

Summary & Conclusions For the Carcinogenicity Studies:

The potential carcinogenicity of modafinil was examined in 2 life-time bioassays one each in mice and rats. The drug was administered as an admixture in the diet for 78wks in the mouse and 104wks in the rat at 6, 30, and 60mg/kg/d doses for both studies. Basis for selection of these doses were 13wk dietary tox studies. From both the rat and mouse studies, it is the opinion of the reviewer that the MTD was not reached. One of the reasons for this, is perhaps auto-induction of modafinil metabolism leading to below-adequate exposure levels. This enzyme induction was prominent with repeated dosing and has been observed in previous tox studies. The inadequate blood levels may have accounted for the minimal drug related effects in these 2 carcinogenicity studies. There was no drug related deaths (in mice and female rats), minimal clinical signs, no effect on food intake, hematology, clinical chemistry, or gross morphology. A sig decr was observed in mean wt of HDm rats (6.5% of cont) on wk80 and mean wt gain (47% of cont) wks 52-80. Mean wt gain was also reduced in MD&HDf rats (26% of cont in each gr) on wks 52-80. However, by the end of the study, mean wts and wt gains were comparable between all drug grs and the cont. There were no drug effects on B.wt or wt gain in mice. A sig and dose-dependent incr was observed in absol and rel wt of the liver in mice and histopath showed hypertrophy without necrosis. A slightly higher incidence of deaths noted in male rats due to increase in CPN. This is a common finding in aged rats usually males but the sponsor indicated that this finding was higher than the historical data and is therefore, drug related. It seems that many of the other lesions were secondary to CPN and not directly drug related. In both the rat and mouse studies, the type of neoplastic lesions were those common in aged animals (spontaneous) and the incidence was similar between cont and drug grs. Based on these results, it is the opinion of the reviewer that a conclusion can not be on the potential tumorigenicity of modafinil in rodents at this time. *reached*

Modafinil plasma levels were measured in these 2 carcinogenicity studies. Technical difficulties and small volume and other problems (see above) led to limited information. Mean plasma levels in mice measured only on wk4 were 102-402ng/ml in males and 23-205ng/ml in female mice and those in male rats 11-171ng/ml and in female rats 30-180ng/ml measured on wks 13, 52, 104. These values represent 0.002-0.04x in mice and 0.001-0.02x in rats, the maximum mean steady state conc of 11ug/ml reached in humans following 400mg dose.

The sponsor recently (Apr 1996) submitted a 3mo tox and TK study in mice to further assess the MTD selection for the carcinogenicity study. This study is reviewed and the reviewer concluded contrary to the sponsor's conclusion, that an MTD was not reached. This is mainly based on lack of adequate exposure due to enzyme induction of modafinil metabolism with repeated administration.

In the attached appendix is all the correspondence between the Division and the Sponsor regarding the adequacy of the carcinogenicity data, arranged in chronological order.

APPEARS THIS WAY ON ORIGINAL

cc.

/Div File/Orig IND# [REDACTED]
/G. Fitzgerald/A. Atrakchi/S. Hardeman

Amendment# 081

IND# [REDACTED]

IND# [REDACTED]
 Drug: Modafinil (Provigil)/CEP1538
 Sponsor: Cephalon, Inc.,
 W. Chester, PA 19380
 Indication: Narcolepsy
 Category: Unknown mechanism, perhaps an $\alpha 1$ agonist
 Sub Date: Mar 31 97
 Rec Date: Apr 3rd 97
 Rev Date: Apr 24 97
 Reviewer: Aisar Atrakchi, Ph.D.
 Team Leader: Glenna Fitzgerald, Ph.D.
 Related IND/NDAs: N20-717

The sponsor conducted an in vitro Morphological Transformation of BALB/3T3 mouse embryo cells to supplement the life-time mouse bioassay.

This assay (GLP) was initiated in June 1996 and completed in Oct 96 at [REDACTED]

A preliminary cytotox assay was conducted at drug conc between 2-2000ug/ml plus vehicle cont (DMSO) and incubated for 3d in -S9 and 4hr in +S9. Following exposure period, cells were washed and prepared; 10d after treatment, cytotox plates were fixed, stained with Giemsa, and scored for colony formation. The high conc for the main assay was selected to give about 20% survival; 3 other conc were also tested. Cytotox was assessed by cloning efficiency and rel CE. The main transformation assay followed standard procedures (Kakunaga, 1973; Heidelberger et al., 1983). The conc tested in the initial assay in -S9 were 150, 300, 600, and 1200ug/ml and those in +S9 were 400, 800, 1200, and 1600ug/ml; a suspension (precipitate) was formed at 1200 and 1600ug/ml. In -S9 in the initial assay solubility hindered the use of conc >600ug/ml and also high toxicity was seen, a repeate cytotox assay conducted concurrently with the main assay, tested the following conc: 38, 75, 150, and 300ug/ml. The positive cont in -S9 was MNNG and dimethylnitrosamine in +S9. Transformed foci were spindle-shaped cells with dense, multilayered, basophilic in staining, random orientation, and invaded the monolayer. The results were expressed as dishes with transformed foci/total dishes, total transformed foci/total dishes, and transformation frequency (# of transformed foci per surviving cell). A positive response is the one where transformation frequency is sig incr over the negative cont in a dose-response pattern (2 consecutive doses) including the HD. A sig incr at the HD only was considered equivocal. Any deviation from these qualifications will produce a neg response. A valid assay is that where the CE of the solvent cont is $\geq 25\%$, the no. of transformed foci will not exceed 3 foci/total (12-15) replicate dishes, and the positive cont should produce its expected incr in no. of foci.

Results:

The rel survival in the initial cytotox assay in -S9 ranged from 0-94% and in +S9 from 6-106%. In the repeate assay, the rel survival in -S9 was 38-87% and in +S9 28-100% (38-300ug/ml conc). In the main assay, modafinil did not produce any transformed foci upto 150ug/ml in -S9 and only 1 foci out of 15 dishes (transformation frequency 0.3 vs. <0.13 in cont) at 300ug/ml. This was not statistically sig from the solvent cont and within the historical data (provided in a table). In +S9, modafinil did induce any foci upto 1600ug/ml. The positive controls produced the expected positive responses. It was concluded that modafinil in this in vitro assay and concentrations did not induce a statistically sig incr in the transformed cells in - or + S9.

cc.

/Div File/Orig IND# [REDACTED]
 /Fitzgerald/S. Hardeman/A. Atrakchi

NDA #20-717
Amendment

Drug: Modafinil
Indication: Narcolepsy
Sponsor: Cephalon, Inc.,
West Chester, PA 344-0065
Corrsp Date: Jul 18 97
Rec Date: Jul 18 97
Rev Date: Jul 31 97 /S/ [REDACTED]
Reviewer: Aisar H. Atrakchi, Ph.D. [REDACTED]
Team Leader: Glenna Fitzgerald, Ph.D.
Related IND/NDA(s): I [REDACTED]

Background:

Apparently, this is an additional study in rats for the abuse potential of modafinil. Two studies, one in rat and another in Rhesus monkey, were submitted with the original IND (Jun 30, 1993). These 2 previous studies showed that modafinil was a re-inforcer for drug discrimination in monkeys (dose-dependent response at 0.03, 0.1, and 0.3mg/kg), and substituted for cocaine in drug discrimination tests in rats (≥ 150 mg/kg).

Submitted Study:**Amphetamine-like Effects of Modafinil in Rats:**

This study was done by [REDACTED] at the [REDACTED] and submitted to [REDACTED] in Jan 1996. This study is similar in design to the previously conducted rat study: rats trained to press lever for food reinforcement under a fixed ratio 32 schedule during the daily 30min sessions. During training, d-amphetamine (1mg/kg) or saline were administered as controls to ensure that the rats were well trained in drug discrimination test. They were dosed before the modafinil and amphetamine dose-response effects were done. Modafinil was tested at 10, 30, 100, and 250mg/kg and amphetamine at 0.1, 0.3, 1.0, and 3mg/kg.

Modafinil at the highest dose of 250mg/kg, caused partial substitution in rats trained to discriminate d-amphetamine from saline. However, the sponsor indicated that this dose was toxic since 1 rat died within 5hr of dosing and others exhibited low response rates at ≥ 24 hr postdose. At ≥ 100 mg/kg no amphetamine-like effects were seen. This conclusion is similar to that mentioned and reviewed previously where modafinil substituted for cocaine at ≥ 150 mg/kg in discrimination tests. Overall, it seems that modafinil re-inforces and substitute for drugs of abuse at doses ≥ 150 mg/kg in rats & monkeys.

cc.

/Div File/Orig NDA# 20-717
/G. Fitzgerald/A. Atrakchi/M. Malandruccho

/S/ [REDACTED] 7/31/97

Modafinil
NDA# 20-717
Cephalon Inc.,

Sep 15 1997 Submission of additional data regarding the carcinogenicity potential of modafinil in mice.

Rev Date: Sep 17 1997

This submission contained:

1. A protocol and results of dermal penetration study,
2. Proposed protocol for a 26wk dermal study of modafinil in TG.AC transgenic mice and,
3. Proposed protocol for 104wk mouse gavage car study in mice.

Also mentioned by the sponsor, an ongoing oral dose-range finding study in FVB-N mice that has been extended to 13wks.

1. Dermal penetration study in FVB-N mice:

The FVB-N is the parent strain of TG.AC it is used here perhaps for economic reasons (less costly than the TG.AC altered variant) and other reasons not mentioned in the protocol. This was a pilot study therefore, non GLP.

Methods:

For the purpose of comparison, an oral dose was also studied. Modafinil was prepared in DMSO at nominal conc of 18&108mg/ml for the dermal application (100ul) and, in [REDACTED] (oral suspending vehicle also used in the CD-1 and OF-1 mice TK study previously submitted & reviewed), at nominal conc of 36mg/ml for the oral gavage (10ml/kg vol administered).

There were 6/sex/dose, for the dermal study, each mouse had 1x2cm of their intrascapular skin region clipped free of hair 24hr pre-application. Doses for the dermal study were 60 & 360mg/kg (note that 60mg/kg was the highest dose used in the 78wk mouse car study), and 360mg/kg for the p.o. study. These doses were applied/administered once and blood collected after 1&4hr postdosing from 2-3/sex/dose. Modafinil, modafinil acid (MA), and modafinil sulfone (MS), 2 major metabolites of modafinil, were measured using [REDACTED]

Results:

Modafinil plasma level following single dermal application incr with dose following 1&4hr measurements but the incr was non-linear (table below from the sponsor); same findings were obtained for the 2 main metabolites. Levels for modafinil and MA clearly declined after 4hr of application rel to the 1hr level, however, level of MS were generally higher for both sexes. Comparison of the same dose of 360mg/kg following dermal & oral dosing at 1hr postdose, showed that modafinil plasma levels after dermal application were 21-26% lower than those after p.o.; the same findings for the MA&MS. The mean plasma level of modafinil after single p.o. dose of 360mg/kg was 105ug/ml which is comparable to those reported earlier in the TK mouse

Pilot Dermal study (Cont.)

study at 38ug/ml after 120mg/kg (C_{1hr} analysis) in CD-1 & OF-1 mice. The same is true for the 2 main metabolites, MA & MS.

Table 1: Mean (Standard Deviation) plasma concentrations of modafinil and metabolites 1 and 4 hours after a single dermal application and 1 hour post oral administration

Route and Dose	Modafinil (µg/mL)	Modafinil Acid (µg/mL)	Modafinil Sulfone (µg/mL)	Modafinil (µg/mL)	Modafinil Acid (µg/mL)	Modafinil Sulfone (µg/mL)
Dermal	1-hour post-application			4-hour post-application		
60 mg/kg						
Male	13.30 (2.73)	0.79 (0.19)	0.53 (0.12)	3.57 (1.80)	0.34*	0.81 (0.26)
Female	14.33 (7.58)	1.04 (0.36)	0.96 (0.64)	0.93 (n=2)	BQL (n=2)	0.54 (n=2)
360 mg/kg						
Male	60.78 (12.05)	2.99 (0.44)	2.94 (1.02)	37.03 (7.06)	2.52 (0.43)	9.15 (2.10)
Female	51.84 (10.43)	3.41 (0.53)	4.47 (1.86)	38.76 (7.22)	2.94 (0.55)	21.33 (2.50)
Oral						
360 mg/kg						
Male	105.06 (16.67)	4.73 (0.37)	19.42 (3.01)	ND	ND	ND

*- Plasma level of one male that had detectable levels of modafinil acid; two males had levels that were below detectable limits
 ND= Not Determined
 BQL= Below quantification limit (< 0.200 µg/mL)

A 4wk dermal range finding in FVB-N mice is planned to assess systemic exposure following repeat application and to select the proper doses for the 26wk dermal car study in TG.AC mice. The reviewer believes this is the same as the ongoing dose range finding that has been extended to 13wks.

APPEARS THIS WAY ON ORIGINAL

Summary & Conclusions:

Single dermal application of modafinil (in DMSO) at 60&360mg/kg to FVB-N mice showed a reasonable systemic exposure to modafinil and its 2 main metabolites, the acid and the sulfone. A concurrent administration of a single gavage dose of 360mg/kg was done for comparison to plasma levels after dermal application and to levels previously measured in a 13wk TK study in CD-1 & OF-1 mice. Modafinil and its metabolite levels were comparable in these studies, but levels were lower after the dermal application.

It can be concluded that single dermal application of modafinil provided reasonable plasma drug levels indicating that the drug readily penetrates the skin and reaches the systemic circulation. Systemic exposure need to be determined following repeat dermal application and the sponsor plans to do so in the near future or the study is ongoing.

2. Proposed protocol for a 26wk dermal study of modafinil in TG.AC transgenic mice:
 [REDACTED] will be the performing lab. The protocol seems to adequately address all the standard parameters in a sub-chronic tox study except for few items (see below). TG.AC mice will be purchased from [REDACTED] at 7-10wks old and will be acclimated for about 2wks. There will be 20mice/sex/dose, using 3 doses (drug prepared in 10% isopropyl alcohol), a control, and a positive cont (TPA 2.5ug, 3X/wk, this cpd will be dissolved in acetone). The doses will be selected based on a 4wk dermal dose-range finding study in the parent strain DVB-N and the Agency's concurrence will be requested.

Comments/Recommendations to the Sponsor:

1. It is recommended that plasma drug levels be measured at 2 time points during the study: perhaps at 2wks and end of study. To do this, it is recommended that additional mice/satellite (both sexes) be included for the TK analysis.
2. Summary table for mean wt changes should be included.
3. Under organ wts, what was the basis for selecting these 5 organs to weigh and not others or more or less?
4. Under histopath, it is unclear whether all tissues will be examined; please clarify.
5. it is unclear what will the negative cont be, is it the vehicle which in this case is 10% isopropyl alcohol or untreated mice.

3. Protocol for 104wk mouse gavage car study in mice
 [REDACTED] will be the performing lab. CD-1 mice will be purchased from [REDACTED], at 6wks old (not more than 8wks), weighs 15-35g, and will be acclimated for about 1wk. There will be 50mice/sex/dose, administered 3 doses and a cont gr.

Comments/Recommendations to the Sponsor:

1. It is recommended that plasma drug levels be measured at 2 wks, 12 & 24months of the study. To do this, it is recommended that additional mice/satellite (both sexes) be included for the TK analysis. The reason for the 2wk, is that modafinil causes autoinduction therefore, an early time point is advisable.
2. Summary table for mean wt changes should be included.

Protocol for the 2yr car study (Cont.)

3. Organ wts should be measured.

4. Histopath from cont and high dose only will be examined as stated in the protocol. Although, it is recommended that histopath done on all drug grs and the cont, however, based on the low tox profile of this drug, it may be acceptable to microscopically examine only the cont and high dose grs and any mouse that died in moribund state, or due to unscheduled death.

cc.

/Div File/NDA# 20-717

/G. Fitzgerald/A. Atrakchi/S. Hardeman

/S/

/S/

APPEARS THIS WAY ON ORIGINAL

COMPLETED AUG 5 1997

Statistical Review and Evaluation

Review of Carcinogenicity Data

AUG 5 1997

DATE:

NDA#: 20-717

APPLICANT: Cephalon, Inc.

NAME OF DRUG: PROVIGIL (modafinil) Tablets

DOCUMENTS REVIEWED: Volumes 8-14 and 17-20 of 33 Containing Data, Results, and Study Reports of the Mouse and Rat Studies, and One Volume Dated 08/07/96 Containing the Data Layout and Diskettes for these Studies.

APPEARS THIS WAY ON ORIGINAL

I. Background

Dr. Aisar Atrakchi (HFD-120) requested from the Division of Biometrics I a statistical review of the rat and mouse studies data as well as an evaluation of the sponsor's findings.

II. The Rat Study

II.a. Design

The drug was studied via dietary administration in Sprague-Dawley rats for 104 weeks with 50 animals per group. There were two control groups receiving the diet only and three treated groups per sex receiving the drug at 6, 30, and 60 mg/kg/day. Diet and water were available ad lib. The liver, kidneys, lungs and gross lesions were examined for all animals of both sexes, the testes, aorta, stomach, and parathyroids for all male animals. For the remaining tissues full histopathological examination was performed only on all control and all high dose animals and on the animals of the low and mid doses which were found dead or killed in extremis.

There were an additional 20 animals per group which were sacrificed at week 52 as part of a toxicity study. The findings of these animals are not part of the evaluation of the tumorigenic potential of modafinil.

II.b. Sponsor's Analyses of the Rat Study

Survival Analysis

The sponsor used Kaplan-Meier survival probability estimates and log-rank tests for group comparisons in survival. High dose males had a slightly higher overall mortality than controls or other treated males with a statistically significant positive trend ($p < .05$). Among the females the mortality experience of the treated animals was comparable.

Tumor Data Analysis

The sponsor performed statistical analyses for selected lesions at the request of the pathologist. For fatal or non-fatal tumors Peto's methods were employed. When all lesions occurred during terminal sacrifice the Cochran-Armitage dose-response test and Fisher-Irwin Exact test with Bonferroni adjustment for pairwise comparisons were used. The sponsor stated that there was no evidence of a treatment-related difference in the incidence, type or distribution of neoplastic lesions.

II.c. Reviewer's Analyses

Survival Analysis

The survival experience of the male rats showed a statistically significant trend at $p=.05$ when using an approximate test for unadjusted positive trend. The probabilities associated with the adjusted Cox test or the generalized Kruskal-Wallis test were not significant. Similarly, the unadjusted comparison between combined controls and the high dose was significant at $p<.03$ but the corresponding Cox or Kruskal-Wallis tests did not reach statistical significance. The mortality experience of the female rats did not display a significant positive trend nor did any pairwise comparisons reach statistical significance (Figures 1 and 2, Table 1).

Tumor Data Analysis

In the analysis of tumor data this reviewer uses the methods described in the paper of Peto et al. (Guidelines for simple sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International Agency for Research against Cancer Monographs, Annex to Supplement, WHO, Geneva, 311-426, 1980) and the method of the exact permutation trend test developed by the Division of Biometrics. The following criteria for the levels of significance ensure a false positive rate of about ten percent for the trend tests of the usual two-species two-sexes studies: Tumors with less than 1.00% occurrence in the control group are considered rare and a positive trend test is statistically significant when it reaches a p-value of $\leq .025$ (one-sided). Higher tumor occurrences in the control group are considered common for these animals and a positive trend is statistically significant when its p-value is less than .005 (one-sided). An approximate permutation trend test is used when fatal and incidental tumors of the same kind are combined and have overlapping time intervals. All tests are survival adjusted and treatment groups are weighted by the actual dose levels. For tissues where not all dose groups were fully necropsied only pairwise comparisons between the high and control groups were performed. The significance criteria for pairwise comparisons are $\alpha \leq .05$ for rare tumors and $\alpha \leq .01$ for common tumors.

In this study all tumors were classified not as fatal and incidental but only as 'undetermined'. It is therefore impossible to do the proper statistical analysis. This reviewer chose to analyze any possible increase in tumor incidence rates with the prevalence method, i.e. the tumors were treated as incidental.

With the exception of liver, kidneys, lungs, and gross lesions in either sex, and the testes, aorta, stomach and parathyroids in the males, the tissues of the terminally sacrificed low and mid dose animals were not examined histopathologically. Therefore, for these tissues a trend test can be performed, for other tissues a pairwise comparison between high dose and combined controls will be performed. There were no trends or pairwise comparisons for either the male or female animals which passed the criteria for statistical significance.

II.d. Validity of the Rat Study

As there are no statistically significant tumor trends among either the male or the female rats, this reviewer evaluated the validity of the study. For this, two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

- (i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?
- (ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following are some rules of thumb as suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol 5, pp 66-78, 1985) had found that on the average, approximately 50 % of the animals in the high dose group survived the two-year study. In a personal communication with Dr. Karl Lin of HFD-715, he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered as a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50 % survival at one year". From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

- (i) "A dose is considered adequate if there is a detectable weight loss of up to 10 % in a dosed group relative to the controls."
- (ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- (iii) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

In another paper, Bart, Chu, and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is a

indication that the treatment has been tested on levels at or approaching the MTD."

Survival at terminal sacrifice ranged from 46 (High dose) - 66 percent for the male rats and from 56-60 percent for the female rats, satisfying the requirement of a sufficient number of animals being exposed for a sufficient length of time to manifest late developing tumors. The body weight gains data showed that the high dose animals gained somewhat less than did their respective controls. The following tables give the mean weight gains, the mean body weights, and their differentials at weeks 52 and 104:

Mean Body Weight Gains

MALES				FEMALES			
Weeks 0- 52*	Controls 493.2 g	High 474.7 g	Difference -18.50 g (3.8 %)	Weeks 0- 52	Controls 270.0 g	High 256.7 g	Difference -13.3 g (4.9 %)
Weeks 0- 104*	Controls 460.2 g	High 412.9 g	Difference -47.3 g (10.3%)	Weeks 0- 104	Controls 371.8 g	High 334.2 g	Difference -37.6 g (10.1 %)

* The results for 0-52 and 0-104 weeks are approximates as they are composites of weight gains for 0-13, 13-26, 26-52, 52-80, and 80-104 weeks.

Mean Body Weights

MALES				FEMALES			
Week	Controls	High	% Controls	Week	Controls	High	% Controls
0	176.6	175.7	99.5	0	136.2	135.1	99.2
52	667.6	650.3	97.4	52	405.6	393.0	96.9
104	627.3	600.3	95.7	104	487.2	450.4	92.4

The survival experience of the high dose male rats was somewhat lower than that of the controls indicating with the other criteria that the high dose was close to the MTD for these animals. The survival experience of high dose female rats was similar across all groups and does not contribute to establishing the high dose as the MTD. However, as body weight gain was up to ten percent less than that of the controls, the MTD may have been reached for these animals too. In addition, the acceptable survival of all animals support the conclusion of a valid study. The pharmacologist may confirm these findings by evaluating the clinical signs and severe histopathological effects of this drug on these animals.

APPEARS THIS WAY ON ORIGINAL

III. The Mouse Study

III.a. Design

This study was conducted in ICO:OF1 [REDACTED] mice for 78 weeks. For each sex there were 50 animals per group. There were two control groups which received diet only and three treated groups which received the drug in the diet at 6, 30, and 60 mg/kg/day. The diet and water was available ad lib. There were an additional 15 animals per control and treatment group which were used for blood sampling and were not part of any survival or tumor analyses. Microscopic examination of tissues was performed only on all gross abnormalities, masses and tissues of all high dose and control (both groups) animals, on all gross abnormalities, masses and tissues of all animals that died or were sacrificed prematurely, and on all gross abnormalities, liver and masses from the intermediate and low dose groups. That is, with the exception of the liver, tissues of the terminally sacrificed low and mid dose animals were not microscopically examined unless gross abnormalities or masses had been noted.

II.b. Sponsor's Analyses of the Mouse Study

Survival Analysis

The sponsor presented cumulative survival in graphical and tabular form. It was concluded that the 'distribution of mortality for each sex was not superior in the treated groups when compared with the respective controls.'

Tumor Data Analysis

For neoplastic findings the sponsor reported that the number of animals with neoplasms, the number of animals with more than one primary neoplasm, and the number of benign and malignant tumors were comparable in all groups. The statistical analysis of neoplastic lesions did not show any positive trends.

III.c. Reviewer's Analyses

Survival Analysis

This reviewer verified the sponsor's conclusion that there was no statistically significant increasing trend in mortality with dose for either sex. (Figures 3 and 4, Table 2).

Tumor Data Analysis

The sponsor investigated possible trends only when there were at least three tumor occurrences in one of the groups. With the exact permutation trend test used by this reviewer this restriction was not necessary and any possible positive trend with dose was tested. A trend test was only

appropriate for any fatal tumor and for incidental liver tumors. None of these reached statistical significance. Pairwise comparisons between high dose and combined controls also did not yield any statistically significant findings.

III.d. Validity of the Mouse Study

Before concluding that the mouse study showed no tumorigenic effect of modafinil the validity of the study needs to be determined following the statistical criteria outline above for the rat study.

At the end of the study more than 50 % (54% HD - 68% Controls) of the male mice had died. Numerically, however, there were 23 HD animals available to manifest any late developing tumors. The mortality among the female mice ranged from 60 - 70 % at the end of the study with the HD animals having the poorest experience. The 15 animals of the HD surviving 1 ½ years may be insufficient to demonstrate any late developing tumors, but may, on the other hand, indicate that the high dose was close to the MTD.

The sponsor provided only individual and mean body weights but not mean body weight gains. The latter could not be computed by this reviewer because the body weight data were not provided on diskette. Using only the mean body weights (see table below), it is not clear whether the observed small differences constitute a drug effect. It rather appears that the high dose may not have been sufficiently close to the MTD.

Mean Body Weights

MALES				FEMALES			
Week	Controls	High	% Controls	Week	Controls	High	%Controls
1	31.5	31.0	98.4	1	23.0	23.0	100.0
50	46.5	46.0	98.9	50	36.0	36.0	100.0
78	47.0	46.0	97.9	78	37.5	36.0	96.0

From the statistical point of view, this study had an insufficient number of females exposed to a drug level which may not have reached the MTD calling the validity of this study into question. However, the numeric increase in mortality with dose would point to the high dose being close to the MTD, but the mean body weight data are inconclusive as there was no difference between controls and High dose animals for the first year. For the male mice there was a sufficient number of animals surviving for 1 ½ years but the high dose did not seem to be close to the MTD. The evaluation of any toxic and severe histopathological findings are left to the expertise of the pharmacologist .

IV. Summary and Conclusion

In this 104 week rat study all tumors were classified as 'undetermined' making a proper analysis impossible. In addition, only selected tissues were examined for all animals limiting possible

trend tests to these tissues. As no statistically significant trends or pairwise comparisons in tumor incidence rates were found the validity of the study had to be assessed. It was found that for either sex a sufficient number of animals lived long enough to manifest any late developing tumors. For the male rats the conclusion was that the high dose was close to the MTD and therefore that a valid study had been conducted. For the female rats the body weight gain data supported this conclusion as well, however, the drug seemed not to have any effect on the mortality of these animals. From a statistical point of view it is not clear whether the MTD was reached for the female rats.

This mouse study was only 78 weeks long. Only a limited number of tissues were examined for all animals making the standard tumor analyses unsuitable. The less powerful pairwise comparison tests for tissues where low and mid doses were not fully necropsied did not find any statistically significant results and neither did any of the trend tests. In the evaluation of the validity of the mouse study this reviewer observed that there were an insufficient number of female mice remaining at week 78 to manifest late developing tumors challenging the validity of the study. The increased mortality of the high dose animals supported the notion that the MTD was reached. However, the lack of differential in weight gain for the first full year casts doubt on this conclusion. The male arm retained a sufficient number of animals at the end of the study but the high dose did not appear to have reached the MTD. Overall this reviewer concluded that the validity of the mouse study is very questionable.

/s/ [Redacted]

Roswitha E. Kelly
Mathematical Statistician

Concur:

/s/ [Redacted]

Todd Sahlroot, Ph. D.
Team Leader

8/1/97

/s/ [Redacted]

George Chi, Ph.D.
Director, DB I

8/5/97

cc: Archival NDA 20-717, PROVIGIL (modafinil) Tablets, Cephalon, Inc.

HFD-120/Division File

HFD-120/Dr. Atrakchi

HFD-120/Dr. Fitzgerald

HFD-120/Mr. Hardeman, CSO

HFD-710/Chron.

HFD-710/Dr. Chi

HFD-710/Dr. Sahlroot

HFD-710/Ms. Kelly

HFD-700/Dr. Fairweather

This review consists of 9 pages of text, 2 tables and 4 figures.

RKELLY/07/28/97/wp-modafinl.rev

APPEARS THIS WAY ON ORIGINAL

Table 1
INTERCURRENT MORTALITY RATES

Weeks	FEMALE RATS			
	0	6	30	60
0- 52	2/100 (2%)	3/50 (6%)	2/50 (4%)	3/50 (6%)
53- 78	9/98 (11%)	1/47 (8%)	4/48 (12%)	5/47 (16%)
79- 92	12/89 (23%)	7/46 (22%)	8/44 (28%)	7/42 (30%)
93-104	17/77 (40%)	11/39 (44%)	7/36 (42%)	7/35 (44%)
Term. Sac.	60/100 (60%)	28/50 (56%)	29/50 (58%)	28/50 (56%)

Weeks	MALE RATS			
	0	6	30	60
0- 52	2/100 (2%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
53- 78	5/98 (7%)	5/49 (12%)	0/49 (2%)	2/50 (4%)
79- 92	12/93 (19%)	11/44 (34%)	9/49 (20%)	7/48 (18%)
93-104	15/81 (34%)	5/33 (44%)	8/40 (36%)	18/41 (54%)
Term. Sac.	66/100 (66%)	28/50 (56%)	32/50 (64%)	23/50 (46%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

Table 2
INTERCURRENT MORTALITY RATES

Weeks	FEMALE MICE mg/kg/day			
	0	6	30	60
0- 52	23/100 (23%)	8/50 (16%)	19/50 (38%)	17/50 (34%)
53- 78	38/77 (61%)	22/42 (60%)	13/31 (64%)	18/33 (70%)
Term. Sac.	39/100 (39%)	20/50 (40%)	18/50 (36%)	15/50 (30%)

Weeks	MALE MICE mg/kg/day			
	0	6	30	60
0- 52	19/100 (19%)	12/50 (24%)	11/50 (22%)	8/50 (16%)
53- 78	49/81 (68%)	19/38 (62%)	19/39 (60%)	19/42 (54%)
Term. Sac.	32/100 (32%)	19/50 (38%)	20/50 (40%)	23/50 (46%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

APPEARS THIS WAY ON ORIGINAL

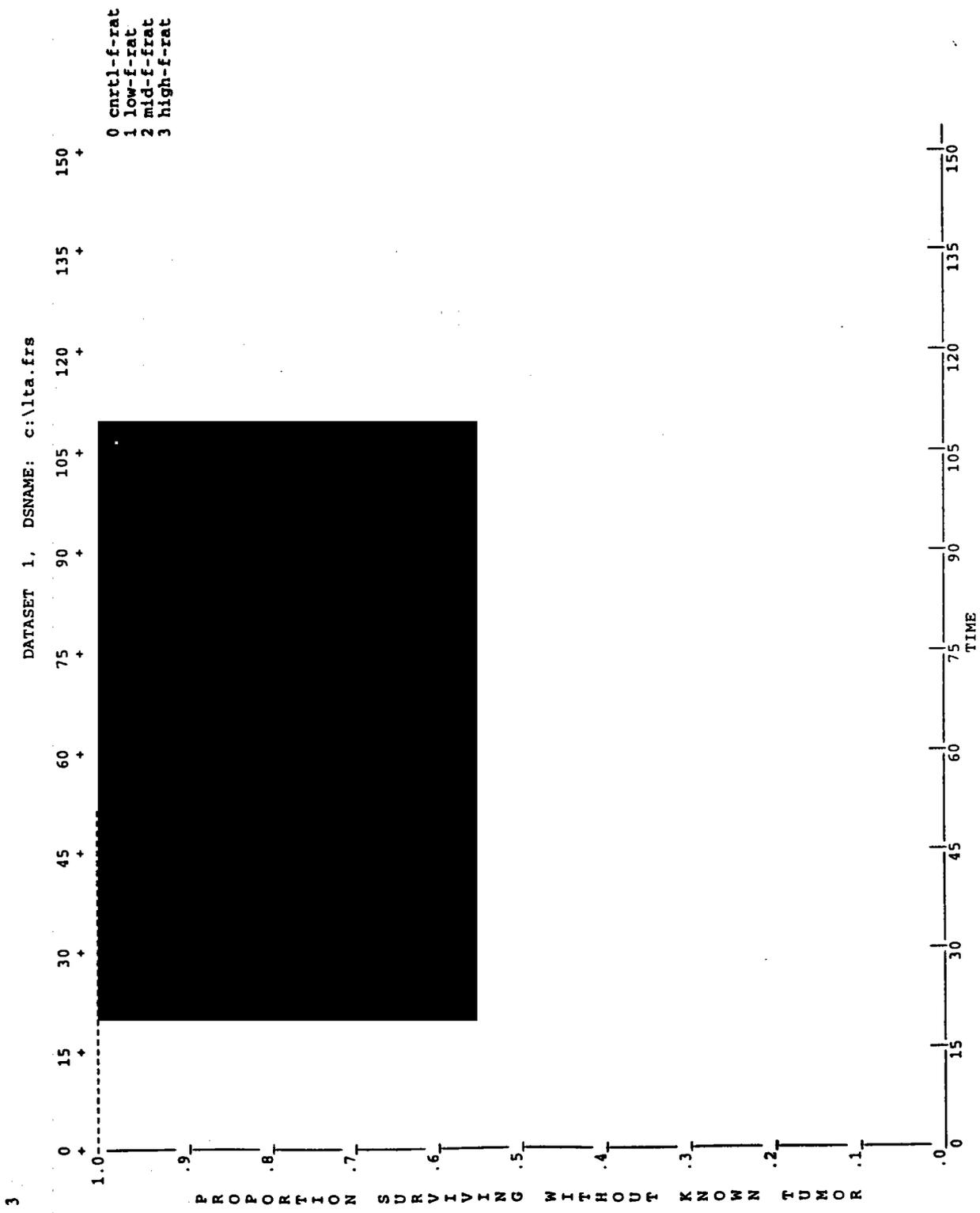
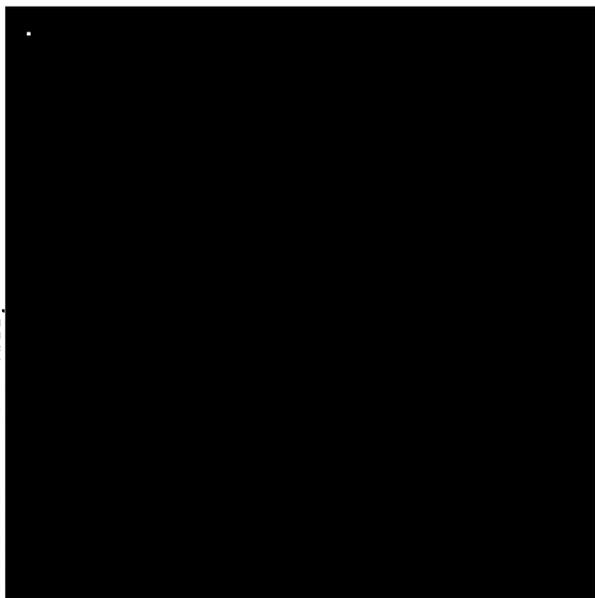


Figure 1

3

DATASET 1, DSNAME: c:\lta.mrs

0 + 15 + 30 + 45 + 60 + 75 + 90 + 105 + 120 + 135 + 150 +



0 cnrt1-m-rat
1 low-m-rat
2 mid-m-rat
3 high-m-rat

PROPORTION SURVIVING WITHOUT KNOWN TUMOR

.9
.8
.7
.6
.5
.4
.3
.2
.1
.0

0 15 30 45 60 75 90 105 120 135 150

TIME

Figure 2

DATASET 1, DSNAME: c:\lta.fms

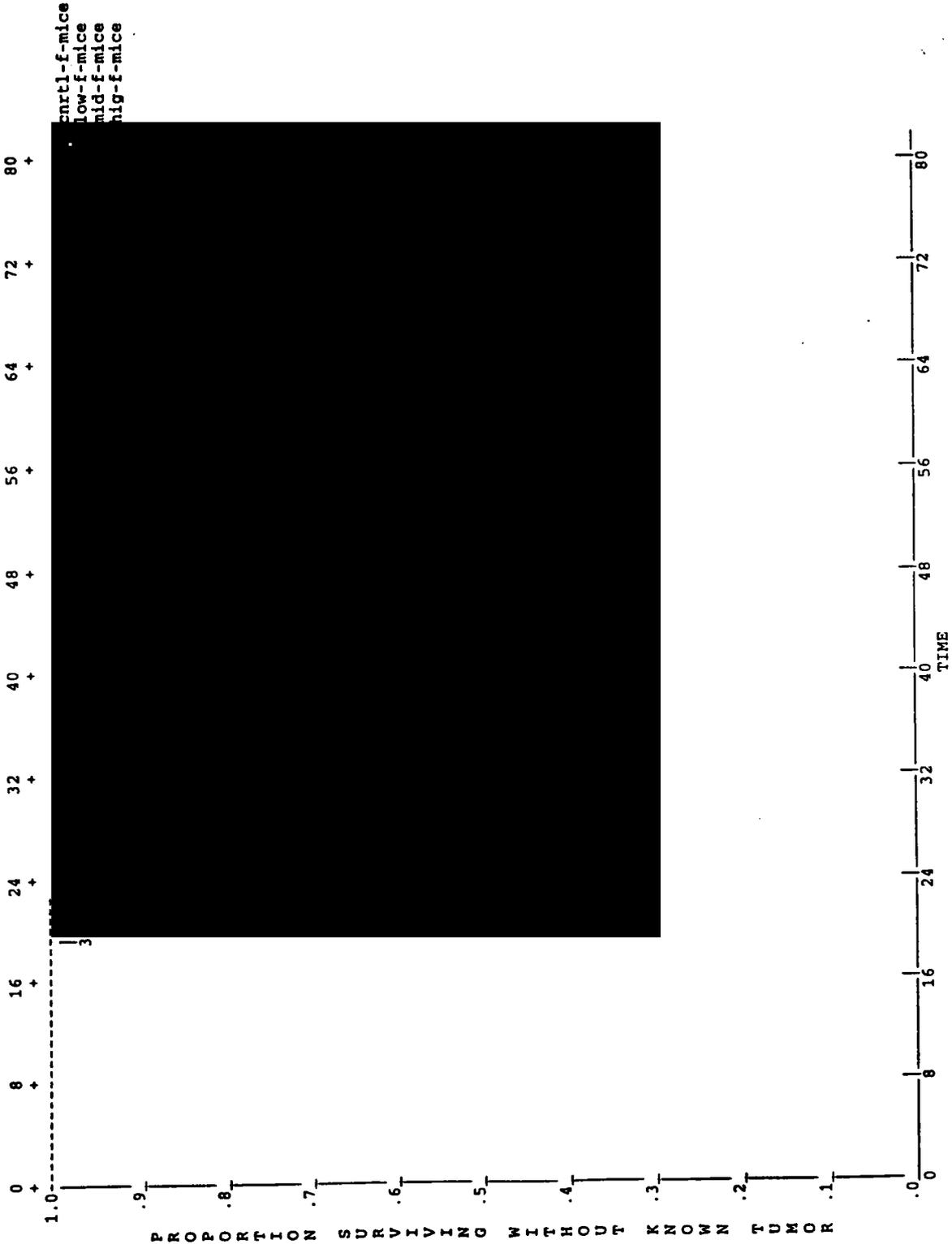


Figure 3

3

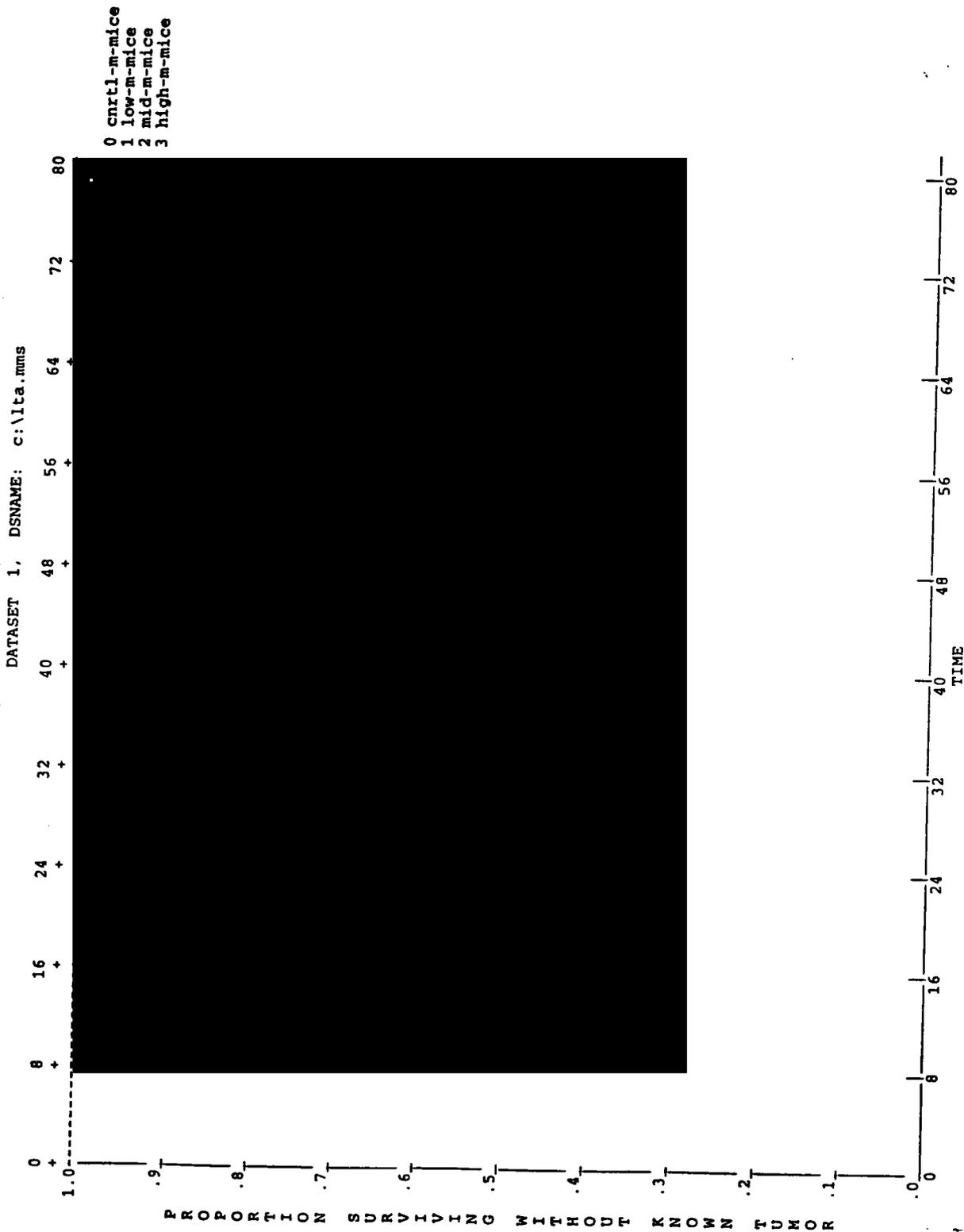


Figure 4

NDA# 20-717
Amendment

Drug: Modafinil - Provigil Tabs - CEP 1538
Indication: Narcolepsy
Category: Mechanism of Action: Unknown. —
Sponsor: Cephalon, Inc.
145 Brandywine Pky
West Chester, PA
Sub Date: Jun 4th 1998
Rec Date: Jun 1998
Rev Date: Jun 1998
Reviewer: Aisar Atrakchia, Ph.D. [redacted] /S/
Team Leader: Glenna Fitzgerald, Ph.D.
Related IND/NDAs: [redacted]

This submission includes study design and summary results of 2 GLP dose range findings of modafinil in the rat to determine the doses to be tested in the main rat fertility and teratology studies. These studies were recommended by the Division to the sponsor in the Dec 29 1997 approvable letter. The Division recommended that the dose range finder studies be initiated prior to drug approval and the main studies be initiated, completed, and final reports submitted in phase 4. Final reports for these dose range finding will be submitted to the Division when available.

Based on the results of the dose range finding studies the doses selected for the both the rat fertility and teratology studies are: 0, 100, 240, and 480mg/kg/d. These studies will follow the ICH document "Detection of Tox to Repro for Medicinal Products".

The reviewer, after review and evaluation of the summary data presented in this submission, concurs with the sponsor on the doses selected for the pivotal rat fertility and teratology studies. The following is presentation of the findings and rationale for dose selection.

- ◆ Oral gavage dose range finding of modafinil in the rat (Cephalon study# DS-98-002)
(Study conducted by [redacted])

SD rats (8/sex/dose) were orally dosed modafinil at 0, 240, 360, or 480mg/kg/d from gd7-17. The cont gr (8/sex) was administered the vehicle, Ora-Plus. Dose volume for all grs was 6ml/kg adjusted daily on basis of each dam's wt. Parameters assessed included clinical signs, B.wt, food intake, and all standard repro parameters to include # and distribution of corpora lutea, implantation sites, uterine wt and contents, early/late resorptions, etc. Fetal parameters included

B.wts, live vs. dead, and, gross external abnormalities. A satellite gr of 4 dams/drug gr was used for TK info. Blood was collected from these dams on gd7 (at 1&24hr postdose) and on gd17 (1hr postdose). These dams were killed after the last collection without further examination.

Results:

Mortality & Clinical Signs: There was no mortality in any gr. Clinical signs included tremors in 4/8 dams dosed 360&480mg/kg and perivaginal staining in a single dam dosed 360mg/kg.

B.wt & Food Intake: mean wt loss was seen in HD dams during gd7-10 (7.7g loss vs. 16g gain in cont)(stats were not presented in these summary reports). This loss in mean wt affected the mean dam wt throughout the dosing period with approximately 29% wt change rel to the corresponding cont (gd7-18; 59±26g vs. 83±27g in corresponding cont). Some rebound in HD

ORAL (GAVAGE) DOSAGE RANGE-FINDING DEVELOPMENTAL TOXICITY
STUDY OF MODAFINIL IN RATS

MATERNAL BODY WEIGHT CHANGES - GESTATION - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE		0.0 MG/KG/DAY	240.0 MG/KG/DAY	360.0 MG/KG/DAY	480.0 MG/KG/DAY
RATS TESTED	N	8	8	8	8
PREGNANT	N(%)	7 (87.5)	7 (87.5)	8 (100.0)	7 (87.5)
MATERNAL BODY WEIGHT CHANGE (G)					
DAYS 0 - 7	MEAN±S.D.	+32.1 ± 8.4	+40.3 ± 6.4	+39.1 ± 6.0	+35.8 ± 8.8
DAYS 7 - 8	MEAN±S.D.	+6.6 ± 5.4	-2.1 ± 6.6	-2.4 ± 4.2	-7.0 ± 5.0
DAYS 8 - 9	MEAN±S.D.	+3.7 ± 2.4	+6.6 ± 2.9	+5.2 ± 6.9	-1.6 ± 5.6
DAYS 9 - 10	MEAN±S.D.	+5.8 ± 3.8	+7.0 ± 2.3	+9.2 ± 3.4	+0.8 ± 6.5
DAYS 7 - 10	MEAN±S.D.	+16.1 ± 5.1	+11.4 ± 5.9	+12.1 ± 5.5	-7.7 ± 9.2
DAYS 10 - 12	MEAN±S.D.	+10.1 ± 4.1	+9.1 ± 3.9	+12.4 ± 5.3	+12.7 ± 9.6
DAYS 12 - 15	MEAN±S.D.	+18.4 ± 5.9	+16.0 ± 6.8	+16.6 ± 9.5	+21.0 ± 5.0
DAYS 15 - 18	MEAN±S.D.	+38.7 ± 18.2	+42.0 ± 5.6	+38.2 ± 8.2	+33.3 ± 12.1
DAYS 7 - 18	MEAN±S.D.	+83.4 ± 26.5	+78.6 ± 6.0	+79.4 ± 10.4	+59.3 ± 26.1
DAYS 18 - 20	MEAN±S.D.	+37.1 ± 12.6	+36.8 ± 17.1	+30.0 ± 15.9	+39.6 ± 12.0
DAYS 7 - 20	MEAN±S.D.	+120.6 ± 28.4	+115.4 ± 21.2	+109.4 ± 14.1	+98.8 ± 37.0
DAYS 0 - 20	MEAN±S.D.	+152.7 ± 32.7	+155.7 ± 21.9	+148.5 ± 18.7	+134.7 ± 36.9

This table restricted to pregnant animals.

DAYS ± DAYS OF GESTATION

wt was seen during gd 18-20 (postdose) but wt gain remained lower (18% lower than the cont) over the gestation period 7-20 (99±37g vs. 121±28g in cont)(table below from sponsor).

The decr in wt was accompanied by decr in food intake. Mean food intake was decr 54% in HD during gd 7-10 and was 18% lower than the corresponding cont throughout the dosing period, gd7-18. The mean intake in HD gd7-10 was 9±4g/d vs. 20±2.5g/d in cont; mean intake during entire dosing period, gd7-18, was 19±2g/d vs. 22±2g/d. The relative food intake (g/kg/d) in HD

dams followed the same pattern as the absolute food consumption reported above: gd7-10: 34±15g/kg/d vs. 71±8g/kg/d; gd7-18: 62±4g/kg/d vs. 71±3g/kg/d for the corresponding cont. **Maternal Parameters:** modafinil had no effect on maternal parameters at any dose except early resorptions were incr in HD rel to the cont (table below from sponsor)(mean±s.d. 2.4±5.6 vs. 0.6±0.8 in cont; n=17 vs. 4 in cont). This was due to a single litter that had 15 early resorptions. The latter consequently affected the litter size which was smaller in HD (14±6) rel to the cont (16±3) and, affected the # of live fetuses (table below).

ORAL (GAVAGE) DOSAGE RANGE-FINDING DEVELOPMENTAL TOXICITY
STUDY OF MODAFINIL IN RATS

CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE		I 0.0 MG/KG/DAY	II 240.0 MG/KG/DAY	III 360.0 MG/KG/DAY	IV 480.0 MG/KG/DAY
RATS TESTED	N	8	8	8	8
PREGNANT	N(%)	7 (87.5)	7 (87.5)	8 (100.0)	7 (87.5)
DIED	N(%)	0	0	0	0
ABORTED AND SACRIFICED	N(%)	0	0	0	0
DELIVERED	N(%)	0	0	0	0
ANIMALS PREGNANT AND CAESAREAN-SECTIONED ON DAY 20 OF GESTATION	N	7	7	8	7
CORPORA LUTEA	MEAN±S.D.	17.8 ± 2.3	17.8 ± 2.0	16.5 ± 2.6	18.0 ± 2.0
IMPLANTATIONS	MEAN±S.D.	16.1 ± 2.7	16.4 ± 1.0	15.9 ± 2.6	16.3 ± 1.0
LITTER TYPE	MEAN±S.D.	16.1 ± 2.7	16.4 ± 1.0	15.9 ± 2.6	16.3 ± 1.0
LIVE FETUSES	N	139	110	122	97
	MEAN±S.D.	15.6 ± 3.2	15.7 ± 1.2	15.2 ± 3.0	13.8 ± 6.2
DEAD FETUSES	N	0	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.6 ± 0.8	0.7 ± 1.0	0.6 ± 1.1	2.4 ± 5.6
EARLY RESORPTIONS	N	4	5	5	17
	MEAN±S.D.	0.6 ± 0.8	0.7 ± 1.0	0.6 ± 1.1	2.4 ± 5.6
LATE RESORPTIONS	N	0	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
DAMS WITH ANY RESORPTIONS	N(%)	3 (42.8)	3 (42.8)	3 (37.5)	3 (42.8)
DAMS WITH ALL CONCEPTUSES DEAD OR RESORBED	N(%)	0	0	0	1 (14.3)
DAMS WITH VIABLE FETUSES	N(%)	7 (100.0)	7 (100.0)	8 (100.0)	6 (85.7)

There were no drug related gross fetal external malformations in any gr. In mid dose, exencephaly was seen in 4 fetuses from 1 litter and protruding tongue in 2 fetuses of 1 litter. In LD, agnathia was seen in 1 fetus from 1 litter., no gross findings in any HD animals.

It was concluded that oral gavage administration of modafinil to rats during organogenesis (gd7-18) caused no deaths upto 480mg/kg/d. Decreases in mean wt gain and food intake rel to the cont were seen in the 480mg/kg dosed dams during dosing. An incr in incidence of early resorptions was seen in HD but wss due to a single litter that had 15 early resorptions. There were no drug related gross malformations in any gr. It was concluded that the doses to be tested in the main teratology study in the rat are 100, 240, and 480mg/kg/d, the 100mg/kg/d is expected to be the NOAEL.

- ◆ Oral gavage 10 day dose range finding of modafinil in the rat (Cephalon study# DS-98-003) (Study conducted by [REDACTED])

SD rats (5/sex/dose) were orally dosed modafinil at 0, 400, 600, or 800mg/kg/d for 10d. The cont gr was administered the vehicle, [REDACTED] dose vol for all animals was 10ml/kg adjusted according to current B.wt measured prior to dosing. Parameters assessed: clinical signs, B.wt, food intake, and complete gross exam.

Results:

Mortality & Clinical Signs: rats died or killed in moribund at doses ≥ 600 mg/kg/d (3/5f 600mg/kg; all m & f in HD). Females in the 600& 800mg/kg grs died within 2-3d of initiation of dosing and males dosed 800mg/kg died between days 3-9 of dosing. Clinical signs seen in all drug grs included: excitation, incr motor activity, repetitive head movement, and repetitive biting. The incidence of signs incr with incr in dose. The following were observed in ≥ 600 mg/kg grs: loss or decr righting reflex, ataxia, and, decr in motor activity; only in HD, licking action.

B.wt & Food Intake: mean B.wt decr linearly with time in Hdm (dosing days 1-8). Mean wt loss ranged between -5.7 ± 12 g on d3-4 to -32 ± 7 g d1-2. Mean wt loss was also seen in LD & MD males during days 1-2&2-3 (-11 ± 7 g to -26 ± 5 g). Mid dose males showed a mean loss for the entire dosing period d1-11 of -27 ± 21 g vs. a gain for the cont gr of 41 ± 26 g. Mean wt loss was also seen in HDF during the 3days they were alive (-12 ± 6 g and -18 ± 4 g over the 3 days). Females in MD lost wt from d1-5 (-5 ± 9 to -11 ± 6 g). However, females in MD showed an overall gain of 30 ± 3 g over the whole dosing period, d1-11. Food intake correlated with the decr in wt in both males and females.

Gross Exam: The sponsor indicated that modafinil had no effect on gross findings.

It was concluded that oral gavage administration of modafinil to male and female rats for 10d caused death at doses ≥ 600 mg/kg within few days of dosing. Clinical signs were seen in all drug grs (LD 400mg/kg/d). Mean wt loss was seen in both sexes dosed ≤ 600 mg/kg/d and in females dosed 400mg/kg/d. Mean wt loss was paralleled by decr in mean food intake. The doses selected for the definitive fertility study are 100, 240, and 480mg/kg/d.

Please note, that the info in this report for these 2 studies are provided as summaries; full data and final reports are to be submitted when available. Therefore, the reviewer's conclusions/recommendations are based on these summary data.

cc.

/Div File/Orig NDA# 20-717

/G. Fitzgerald/A. Atrakchi/AM. Homonnay [REDACTED] APPEARS THIS WAY ON ORIGINAL

/S/ [REDACTED]

/S/ [REDACTED]

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 17, 1998

FROM: Glenna G. Fitzgerald, Ph.D. /S/ [REDACTED]
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-717
Provigil (modafinil)
Cephalon, Inc.

SUBJECT: November 11, 1998 labeling submitted by sponsor

The sponsor's newly submitted labeling has been discussed with the primary reviewer, Dr. Aisar Atrakchi, and the following recommendations for the preclinical sections are made.

DESCRIPTION

Page 1, lines 4 & 5: Do not delete DRAFT LABELING [REDACTED]

CLINICAL PHARMACOLOGY

Page 2, lines 20 through 24 and 31 through 40: Sponsor's changes are acceptable.

Page 3, lines 47 through 52: Sponsor's changes are acceptable.

lines 53 through 55: Delete sentence DRAFT LABELING [REDACTED]

DRAFT LABELING [REDACTED] No reference to this effect is available.

lines 58 through 73: Sponsor's changes are acceptable.

Page 4, lines 74 through 79: Agree with deletion. But replace with [REDACTED]

DRAFT LABELING [REDACTED]

DRAFT LABELING [REDACTED]

[REDACTED] substituted for cocaine in drug administration

[REDACTED] [Note to clinicians: At the time of the AE action, Drug Abuse staff felt that information about abuse potential should be included in the Clin Pharm section as well as under Abuse Potential. They wrote the portions which appeared in our AE labeling in both locations, and which the sponsor has deleted on both pages. Dr. Atrakchi prefers the inclusion of specific information from animal studies, rather than the more general statements originally used, and has written the replacement statements. The sponsor does not want any of the above. I believe the information should be included, but defer to the clinical team to decide which style should be used.]

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Pages 20 through 22: Sponsor's changes are acceptable

ABUSE POTENTIAL AND DEPENDENCE

Page 28, lines 719 through 726: Sponsor's deletion is acceptable. In its place add the following text: **DRAFT LABELING** [REDACTED]

[REDACTED]

Page 28, lines 727 through 733: Sponsor's changes are acceptable.

NDA 20-717

c.c.\Div File

\Katz\Freiman\Atrakchi\Homonnay\Fitzgerald

APPEARS THIS WAY ON ORIGINAL