Provides minor editorial revisions.

#### Amendment 3:

The exact date of this amendment is not clear from the submission. However, it appears to have been entered into the protocol at the same time as amendments 2 and 4, which would make the date 3/5/96. It consists of two features:

- 1) Changes one clinical monitor and adds one new clinical monitor.
- 2) Allows for the use of 200 mg tablets of modafinil containing a logo during the extended open label phase of the protocol.

**Amendment 4:**

This amendment was dated 3/5/95. It revises the statistical analysis section of the protocol as follows:

There are two primary measures of efficacy: The MWT and the CGI-C score. The primary hypothesis will be that treatment with modafinil at 400 mg/day for up to nine weeks will result in a statistically significant (5% level of significance, two sided test) increase in sleep latency compared to placebo on the MWT and a statistically significant improvement in the CGI-C score compared to placebo. The analysis population will include all randomized patients who receive study medication and have at least one post-baseline measurement for both MWT and CGI-C. 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 and baseline sleep latency.

The CGI-C score will be analyzed with a generalized Cochran-Mantel-Haenszel (CMH) test (Mantel's Test) for ordinal categorical data, including effects for treatment and baseline CGI severity. Severity will be measured with three strata: normal or borderline ill or slightly ill; moderately ill; markedly ill or extremely ill.

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

- 1) MWT
  - a) sleep latency (min.) (by test)
  - b) sleep latency (percentage of patients remaining awake 20 minute {complete success} for 0, 1, 2, 3 or 4 tests)
  - c) sleep latency to 10 seconds (average of 4 tests, by test)
  - d) total sleep time (average of 4 tests, time of day)
  - e) patient subjective evaluation of sleep latency (average of 4 tests, by test)
- 2) MSLT
  - a) sleep latency (min.)(average of 4 tests, by test)
  - 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 of 4 tests, by test)
  - d) latency to REM sleep (average of 4 tests, by test)
  - e) Stage II latency (average of 4 tests, by test)
  - f) Stage III latency (percentage of patients with "NO" for 0, 1, 2, 3 or 4 tests)
  - g) patient subjective evaluation of sleep latency (average of 4 tests, by test)
- 3) Epworth Sleepiness Score (ESS)

- total ESS score (0-24) from eight questions
- 4) SCPT
  - number of obstacles hit, percentage hit and obstacles passed, percentage passed in the 30 minute test period
- 5) Nocturnal Polysomnography
  - a) time variables (time in bed, time awake after sleep onset, total REM sleep, sleep latency, REM latency, etc.)
  - b) duration variables (sleep Stages I, II, III, IV, time in bed, minutes and percentages, etc.)
  - c) counts (numbers of awakenings, awakenings > 2 min., arousals, periodic leg movements in sleep [PLMS], PLMS with arousals, PLMS with awakening, respiratory disturbance index, etc.)
- 6) QOLIN
  - a) qualitative questions scored on an ordinal scale of worst to best
  - b) Visual Analog Scale (VAS) with consecutive ovals representing scale from worst to best
- 7) Patient Daily Sleep Log
  - a) time variables (total time asleep, time to fall asleep, etc.)
  - b) counts (number of episodes of unwanted sleep, number of episodes of desire for sleep, number of episodes of sleep paralysis, etc.)
  - c) qualitative variables (feeling of tension/anxiety when getting up in the morning, feeling of sleepiness when getting up in the morning, etc.)

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.

In addition, as the CGI-C, SCPT, ESS and Patient Daily Sleep Log will be measured after one week of treatment when all patients randomized to study drug will be receiving modafinil 100 mg, an analysis of treatment effect will be performed for these measures for that timepoint.

Following the Treatment Withdrawal Period (Weeks 9 through 11), at Week 11, the MWT, CGI-S, SCPT, ESS, QOLIN and Patient Daily Sleep Log will be performed. The effect of withdrawal of modafinil treatment will be assessed by analyzing the change from Week 9 to Week 11 within modafinil dose groups, and by comparing modafinil/placebo patients to placebo/placebo patients at Week 11.

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 baseline value of the variable as a covariate.

Exploratory hypotheses will be performed for the primary and secondary efficacy variables. A multivariate ANCOVA and a step-wise selection procedure will be utilized to identify important covariates with a statistical criterion for inclusion of  $p < 0.10$ .

\*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. Since modafinil 400 mg is expected to be more superior to placebo than modafinil 200 mg, the comparison of modafinil 200 mg versus placebo will be tested as secondary hypothesis. In addition, a comparison of the combined doses of modafinil (200 mg, 400 mg) will be tested versus placebo as a secondary hypothesis.

\*For all continuous analyses, pairwise comparisons among the treatment groups...will be performed with variance estimated from the model mean square error (MSE) without adjustment. Dose response will be tested by partitioning the treatment sum of squares into single degree of freedom tests for linear and quadratic trend. For CGI-C, pairwise comparisons among treatment groups...will be performed by including only the pairwise groups in the CMH test. Dose response will be tested with modafinil 400 mg, modafinil 200 mg and placebo included in the CMH test. All tests are two-sided 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 Fisher's Exact Test." [Item 8, Vol. 18, p. 07666-7]

#### **Section 7.2.2.4 Conduct of Study:**

##### Patient Distribution/Disposition:

Of the 273 patients randomized, 271 (99%) received study medication and were considered to be evaluable for the safety analyses. Two patients were not evaluable for safety or efficacy analyses. Patient 0907 (modafinil 400 mg) and Patient 1205 (modafinil 200 mg) were randomized prior to receiving results of the baseline urine drug screen (UDS) and were instructed not to begin taking study medication until they had been cleared for entry. Both patients had positive UDS results and returned all study medication unopened.

Of the 273 patients randomized, 257 (94%) 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):

**Table 18. Patients Excluded from Efficacy Evaluable Population**

Patient Number	Treatment Group	Missing Evaluation
0110 <sup>a</sup>	Modafinil 200 mg	CGI-C and MWT
0210 <sup>b</sup>	Placebo	CGI-C and MWT
0710 <sup>c</sup>	Placebo	MWT
0802 <sup>c</sup>	Modafinil 400 mg	MWT
0907 <sup>d</sup>	Modafinil 400 mg	All Evaluations
1003 <sup>a</sup>	Modafinil 200 mg	MWT
1102 <sup>e</sup>	Placebo	CGI-C and MWT
1205 <sup>d</sup>	Modafinil 200 mg	All Evaluations
1209 <sup>f</sup>	Modafinil 200 mg	CGI-C and MWT
1303 <sup>a</sup>	Placebo	MWT
1409 <sup>c</sup>	Modafinil 200 mg	CGI-C and MWT
1503 <sup>c</sup>	Modafinil 200 mg	CGI-C and MWT
1514 <sup>c</sup>	Placebo	CGI-C and MWT
1518 <sup>c</sup>	Modafinil 400 mg	MWT
2011 <sup>a</sup>	Modafinil 200 mg	MWT
2306 <sup>a</sup>	Modafinil 400 mg	CGI-C

<sup>a</sup>Patient discontinued due to AE  
<sup>b</sup>Data accidentally destroyed  
<sup>c</sup>Patient withdrew consent  
<sup>d</sup>Patient did not receive study medication and was excluded from both Safety and Efficacy Evaluable Populations  
<sup>e</sup>Baseline CGI-S not done because "raters could not be located"  
<sup>f</sup>Patient discontinued due to non-compliance

[based on sponsor's Table 6A, Item 8, Vol. 14., p. 06053]

Five patients (6%) in the modafinil 400 mg group discontinued the study compared to 12 patients (13%) in the modafinil 200 mg group and 11 patients (12%) in the placebo treatment group. One patient in the modafinil 400 mg group, six patients in the modafinil 200 mg group, and three patients in the placebo group discontinued for AE's. The following table summarizes patient disposition:

**Table 19. Patient Disposition**

	<b>Modafinil 400 mg</b>	<b>Modafinil 200 mg</b>	<b>Placebo</b>
Total Patients Randomized	90	90	93
Patients Who Did Not Receive Study Drug	1 (1%)	1 (1%)	0
Patients Evaluable for Safety	89 (99%)	89 (99%)	93 (100%)
Patients Evaluable for Efficacy	86 (96%)	83 (92%)	88 (95%)
Completed Double Blind Phase	84 (93%)	77 (86%)	82 (88%)
Early Discontinuations:	5 (6%)	12 (13%)	11 (12%)
Adverse Clinical Experiences	11 (12%)	6 (7%)	3 (3%)
Protocol Violation	1 (1%)	0	1 (1%)
Patient Withdrew Consent	3 (3%)	3 (3%)	3 (3%)
Patient Noncompliance	0	1 (1%)	1 (1%)
Lack of Study Medication Efficacy	0	2 (2%)	2 (2%)
Other	0	0	1 (1%)

[based on sponsor's Table 6B, Item 8, Vol. 14, p. 06054]

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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 20. Patient Specific Protocol Violations**

Protocol Violation	Treatment	Patient Numbers
<b>Entry Criteria:</b>		
MSLT at Baseline > 8 min	Modafinil 400 mg	0611, 1206
	Modafinil 200 mg	0609, 0610, 1507
	Placebo	1517
Patient was > 65 years old	Modafinil 400 mg	2021, 2022
	Modafinil 200 mg	1301
	Placebo	0103, 0303
Patient was < 18 years old	Placebo	0521
<b>Primary Efficacy Assessment at Baseline</b>		
CGI-S not done	Modafinil 200 mg	1102*
* Patient not in efficacy evaluable population		

[based on sponsor's Table 6C, Item 8, Vol. 14, p. 06055]

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Demographics:

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

**Table 21. Demographics - Safety Evaluable Population**

	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo
Age (years)	n	89	89	93
	mean	42	42	41
	s.d.	13	13	13
	median	42	45	41
Women	%	51	58	54
Face:				
Caucasian	n (%)	75 (84%)	79 (89%)	81 (87%)
African-American	n (%)	6 (7%)	9 (10%)	9 (10%)
Hispanic	n (%)	7 (8%)	1 (1%)	3 (3%)
Other	n (%)	1 (1%)	0	0
Weight (lb)	n	89	89	93
	mean	181	174	149
	s.d.	39	44	38
	median	182	177	173
Height (in)	n	89	89	93
	mean	67	67	67
	s.d.	4	4	4
	median	68	67	67

[based on sponsor's Table 6E, Item 8, Vol. 14, p. 006057]

Patients ranged from 17 to 67 years. 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 (except for marital status) with all p values  $\geq 0.050$ .

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 22. Baseline Narcolepsy History -Safety Evaluable Population**

Characteristic	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo
Total # Patients	n	89	89	93
Years Since Initial Diagnosis	n	89	88	93
	mean	6.6	7.6	8.1
	s.d.	9.2	10.8	11.4
	median	3	3	3
	minimum	0	0	0
	maximum	33	49	44
Years Since Onset	n	84	86	89
	mean	22.0	21.8	24.8
	s.d.	14.8	14.5	15.7
	median	17	17	24
	minimum	1	1	1
	maximum	66	49	51

[based on sponsor's Table 2.1.0, Item 8, Vol. 15, p. 06222]

All three treatment groups had similar severities of illness at baseline, as measured by the CGI-S. However, the difference between the modafinil 400 mg group and the modafinil 200 mg group was statistically significant ( $p = 0.009$ ) in a pairwise comparison. These findings are summarized in the following table:

**Table 23. CGI-S at Baseline - Efficacy\* Evaluable Population**

	Modafinil 400 mg	Modafinil 200 mg	Placebo
Total number patients	86	83	88
no signs illness	0	0	0
borderline ill	1 (1%)	4 (5%)	5 (6%)
slightly ill	11 (13%)	18 (22%)	12 (14%)
moderately ill	39 (45%)	38 (46%)	38 (43%)
markedly ill	30 (35%)	19 (23%)	26 (30%)
extremely ill	5 (6%)	4 (5%)	7 (8%)

[based on sponsor's Table 6F, Item 8, Vol. 14, p. 06059]

There were slight differences among treatment groups at some levels of severity for the related narcolepsy symptoms of excessive daytime sleepiness, sleep attacks during the day, and interrupted sleep at night. However, there were more notable Baseline differences among treatment groups in the percentage of patients experiencing hypnagogic hallucinations, sleep paralysis and cataplexy, at some levels of severity. The following table summarizes these differences:

**Table 24. Baseline Disease Characteristics**

Symptoms	Modafinil 400 mg	Modafinil 200 mg	Placebo
Total number patients	89	89	93
Number of patients with:			
hypnagogic hallucinations	42 (47%)	37 (42%)	53 (57%)
sleep paralysis	34 (38%)	39 (44%)	48 (52%)
cataplexy	36 (40%)	49 (55%)	47 (51%)

[based on sponsor's Table 6G, Item 8, Vol. 14, p. 06060]

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 25. Prior Medications - Safety Evaluable Population**

	Modafinil 400 mg	Modafinil 200 mg	Placebo
Total number of patients	89	89	93
Number of patients taking prior medications	81 (91%)	84 (94%)	83 (89%)
Number of patients taking narcolepsy medications	65 (73%)	66 (74%)	64 (69%)

[based on sponsor's Table 6H, Item 8, Vol. 14, p. 06061]

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 26. Concomitant Medications with CNS Activity - Safety Evaluable Population**

	Modafinil 400 mg	Modafinil 200 mg	Placebo
Total number of pts.	89	89	93
Any concomitant meds	75 (84%)	84 (94%)	77 (83%)
Narcolepsy meds <sup>a</sup>	6 (7%)	5 (6%)	9 (10%)
Cataplexy meds <sup>b</sup>	0	2 (2%)	1 (1%)
Other drugs with stimulant effect:			
pseudoephedrine <sup>c</sup>	3 (3%)	0	0
Drugs with sedative effect:			
antihistamines <sup>d</sup>	15 (17%)	12 (13%)	8 (9%)
diazepam	1 (1%)	0	0

<sup>a</sup> dexamphetamine, caffeine, pemoline, methylphenidate, methamphetamine  
<sup>b</sup> imipramine, amitriptyline  
<sup>c</sup> either alone or as component of combination drug  
<sup>d</sup> astemizole, brompheniramine, chlorpheniramine, diphenhydramine, loratadine, terfenadine, triprolidine

[based on sponsor's Table 6I, Item 8, Vol. 14, p. 06062]

**Section 7.2.2.5 Sponsor's Efficacy Results:***Treatment-by-site Interaction:*

The analyses performed to evaluate possible treatment-by-site interaction effects for each narcolepsy test (MWT, MSLT, ESS, SCPT) were not significant (all p-values >0.100).

*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 27. 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	83	88	
MWT Average Sleep Latency (min)*	mean	7.86	8.28	5.35	< 0.001
	s.d.	5.28	5.89	4.49	
* mean of four tests taken at each visit					

[based on sponsor's Table 7A, Item 8, Vol. 14, p. 06064]

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:

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**Table 28. 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	83	88	
very much improved	5 (6%)	7 (8%)	0	0.016
much improved	24 (28%)	21 (25%)	12 (14%)	
minimally improved	23 (27%)	20 (24%)	21 (24%)	
no change	26 (30%)	27 (33%)	42 (48%)	
minimally worse	5 (6%)	7 (8%)	9 (10%)	
much worse	3 (3%)	1 (1%)	4 (5%)	
very much worse	0	0	0	

[based on sponsor's Table 7A, Item 8, Vol. 14, p. 06064]

*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, except REM Sleep Latency, 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.

For both active treatment groups there were statistically significant increases from Baseline in MWT Average Sleep Latency at Week 3 and throughout the remainder of the study (all p-values < 0.001). Changes from Baseline for MWT Average Sleep Latency times for patients in the placebo treatment group were no statistically significant.

Modafinil 400 mg vs. modafinil 200 mg was not significant for MWT average sleep latency at

any timepoint. All p-values were > 0.200. Treatment group comparisons were also not significant at baseline, with all p-values > 0.700. This data is summarized in the following table:

**Table 29. MWT Average Sleep Latency (min.) by Visit - Efficacy Evaluable Population**

Visit	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo
Baseline	n	86	83	88
	mean ± s.d.	5.86 ± 4.37	6.08 ± 4.86	6.00 ± 4.97
Week 3	n	86	83	87
	mean ± s.d.	9.29 ± 5.63	8.89 ± 5.75	5.47 ± 5.13
Week 6	n	83	78	87
	mean ± s.d.	8.96 ± 5.69	8.90 ± 5.70	6.08 ± 4.90
Week 9	n	84	78	83
	mean ± s.d.	7.82 ± 5.34	8.20 ± 5.88	5.53 ± 4.54
Endpoint	n	86	83	88
	mean ± s.d.	7.86 ± 5.28	8.28 ± 5.89	5.35 ± 4.49

[based on sponsor's Table 7B, Item 8, Vol. 14, p. 06066]

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, the modafinil 200 mg treatment group, and the modafinil combined treatment groups were significantly better than placebo for Tests 2, 3 and 4 (all p-values < 0.050). No significant difference was found between the active treatment groups for any individual test with the exception of Test 1, Week 3 (p-value = 0.043).

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. The sponsor's Tables 8.1.0 through 8.1.9 (Item 8, Vol. 15, p. 06267-06286) confirm this conclusion.

#### REM SLEEP LATENCY

The sponsor reports that there were no strong trends towards statistical significance for REM Sleep Latency. The sponsor's Tables 8.2.0 through 8.2.9 (Item 8, Vol. 15, p. 06287-06306) confirm this conclusion.

#### TOTAL SLEEP TIME

The sponsor reports that on average, patients in the modafinil 400 mg treatment group exhibited lower Total Sleep Time (8.11 min.) than patients in the placebo treatment group (9.92 min.) at Endpoint. Patients in the modafinil 200 mg treatment group exhibited lower Total Sleep Time (7.88) than either high dose or placebo patients. Other than Test 2, Week 3, no significant differences were found between the two active study medication groups for any individual test or on average at Endpoint. The results for scheduled visits were similar to those seen at Endpoint. The sponsor's Tables 8.3.0 through 8.3.9 (Item 8, Vol. 15, p. 06307-6326) confirm these findings.

#### PATIENT SUBJECTIVE EVALUATION OF SLEEP LATENCY

Patients were asked to estimate how long they were able to stay awake at the end of each test period. The sponsor reports that both treatment arms and the combined treatment groups values were all significantly greater than the placebo group values on Tests 2, 3, 4, and on average (p-values <0.010) at Endpoint; and that (with the exception of Test 2 at Week 3) no significant difference was found between the two active treatment groups for any individual test or on average. They also state that similar comparisons were made for each scheduled study visit, and that the results were similar to those seen at Endpoint. The sponsor's Tables 8.4.0 through 8.4.9 (Item 8, Vol. 15, p. 06327-6346) confirm these findings with the following exception: 1) modafinil 200 mg compared to the placebo group for Test 4, Week 6 (10.628 min. vs. 9.519 min., respectively, p = 0.252); 2) modafinil 400 mg compared to placebo group for Test 4, Week 6 (11.148 min. vs. 9.519 min., respectively; p = 0.067); and 3) combined active treatment groups compared to placebo group for Test 4, Week 6 (11.146 min./10.628 min. [400 mg/200 mg] vs. 9.519, respectively, p = 0.086 .

The sponsor also reports that their analysis comparing the number of tests for which patients subjectively evaluated themselves as having stayed awake during the entire test revealed that the modafinil 400 mg, 200 mg and combined treatment groups all exhibited significantly more patients reporting staying awake at Endpoint than patients in the placebo group (all p-values < 0.010). They also note that similar comparisons were made for all other scheduled visits, and that the results were similar to those seen at Endpoint. Review of the sponsor's Table 8.4.10 (Item 8, Vol. 15, p. 06347-6349) confirms these findings with the following exception: modafinil 200 mg compared to placebo for Week 6, p = 0.158).

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**CGI-C:**

Patients in both active treatment groups had significantly greater improvement than patients in the placebo group at each visit. These results are summarized in the following table:

**Table 30. Patients Improved in CGI-C - Efficacy Evaluable Population**

Visit	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo
Week 3	n (%)	60 (70%)	45 (55%)	33 (38%)
	p-value*	< 0.001	0.022	
Week 6	n (%)	51 (62%)	55 (71%)	38 (44%)
	p-value*	0.038	0.001	
Week 9	n (%)	51 (61%)	46 (58%)	32 (38%)
	p-value*	0.016	0.023	
Endpoint	n (%)	52 (60%)	48 (58%)	33 (38%)
	p-value*	0.016	0.012	

\* Modafinil 400 mg or 200 mg compared to placebo

[based on sponsor's Table 7E, Item 8, Vol. 15, p. 06072]

A statistically significant difference between the modafinil 200 mg and 400 mg treatment groups for baseline CGI-S ( $p = 0.009$ ) was noted. However, the comparison of modafinil 400 mg and 200 mg was not significant at any timepoint for CGI-C. A greater percentage of patients treated with modafinil 100 mg showed improvement (64%) compared to patients in the placebo group (36%) at Week 1 ( $p < 0.001$ ).

**MSLT:****SLEEP LATENCY (16 SEC)**

Patients in the modafinil 400 mg treatment group exhibited a longer average Sleep Latency (16 sec), i.e. to the first 16 seconds of continuous sleep, time (5.14 min.) than patients in the modafinil 200 mg (4.99 min.) or placebo (3.46 min.) treatment groups at Endpoint. The sponsor's analyses found statistically significant treatment effects for the 400 mg treatment group when compared to the placebo group for Tests 2 and 3 at Endpoint (all  $p$ -values  $< 0.050$ ). Modafinil 200 mg was significantly different from placebo only for Test 2 at Endpoint ( $p = 0.014$ ). The combined treatment groups and placebo group comparisons resulted in a significant difference only for Tests 2 and 3 at Week 9 and Endpoint (all  $p$ -values  $< 0.01$ ). The

sponsor also notes statistically significant increases from Baseline in the active treatment groups of 1.99 min. in the 200 mg group and 2.32 min. in the 400 mg group (p-values both <0.001). No significant differences were found between the two active treatment arms. Review of the sponsor's Tables 9.0.0 through 9.0.9 (Item 8, Vol. 15, p. 06350-06360) confirms these findings.

The sponsor reports that there were no significant differences between treatment groups for the Number of Patients Staying Awake for 0 to 4 Tests at Week 9 or Endpoint with all p-values > 0.050. This is confirmed by review of the sponsor's Table 9.0.10 (Item 8, Vol. 15, p. 06360-06361).

#### REM SLEEP LATENCY

There was a significant difference between the modafinil 400 mg group and the placebo group at Endpoint (p = 0.029). The average REM Sleep Latency at Endpoint was greater for the modafinil 400 mg group (12.78 min.) compared to either the modafinil 200 mg treatment group (11.89 min.) or the placebo group (10.61 min.). All three treatment groups (including placebo) exhibited significant increases in mean Rem Sleep Latency time from the Baseline results (all p-values <0.010) with increases of 3.48 min. for modafinil 400 mg, 2.22 min. for modafinil 200 mg, and 1.84 min. for placebo. When the individual Tests were analyzed, the 400 mg, 200 mg and combined active treatment groups were significantly better than placebo only for Test 2 (p = 0.002) at Week 9 and Endpoint. There were no significant differences between the active treatment groups for any individual test or on average. These findings are confirmed by review of the sponsor's Tables 9.1.0 through 9.1.9 (Item 8, Vol. 15, p. 06362-6371).

#### FIRST CONTINUED SLEEP LATENCY

The sponsor reports that these results are similar to those for the Sleep Latency (16 sec). That is confirmed by review of the sponsor's Tables 9.2.0 through 9.2.9 (Item 8, Vol. 15, p. 06372-06381).

#### STAGE 2 AND STAGE 3 SLEEP LATENCY

The sponsor reports that there were no significant differences between the two treatment groups for Stage 2 Sleep Latency, average of four tests (all p-values > 0.500). No consistent treatment group differences were noted for individual MSLT assessments. These conclusions are confirmed by review of the sponsor's Tables 9.3.0 through 9.3.9 (Item 8, Vol. 15, p. 06382-06391).

Data was also collected regarding Stage III sleep. Similar results were reportedly seen in each treatment group. Twenty percent or less of patients did not achieve Stage III sleep during one or more tests. No significant differences were found in any treatment group comparisons (all p-values > 0.100). These results are confirmed by review of the sponsor's Table 9.4.0 (Item 8, Vol. 15, p. 06392-06393).

PATIENT SUBJECTIVE EVALUATION OF SLEEP LATENCY

The sponsor reports that the modafinil 400 mg treatment group had a significantly greater average Patient Subjective Evaluation of Sleep Latency (8.66 min.) compared to either the modafinil 200 mg group (8.06 min.) or the placebo group (5.81 min.) at Endpoint. The modafinil 400 mg, 200 mg and combined treatment groups were significantly different from placebo for Tests 2 and 3. No significant differences were found between the two active study medication groups for any individual test or the average of all four tests (all p-values >0.050). There were significant increases from Baseline in Patient Subjective Evaluation of Sleep Latency for all three treatment groups at Endpoint: 2.80 min. for the modafinil 400 mg group; 1.95 min. for the modafinil 200 mg group; and, 1.04 min. for the placebo group (p-values <0.001, 0.001 and 0.016, respectively). These results are confirmed by review of the sponsor's Tables 9.5.0 through 9.5.9 (Item 8, Vol. 15, p 06394-06403).

ESS:

ESS scores from patients in the modafinil 400 mg and 200 mg treatment groups were significantly lower than scores from patients in the placebo group. This indicates less likelihood of falling asleep or dozing during the listed activities. These results are summarized in the following table:

**Table 31. Observed Values for ESS Score by Visit - Efficacy Evaluable Population**

Visit	Statistic	Modafinil 400 mg	Modafinil 200 mg	Placebo
Baseline	n	85	83	86
	mean ± s.d.	18.0 ± 3.4	17.4 ± 3.8	17.6 ± 4.0
Week 3	n	84	80	87
	mean ± s.d.	12.8 ± 4.9 <sup>ab</sup>	13.4 ± 5.3 <sup>ab</sup>	16.0 ± 4.8 <sup>b</sup>
Week 6	n	83	79	85
	mean ± s.d.	12.3 ± 5.4 <sup>ab</sup>	13.0 ± 5.4 <sup>ab</sup>	15.6 ± 4.7 <sup>b</sup>
Week 9	n	82	79	85
	mean ± s.d.	12.3 ± 5.1 <sup>ab</sup>	13.0 ± 5.1 <sup>ab</sup>	15.8 ± 4.8 <sup>b</sup>
Endpoint	n	85	83	88
	mean ± s.d.	12.3 ± 5.1 <sup>ab</sup>	13.1 ± 5.1 <sup>ab</sup>	15.9 ± 4.7 <sup>b</sup>
<p><sup>a</sup> significantly different from placebo (p &lt; 0.001)  <sup>b</sup> significantly different from Baseline (p &lt; 0.001)</p>				

[based on sponsor's Table 7G, Item 8, Vol. 15, p. 06078]

Comparisons between treatment groups showed modafinil 400 mg, modafinil 200 mg and

modafinil combined treatment group ESS scores were all significantly lower than placebo at Endpoint (all p-values < 0.001). Patients in the modafinil 400 mg group had lower ESS scores on average (12.3) compared to patients in the 200 mg group (13.1) and the placebo group (15.9). All three treatment groups had significant mean score decreases from Baseline to Endpoint (5.7, 4.3 and 1.7, respectively; all p-values < 0.001). No significant difference was found between the two active treatment groups for any scheduled visit or at Endpoint. The combined treatments groups (each having received 100 mg during the first week) had a significantly lower mean ESS score (13.9) compared to the placebo group (15.8) at Week 1 (p < 0.001). These findings are confirmed by review of the sponsor's Tables 10.0.0 through 10.0.3 (Item 8, Vol. 15., p. 06407-06411).

#### SCPT:

On average the patients in the modafinil 200 mg treatment group hit a smaller percentage of obstacles at Endpoint (4.5%) than either the modafinil 400 mg treatment group (4.8%) or the placebo treatment group (9.2%). There were significant treatment group comparisons to the placebo group for the 400 mg group (p = 0.029), 200 mg group (p = 0.011), and the combined treatment group (p = 0.006) at Endpoint for the percentage of obstacles hit. Improvement from Baseline to Endpoint was significant for the modafinil 400 mg and 200 mg groups, at 1.7% (p = 0.018) and 2.3% (p = 0.016), respectively. No difference was detected between the modafinil combined treatment groups and the placebo group at Week 1 (following the 100 mg treatment period) for the percentage of obstacles hit (p = 0.129). These findings are confirmed by review of the sponsor's Table 7H (Item 8, Vol. 14, p. 0 6081) and Tables 11.1.0 and 11.1.3 (Item 8, Vol.15, p. 06418-06423).

#### Nocturnal Polysomnography Results:

There was an increase from Baseline to Endpoint in periodic leg movements of sleep (PLMS) with awakenings for the modafinil 400 mg treatment group only. This mean increase was largely due to a single modafinil 400 mg patient (#2021) whose number of PLMS with awakenings increased from 4 and 22 at the first and second baseline assessments to 145 and 265 at the first and second Endpoint assessments. Differences from baseline and between treatment groups for other parameters were not significant. These findings are confirmed by review of the sponsor's Tables 12.0.0 through 12.5.13 (Item 8, Vol. 15, p. 06424-06484).

#### Patient Sleep Logs:

The sponsor has found that patients in the modafinil 400 mg and 200 mg treatment groups reported, at Endpoint and all post-Baseline visits, fewer minutes of sleep during the day than patients on placebo. Although the same treatment group relationships were observed at Baseline, the changes from Baseline to Endpoint in the average number of minutes of sleep during the day were decreases for the modafinil groups and remained approximately the same for the placebo treatment group. They also note that differences between modafinil and placebo treatment groups were not clinically meaningful for number of episodes of unwanted sleep, number of episodes of desire for sleep, number of cataplexy attacks, ability to resist sleep, and general alertness.

Other findings noted by the sponsor included:

- The change from Baseline to Endpoint for the average number of minutes to fall asleep at night decreased for all treatment groups. However, there was a larger decrease observed for the two active treatment groups compared to the placebo group.
- The change from Baseline to Endpoint for average number of minutes of sleep before first awakening was clinically meaningful only for the modafinil 400 mg treatment group.
- Patients receiving modafinil 100 mg for the first week had a larger decrease in the number of minutes of sleep during the day and the number of minutes of sleep before first awakening compared to the patients in the placebo group.
- The change in the average number of minutes to fall asleep at night from Baseline to Week 1 was similar for patients receiving 100 mg and patients in the placebo group.

The sponsor did not report the results of any statistical analyses of this data.

QOLIN:

Higher numbers of patients in the two active treatment groups, compared to patients in the placebo group, responded positively to questions regarding "feelings about life as a whole", "quality of life during the past week", and "productivity."

All three treatment groups responded similarly when asked to rate their general health at Endpoint. While the percentage of patients whose physical health or emotional problems interfered with their normal social activity "Quite a bit" or "Extremely" during the past week decreased from Baseline to Endpoint for the modafinil 400 mg and 200 mg treatment groups and increased for the placebo group, the percentage of patients whose physical health or emotional problems interfered "All of the time" or "Most of the time" decreased for the modafinil 400 mg group but increased for the 200 mg and placebo groups.

In rating bodily pain during the past week, the percentage of patients reporting "moderate", "severe", or "very severe" pain increased from Baseline to Endpoint for the modafinil 200 mg group, stayed the same for the 400 mg group and decreased for the placebo group. The percentage of patients reporting the amount that pain interfered with their work as at least "moderately" during the past week increased from Baseline to Endpoint for the 400 mg group and the 200 mg group, but decreased for the placebo group.

Although the sponsor notes that responses regarding driving capacity favored the active treatment groups over placebo, review of their summary reveals rather mixed results. However, the "time patients felt they could drive safely without a nap" improved for both active groups and stayed the same for the placebo group, and those patients reporting being able to drive less than 30 minutes safely without a nap decreased for the treatment groups.

The sponsor did not report the results of any statistical analyses of this data.

**Section 7.2.2.6 Reviewer's Efficacy Discussion:**

For this study the sponsor chose two primary efficacy variables, average sleep latency at Endpoint on the MWT and improvement of the CGI-C score. Both variables compared modafinil 400 mg to placebo. By their analyses, modafinil 400 mg was proven effective for the treatment of excessive daytime sleepiness in the narcoleptic patient, with  $p < 0.001$  and  $p = 0.016$  for average sleep latency and improvement of CGI-C score, respectively

There were numerous secondary efficacy variables. Sleep latency results on the MWT supported the efficacy of modafinil over placebo, but did not support a difference between the two modafinil doses, 200 mg and 400 mg. REM latency did not show a significant difference between treatment groups. The Total Sleep Time documented increases in improvement in ability to stay awake for both active treatment groups, but with patients in the lower dose group exhibiting the lower Total Sleep Time compared to patients in the higher dose group. There were no consistently significant differences between the two active dose groups. Subjective evaluation by patients and CGI-C confirmed the above findings.

The MSLT REM latencies were somewhat more supportive with the 400 mg group showing significant increases in the average REM sleep latency compared to the placebo group at Endpoint. There were no significant differences between the active groups at any point. Modafinil did not appear to affect Stage II or III sleep latency. Subjective patient evaluations of sleep latency on the MSLT resulted in the modafinil 400 mg treatment group having a significantly greater average sleep latency compared to either the 200 mg or placebo groups at Endpoint. No significant differences between the two active treatment groups were noted. Scores on the ESS showed significant improvement with either the combined treatment group versus placebo or the individual dose groups versus placebo. No significant difference was found between the two active treatment groups. SCPT results noted a trend towards improvement with low dose treatment, but no significant pairwise comparisons were observed. Patient Sleep Log results and QOLIN results did appear to find trends towards improvement with either dose compared to placebo, but the results are difficult to interpret.

Discussion with Dr. David Hoberman, statistical reviewer for this NDA, confirmed the sponsor's conclusions regarding the statistical analyses of the primary efficacy variable data.

**SECTION 7.2.3 OTHER SUPPORTING CLINICAL TRIALS:**

There are six completed foreign clinical studies which were not sponsored by Cephalon but have been submitted by Cephalon as supportive of clinical efficacy. Three of these studies were controlled clinical trials (MOD-024, MOD-025 and MOD94003) and three were uncontrolled (MOD-026, MOD-027 and MOD-028). The final study report for MOD94003 was not available at the time of NDA submission. These six studies are summarized below.