

RESULTS

A total of 273 patients were randomized, with 271 receiving treatment. The following chart displays patient flow (adapted from Dr. Rappaport, page 48):

	Modafinil 400	Modafinil 200	Placebo
Patients randomized	90	90	93
Patients treated	89	89	93
Patients in Efficacy Analysis	86	83	88
Completers	84 (93%)	77 (86%)	82 (88%)

Patients were not included in the efficacy analysis, as noted above, because they did not have at least 1 on-treatment assessment consisting of both measures (MWT & CGI-C). In this study, most of the dropouts were in the 200 mg/day group.

Groups were comparable at baseline on demographics and disease parameters. In particular, patients enrolled in this trial were on average 41-42 years old with a mean duration of symptoms of about 22-25 years (with a mean time since diagnosis of 7-8 years).

Groups were also relatively comparable at baseline with regard to prior medication use and disease severity, although there was a slight maldistribution on the CGI-S between the Modafinil 400 and 200 mg groups. Specifically, there were fewer slightly ill patients in the 400 compared to the 200 mg groups (13% vs 22%, respectively), and more markedly ill patients in the 400 compared to the 200 mg groups (35% vs 23%; see Dr. Rappaport's review, page 51-52).

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Primary Outcomes

Sleep Latency (MWT)

The following table displays the results:

	Baseline	Endpoint	P-value
Placebo (N=88)	6.0	5.4	
M 200 mg/d (N=95)	6.1	8.3	<0.001
M 400 mg/d (N=86)	5.9	7.9	<0.001

The analysis used was a simple ANCOVA with baseline latency as the only covariate (as described in the protocol, but with no additional covariates included).

As can be seen in Dr. Hoberman's Figure 1, these differences were apparent at Week 3 (the first on-treatment visit) and persisted with little change over the duration of the study. Dr. Rappaport's Table 29, page 55-56 describes the same information, and notes that the p-values for each dose comparison to placebo at each of these timepoints was <0.001.

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CGI-C

There was a marked change in the distribution of change scores, as outlined in the following table:

	Modafinil 400 (N=86)	Modafinil 200 (N=83)	Placebo (N=88)
Very much improved	6%	8%	0%
Much Improved	28%	25%	14%
Minimally Improved	27%	24%	24%
No change	30%	33%	48%
Minimally Worse	6%	8%	10%
Much Worse	3%	1%	5%
Very Much Worse	0%	0%	0%
P-value	0.02	0.01	

The model used baseline severity as a covariate with no other covariates used.

The proportion of patients who improved from baseline at endpoint for each dose group was 60%, 58%, and 38%, for Modafinil 400, Modafinil 200, and Placebo, respectively. These differences yielded p-values for each dose comparison to placebo of <0.01. The differences between each dose and placebo in the proportion of patients improved from baseline yielded p-values less than 0.05 at all time points (weeks 3, 6, and 9).

Secondary Measures

A number of secondary outcomes were assessed.

MWT

Multiple other parameters derived from data measured during the MWT were used to compare drug and placebo. These included latency to sleep lasting at least 10 seconds (a standard measure), REM sleep latency, total

sleep time, and patient's subjective evaluation of sleep latency. The Agency has not performed independent analyses of these outcomes, but according to the sponsor, the results generally mirror those on the primary outcomes, although for some (total sleep time) the differences, though numerically favoring drug in both dose groups compared to placebo, were not statistically significant (in fact, results on this parameter numerically favored the 200 mg group over the 400 mg groups). For, REM sleep latency, there were no strong trends in favor of either dose group compared to placebo.

MSLT

Again, multiple parameters are measured in this test. These include sleep latency (to the first 16 seconds of continuous sleep), REM sleep latency, first continued sleep latency, latency to Stage 2 and 3 sleep, and patient's subjective evaluation of sleep latency. Again, the Agency has not performed independent analyses of these measures. The sponsor reports scattered nominally significant differences between various dose groups and placebo on some individual tests, but no consistently significant between treatment differences favoring either the 400 mg or 200 mg groups compared to placebo on any of the parameters listed.

ESS

ESS scores for each Modafinil group were significantly different from placebo ($p < 0.001$) at endpoint, as well as at Weeks 3, 6 and 9.

SCPT

Between treatment differences between each drug and placebo were significant at endpoint.

Polysomnography

There were no consistent significant differences between either drug group and placebo on any parameters.

Patient Sleep Log

In general, the sponsor reports changes favoring drug on various sleep related measures, but no statistical analyses were presented.

QOLIN

Although the sponsor reports changes in favor of drug, no statistical analyses were reported.

SAFETY

A total of 2305 subjects have been treated with Modafinil for whom CRFs are available to the sponsor. These subjects were enrolled either in Cephalon sponsored Phase 1, 2, or 3 studies (controlled and uncontrolled), or in foreign, non-Cephalon sponsored studies.

A total of 559 patients have received the drug for at least 6 months, and 537 have received doses of between 200-400 mg/day for this duration. A total of 225 subjects have received treatment for at least 1 year, with 207 of these receiving doses of between 200-400 mg/day. For these totals, the sponsor has not submitted a further dose by duration breakdown.

The sponsor has submitted more detailed dose and duration data for the database with the Cephalon sponsored uncontrolled Phase 3 data excluded (this display can be found as Dr. Rappaport's Table 34, page 75-76).

Although this table does not represent the complete database, it contains the only data that we currently have that permit an estimate of the total exposure at doses close to 400 mg/day (375-424 mg/day), the maximum dose the sponsor proposes be permitted in labeling. As can be seen, the amount of experience at this dose for extended durations is relatively small. For example, for all studies combined (all Phases, Cephalon and non-Cephalon sponsored), 197 subjects have received this dose for greater than 28 days (177 of these have received this dose for between 29-90 days). An additional 13 subjects have received doses greater than 424

mg/day for at least 29 days.

As Dr. Rappaport notes, there are 2 potential problems in the interpretation of the safety experience as submitted, both related to the foreign experience. First, he notes that the sponsor is not certain that all patients described in the foreign experience are unique (presumably this means that the numbers that appear in cells that should be mutually exclusive may not be). Second, most of the foreign data was derived in settings in which the total daily dose was given as a twice a day regimen, whereas the Cephalon sponsored data was as a single daily dose, the regimen shown to be effective in the 2 effectiveness trials.

DEATHS

A total of 5 subjects died while receiving Modafinil; none occurred in Cephalon sponsored studies (see Dr. Rappaport's review, Table 32, page 70). This yields a crude mortality of 0.2%. None of the deaths occurred in patients with narcolepsy. Three (3) of the patients were being treated for depression, and one each had ALS and age associated memory impairment (AAMI).

Two (2) of the patients with depression were treated with 200 mg/day; one died after an episode of syncope after treatment for an unknown duration (65 yo), and one died after 8 days of treatment presumably due to progressive cirrhotic complications (58 yo). The other patient with depression (82 yo) was treated with 150 mg/day for 1 day, and died from events listed as heart failure, pain, and kidney function abnormality.

The patient with ALS (40 yo) had been treated with 200 mg/day for an unknown duration, from an event listed as "aggravation reaction". Finally, the patient with AAMI (68 yo) had been treated with 400 mg/day for an unknown duration and died from a myocardial infarction.

DISCONTINUATIONS

In Cephalon sponsored Phase 3 controlled trials, the most common single adverse events leading to discontinuation were headache and cataplexy, each occurring in 4/369 (1.1%) of modafinil treated patients, compared to

0 and 1/185 (0.5%) of placebo patients, respectively. No other single adverse event was responsible for more than 0.5% of patients discontinuing treatment with modafinil in these studies, although 3% of patients reported discontinuing treatment due to ADRs involving the Nervous System, with ADRs of the Body as a Whole accounting for discontinuation of 1.4% of patients, Digestive System ADRs accounting for discontinuation of 1.1% of patients, and Respiratory System ADRs accounting for discontinuation of 0.8% of patients.

Dr. Rappaport reproduces the sponsor's summary table of discontinuations due to ADRs (reprinted in his review as Table 36, page 78) in the US as well as foreign databases, excluding Cephalon sponsored Phase 3 uncontrolled experience. Unfortunately, the comparative dropout rates (drug vs placebo) due to specific events in the foreign controlled trials cannot be examined, because it appears that the sponsor has combined controlled and uncontrolled data in the same table. Nonetheless, as presented here, no single ADR accounts for more than 0.6% of dropouts in the foreign narcolepsy patients (N=533), or 2.1% (insomnia) in the foreign non-narcolepsy patients (N=1171). In all of these foreign studies, the Nervous System was the body system in which the greatest number of events leading to discontinuation occurred (6.4% of patients in the foreign, non-narcolepsy patients).

SERIOUS ADVERSE EVENTS

In Cephalon sponsored Phase 3 controlled trials, 9/369 (2.4%) of modafinil treated patients experienced a serious adverse event, compared to 5/185 (2.7%) of placebo treated patients. Of the 9 modafinil treated patients, the sponsor considered 6 patients to have experienced a serious adverse event that was possibly, probably, or presumably definitely related to treatment (see Dr. Rappaport's Table 33, page 72).

Dr. Rappaport has reviewed all narrative summaries of all ADRs resulting in discontinuations as well as those for all serious ADRs, regardless of the investigators' causality assessments. In his view, only 3 events (in 2 patients) were both clinically significant and likely related to treatment; they occurred in patients in Cephalon sponsored Phase 1,2 studies.

One was a 22 year old man who experienced an acute psychotic episode after one week of treatment with 600 mg/day (after initiating treatment with 200 mg/day on Day 1 and 400 mg/day on Day 2). The episode resolved 3 days after treatment discontinuation.

The others were tachycardia (from 77-98 at baseline to 133-147) 8 hours after a single 800 mg dose, and hypertension (125/89 at baseline [supine] to 143/103) also after the single dose, in a 21 year old man.

ADVERSE EVENTS

In Cephalon sponsored Phase 3 controlled trials, ADRs that occurred in at least 2% of Modafinil treated patients and that were more frequent in the modafinil treated patients compared to the placebo treated patients were (taken from Table 39 in Dr. Rappaport's review, pages 83-84):

Event	Modafinil % (N=369)	Placebo % (N=185)
Headache	50%	
Nausea	13%	40%
Rhinitis	11%	4%
Diarrhea	8%	8%
Nervousness	8%	4%
Pharyngitis	6%	6%
Dry Mouth	5%	3%
Anorexia	5%	1%
Dizziness	5%	1%
Depression	4%	4%
Anxiety	4%	3%
Lung Disorder	4%	1%
Cataplexy	3%	2%
Insomnia	3%	2%
Paresthesia	3%	1%
LFT Elevation	3%	1%
Amblyopia	2%	2%
Chest Pain	2%	1%
Vision Abnormal	2%	1%
Dyspnea	2%	0%
		1%

	Modafinil	Placebo
Hypotension	2%	1%
Hypertension	2%	0%
Neck Pain	2%	1%
Chills	2%	0%
Vomiting	2%	1%
Dyskinesia	2%	0%
Hypertonia	2%	0%

In general, the ordering of these ADRs was about the same in the foreign experience, although the total number of patients reporting ADRs was generally greater in the Cephalon sponsored studies (with exceptions; for example, in the foreign, non-narcolepsy patients, a total of 11% reported insomnia, presumably, though, including uncontrolled experience-see Dr. Rappaport's Table 38, page 82).

Most of any dose response seen in ADRs was seen at doses greater than 400 mg/day.

LABORATORY VALUES

The sponsor reported the results of laboratory tests only for the Cephalon sponsored studies.

Clinical Chemistry

In the Phase 3 controlled trials, there were no important differences between drug and placebo (not broken down by dose) in the incidence of abnormally increased LFTs (ALT, AST, GGT, bilirubin >3X ULN), or any other routine chemistry test (see Dr. Rappaport's Table 40, page 88). There was a dose dependent increase in any elevation of GGT in these studies (placebo-5%, 200 mg/day-4%, 400 mg/day-10%), although, as noted by Dr. Rappaport, a number of these patients had abnormal screening or baseline levels, other causes for the elevations, and/or decreases with continued treatment. In the Phase 1,2 studies, the only finding of interest was the incidence of elevated Bicarbonate in Modafinil treated subjects (5/66 or

8%) compared to 0/20 placebo patients.

In the open label experience, 2.4% of patients had at least one abnormal GGT.

Hematology

There were no important hematologic abnormalities.

Other Safety concerns

No other significant safety concerns have been noted. Study 302 examined the effects of drug withdrawal. Although there appeared to be a slight increase in daytime sleepiness in patients who withdrew from either 400 mg or 200 mg/day compared to placebo, there was no between treatment difference in other ADRs of importance (see Dr. Rappaport's review, page 94).

PHARMACOLOGY

As Dr. Fitzgerald notes in her supervisory review of 11/7/97, the sponsor has submitted the results of 2 life time in vivo carcinogenicity studies, only one of which has been found to be acceptable. Specifically, the study in rats was acceptable, but the mouse study was not, because the doses were too low.

[REDACTED]

[REDACTED] This is a dermal application model, and a preliminary study performed by the sponsor suggests that reasonable plasma levels of the parent and 2 major metabolites could be obtained. As Dr. Fitzgerald points out, the sponsor must now perform a study to determine the doses and endpoints to be examined in the definitive study.

Further, Dr. Fitzgerald notes that the fertility (rats) and teratogenicity studies (rats and rabbits) submitted are essentially inadequate, because the doses used were too low, and they were not GLP studies. Despite the inadequacies, the rat teratology study did define a threshold dose for

teratogenic effects (200 mg/kg).

A peri- and post-natal study was performed in 1995 according to ICH guidelines, and is acceptable, but a final report has not yet been submitted to the Agency. Based on a desk copy of the report received on 11/6/97, which did not contain plasma level data, Dr. Fitzgerald has concluded that no adverse effects occurred at doses up to 200 mg/kg.

In sum, Dr. Fitzgerald concludes that the NDA can be considered approvable, with the sponsor's commitment to submit the results of an acceptable alternative carcinogenicity assay, and appropriate reproduction and teratology studies. I agree.

CHEMISTRY

A letter outlining minor deficiencies was sent to the sponsor on 5/12/97, to which they responded. Dr. Heimann reviewed the response (review dated 12/2/97) and finds the responses acceptable. However, there are minor problems with the data submitted by the DMF holder, (not the sponsor), the details of which cannot be made known to the sponsor. However, these outstanding deficiencies have been relayed to the DMF holder.

BIOPHARMACEUTICS

Dr. Yuan has several comments. Of interest is her finding that levels of the metabolite modafinil acid (presumed to be inactive) were markedly increased in patients with renal impairment (N=10, mean Cl_{cr} =16.6) compared to normals (N=12) after a single 200 mg dose. Specifically, while parent levels were unchanged, modafinil acid AUC increased by 8 fold and C_{max} by 3 fold.

Additionally, patients with "severe" cirrhosis (N=9) had a doubling of half-life and C_{max} after 8 days of 200 mg (Days 1 and 8, 200 mg single dose; Days 2-7, 100 mg BID) compared to normals (N=6).

SCHEDULING

The sponsor has requested that modafinil be placed in Schedule IV of the Controlled Substances Act. HFD-170 has reviewed the abuse and dependence data and agrees with this placement (see Dr. Klein's review of 12/1/97).

COMMENTS

The sponsor has submitted the results of 2 parallel group, placebo controlled, multi-center trials examining the effectiveness of Modafinil, 400 mg/day and 200 mg/day, given as a single dose to patients with narcolepsy. In addition, they have submitted data on the safety of Modafinil in a cohort of over 2000 patients.

In my view, the controlled trial data clearly provide substantial evidence of effectiveness of 400 mg/day and 200 mg/day of Modafinil in this population, at least on the symptom of daytime sleepiness. The primary outcome measure used to assess this effect (MWT) is widely regarded as an appropriate measure of this symptom, and the results seen on the CGIC suggest that the effects are of clinical utility. There is no compelling evidence that a dose of 400 mg/day provides additional benefit beyond that conferred by a single daily dose of 200 mg/day.

No important safety issue has been identified. However, limitations in the sponsor's submission have made it impossible to reach a definitive conclusion on the safety of this product.

Specifically, much of the safety data is from foreign sources. We have already seen that the sponsor has not been able to confirm that the numbers of patients they report to have been exposed to various doses/durations represent separate, discrete individuals, as one would assume from the submission. For this reason, the sponsor should be asked to give a complete and accurate accounting of the exact number of patients who have received drug, as well as accurate dose/duration data for this cohort.

In addition, the sponsor has not given sufficiently detailed dose/duration

data for the database that includes the Cephalon sponsored Phase 3 uncontrolled studies (the entire safety database). As has been noted, for example, we cannot know from the sponsor's presentation how many patients received doses close to 400 mg/day for at least 6 months.

The fact that much of the foreign data was gained with twice a day dosing is problematic. It is not immediately obvious that a daily dose of 400 mg, given as 200 mg twice a day, provides relevant data to support the safety of a 400 mg/day dose, given as a single dose (the dosing regimen shown to be effective).

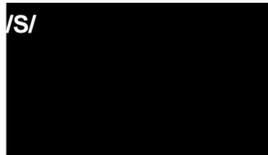
For these reasons (lack of additional benefit of a 400 mg/day dose, inadequate description of the exposure at the higher dose, potential inability of the foreign data to support the safety of this dose), I recommend that the product be labelled for use as a single 200 mg daily dose. If the sponsor can adequately describe sufficient safety experience at a single dose of 400 mg, a statement to the effect that such a dose is reasonably well tolerated may be permitted in labeling, but it may not be recommended as a dose that is likely to be more useful than the 200 mg/day dose.

Additionally, as Dr. Rappaport points out in his review (page 87), the sponsor has not submitted laboratory data for the foreign studies; they must do so.

Finally, the Pharmacology and Biopharmaceutics comments should be transmitted to the sponsor.

RECOMMENDATIONS

The sponsor should be sent an Approvable letter with attached draft labeling.

/s/ 

Russell Katz, M.D.

APPEARS THIS WAY ON ORIGINAL

Cc:

NDA 20-717

HFD-120

HFD-120/Katz/Leber/Rappaport/Malandrucco/Fitzgerald

APPEARS THIS WAY ON ORIGINAL

REVIEW AND EVALUATION OF CLINICAL DATA
NDA 20-717

Sponsor: Cephalon, Inc.
Drug: Provigil (modafinil) Tablets
Proposed Indication: Narcolepsy
Material submitted: Information amendment
Date received: 9/29/97

This amendment includes information for the Division of Anesthetic, Critical Care and Addiction Drug Products for review of the abuse potential of modafinil. In addition, it contains a summary of efficacy for the 40 week, open label extension phase of the Phase 3 clinical trials conducted under protocols C1538a/301/NA/US and C1538a/302/NA/US and an analysis of the quality of life in narcolepsy (QOLIN) for the double blind portion of these studies. The submission is divided into four sections.

1. This is a brief summary of the [REDACTED] post-marketing safety assessment of AE's which would commonly be reported in association with stimulant use, abuse or overdose. This section also includes a line listing of all AE's by system for modafinil, narrative summaries of all ninety AE's and an estimate of the number of treatment days.

Based on a formula using incidence of AE's and imputability (according to specific rules used in France), [REDACTED] has reported "Relationship Weighed Mean" scores of 1.5 for "increased pulse rate/tachycardia", 2 for "excitation/agitation/nervousness", 1.3 for "loss of appetite/anorexia" and 0 for "increased alertness", "increased blood pressure", "dilated pupils", "euphoria", and "insomnia." Interpretation of these scores is impossible as no further information is provided.

Additionally, [REDACTED] reports that no agitation, increase in body temperature, hallucinations, convulsions or deaths were reported in any of the six cases of higher daily doses of modafinil, 500 or 600 mg/day; and that no case of "withdrawal syndrome" has been reported since the drug has been on the market.

The line listing notes a total of ninety reported AE's. Of these, only nine are considered "imputability likely". These are: one case each of cephalgia (200 mg/d), hypoglycemia (300 mg/d), tachycardia (200 mg/d) and sweating (500 mg/d); two cases each of nervousness (300 and 100 mg/d) and rash (300 and 200 mg/d); and one case of "increased therapeutic response" believed to be due to an interaction between modafinil and cyclosporine [see biopharm review for this NDA] at a dose of 200 mg/d. None of the above AE's was considered serious and all resolved.

There were four SAE's listed: one case each of hemiplegia, gastritis hemorrhagic, malaise and asthenia. All of these were listed as "imputability doubtful."

The actual narrative summaries are difficult to interpret due to the fact that imputability scores are based on "chronological and semeiological" criteria which are not defined.

The "Number of Treatment's Days" table is uninterpretable as the population is not defined, and the formula used not provided.

2. The following conclusions were drawn by the sponsor from the results of their efficacy assessments of the open label, extension trials:

- The efficacy of modafinil demonstrated in the double blind study is maintained with long term treatment at flexible or fixed, patient optimized dosage levels;
- Placebo patients showed relatively little change in any parameter during the double blind phase, but were greatly improved during the open label phase;
- Most patients improved with long term treatment at 200 to 400 mg daily doses as indicated by a 14% discontinuation rate due to lack of efficacy in Study 301 and a 9% discontinuation rate due to lack of efficacy in Study 302;
- Overall quality of life is improved and maintained with long term therapy as indicated by reported improvement in feeling about life, overall quality of life, and standardized Physical Health and Mental Health SF-36 factors;
- Modafinil in 200 to 400 mg daily doses was effective for the treatment of excessive daytime sleepiness in narcolepsy for up to 51 weeks of therapy.

Review of the data submitted supports the sponsors conclusions. However, the true value of this data is difficult to assess as the studies were uncontrolled and open label.

3. Attachment 3 provides a description of the effects that smart drug and anorectic properties of modafinil will have on abuse potential. The sponsor has concluded that, "There is minimal evidence to suggest that modafinil might be a nootropic agent." There has been no evidence supporting it's abuse found by the drug's manufacturer in France, or by Interpol, since it's introduction in 1994.

The sponsor also concludes that long term use of modafinil in narcoleptic patients fails to demonstrate evidence of clinically meaningful alterations in weight. They note that "modafinil has predictable, dose-related acute effects on appetite during single-dose administration in rodents...and in poly-substance abusing human research subjects...However, in long-term clinical trials modafinil failed to demonstrate evidence of clinically meaningful, dose-related, or predictable effects on weight or on appetite in human narcolepsy subjects."

4. This is the report of the study conducted under protocol C1538a/201/AB/US. This study was entitled: "An Evaluation of Potential Abuse Liability of Orally Administered Modafinil Using Methylphenidate as a Reference Agent (Phase B)." A brief summary of this study follows.

This was a double blind, placebo controlled, 6 x 6 Latin square crossover, abuse liability evaluation of modafinil compared with methylphenidate. Male and female subjects with a history of polysubstance abuse including cocaine were selected. Each subject participated in six inpatient drug evaluation sessions that were separated by two washout days. Each subject received two doses of methylphenidate (45 and 90 mg), three doses of modafinil (200, 400, 800 mg), and placebo, in a randomized, double blind manner. The doses were chosen based on the results of Phase A, the dose ranging segment of the protocol. Each treatment was administered as one dose on the morning of the first day of each treatment session, followed by two days without any drug.

Number of Subjects	Male n (%)	Female n (%)	Total n (%)
Entered	25 (100)	12 (100)	37 (100)
Discontinued*	1 (4)	0 (0)	1 (3)
Completed all treatments	24 (96)	12 (100)	36 (97)
Evaluable for safety	25 (100)	12 (100)	37 (100)
Evaluable for abuse liability	24 (96)	12 (100)	35 (97)

* One male subject discontinued after receiving only one treatment (90 mg methylphenidate); therefore, 25 male subjects and 12 female subjects are evaluable for safety of 90 mg methylphenidate, and 24 male and 12 female subjects are evaluable for safety of all other treatments and for the abuse liability potential of modafinil

Abuse potential was assessed by the use of the following selected measures of amphetamine like effect: 1) the Addiction Research Center Inventory (ARCI); 2) Drug Rating Questionnaire (Subject, Observer); 3) Drug Identification Questionnaire; 4) comparison of the profile of signs and symptoms on the Drug Response Questionnaire (Subject, Observer); 5) number of actual (observer) and estimated (subject) hours of sleep on dosing day(s); 6) amount of kilocalories consumed at the noon meal, and evening meal on dosing days, and 7) supine and standing pulse rate and blood pressure.

Separate analyses of drug abuse liability were conducted for the male and female subject populations. The female subjects, in error, had a treatment randomization that was different from that of the male subjects. Therefore, the statistical analysis model for the female subjects was different from that for the male subjects.

Based on their analyses, the sponsor has concluded the following:

"Modafinil at the therapeutically relevant doses of 200 mg, 400 mg, and 800 mg,

appears to be less amphetamine-like than 45 mg or 90 mg methylphenidate when administered to male polysubstance abusers. On nonphysiological measures of abuse liability (subjective and behavioral) in male subjects, the responses for modafinil 200 mg and 400 mg were consistently lower than those of the methylphenidate 45 mg and 90 mg. The responses for modafinil 800 mg were generally similar to methylphenidate 45 mg or intermediate to methylphenidate 45 mg and 90 mg. In female subjects, no consistent dose response was present for the 200 mg and 400 mg doses, while modafinil 800 mg generally produced the largest overall response on the nonphysiological measures of abuse liability. In contrast, for the physiological measures of supine and standing systolic and diastolic blood pressure and pulse rate, good dose-response patterns were observed for both modafinil and methylphenidate in male and female subjects. The order of response on the physiological measures was generally methylphenidate 90 mg > modafinil 800 mg > modafinil 400 mg > methylphenidate 45 mg > modafinil 200 mg. The responses for modafinil 200 mg were similar to those of placebo...Several issues must be considered in the interpretation of the nonphysiological abuse liability results in females: i) These drug abuse evaluation assessments have never been validated in female subjects, ii) the effects were not dose-dependent across all three doses, and iii) the randomization schedule was not balanced for the female subjects."

There were no deaths or SAE's. No subject was discontinued due to an AE, although one subject who had received a single dose of methylphenidate withdrew his consent, complaining of flu-like symptoms. The most frequent AE for all treatment groups was somnolence. Methylphenidate administration resulted in an increased incidence of somnolence, euphoria, anorexia, tremor, nervousness, dry mouth, sweating, and dizziness relative to modafinil. Modafinil administration resulted in an increased incidence of headache relative to methylphenidate.

APPEARS THIS WAY ON ORIGINAL

Conclusions:

1. Limited useful information is available in this post-marketing review from France. The data and methods of analysis are poorly defined. There do not appear to be any new AE's of clinical significance. Nor does there appear to be an increased incidence of any clinically significant AE.
2. Long term efficacy is difficult to assess based on these open label extension studies. However, there does appear to be a maintenance of efficacy over the time period.
3. The information provided in the original NDA does support the sponsor's conclusion that modafinil does not appear to have a clinically significant anorectic effect. The abuse potential data will be analyzed in detail by the Abuse Potential Team of the Division of Anesthetic, Critical Care and Addiction Drug Products.
4. As noted above, the abuse potential of modafinil (as evaluated in Study 201) will be analyzed in detail by the Abuse Potential Team. The safety portion of this study raises no particular concerns in the polysubstance abuse population and no new concerns for the use of modafinil, in general.

Recommendations:

No action is indicated at this time.

/S/

Bob A. Rappaport, M.D.
Medical Reviewer
November 18, 1997

cc: orig. NDA
HFD-120 file
HFD-120
Leber
Katz
Rappaport
Malandrucco

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NDA 20-717
ADDENDUM 11/20/97

Sponsor:	Cephalon, Inc.
Drug:	Provigil (modafinil) Tablets
Proposed Indication:	Narcolepsy
Material submitted:	Original NDA
Date received:	12/30/96

The following are the sponsor's descriptions of the Maintenance of Wakefulness Test (MWT) and Multiple Sleep Latency Test (MSLT) as performed in the pivotal Studies 301 and 302 [Item 8, Vol. 11, pp. 04553-04554]:

MWT

"Four 20-minute trials of the MWT will be performed at 2-hour intervals beginning approximately 2 hours after the nocturnal polysomnographic session is completed...The nocturnal polysomnography montage, excluding respiratory airflow and leg EMG will be maintained throughout each MWT trial. Patients will be allowed access to their usual amount of caffeine beverages and food. The patient will be dressed and sitting semirecumbent on a reading pillow in bed in a dark room. They will be asked to remain awake, but not to use extraordinary measures such as slapping the face or singing. The time to sleep onset (sleep latency) will be scored based on standard Rechtschaffen and Kales criteria defined by either of the following: (a) 3 consecutive 30 second epochs of Stage 1 of sleep; or (b) any single, 30-second epoch of Stage 2, 3, 4, or REM sleep. Each MWT trial will be terminated after 20 minutes if no sleep occurs or 10 minutes after sleep onset. Sleep latency for each trial and average sleep latency for the four trial will be tabulated."

MSLT

"Four 20-minute trials of the MSLT will be performed at 2-hour intervals beginning approximately 2 hours after the nocturnal polysomnographic session is completed. The MSLT will be done according to previously established procedures. The nocturnal polysomnography montage, excluding respiratory airflow and leg EMG, will be maintained throughout each MSLT trial. Patients will be allowed access to their usual amount of caffeinated beverages and food. The patient will be dressed in non-constricting day clothes. The patient will be instructed to lie quietly and attempt sleep [sic]. Sleep latency will be scored according to the newest MSLT scoring criteria as the first 16 seconds of any sleep. The time to sleep onset will also be tabulated and is based on standard Rechtschaffen and Kales criteria defined by either of the following: (a) 3 consecutive 30 second epochs of Stage 1 sleep; or (b) any single 30 second epoch of Stage 2, 3, 4, or REM sleep. According to the clinical protocol of the MSLT, each trial will be terminated after 20 minutes if no sleep occurs, or 15 minutes after sleep onset. Sleep latency for the four trials will be tabulated."

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Bob A. Rappaport, M.D.
Medical Reviewer
November 20, 1997

cc: orig. NDA
HFD-120 file
HFD-120

Leber

Katz

Rappaport

Malandrucco

APPEARS THIS WAY ON ORIGINAL

**NDA 20-717
ADDENDUM 12/11/97**

Sponsor:	Cephalon, Inc.
Drug:	Provigil (modafinil) Tablets
Proposed indication:	Narcolepsy
Material submitted:	Original NDA
Date received:	12/30/96

As part of the Patient Daily Sleep Logs, subjects recorded the following:

1. Total minutes of sleep during day (naps)
2. Number of episodes of unwanted sleep
3. Number of episodes of desire for sleep
4. Number of cataplexy attacks
5. Number of minutes to fall asleep
6. Number of minutes of sleep before first awakening
7. Number of minutes awake (not counting time to fall asleep)
8. Number of hours slept
9. Number of times awakened
10. Number of hypnagogic hallucinations; and
11. Number of episodes of sleep paralysis

In regard to #'s 4, 9, 10 and 11, the common associated symptoms in narcoleptics, the sponsor reported the following:

Study 301:

*Patients receiving modafinil 400 mg and 200 mg reported more cataplectic attacks per day than did patients receiving placebo (averages of 0.98 and 0.82 versus 0.74, respectively) at Endpoint. However, this was also true at Baseline: the modafinil 400 mg and 200 mg groups had averages of 1.31 and 0.96 cataplectic attacks per day, respectively at Baseline, compared with 0.79 for the placebo group. The incidence of daily reported cataplectic attacks decreased during

the study for both modafinil 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.

"There was no reported negative effect of modafinil treatment on nightly sleep. Modafinil groups reported awakenings ('woke up') at night on fewer occasions, and experienced fewer episodes of hypnagogic hallucinations and of sleep paralysis." [Item 8, Vol. 8, p. 03078]

Review of the sponsor's Table After Text 14.0.3-14.1.6, Item 8, Vol. 9, pp. 03479-03498, confirm the above findings for Endpoint evaluations. No statistical analyses are reported and the positive results appear to be a trend of small amplitude.

Study 302:

"Differences between modafinil treatment groups and the placebo treatment group were not clinically meaningful for number of...cataplexy attacks...

"...Differences between treatment groups for other parameters [number of times awakened, number of hypnagogic hallucinations, number of episodes of sleep paralysis, and others] were not clinically significant." [Item 8, Vol. 14, p. 06083]

Review of the sponsor's Table After Text 14.0.6-14.1.12, Item 8, Vol. 16, pp. 06506-006534, does not reveal any obvious negative or positive trends. No statistical analyses are reported.

/s/

Bob A. Rappaport, M.D.
Medical Reviewer
December 11, 1997

cc: orig. NDA
HFD-120 file
HFD-120

Leber
Katz
Rappaport
Malandrucco

APPEARS THIS WAY ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

DATE: December 1, 1997

TO: Addressees (below)

THRU: Cynthia McCormick, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)

FROM: Michael Klein, Ph.D., Team Leader
Controlled Substances Evaluation Team (HFD-170)

SUBJECT: Recommendation: Placement of MODAFINIL in Schedule IV
of the Controlled Substances Act (CSA)

Attached is the document entitled *Basis for the Recommendation for Control of Modafinil in Schedule IV of the Controlled Substances Act (CSA)*. NDA #20-717 sponsored by Cephalon, Inc. has a PDUFA due date of December 27, 1997. The sponsor has recommended that modafinil be scheduled in Schedule IV. That recommendation and other supporting documentation is attached.

After your review and concurrence of the attached scheduling document, please return signed document to Corinne Moody, HFD-170, **ASAP**. We will then forward the recommendation to the Office of Health Affairs for coordination with the Commissioner of Food and Drugs and the Director of the National Institute on Drug Abuse, per the 1985 MOU with NIDA. Their concurrence will then be transmitted to the Assistant Secretary for Health. The recommendation ultimately will be directed to the DEA, which has administrative responsibility for the CSA.

The sponsor is hopeful that this control action can move along expeditiously so that marketing of modafinil will not be delayed.

Addressees:

HFD-170/C. McCormick/C. Moody/B. Hayes/S. Calderon/ I. Cerny/ M. Klein
HFD-120/P. Leber/R. Katz/ M. Mallandrucco/B. Rapaport
ODEIII/P. Botstein/ B. Collier
ODEI/R. Temple
HFD-1/ J. Woodcock/ M. Lumpkin
HFY-1/ S. Nightingale/ N. Reuter

Non-Concur: _____

**BASIS FOR THE RECOMMENDATION
FOR CONTROL OF MODAFINIL IN SCHEDULE IV
OF THE CONTROLLED SUBSTANCES ACT (CSA)**

Modafinil is a new chemical entity and a central nervous system (CNS) stimulant that is being considered for approval by the Food and Drug Administration (FDA) under the trade name PROVIGIL[®] (NDA #20-717). The indication being proposed for modafinil is to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy. Chemically, the substance is 2-[(diphenylmethyl)-sulphonylacetamide], molecular formula C₁₅H₁₅NSO₂, with a molecular weight of 273. PROVIGIL[®] is a tablet containing 100 mg or 200 mg of modafinil. PROVIGIL[®] is sponsored by Cephalon, Inc. The drug has been marketed in France, though approvals are pending in Canada, Belgium, Denmark, Greece, Ireland, Italy, Netherlands, Portugal, Spain and the U.K.

Under 21 U.S.C. 811(f), the Secretary of the Department of Health and Human Services is required to forward information about the abuse potential of a drug for which a new drug application has been submitted to the Secretary, if such drug has a stimulant, depressant or hallucinogenic effect. Pursuant to 21 U.S.C. 811(b), the Secretary is required to consider in the scientific and medical evaluation eight factors determinative of control or removal of a drug or other substance from the schedules of the CSA. Following consideration of the eight factors, if it is appropriate, the Secretary must make three findings to recommend to schedule a substance in the CSA. The findings relate to a substance's abuse potential, legitimate medical use, and dependence liability.

Administrative responsibilities for evaluating a substance for control under the CSA are performed by the FDA, with the concurrence of the National Institute on Drug Abuse (NIDA), as described in the Memorandum of Understanding (MOU) of March 8, 1985 (50 FR 9518-20).

Accordingly, the FDA recommends that modafinil be controlled in Schedule IV of the CSA. Pursuant to 21 U.S.C. 811(c), the eight factors pertaining to scheduling the product are considered below:

1. Its actual or relative potential for abuse.

The following factors have been considered in the assessment of modafinil's abuse potential:

- i. In *in vitro* binding studies, modafinil was active at the dopamine reuptake site, and displayed some binding affinity for the dopamine receptors. Modafinil was approximately 100-fold less potent than cocaine in stimulating the release of ³H-dopamine.
- ii. Modafinil is reinforcing, as evidenced by its being shown to be self-administered by primates that were trained to self-administer cocaine. This behavioral response is a major preclinical indicator that a drug is likely to possess abuse potential and that it will produce psychological and/or physical dependence.
- iii. Modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other scheduled CNS stimulants.
- iv. Modafinil has a quick onset and short duration of action.
- v. As a CNS psychostimulant, its diversion from pharmacies, hospitals, and physicians' offices for purposes of abuse would be considered a likely prospect.
- vi. Although modafinil has not been studied in children, its use in the treatment of attention deficit disorder in children is possible. Its use for other off-label applications including as an aid in weight loss or performance enhancement are possible.
- vii. [REDACTED]

viii. Modafinil lacks water solubility and decomposes with heat, and therefore would not likely be abused by parenteral, intranasal, or inhalation routes, as are cocaine, methylphenidate, and

amphetamine.

ix. Relative potency differences between modafinil and other CNS psychostimulants are significant. Although in primates modafinil functioned as a positive reinforcer at doses 22- and 66-folds lower than the proposed therapeutic dose (400 mg/day; 6.67 mg/kg), it is considerably less potent than amphetamine and methylphenidate.

x. In preclinical drug discrimination studies, modafinil only partially discriminated to cocaine and d-amphetamine.

2. Scientific evidence of its pharmacological effect, if known.

PRECLINICAL PHARMACOLOGY. The precise biochemical mechanism by which modafinil elicits its wake-promoting effects has not been clearly defined. Available data indicate that modafinil does not act directly on any single neurotransmitter system, but rather, modafinil appears to indirectly affect dopaminergic, serotonergic and GABA systems, or a combination of these systems and requires an intact $\alpha 1$ -adrenergic system. The drug's effects on the dopaminergic system appear to be mediated by its ability to modulate GABAergic transmission. Using microdialysis in the nucleus accumbens, modafinil (30, 100 and 300 mg/kg, s.c.) dose-dependently increased the release of dopamine while decreasing the release of GABA in rats. Local infusion of the GABA_B antagonist phaclofen, the GABA_A agonist muscimol, and the GABA reuptake inhibitor SKF589976A decreased modafinil-induced release of dopamine from the nucleus accumbens. In contrast, the GABA_B agonist baclofen increased the modafinil-induced release of dopamine.

The affinity of modafinil for various receptors has been evaluated in the *Nova Screen*, an *in vitro* radiolabeled binding study screen. Results demonstrated that modafinil (0.1 mM) does not inhibit more than 37% of the binding to any of the panel of receptors tested. These included the following types of sites: adenosine, adrenergic, benzodiazepine, dopamine (non-selective), GABA_A and GABA_B, glutamate AMPA, kainate, NMDA, glycine site, and MK-801), strychnine-sensitive glycine, histamine (H1 and H2), muscarinic (non-selective, central and peripheral), nicotinic, 5-HT, sigma, opiate (non selective), ion channels (i.e., calcium channel, (L and N), chloride channel, potassium channel (ATP sensitive, voltage sensitive and insensitive)), NE, and 5-HT uptake/transporter, and second messengers systems (adenylate cyclase, inositol triphosphate and protein kinase C).

Modafinil (0.1mM) displayed some binding affinity for the dopamine receptors; and it showed 100% inhibition of dopamine uptake ($IC_{50} = 3.10\mu M$; $K_i = 1.93\mu M$). Modafinil also lacked affinity for the A₁ or A₂ adenosine receptors. Modafinil (0.001 - 10.0 μM) did not inhibit the binding of [³H]DPCPX (A₁ receptors) or [³H]CGS-21680 (A₂ receptors) to the adenosine receptors in whole brain membranes preparations (except cerebellum).

In a second set of studies, the affinity of modafinil for various uptake sites was evaluated. These studies included evaluation of norepinephrine (³H-desipramine in rat cortex), serotonin (³H-Citalopram) and dopamine (³H-mazindol in rat striatum and ³H-WIN in guinea pig striatum) uptake sites. Except for binding at the dopamine uptake site, binding inhibition was not obtained. In radioreceptor studies using ³H-mazindol, the affinity of modafinil for the dopamine uptake site was approximately five-fold lower than affinity of cocaine, 16-fold lower than d-amphetamine, 30- and 60-fold lower than the affinity showed by nomifensine and GBR-12909 [K_i (nM): 2,050 \pm 30, vs. 375 \pm 28 for cocaine; 132 for d-amphetamine; 68 \pm 10 for nomifensine and 24 \pm 5.6 for GBR 12909] (Table I).

Table I. Effect of Modafinil on Dopamine (DA), Serotonin (5-HT), and Norepinephrine (NE) Uptake.

COMPOUND	K _i (nM) INHIBITION OF ³ H-MAZINDOL BINDING	IC ₅₀ (nM) INHIBIT DA UPTAKE		IC ₅₀ (nM) INHIBIT DA UPTAKE
	Striatum	Striatum	Cortex	Cortex
GBR 12909	24	-	-	-
Nomifensine	68	89	47	24
d-Amphetamine	132 (K _H); 29,400 (K _L)	-	-	-
Cocaine	375	IC ₅₀ 5-Fold greater than nomifensine	-	-
Modafinil	2050	6,800	6,500	8,300
Modafinil acid	-	> 1,000,000	66,000	15,000
Modafinil sulfone	-	> 500,000	68,000	2,800

The ability of modafinil to affect the release of dopamine was examined in both mice and rat striatum. The effects of modafinil to stimulate the release of [³H]DA from mouse striatum was compared to that of d-amphetamine. In contrast to observations with d-amphetamine (10 μM), modafinil (10 μM) did not stimulate release of [³H]dopamine from the synaptosomes. In rat striatal slices preloaded with ³H-dopamine, the ability of modafinil (300 μM), cocaine (3-30 μM), d-amphetamine (3.0-30.0 μM), and nomifensine (30-300 μM) to increase spontaneous and electrically-evoked release of dopamine was evaluated. Under basal conditions, modafinil was less potent than nomifensine (10 and 30 μM) and cocaine (3 and 10 μM) in stimulating [³H]dopamine release. Using electrical stimulation to stimulate the release of [³H]dopamine from rat striatal slices, modafinil was less potent than nomifensine (10 and 30 μM) and cocaine (10 μM) in blocking the release of [³H]dopamine following electrical stimulation. Results from these studies indicated that modafinil was approximately 100-fold less potent than nomifensine or cocaine in stimulating the release of ³H-dopamine.

Although dopamine uptake inhibition or stimulation of dopamine release is believed to be an important property of most amphetamine-like stimulants, the implication of the low affinity shown by modafinil for dopamine uptake sites and the negligible affinity for other receptor systems in the psychopharmacological profile of modafinil is unknown. The hypothesis currently espoused regarding the mechanism of action of modafinil is that stimulation of α1 adrenergic sites are involved. This is based on the observation that the modafinil induced increase in motor activity in mice is antagonized by central α1-antagonists such as prazosin, but not by dopamine antagonists, although modafinil does not bind to α1-receptors *in vitro* at concentrations up to 10 μM, using [³H]-prazosin in canine cortical membranes.

Modafinil was studied preclinically for effects on arousal and locomotor activity. In rats, the effects of modafinil on wakefulness were compared to that of methamphetamine. Modafinil (30-300 mg/kg) promoted EEG-defined wakefulness in a dose-dependent manner. Modafinil was less potent than methamphetamine in inducing a state of wakefulness; a dose of 300 mg/kg of modafinil was equipotent to 1.0 mg/kg of methamphetamine. In contrast to methamphetamine, modafinil did not produce an increased drive for compensatory sleep (i.e., NREM). In another study, the effects of modafinil (64 and 128.0 mg/kg, i.p.) and d-amphetamine (2.5 and 5.0 mg/kg i.p.) on sleep/waves

cycles (duration), slow wave sleep (SWS), paradoxical sleep (PS) and wakefulness were evaluated in Sprague Dawley rats (Touret *et al.*, 1995). Both modafinil and d-amphetamine dose-dependently increased wakefulness; modafinil was approximately 51-times less potent than d-amphetamine. Similar effects were seen with 128 mg/kg modafinil and 2.5 mg/kg amphetamine. d-Amphetamine wakefulness was followed by recovery of lost PS rebound on the day of administration, whereas modafinil did not produce this effect. In contrast to d-amphetamine, modafinil did not affect the sleep patterns of the rats one day post-treatment. In modafinil-treated rats, sleep pattern on post-injection day was similar to that of controls, while that of d-amphetamine-treated rats was modified.

The effects of modafinil on arousal were also evaluated in sleep deprived rats. Results from this study demonstrated that modafinil was effective in reducing preexisting sleep deficit brought on by forced wakefulness and the accumulation of additional REM sleep debt incurred during sleep deprivation. When modafinil (100 and 300 mg/kg) was administered to rats deprived of sleep for six hours, modafinil prolonged EEG-defined wakefulness without increasing NREM sleep or the desire to recover lost NREM. At a dose of 300 mg/kg, the amount of lost NREM and REM recovered after the extended period of sleep deprivation was reduced by modafinil. Modafinil at a dose of 300 mg/kg did not alter levels of sleep, wakefulness, or locomotor activity two days post-treatment.

In another rat study, effects of modafinil on sleep/wake cycles were examined in anesthetized rats. Modafinil (32.0 to 250 mg/kg) increased the duration of wakefulness and the latency to the first appearance of REM sleep in a dose-dependent manner. The SWS was also decreased in a dose-dependent manner. Modafinil (64 and 128 mg/kg) and d-amphetamine (2.5 and 5.0 mg/kg) produced similar results on recovery of paradoxical sleep in rats implanted with electrodes. Modafinil and d-amphetamine each caused a dose-dependent increase in wakefulness. In contrast to d-amphetamine, the wakefulness induced by modafinil was not followed by recovery of lost paradoxical sleep.

Effects of modafinil on sleep and wakefulness were examined in two standard dog models. In the English bulldog model of hypersomnolence, the effects of modafinil (10.0 mg/kg, i.v.) on sleep [parameters measured included total sleep time; sleep latency (total minutes till onset of NREM); sleep disordered breathing index] and wakefulness were evaluated. Modafinil significantly ($p < 0.005$) produced marked wakefulness and increased sleep latency (346 ± 105 min for modafinil vs 71 ± 40 min. for vehicle control). In the dobermans narcoleptic model, the effects of modafinil (0.125-10.0 mg/kg, i.v.) and d-amphetamine (2.5-200.0 μ g/kg, i.v.) on cataleptic sleep locomotor activity, and cardiovascular parameters were examined. Modafinil at a dose of 10.0 mg/kg and d-amphetamine 200 μ g/kg showed equal efficacy in increasing wakefulness and decreasing sleep in both the normal and narcoleptic dogs. Unlike d-amphetamine, modafinil significantly reduced REM in both normal and narcoleptic dogs. Modafinil, up to 10 mg/kg, had no effects on suppressing or decreasing cataplexy.

REINFORCING EFFICACY. The ability of modafinil to function as a positive reinforcer was evaluated in primates. Using the standard self-administration paradigm, the reinforcing efficacy of modafinil was evaluated in four rhesus monkeys that were trained to self-administer cocaine (0.02 mg/kg/infusion in one monkey; 0.05 mg/kg/infusion in three monkeys) under a fixed-ratio 10 schedule of drug delivery. Using the standard substitution procedure, vehicle (ethanol-emulphor), saline, modafinil (0.03, 0.1, and 0.3 mg/kg/injection), d-amphetamine (0.01 or 0.03 mg/kg/injection), and l-ephedrine (0.1 mg/kg/infusion) were substituted for cocaine. Once stable responding was obtained, test drugs were substituted for four consecutive days. Between substitutions, the monkeys were returned to cocaine baseline conditions for at least three sessions.

Modafinil functioned as a positive reinforcer at doses that were 22- and 66-folds lower than the proposed therapeutic dose (400 mg/day; 6.67 mg/kg). In all monkeys, at least one dose of modafinil maintained number of infusions above the range of infusions obtained for saline and vehicle. Modafinil at a dose of 0.3 mg/kg/injection was self-administered by all four monkeys; and 0.1 mg/kg/infusion

modafinil was self-administered by two monkeys. These doses of modafinil were self-administered at rates equal to or greater than the rates of baseline cocaine infusions. Generally, as the dose of modafinil was increased, the number of infusions obtained first increased and then decreased for the monkeys self-administering modafinil, resulting in an inverted U-shaped function relating infusion number to dose. As the dose per infusion was increased, intake (mg/kg/1-hr session) of modafinil increased; the mean intake of modafinil for all four monkeys ranged from 0.4 mg/kg to 34.7 mg/kg at the 0.03 mg/kg/infusion and 0.3 mg/kg/infusion, respectively.

The pattern of responding maintained by modafinil differed from that observed with cocaine. Analysis of the within session time course of cocaine infusions under baseline conditions revealed that in three of four monkeys, the greatest number of infusions occurred during the first quarter of the session. The fourth monkey maintained responding for cocaine at a similar rate throughout the entire session. In contrast, when modafinil (0.1 and 0.3 mg/kg/injection) was available, in some monkeys the rate of self-administration was the greatest in the first 2 quarters of the session; whereas in some monkeys it was distributed fairly evenly throughout the entire one hour session.

As a positive test, d-amphetamine and l-ephedrine were substituted for cocaine in three monkeys. Results clearly showed that both d-amphetamine and l-ephedrine maintained rates of responding higher than that of saline; that is, they were positive reinforcers. In all three monkeys, the mean number of d-amphetamine and l-ephedrine infusions were comparable to the cocaine baseline.

To assess the role of the adrenergic system in the reinforcing effects of modafinil, an antagonism test with prazosin was conducted. Prazosin (0.1 mg/kg) was administered intravenously 15 minutes prior to the self-administration substitution session with modafinil (0.05 and 0.3 mg/kg/injection) or vehicle (1:1 ethanol:emulphor). Prazosin had no significant effect on modafinil maintained behavior.

DISCRIMINATIVE STIMULUS PROPERTIES. Drug discrimination studies are routinely used to demonstrate whether or not a new drug is recognized as being pharmacologically equivalent to known drugs of abuse. In animals, if a new drug exhibits similar stimulus properties to known drug of abuse, there is a strong possibility that the new drug would be similarly abused by humans. The stimulus properties of modafinil were evaluated in rats trained to discriminate cocaine from saline and in another group of rats trained to discriminate amphetamine from saline.

The discriminative stimulus properties of modafinil were evaluated in rats trained to discriminate cocaine (10 mg/kg, ip) from saline in a two-lever operant procedure under a fixed-ratio (FR) 32 schedule of reinforcement during daily 30-minute sessions. After criterion was established, substitution tests were conducted. On substitution test sessions, doses of modafinil (3.0-250 mg/kg; 30 minutes pretreatment time), d-amphetamine (0.1-3.0 mg/kg, 10 minutes pretreatment time), or l-ephedrine (3.0 - 30.0 mg/kg, 10 minutes pretreatment time) were administered prior to the behavioral session. To assess the role of the adrenergic system in the discriminative stimulus effects of modafinil, an antagonist test session with prazosin was conducted after the substitution test sessions were completed, in a similar manner as described above. During the antagonism test, prazosin (0.3 mg/kg) alone or prazosin (0.3 mg/kg) 10 minutes prior to 250 mg/kg of modafinil was evaluated. The behavioral session was conducted 30 minutes after the subjects received the modafinil injection and 40 minutes after receiving prazosin only. Both d-amphetamine and l-ephedrine dose-dependently substituted for the stimulus cue of cocaine. The highest dose of d-amphetamine tested elicited 100% cocaine-lever responding; whereas the highest dose of l-ephedrine tested only elicited approximately 80% cocaine-appropriate responding and this was associated with marked behavioral disruption (i.e., a substantial decrease in rate of responding).

Following modafinil (3-100 mg/kg) substitution for cocaine, subjects responded exclusively on the saline lever. However, cocaine-appropriate responding was observed when 150 and 250 mg/kg of modafinil was tested. Modafinil (150 mg/kg) only substituted for cocaine in one out of six rats tested;

four of six rats elicited cocaine-lever responding at a dose of 250 mg/kg. However, this high dose tested also reduced rates of responding by 59% as compared to control response rate.

In the antagonism test, prazosin (0.3 mg/kg) was studied alone and in combination with modafinil (250 mg/kg). Prazosin alone elicited exclusively saline-appropriate responding. When prazosin was administered 10 minutes prior to modafinil, prazosin failed to attenuate either the cocaine-like discriminative stimulus effects or the response rate effects of this dose of modafinil.

The discriminative stimulus properties of modafinil were evaluated in rats trained to discriminate d-amphetamine (1.0 mg/kg, ip) from saline in a two-lever operant procedure under a FR 32 schedule of reinforcement during daily 30-minute sessions. After criterion was established, substitution tests were conducted. Substitution test sessions were conducted with modafinil (10.0, 30.0, 100.0, and 250.0 mg/kg), and d-amphetamine (0.1, 0.3, 1.0 and 3.0 mg/kg). d-Amphetamine dose-dependently substituted for the training dose (1.0 mg/kg) of d-amphetamine. Only saline-appropriate responding was observed when 10, 30, and 100.0 mg/kg of modafinil was substituted for d-amphetamine. Partial amphetamine-appropriate responding was elicited by 250.0 mg/kg of modafinil; only 51.4% d-amphetamine-lever responding was measured. However, a substantial decrease in rates of responding was observed and one rat died within 5 hours of modafinil administration.

CLINICAL TRIALS. Modafinil has been studied in adult (17-65 yrs) patient populations, for use in treatment of narcolepsy in a dosage of 200-400 mg/day. No study has been specifically designed to evaluate the metabolism, safety, or efficacy of modafinil in geriatric or pediatric patients with narcolepsy.

Safety and efficacy were assessed in two 9-week placebo-controlled, double-blind, randomized, parallel-group studies of safety and efficacy of 200 mg and 400 mg of oral modafinil in patients with narcolepsy followed by a 40-week, open-label, flexible-dose continuation study with and without a 2-week discontinuation segment between the blinded and open label parts of the study. The protocol called for three groups of 95 patients each to be randomly assigned to one of three treatment arms. Eligible patients received a specified number of tablets to be taken daily for 9 consecutive weeks. Of 285 patients randomized, 283 (99%) received study medication and were considered to be evaluable for the safety analyses. Two patients were not evaluable. One 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 drug supply was returned 12 tablets were missing. The database did not include study medication of AE data (other than a note stating patient did not have any AE's) (0.35% possible drug abuse in clinical trial). The other patient was discontinued when the investigator determined that the patient did not meet inclusion criteria. Fourteen patients (15%) in the modafinil 400 mg group discontinued study compared to 3 patients (3%) in the modafinil 200 mg group and 5 patients (5%) in the placebo treatment group. Eleven of 14 patients who discontinued from 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 because of AE's. During the study, the blind for Patient 1403 was broken by the investigator because of concerns that the patient had taken another stimulant.

EFFICACY SUMMARY. For the majority of study sites (12/18), the mean sleep latencies were higher in both modafinil treatment groups (200 mg, 400 mg) compared to the placebo group. Patients in the modafinil 400 mg treatment group were able to stay awake for a significantly longer time and had greater clinical improvement. Patients in the modafinil 400 mg and 200 mg treatment groups were able to stay awake significantly longer as measured by all parameters when compared to patients in the placebo treatment group.

Patients were asked to provide subjective responses by estimating how long they were able to stay awake at the end of each test period. 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 ($p < 0.050$). Patients in both active treatment groups had significantly greater improvement than patients in the placebo group at each visit. Patients in the modafinil 400 mg treatment group had significantly greater improvement than patients in the modafinil 200 mg treatment group only at Weeks 3 and 6. No significant differences were found between the two active treatment arms. 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". None was reported statistically.

Discontinuation evaluations at the end of Weeks 10 and 11 include recording of concomitant medications and AE's. Effect of modafinil treatment was assessed by analyzing change from Week 9 to 11 within modafinil dose groups, and by comparing modafinil/placebo patients to placebo/ placebo patients at Week 11.

Of the 273 patients randomized, 271 (99%) received medication and were evaluable for safety analyses. Two patients were not evaluable for safety or efficacy analyses. Two patients had positive urine drug screens and returned all study medications unopened. Approximately 50% of the patients in each treatment arm reported light to moderate use of caffeine. Half in each treatment group reported light to moderate alcohol use.

Patients in modafinil 400 mg treatment group were able to stay awake for a significantly longer time at endpoint compared to patients in the placebo treatment group. More patients in the Modafinil 400 mg treatment group had clinical improvement in symptoms when compared to patients on placebo. Patients in the modafinil 400 and modafinil 200 treatment groups could stay awake significantly longer, except as measured by REM Sleep Latency, as compared to patients on placebo. 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 & 9, and at Endpoint ($p < 0.001$).

On average, patients in the modafinil 400 group exhibited lower Total Sleep Time (8.11 minutes) than patients on placebo (9.92 minutes) at Endpoint. Patients in the modafinil 200 group exhibited lower Total Sleep Time (7.88 minutes) than either high dose or placebo patients.

PATIENT SUBJECTIVE EVALUATION OF SLEEP LATENCY. Patients in both active treatment groups had significantly greater improvement than patients on placebo at each visit. A greater percentage of patients treated with modafinil 100 mg showed improvement (64%) compared to patients in the placebo group (36%) at Week 1 ($p < 0.001$). Other clinical trials demonstrated a comparative decrease in excessive daytime somnolence by 80% for modafinil 400 mg, 66% on modafinil 200 mg and 34% for subjects on placebo.

DEATHS, DRUG OVERDOSES, ADVERSE EVENTS. Five deaths were reported in the clinical studies by modafinil-treated subjects. Causes of death were primarily "asthenia" or "myocardial infarction" (Table II).