CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-875

PHARMACOLOGY REVIEW

June 14, 2007

Review and Evaluation of Pharmacology and Toxicology
Complete Response to Approvable Letter

NDA: 21-875

Sponsor: Cephalon
West Chester, PA

Received: April 16, 2007

Drug: Nuvigil (armodafinil; R-modafinil) Tablets

Category: stimulant

Related INDs and NDAs: 68,517; 42,873; 20-717

Summary and Recommendations:

The sponsor has committed to perform a repeat 2-year mouse carcinogenicity study, as requested by the Division in the Approvable Letter, and their proposed timeline for completion of this study is considered acceptable. The following changes to the Clinical Pharmacology and Pregnancy sections of labeling are recommended (in red):

b(4)
b(5)

b(4)
b(5)

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✔ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Fisher
6/14/2007 01:20:28 PM
PHARMACOLOGIST

Lois Freed
6/14/2007 02:14:27 PM
PHARMACOLOGIST

March 8, 2007

Review and Evaluation of Pharmacology and Toxicology
Response to approvable letter

NDA: 21-875

Sponsor: Cephalon
West Chester, PA

Received: June 30, 2006

Drug: Nuvigil (armodafinil; R-modafinil) Tablets

Category: stimulant

Related INDs and NDAs: 68,517; 42,873; 20-717

Summary and Recommendations:

Armodafinil (R-modafinil; levorotary enantiomer of modafinil) is the R-enantiomer of racemic modafinil (Provigil; IND 42,873; NDA 20-717), a drug approved for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and "shift work sleep disorder." An abbreviated nonclinical toxicology package was submitted with the application, consisting of 13-week bridging toxicity studies in rats and dogs, a developmental toxicology study in rats, and cardiovascular and CNS safety evaluations as well as postapproval studies conducted with modafinil (Tg.AC mouse carcinogenicity study, rat reproductive toxicity study, rabbit embryofetal development study). The studies of R-modafinil submitted with the NDA indicated that that there is no significant difference in toxicity between R-modafinil and racemic modafinil at comparable exposures in studies of up to 3 months duration. But the bridging strategy rests on the premise that the toxic potential of modafinil is understood, and questions about the adequacy of the toxicity evaluation of modafinil were raised. Deficiencies in the developmental toxicity and carcinogenicity assessments of modafinil were considered of primary importance. The pre- and postnatal development studies of modafinil submitted with NDA 20-717 were non-standard in that neurobehavioral assessments were not conducted on offspring exposed for the currently recommended period of development, ie, implantation through weaning, and were thus considered inadequate. Carcinogenicity studies conducted with the racemate (NDA 20-717) were relied upon for this application (agreed to in principle by Division). The original mouse carcinogenicity study of racemic modafinil had been judged inadequate, and the drug was approved with the stipulation that another mouse study be performed Phase 4. In order to fulfill this requirement, modafinil was evaluated in a 26-week Tg.AC transgenic mouse bioassay. While the topical Tg.AC assay was apparently considered appropriate for evaluation of an oral drug at the time it was accepted (by full CAC, 10/97), it is not now. In addition, the rat carcinogenicity study of modafinil was considered only marginally adequate. Thus, the assessment of carcinogenic potential for modafinil, and by extension armodafinil, was considered incomplete. Therefore, the NDA was deemed approvable with respect to the pharmacology/toxicology portion on the condition that a carcinogenicity assessment [redacted] be conducted Phase 4. The letter (dated 4/28/06) contained the following pharm/tox request: b(4)

You submitted two pre- and post-natal studies of modafinil. In Study DS-93-017, modafinil was administered to rats at doses up to 100 mg/kg/day from gestation day 15 through postpartum day 21. That study was inadequate due to the lack of any maternal toxicity and insufficient duration of dosing. In Study DS-95-022, modafinil was administered at higher doses (up to 200 mg/kg/day) from gestation day 7 through postpartum day 20. Although Study DS-95-022 was otherwise adequate, it does not appear that neurobehavioral parameters were assessed. b(4)

c: [redacted] to current ICH standards (cf. Guideline for Industry Detection of Toxicity to Reproduction for Medicinal Products ICH-S5A September 1994).

Regarding the assessment of carcinogenic potential, you have conducted a 78-week dietary study in mouse, a 104-week dietary study in rat, and a 26-week dermal study in the Tg.AC transgenic mouse with modafinil. The Tg.AC mouse assay was conducted to fulfill a Phase 4 requirement for modafinil due to the inadequacy of the 78-week dietary study. We acknowledge that you received concurrence on the use of this model from both the Agency and the Carcinogenicity Assessment Committee; however, the dermal Tg.AC is not currently considered appropriate for evaluation of an oral drug, based on the potential inability of the dermal model to adequately assess the carcinogenic potential of metabolites (formed following oral administration) or in a full battery of tissues (i.e., the Tg.AC strain is genetically 'initiated' for skin carcinogenicity; cf. Leder A et al. *Proc Natl Acad Sci USA* 87:9178- 9182, 1990; Holden HE et al. *J Appl Toxicol* 18(1):19-24, 1998). Considering the intended patient population, we consider it critical that the assessment of carcinogenic potential of armodafinil be adequate. Therefore, either a 2-year study or an appropriate alternative assay on armodafinil needs to be conducted.

[redacted] the carcinogenicity studies may be conducted post marketing; a time line should be proposed for study conduct and submission of a final study report for each study. If you believe that you have additional information that would justify the adequacy of the available nonclinical data regarding these two issues, please submit them for review. b(4)

Subsequent to the issuance of the approvable letter, it was determined that an adequate rat pre- and postnatal development study of modafinil had been conducted. This requirement has thus been met. The current response to the approvable letter contains the sponsors' arguments for the adequacy of the carcinogenicity assessment of modafinil, summarized as follows:

> Cephalon recognizes that the dermal Tg.AC alternative bioassay is not currently considered by FDA as an appropriate evaluation of the carcinogenic potential of an orally administered drug. However, based on the preponderance of nonclinical safety data that has been generated with modafinil (the racemate of armodafinil [or R-modafinil]) and summarized below clearly indicating that modafinil is not a carcinogenic compound, Cephalon considers that the carcinogenic potential of armodafinil (the levorotatory isomer of modafinil) has been adequately evaluated and is proposing removal of the recommendation by The Agency for the initiation of a carcinogenicity bioassay (either a 2-year oral or an appropriate alternative bioassay) with armodafinil....
>
> In summary, the previous carcinogenicity investigations as well as two *in vitro* studies (cell transformation and unscheduled DNA synthesis) having the capability to detect potential *in vivo* carcinogenicity that have been performed have demonstrated that the racemate of armodafinil is not carcinogenic. Chronic (> 6-month) systemic toxicology administration of modafinil in both rats and dogs have not resulted in any potential (or real) preneoplastic organ/tissue changes. The recognized drug-metabolizing capability of the skin would suggest

that both primary circulating metabolites observed consistently with the systemic administration of modafinil in nonclinical and clinical studies, i.e., the acid and sulfone metabolites, would have likely been present in skin to some extent following daily dermal application of modafinil in the Tg.AC mouse model for 26 weeks. Lastly, the general (historical) lack of regulatory-driven carcinogenicity concerns on the basis of results from looking at mouse data alone should strongly preclude the initiation of yet another long-term carcinogenicity bioassay in this species. Therefore, based then on these aforementioned reasonings, Cephalon requests that FDA reconsider their request to conduct a murine (standard 104-week or alternative bioassay in a transgenic mouse model) carcinogenicity study with armodafinil.

All of the information contained in the sponsor's response has been considered previously; no new data were submitted to address the deficiency in the carcinogenicity assessment noted in the approvable letter. Not all animal carcinogens have been found positive in genotoxicity screens or capable of producing preneoplastic changes in general toxicity studies (including chronic). As stated by Jacobs in a recent review article (Tox Sci 88(1)18-23,2005): "Many of the mechanisms of carcinogenesis found with pharmaceuticals may not be amenable to early prediction at this time. Many of the mechanisms identified to date appear to be nongenotoxic and may require prolonged treatment to be expressed. Current results available to the FDA do not support the idea that short-term studies accurately predict the neoplastic findings in long-term assays of pharmaceuticals." The sponsor acknowledges that the dermal Tg.AC alternative bioassay is not currently considered an appropriate model for evaluation of the carcinogenic potential of an orally administered drug. Even if the major metabolites of modafinil are produced in the skin (which has not been demonstrated), the exposures are unknown and would likely be limited to the skin. Although implied, since there is a marginally valid rat study but no valid mouse carcinogenicity study of modafinil, the test species for the requested carcinogenicity study of armodafinil was not specified in the letter. However, it is not true that there is a lack of "regulatory-driven carcinogenicity concerns" based on mouse data alone. The mouse would also appear to be the appropriate choice based on PK, although exposure data in mice are limited (see original NDA review). R-modafinil is more rapidly cleared than S-modafinil in rats, while the opposite is true in mice (and humans). Exposure margins achieved in the rat studies of both modafinil and armodafinil were small (or non-existent). Therefore, the mouse should be used for this study unless it can be shown that significantly higher exposures could be achieved in rats.

J.E. Fisher, Ph.D.

cc:
NDAs (21-875)
Div File
HFD-120/LFreed/CCalder/EFisher

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Fisher
3/14/2007 03:48:16 PM
PHARMACOLOGIST

Lois Freed
3/14/2007 04:04:07 PM
PHARMACOLOGIST

April 28, 2006

Review and Evaluation of Pharmacology and Toxicology

NDA: 21-875

Sponsor: Cephalon
West Chester, PA

Received: March 31, 2005

Drug: Nuvigil (armodafinil; R-modafinil) Tablets

Category: stimulant

Related INDs and NDAs: 68,517; 42,873; 20-717

Background: Armodafinil (R-modafinil; levorotary enantiomer of modafinil) is the R-enantiomer of racemic modafinil (Provigil; IND 42,873; NDA 20-717), a drug approved for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. In accordance with an abbreviated nonclinical toxicology program agreed to by the Division (see 10/22/04 pre-NDA meeting minutes), bridging studies consisting of 13-week toxicity studies in rats and dogs, a developmental toxicology study in rats, and cardiovascular and CNS safety evaluations were submitted. In addition, b(4) and postapproval (Phase 4) studies conducted with modafinil (Tg.AC mouse carcinogenicity study, rat reproductive toxicity study, rabbit embryofetal development study) were included in the application.

Contents:

I. PHARMACOLOGY

In studies that compared the enantiomers and racemate, the pharmacological properties of armodafinil (R-modafinil; l-modafinil; CEP-10953 [redacted] 0982; the levorotary enantiomer of modafinil) were qualitatively similar to those of the S-enantiomer (d-modafinil; CEP-10952 [redacted] 0983) and racemate (R,S-modafinil; CEP-1538; [redacted] 40476). Experiments in mice and rats have shown that all 3 were similar in producing behavioral stereotypy, increasing spontaneous locomotor activity, enhancing EEG/EMG-based wakefulness, and binding to the DA transporter (IC50 value ≈ 4 uM), although there were some quantitative differences for some measures. b(4)

A. Wake Promoting Activities of Modafinil Racemate (CEP-1538), (S)-Modafinil, (CEP-10952), and (R)-Modafinil (CEP-10953) (Study No. DRR-2003-04; conducted by Cephalon, West Chester, PA; report dated 10/03; non-GLP)

Waking activity was evaluated in the rat by recording cortical EEG activity and nuchal (dorsal neck muscle) electromyographic (EMG) activity. Experiments comparing racemic modafinil (CEP-1538) and its (*S*)- and (*R*)-enantiomers (CEP-10952 and -10953, respectively) demonstrated that all 3 compounds produced a significant wake-enhancing effect at 100 mg/kg ip in rats, but that CEP-10952 showed significantly greater waking activity than either CEP-1538 or CEP-10953 (**Figure I.A1**). The difference in pharmacological activity between the *(S)*- and *(R)*-enantiomer was thought be at least partly due to pharmacokinetic differences. In the rat there are significant differences in the rate of clearance of *(S)*- vs *(R)*-modafinil; ie, when the racemate is given by iv injection, the t1/2 of the (*S*)-enantiomer is about 30% greater than that of the (*R*)-enantiomer, and the rate of clearance is significantly less. The situation is reversed in humans, where the (*R*)-enantiomer has a longer half-life (this is the stated basis for developing the R-enantiomer).

Figure I.A1

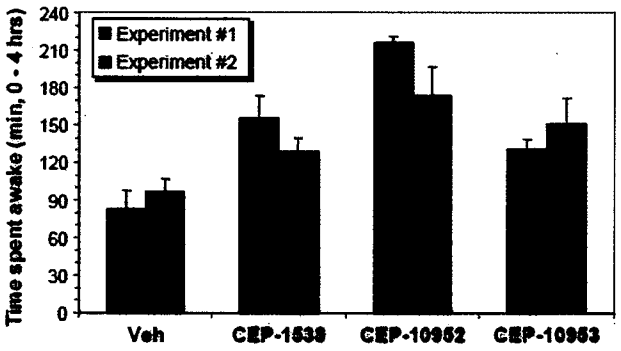


Fig. 3. Total minutes spent awake between 0 and 4 hours post dosing (AUC; 240 min. maximum) in individual experiments. N= 4 rats / group; error bars = SEM.

B. Comparative Activity of Modafinil and its R- and S- Enantiomers for Increased Locomotor Activity and Decreases in Barbital-induced Sleep (Report # DRR-2004-34; conducted by [redacted], report dated 2/17/86; non-GLP) b(4)

When modafinil [redacted] 0476) and its R- and S-enantiomers [redacted] 40982 and 40983) were compared for effects on spontaneous locomotor activity in mice, a dose of 64 mg/kg

ip increased locomotor activity 30 minutes post administration for all 3 compounds compared to control. At a dose of 128 mg/kg, all compounds increased locomotor activity 4 hours post administration (**Table I.B1**). Although no significant difference in effect was found between treatment groups in either trial, the S-enantiomer appeared somewhat more potent. Similar results were seen in other studies.

Table I.B1 Effects of modafinil and its enantiomers on locomotor activity

Compounds	mg/kg I.P.	Cumulative Number of crossed beams										%	
												Controls	Variation
-4 hrs		1 min.	2 min.	3 min.	4 min.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.		
[illegible]	-	29	49	69	90	116	204	271	357	394	439±28.6	100	-
[illegible]	128	37 NS	66 *	93 *	121 *	145 NS	270 *	348 *	485 **	573 **	659±39.8 **	151 **	+51 **
[illegible]	128	36 NS	59 NS	84 NS	109 NS	138 NS	254 *	364 *	460 **	538 **	620±44.6 **	142 **	+42 **
[illegible]	128	40 **	70 ***	100 ***	131 ***	160 **	297 ***	432 ***	534 ***	635 ***	713±45.9 ***	163 ***	+63 ***

b(4)

C. Cardiovascular Effects of CEP-10953 (R-Modafinil) In Conscious, Telemetered Beagle Dogs (Cephalon Ref. No. DS-03-004; Conducted by [illegible] Report Dated 10/04; GLP)

1. Methods

Four male beagle dogs (implanted with telemetry transducers for the assessment of arterial blood pressure and lead II ECG) received oral doses (2.5 ml/kg) of 0 (vehicle, Ora-Plus), 7.5, 20, and 50 mg/kg on days 1, 4, 8, and 11, respectively. Data collection for each dose started at 30 min before dosing and ended approximately 6 h after dosing. Systolic and diastolic blood pressure (SBP and DBP), HR, and all lead II ECG variables (PR interval, QRS duration, RR interval, and QT interval) were measured continuously for each animal. Mean arterial blood pressure (MAP) was calculated as (DBP + 1/3(SBP - DBP)) and QTc interval was calculated according to Fridericia's method (QTcF) from lead II ECG. Blood was collected from each dog predose and 1, 4, 9, and 24 h postdose following each dose for TK analysis.

2. Results

There was no change in SBP at any dose. A significant decrease in DBP was seen at the end of dosing with HD, but the effect was not thought to be drug-related, since the value was not different from baseline. DBP appeared to be increased somewhat at 20 and 50 mg/kg compared to C and baseline (statistically significant at 90 min following treatment with 50 mg/kg). MAP followed the same pattern as DBP, with a significant decrease at the zero-min time point and a significant increase at 90-min after 50 mg/kg. The effect at the zero-min timepoint was not thought to be drug-related. Although vehicle control values were extremely variable, it appeared that HR was increased by treatment at the MD and HD (**Table I.C1**).

In the ECG analysis, PR interval tended to be decreased somewhat (SS at 30 min after HD) compared to C, which were again highly variable. RR interval was decreased at all

doses compared to C, but was not clearly changed from baseline (-15 min values significantly lower than C in all treatment groups; **Table I.C2**). QT interval was decreased at MD and HD (SS at most time points; **Table I.C3**), and QTcF was decreased slightly at 240 min (**Table I.C4**). The ECG waveform analysis did not indicate any effects on lead II ECG waveforms or rhythm.

PK parameters for (R)-modafinil and the metabolites (R)-modafinil acid and modafinil sulfone are shown in **Table I.C5**. The increases in Cmax across this dose range were approximately dose-proportional, whereas the increases in AUC were greater than dose-proportional. Similar dose-related increases were observed for the primary circulating metabolites, R-modafinil acid and modafinil sulfone.

Table I.C1

Table 4. Effects of Vehicle and CEP-10953 on Heart Rate in Conscious, Telemetered Male Beagle Dogs

Time (min)	Heart Rate (bpm)			
	Vehicle 2.5 mL/kg	CEP-10953 7.5 mg/kg	CEP-10953 20 mg/kg	CEP-10953 50 mg/kg
-15	69 ± 12	110 ± 18***	113 ± 18*	89 ± 10
0	133 ± 13	118 ± 11	123 ± 8	157 ± 18
30	74 ± 7	106 ± 9	115 ± 9	135 ± 9***
60	118 ± 26	115 ± 15	144 ± 18	158 ± 28
90	60 ± 10	91 ± 14	111 ± 9	151 ± 20***
120	52 ± 5	90 ± 9	111 ± 7*	160 ± 19***
180	73 ± 12	98 ± 8	118 ± 10*	157 ± 18***
240	128 ± 29	132 ± 19	132 ± 24	152 ± 35
300	59 ± 8	94 ± 10	122 ± 14*	156 ± 12***
360	64 ± 9	84 ± 3	125 ± 11***	161 ± 12***

The vehicle (2.5 mL/kg Ora-Plus®) and CEP-10953 were administered by gavage at time zero.

Data for the vehicle and 7.5-mg/kg dose level are mean ± standard error of the mean of results obtained from four doses in three animals. Data for the 20- and 50-mg/kg dose levels are mean ± standard error of the mean of results obtained from four doses in four animals.

* and *** denotes $p < 0.05$ and $p < 0.001$ versus the time-matched vehicle.

Table I.C2

Table 7. Effects of Vehicle and CEP-10953 on RR Interval in Conscious, Telemetered Male Beagle Dogs

Time (min)	RR Interval (ms)			
	Vehicle 2.5 mL/kg	CEP-10953 7.5 mg/kg	CEP-10953 20 mg/kg	CEP-10953 50 mg/kg
-15	1006.2 ± 165.0	655.1 ± 117.8***	639.9 ± 100.3***	770.0 ± 85.3*
0	518.6 ± 75.3	564.7 ± 57.8	518.4 ± 37.1	457.5 ± 41.8
30	906.4 ± 74.9	668.5 ± 69.8	573.8 ± 56.4	446.8 ± 13.8*
60	674.5 ± 130.1	550.8 ± 80.8	481.1 ± 56.0	462.2 ± 43.6
90	1072.4 ± 129.6	749.9 ± 112.4	572.6 ± 55.3	454.7 ± 72.0*
120	1233.0 ± 49.4	741.3 ± 71.0	590.7 ± 44.3***	414.7 ± 45.7***
180	987.0 ± 166.3	703.2 ± 72.4*	576.7 ± 31.6*	412.1 ± 55.3***
240	633.1 ± 149.8	593.9 ± 35.3	565.5 ± 53.5	489.3 ± 77.8
300	1127.7 ± 85.7	701.8 ± 70.6	538.2 ± 59.4*	456.0 ± 41.9*
360	1026.8 ± 71.2	797.2 ± 13.7	524.0 ± 49.7***	387.4 ± 20.7***

The vehicle (2.5 mL/kg Ora-Plus®) and CEP-10953 were administered by gavage at time zero.

Data for the vehicle and 7.5-mg/kg dose level are mean ± standard error of the mean of results obtained from four doses in three animals. Data for the 20- and 50-mg/kg dose levels are mean ± standard error of the mean of results obtained from four doses in four animals.

* and *** denotes $p < 0.05$ and $p < 0.001$ versus the time-matched vehicle.

Table I.C3

Table 8. Effects of Vehicle and CEP-10953 on QT Interval in Conscious, Telemetered Male Beagle Dogs

Time (min)	QT Interval (ms)			
	Vehicle 2.5 mL/kg	CEP-10953 7.5 mg/kg	CEP-10953 20 mg/kg	CEP-10953 50 mg/kg
-15	239.7 ± 13.2	212.8 ± 14.4*	205.5 ± 12.0*	226.2 ± 9.7
0	197.5 ± 9.9	200.9 ± 7.6	192.6 ± 5.5	186.0 ± 7.4
30	233.3 ± 7.3	213.3 ± 7.1	200.7 ± 5.3*	190.7 ± 3.5***
60	225.1 ± 11.8	195.4 ± 7.4	185.9 ± 8.7*	183.8 ± 6.3*
90	244.7 ± 9.4	217.8 ± 7.8	199.1 ± 3.8*	179.6 ± 10.4***
120	254.3 ± 5.2	221.3 ± 4.7	201.5 ± 2.4***	178.4 ± 7.7***
180	243.4 ± 6.2	215.3 ± 7.5	197.1 ± 1.2***	179.2 ± 6.7***
240	211.5 ± 17.6	197.9 ± 7.8	186.3 ± 7.5	178.7 ± 10.4
300	245.7 ± 4.5	218.7 ± 4.7	197.6 ± 5.3***	179.3 ± 3.1***
360	241.4 ± 4.2	227.0 ± 2.6	196.8 ± 7.3***	178.0 ± 4.0***

The vehicle (2.5 mL/kg Ora-Plus®) and CEP-10953 were administered by gavage at time zero.

Data for the vehicle and 7.5-mg/kg dose level are mean ± standard error of the mean of results obtained from four doses in three animals. Data for the 20- and 50-mg/kg dose levels are mean ± standard error of the mean of results obtained from four doses in four animals.

* and *** denotes $p < 0.05$ and $p < 0.001$ versus the time-matched vehicle.

Table I.C4

Table 9. Effects of Vehicle and CEP-10953 on QTcF Interval in Conscious, Telemetered Male Beagle Dogs

Time (min)	QTcF Interval (ms)			
	Vehicle 2.5 mL/kg	CEP-10953 7.5 mg/kg	CEP-10953 20 mg/kg	CEP-10953 50 mg/kg
-15	241.8 ± 4.7	247.4 ± 6.6	240.7 ± 4.0	247.8 ± 1.2
0	247.6 ± 3.8	243.9 ± 3.2	240.1 ± 3.2	242.0 ± 4.7
30	241.8 ± 4.3	244.8 ± 1.0	242.5 ± 4.6	249.4 ± 2.5
60	259.9 ± 4.1	240.5 ± 5.9	238.3 ± 3.1	238.5 ± 4.3
90	241.1 ± 9.2	242.2 ± 5.0	241.0 ± 4.7	235.4 ± 5.8
120	237.5 ± 7.0	245.9 ± 6.4	240.9 ± 3.8	240.1 ± 1.6
180	248.3 ± 9.6	243.3 ± 7.0	237.2 ± 3.6	242.7 ± 4.3
240	250.3 ± 7.3	235.6 ± 6.2	225.9 ± 6.0***	228.7 ± 6.8***
300	237.0 ± 7.1	247.6 ± 6.3	244.4 ± 5.1	234.0 ± 5.0
360	240.4 ± 9.2	244.9 ± 3.9	244.9 ± 3.7	244.4 ± 3.4

The vehicle (2.5 mL/kg Ora-Plus®) and CEP-10953 were administered by gavage at time zero.

Data for the vehicle and 7.5-mg/kg dose level are mean ± standard error of the mean of results obtained from four doses in three animals. Data for the 20- and 50-mg/kg dose levels are mean ± standard error of the mean of results obtained from four doses in four animals.

*** denotes $p < 0.001$ versus the time-matched vehicle.

Table I.C5

Mean ± SD pharmacokinetic parameters of (R)-modafinil, (R)-modafinil acid, and modafinil sulfone in male beagle dogs ($n = 4$) administered single oral doses of (R)-modafinil at 7.5, 20, or 50 mg/kg

Compound	Parameter	(R)-Modafinil Dose		
		7.5 mg/kg	20 mg/kg	50 mg/kg
(R)-Modafinil	C_{max}, µg/mL	6.5 ± 0.7	17.4 ± 2.3	39.8 ± 4.6
	t_{max}, h[a]	1.0 [all 1.0]	1.0 [1.0 - 4.0]	2.5 [1.0 - 4.0]
	AUC_{0-t}, µg·h/mL	25.1 ± 13.2	106.6 ± 23.3	264.8 ± 26.9
(R)-Modafinil Acid	C_{max}, µg/mL	BLQ	0.4 ± 0.1	0.8 ± 0.3
	t_{max}, h[a]	NC	4.0 [1.0 - 4.0]	4.0 [all 4.0]
	AUC_{0-t}, µg·h/mL	0.0 ± 0.0	1.2 ± 0.2	4.3 ± 2.5
Modafinil Sulfone	C_{max}, µg/mL	1.3 ± 0.2	4.0 ± 0.3	12.7 ± 2.7
	t_{max}, h[a]	4.0 [1.0 - 4.0]	9.0 [4.0 - 9.0]	6.5 [4.0 - 9.0]
	AUC_{0-t}, µg·h/mL	6.6 ± 3.0	26.4 ± 1.7	116.8 ± 78.2

[a] Median [range]

NC = not calculable

BLQ = below the limit of quantitation (<0.20 µg/mL)

3. Conclusions

Apparent treatment-related changes consisted of increases in HR and decreases in the RR interval, QT interval, and QTcF interval, primarily at doses of 20 mg/kg or greater. The HD (50 mg/kg) may have also increased DBP and MAP. All changes were small, and statistical significance was often related to the variability of the control values. The ECG waveform analysis did not indicate any effects on lead II ECG waveforms or rhythm. The HD produced an R-modafinil AUC about 2 times that in human volunteers given the highest recommended dose of 250 mg (AUC = 148 ug.h/ml in study C10953a/102/PK/UK).

D. Effect of R-modafinil on action potential parameters in isolated dog Purkinje fibers (Study No. 1263DC36.001; Cephalon Study No. DS-03-001; conducted by [redacted], report dated 2/04; GLP)

1. Methods

The effects of R-modafinil (50, 150 and 300 uM) on intracellularly recorded action potential parameters was evaluated in an isolated dog Purkinje fiber preparation (4 Purkinje fibers isolated from the hearts of 4 Beagle dogs) electrically paced at 1 and 0.5 Hz. Fibers were exposed to the vehicle (0.2% DMSO) and each concentration of drug for at least 25 min or until response had reached steady state and electrophysiological responses were recorded at stimulation frequencies of 1 and 0.5 Hz. The following action potential parameters were measured: resting membrane potential (RMP), action potential amplitude (APA), maximum rate of depolarization of the action potential upstroke (Vmax), and action potential duration at 30, 50, and 90% (APD30, APD50, and APD90) repolarization. A positive control was not used in this study.

2. Results

Concentrations of 50, 150 and 300 ug/ml produced concentration-dependent reductions in APD at all doses (APD50 by up to 56% and APD90 up to 29% at HD; **Tables I.D1** and **I.D2**). Apparent (but not SS) reductions in RMP, APA, and Vmax were also seen at 0.5 Hz. The effects on APD were partially reversed following the washout period.

3. Conclusions

Concentrations of 50, 150 and 300 uM produced a concentration-dependent reduction in action potential duration in Purkinje fibers, which does not indicate a potential to prolong QT interval in vivo.

Table I.D1

b(4)

Effect of CEP-10953 on Action Potential Parameters in Isolated Dog Purkinje Fibers
Study Number: 1263DC36.001
Cephalon Study Number: DS-03-001

1.0 Hz

Treatment	n	RMP (mV)	OS (mV)	APA (mV)	V_{max} (mV/ms)	APD_{30} (ms)	APD_{50} (ms)	APD_{50} (% Change)#	APD_{90} (ms)	APD_{90} (% Change)#
Control	4	-91.3± 1.11	28.4± 1.10	119.6± 0.60	580.9± 59.74	75.7± 6.85	191.4± 6.69	0.0± 0.00	256.4± 1.65	0.0± 0.00
DMSO (0.2%)	4	-90.7± 1.16	27.4± 1.36	118.2± 0.99	549.2± 49.64	74.1± 10.99	190.3± 7.98	-0.6± 2.68	257.8± 3.00	0.5± 0.68
CEP-10953 (50 µM)	4	-90.2± 0.68	27.9± 1.45	118.1± 1.20	523.1± 56.96	63.7± 14.16	168.4± 11.86	-11.8± 3.28	240.5± 6.02	-6.7± 2.14*
CEP-10953 (150 µM)	4	-88.5± 0.71	26.3± 2.53	114.8± 2.04	497.9± 76.79	52.0± 10.39	133.0± 12.94*	-30.5± 4.99*	214.9± 3.89*	-16.6± 1.46*
CEP-10953 (300 µM)	4	-88.4± 1.83	27.4± 2.76	115.8± 0.97	536.5± 72.71	30.2± 4.60	98.9± 8.68*	-48.3± 3.00*	193.7± 2.73*	-24.9± 0.57*
Washout	4	-90.5± 1.21	28.3± 2.44	118.8± 1.73	550.8± 58.33	63.3± 14.33	174.1± 14.25	-8.9± 4.89	249.6± 4.34	-3.2± 0.84

Data are expressed as mean ± standard error of the mean
RMP = Resting Membrane Potential
OS = Overshoot
APA = Action Potential Amplitude
V_{max} = Maximum Rate of Depolarization of the Action Potential Upstroke
#Percentage changes for test article and washout were calculated from DMSO values.

APD_{30} = Action Potential Duration at 30% repolarization
APD_{50} = Action Potential Duration at 50% repolarization
APD_{90} = Action Potential Duration at 90% repolarization
* Statistically significant (P<0.05) change when compared to the DMSO group- ANOVA followed by Tukey HSD Multiple Comparison Test

Table I.D2

b(4)

Effect of CEP-10953 on Action Potential Parameters in Isolated Dog Purkinje Fibers
Study Number: 1263DC36.001
Cephalon Study Number: DS-03-001

0.5 Hz

Treatment	n	RMP (mV)	OS (mV)	APA (mV)	V_{max} (mV/ms)	APD_{30} (ms)	APD_{50} (ms)	APD_{50} (% Change)#	APD_{90} (ms)	APD_{90} (% Change)#
Control	4	-88.3± 1.21	28.3± 1.24	116.6± 1.11	547.2± 47.58	70.8± 10.77	213.5± 8.85	0.0± 0.00	289.1± 3.51	0.0± 0.00
DMSO (0.2%)	4	-88.4± 1.16	27.4± 1.43	115.8± 1.16	522.6± 52.59	66.7± 14.00	210.2± 10.02	-1.5± 3.38	288.7± 2.44	-0.1± 1.03
CEP-10953 (50 µM)	4	-88.3± 0.71	27.0± 1.54	115.3± 1.41	485.1± 51.69	57.6± 16.28	178.4± 14.37	-15.4± 3.86*	261.0± 8.33*	-9.5± 3.25*
CEP-10953 (150 µM)	4	-87.1± 1.51	26.4± 2.58	113.5± 1.89	512.9± 50.99	40.7± 10.28	138.9± 7.91*	-34.0± 0.67*	229.4± 1.70*	-20.5± 1.24*
CEP-10953 (300 µM)	4	-85.4± 2.37	27.1± 2.73	112.5± 0.48	442.6± 46.79	12.2± 2.05	92.2± 6.83*	-56.3± 1.50*	203.6± 2.16*	-29.4± 1.19*
Washout	4	-87.6± 1.10	28.4± 2.58	116.0± 1.79	537.5± 55.49	55.9± 16.82	188.4± 17.17	-10.9± 4.84	277.2± 2.50	-4.0± 0.62

Data are expressed as mean ± standard error of the mean
RMP = Resting Membrane Potential
OS = Overshoot
APA = Action Potential Amplitude
V_{max} = Maximum Rate of Depolarization of the Action Potential Upstroke
#Percentage changes for test article and washout were calculated from DMSO values.

APD_{30} = Action Potential Duration at 30% repolarization
APD_{50} = Action Potential Duration at 50% repolarization
APD_{90} = Action Potential Duration at 90% repolarization
* Statistically significant (P<0.05) change when compared to the DMSO group - ANOVA followed by Tukey HSD Multiple Comparison Test

E. Effects of CEP-10953 (R-modafinil) in the Irwin Test in Sprague Dawley Rats (Cephalon Study No. DS-03-002; conducted by [redacted], report dated 8/04; GLP) b(4)

1. Methods

Male rats (S-D; 6/dose) were administered (oral gavage) a single dose of 100, 300, or 1000 mg/kg CEP-10953; 20 mg/kg chlorpromazine; or vehicle (· s Suspending Vehicle) for the Irwin test. The parameters defined in the Irwin test were systematically evaluated for each rat at 1, 2, 4, and 8 h after dosing. In addition, 9 rats (3/dose) were included for T-K.

2. Results

Following treatment with CEP-10953, increased locomotor activity and increased startle response were observed at the LD or higher. In addition, stereotypic behavior characterized by sniffing at the bottom of the cage in 2/6 animals and straub tail in all animals was observed at the MD or greater. These effects were observed over the first 4

h of the study, returning to normal by 8 h postdose. The HD produced stereotypic behavior in all animals, however, by 8 h postdose, sensoromotor responses (reactions to sensory input) were decreased. Decreases in body tone were also observed. The signs of stereotypic behavior ranged from mild to severe between 2 and 8 h postdose. Mydriasis was observed at 8 h postdose in 3/6 animals. Dose-dependent increased activity was seen, and the peak effect for increased locomotor activity and stereotypy occurred at 4 h postdose. These effects were considered to be related to an exaggerated pharmacological (CNS) response. Plasma concentrations of R-modafinil and two primary circulating metabolites, R-modafinil acid and modafinil sulfone indicated nearly dose-proportional increases in systemic exposure to all three over the dose range. The AUC0–4 hr for R-modafinil, estimated from the mean plasma concentrations, was approximately 89, 268, and 618 ug.hr/ml at the LD, MD, and HD, respectively. Chlorpromazine (20 mg/kg, oral) produced effects consistent with its known pharmacological activity, attesting to the validity of the test system.

3. Conclusions

Following treatment with CEP-10953 at 100, 300, or 1000 mg/kg, general signs of central nervous system (CNS) stimulation were observed, including increased locomotor activity, increased startle response, and stereotypic behavior. In addition, at the MD or greater stereotypic behavior characterized by sniffing at the bottom of the cage in 2/6 animals and straub tail in all animals was observed. In the LD and MD these effects were observed over the first 4 h of the study, returning to normal by 8 h postdose; whereas in the HD, sensorimotor responses were decreased. The observed signs of CNS stimulation were consistent with an exaggerated pharmacologic effect.

II. PHARMACOKINETICS (primarily from sponsor's summary)

Pharmacokinetics for single oral doses of armodafinil (R-modafinil; suspension in [redacted] are shown below. b(4)

Table II.1

Table 2: Pharmacokinetic Parameters of Armodafinil after Single Oral Doses to Mice, Rats, and Dogs

	CD-1 mice[a] (n=4/timepoint)	Sprague Dawley rats (n=4/timepoint)			Beagle dogs[b] (n=4)	
Parameter[c,d]	50 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	10 mg/kg	25 mg/kg
C_{max} (µg/mL)	35.9	23.6	33.5	75.8	7.9 ± 0.7	21.0 ± 3.6
t_{max} (hr)	0.5	0.25	0.25	0.50	1.0 (0.25-1.5)	0.5 [0.5-1.0]
$t_{1/2}$ (hr)	1.4	0.32	0.55	0.63	1.5 ± 0.2	1.6 ± 0.2
$AUC_{0-\infty}$ (µg·hr/mL)	75.0	18.2	32.8	147.1	29.0 ± 5.1	91.2 ± 13.0
F (%)	ND[e]	57.7	52.0	116.6	108.1 ± 19.5	136.3 ± 22.9

[a] The parameter values shown for mice were obtained from preliminary experiments and are therefore considered to be estimates.
[b] Mean ± standard deviation, except median [range] for t_{max}
[c] C_{max}=maximum observed concentration; t_{max}=time of occurrence of C_{max}; $AUC_{0-\infty}$=area under the plasma concentration versus time curve from t=0 to infinity; $t_{1/2}$=elimination half-life; F=fraction bioavailable
[d] Calculated from composite data in mice and rats and for individual animals in dogs.
[e] ND=not determined.

The results of studies conducted for this application and the previous racemic modafinil NDA (20-717) indicate that R-modafinil is well absorbed and eliminated predominantly through metabolism via both hydrolytic and oxidative pathways, with primarily renal elimination of the metabolites. There were 2 major metabolites in all species examined: modafinil acid and modafinil sulfone. Neither was pharmacologically active in rodents. The hydrolytic reaction (hydrolysis of the amide to the corresponding acid) is esterase/amidase-catalyzed and enantioselective, but the relative preferences of the hydrolytic enzymes for R- or S-modafinil are species-specific. To a lesser extent oxidative microsomal enzymes also demonstrated some enantioselectivity. In rats and mice, the enantioselectivities for disappearance of parent compound observed in vitro in incubations of liver and plasma preparations were in opposing directions, with liver being enantioselective for R-modafinil and plasma for S-modafinil in both species. In vivo, S-modafinil was more rapidly cleared in mice than R-modafinil, while the opposite was true in rats, indicating that the competing enantioselective processes that control the elimination of the enantiomers have different balance points in the two species. In contrast, in dogs and humans, there was a clear preference for S-modafinil as a substrate in vitro, which is consistent with the longer half-life for R-modafinil in these species in vivo. There is minimal esterase/amidase activity in the plasma of the nonrodents. Like racemic modafinil, R-modafinil can induce hepatic CYP enzyme activity in vivo in mice, rats, and dogs, although it appeared to be a less potent inducer in mice and rats than the racemate or S-isomer. During studies of R-modafinil in rats and dogs, plasma concentrations of the parent compound generally decreased, sometimes markedly, after multiple doses, indicating auto-induction. The ratios of the concentrations of the parent compound to those of the 2 circulating metabolites did not consistently change after multiple-dose administration, suggesting either that the enzymes producing those metabolites did not change or that their elimination pathways were also being induced. At high doses in rats and dogs, there is evidence of saturability of elimination pathway(s).

In contrast to the substantial interspecies differences, as well as the differences between plasma and liver microsome activities, in the enantioselectivity observed in the hydrolysis of modafinil to modafinil acid, there was a clear preference for the S-enantiomer of modafinil as a substrate for conversion to modafinil sulfone in all the species tested. Formation rates of modafinil sulfone ranged from 50% (human) to 136% (rat) higher for S- vs R-modafinil, with relative rates in incubations with mouse liver microsomes nearly double those of dog or rat liver microsomes, and rates in human liver microsomes nearly an order of magnitude lower than the other species tested. This preference for S-modafinil conversion to modafinil sulfone in mice could at least

partially explain the in vivo results in that species, although it is possible that the lower plasma levels of S-modafinil could be due to absorption interactions between enantiomers.

Thus, there appear to be pharmacokinetic interactions between the two enantiomers of modafinil in vivo in rodents, particularly rats, that are not readily predicted from in vitro metabolism studies and could involve clearance mechanisms other than metabolism. In contrast, in vivo and in vitro results for dogs and humans are consistent, in that the metabolism of R-modafinil to either modafinil acid or modafinil sulfone predicts the greater in vivo plasma clearance of this enantiomer. There was no evidence of interconversion of the R and S enantiomers in vitro or in vivo.

Rodent

When oral doses of each enantiomer of modafinil were administered individually or together at the same dose as the racemate to rats and mice and plasma concentrations were determined, the resulting PK parameters for S-(d-) and/or R-(l-) modafinil after each dose are shown in **Table II.2**. After individual oral doses of 100 mg/kg of each enantiomer to rats, Cmax was nearly identical between the enantiomers. However, the R-enantiomer of modafinil was cleared (CL/F) twice as fast from plasma, with a correspondingly lower AUC. The difference in the plasma levels of the enantiomers was much reduced when the compounds were dosed together as the racemate. The mean Cmax for both compounds was reduced relative to that after individual dosing, but the difference was only statistically significant for S-modafinil. Although the AUC was still significantly different between the enantiomers when dosed as the racemate, it was reduced for S-modafinil, but increased for R-modafinil, as compared to dosing individually. In addition, the CL/F of R-modafinil after oral dosing as the racemate was significantly reduced relative to that after individual dosing. As opposed to the results in rats, levels of S-modafinil in mice were slightly, but not significantly, lower than those for R-modafinil after an oral dose of 100 mg/kg of the racemic mixture (**Table II.3**). Also unlike rats, the concentrations of both modafinil acid enantiomers in mice were substantial and showed relatively the same differences in levels throughout the experiment as were observed for the parent enantiomers (R/S ratio for both modafinil and modafinil acid was approximately 1.5). As previously observed in vitro, there was no evidence of interconversion of the enantiomers of modafinil in vivo, nor was the opposite enantiomer of modafinil acid detected when the compounds were dosed individually in either rats or mice.

Table II.2

Rats oral dose	C_{max} (µg/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	AUC_{0-inf} (µg·hr/mL)	CL/F (L/hr/kg)	MRT_{inf} (hr)
100 mg/kg of *d*-modafinil	29.38 1.99	0.5 0.0	0.96 0.25	52.49 12.42	1.99 0.55	1.78 0.59
d-modafinil after 200 mg/kg racemate	14.15[a] 0.52	0.7 0.3	1.87 0.51	43.80 12.26	2.41 0.64	2.98 0.88
100 mg/kg of *l*-modafinil	22.55 8.96	0.5 0.0	1.25 0.16	18.71[b] 3.90	5.52[b] 1.22	0.97 0.11
l-modafinil after 200 mg/kg racemate	13.68 1.31	0.5 0.0	1.38 0.51	26.34[b] 6.08	3.94[a,b] 0.85	2.32 0.94

Table II.3

Mice (composite values)	C_{max} (µg/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	AUC_{0-inf} (µg·hr/mL)	CL/F (L/hr/kg)	MRT_{inf} (hr)
d-modafinil (100 mg/kg of racemate)	17.79	1.0	1.61	55.38	0.90	2.63
l-modafinil	26.11	1.0	1.76	86.82	0.58	2.83

Dog

The pharmacokinetics of modafinil was evaluated in male beagle dogs after single oral (5, 15, or 30 mg/kg) or intravenous (5 mg/kg) doses. The samples were analyzed using a validated HPLC-UV method for total modafinil (R+S) and its 2 circulating metabolites, modafinil acid (R+S) and modafinil sulfone. In addition, the samples obtained after the 30-mg/kg oral dose and the second intravenous dose were analyzed for R-modafinil and S-modafinil. After an oral dose, the mean Cmax and AUC for total modafinil were dose-related but only the AUC was dose-proportional. The mean tmax for modafinil at the 3 dose levels was 1.8-2.2 hr postdose. The oral bioavailability of the 5-mg/kg oral dose was 74.5%. The mean apparent half-life was 1.70, 2.41, and 4.29 hr at 5, 15, and 30 mg/kg, respectively. After the iv dose, modafinil was eliminated in a virtually monophasic manner, with a mean half-life of 2.09 hr. Both modafinil acid and modafinil sulfone were detected after each oral or intravenous dose, at lower concentrations than those of the parent compound. When samples were re-analyzed using a [redacted] method for determination of the concentrations of the R- and S- enantiomers of modafinil, the AUC was larger and the half life longer for R- than for S-modafinil. After the oral dose, the mean Cmax was similar for the 2 enantiomers, but the AUCs for R- and S-modafinil were 70.0 and 38.1 µg·hr/ml, respectively **(Table II.4). The respective t1/2's were 5.01 and 3.52 hr. After the iv dose, the AUCs for R- and S-modafinil were 10.7 and 9.2 µg·hr/ml, respectively, and the respective t1/2's were 2.54 and** 2.09 hr.

b(4)

Table II.4

Table 24-1 Pharmacokinetic parameters of MO after a single oral administration (30 mg/kg)

Animal No.	Cmax	tmax	t1/2	AUC_{0-24}	$AUC_{0-\infty}$	CL/F	Vd/F
	µg/mL	hr	hr	µg·hr/mL	µg·hr/mL	mL/min	L
1	11.33	2.0	5.80	94.84	102.02	4.90	2.46
2	11.71	3.0	3.67	72.64	71.08	7.03	2.24
3	19.79	2.0	1.95	104.87	103.15	4.85	0.82
4	19.39	2.0	4.04	149.32	148.67	3.36	1.18
5	9.80	2.0	5.99	80.71	88.67	5.64	2.92
n	5	5	5	5	5	5	5
Mean	14.40	2.2	4.29	100.47	102.72	5.16	1.92
S.D.	4.79	0.4	1.66	30.01	28.77	1.34	0.89

Table 24-2 Pharmacokinetic parameters of MOA after a single oral administration (30 mg/kg)

Animal No.	Cmax	tmax	t1/2	AUC_{0-24}	$AUC_{0-\infty}$
	µg/mL	hr	hr	µg·hr/mL	µg·hr/mL
1	6.05	2.0	3.67	44.29	43.54
2	6.19	3.0	3.59	39.97	38.92
3	13.12	3.0	1.78	72.90	71.46
4	16.34	3.0	1.95	102.44	99.18
5	5.28	2.0	7.22	47.54	56.70
n	5	5	5	5	5
Mean	9.40	2.6	3.64	61.43	61.96
S.D.	5.01	0.5	2.19	26.27	24.36

Table 24-3 Pharmacokinetic parameters of MOS after a single oral administration (30 mg/kg)

Animal No.	Cmax	tmax	t1/2	AUC_{0-24}	$AUC_{0-\infty}$
	µg/mL	hr	hr	µg·hr/mL	µg·hr/mL
1	2.56	8.0	-	35.96	-
2	2.50	5.0	4.95	25.96	27.19
3	5.19	5.0	2.62	43.47	41.99
4	4.28	5.0	14.85	59.30	109.88
5	2.20	5.0	12.63	27.82	45.42
n	5	5	4	5	4
Mean	3.35	5.6	8.76	38.90	56.12
S.D.	1.32	1.3	5.89	13.56	36.78

-: Not calculable

Table 24-4 Pharmacokinetic parameters of *d*- MO after a single oral administration (30 mg/kg)

Animal No.	Cmax	tmax	t1/2	AUC_{0-24}	$AUC_{0-\infty}$	CL/F	Vd/F
	µg/mL	hr	hr	µg·hr/mL	µg·hr/mL	mL/min	L
1	5.22	2.0	4.14	34.12	34.09	7.33	2.63
2	5.37	3.0	3.68	30.68	29.98	8.34	2.66
3	9.44	1.0	1.93	40.09	40.92	6.11	1.02
4	9.56	2.0	2.51	50.63	49.15	5.09	1.10
5	4.64	2.0	5.35	34.05	36.14	6.92	3.20
n	5	5	5	5	5	5	5
Mean	6.85	2.0	3.52	37.91	38.06	6.76	2.12
S.D.	2.44	0.7	1.35	7.87	7.35	1.23	0.99

Table 24-5 Pharmacokinetic parameters of *l*-MO after a single oral administration (30 mg/kg)

Animal No.	Cmax	tmax	t1/2	AUC_{0-24}	$AUC_{0-\infty}$	CL/F	Vd/F
	µg/mL	hr	hr	µg·hr/mL	µg·hr/mL	mL/min	L
1	6.28	2.0	6.80	63.03	71.52	3.50	2.06
2	6.44	3.0	3.61	41.65	40.71	6.14	1.92
3	11.31	2.0	3.21	63.45	71.44	3.50	0.97
4	11.40	2.0	5.29	107.89	113.28	2.21	1.01
5	5.61	2.0	6.12	48.03	52.98	4.72	2.50
n	5	5	5	5	5	5	5
Mean	8.21	2.2	5.01	64.81	69.99	4.01	1.69
S.D.	2.89	0.4	1.56	25.88	27.50	1.48	0.67

*: p<0.05 (t-test, d-MO vs. l-MO, two-sided, paired)

Human

Racemic modafinil is currently approved for the treatment of excessive sleepiness associated with OSAHS, SWSD, or narcolepsy. Its therapeutic effects have been reported to diminish for some patients later in the day. In clinical pharmacology studies, in which racemic modafinil was administered and enantioselective bioanalysis for the individual enantiomers (R-modafinil and S-modafinil) was performed, it was observed that systemic exposure to R-modafinil is greater than that to S-modafinil and the t½ of R-modafinil is substantially longer than that of S-modafinil (approximately 15 and 4 hours, respectively; **Table II.5**). In PK studies with R-modafinil, systemic exposure to R-modafinil following multiple daily doses of armodafinil at 150 or 250 mg was found to be comparable to systemic exposure to R,S-modafinil following multiple daily doses of racemic modafinil at 200 or 400 mg. However, according to the sponsor, "R-modafinil and racemic modafinil have distinct plasma concentration-time profiles due to different rates of clearance between the R and S enantiomers, despite similar overall exposure. R-modafinil exhibits a lower peak concentration, which is offset by higher concentrations of R-modafinil at later times in the profile relative to modafinil." Therefore, it was theorized that the difference in the pharmacokinetics of racemic modafinil and R-modafinil may result in better tolerability, due to a lower maximum plasma concentration (Cmax), and more sustained effect. In addition, lower peak concentrations might reduce the potential for drug-drug interactions.

PK parameters for R-modafinil after oral administration of 100, 150, 200, 250, or 300 mg to healthy young men are shown in **Table II.6**. PK was essentially linear (dose-independent), with a tmax in each of the dose groups of ~6 hr. Levels of R-modafinil acid and modafinil sulfone were also measured; AUCs for these metabolites at 250 mg on Day 7 were 11.9 and 58.9 ug.h/ml, respectively (8 and 40% of parent). The tmax for all doses was longer than the tmax for (RS)-modafinil (~6 hours compared to 2 hours). After single oral doses of 50 to 400 mg in fasted young men (**Table II.7**), the PK of R-modafinil was essentially linear, with approximately dose-proportional increases in mean Cmax and AUC0-∞ in this dose range. R-modafinil appeared to be at or near steady state after 7 days of administration; however, the AUCs on days 7 and 14 of administration were slightly greater than would be predicted on the basis of the day-1 data (ie, CL/F was decreased).

The recommended dose of R-modafinil is 150 or 250 mg given once a day for patients with OSAHS or narcolepsy, and 150 mg/day for patients with SWSD. The recommended dose of Provigil is 200 mg/day, but doses up to 400 mg/day were well-tolerated in clinical trials (label).

Table II.5

Table A2: Tabular Summary of PROVIGIL Studies Contributing Pharmacokinetic Data on R-Modafinil

Study ID No. of centers Location Principal investigator Publications Start date Status	Primary study objective Study design	Number of subjects[a] Sex (M/F) Age: mean (range) (y)	Treatment : oral PROVIGIL dose (mg/day) (Fasting/fed)	N	Mean±SD pharmacokinetic parameters of R-modafinil[b]			Mean±SD pharmacokinetic parameters of S-modafinil[b]		
					C_{max} (µg/mL)	$t_{½}$ (h)	$AUC_{0-\infty}$ (µg·h/mL)	C_{max} (µg/mL)	$t_{½}$ (h)	$AUC_{0-\infty}$ (µg·h/mL)
CEP-2101 1 USA Keesal None 7 Aug 1993 Completed	Safety of modafinil, and pharmacokinetics of modafinil, R-modafinil, and S-modafinil after 7-day administration of modafinil Randomized, placebo-controlled, double-blind, ascending multiple-dose study	32 (32M/0F) 26 (20–39)	200 (fed day 1) 200 (fed day 7) 400 (fed day 1) 400 (fed day 7) 600 (fed day 1) 600 (fed day 7) 800 (fed day 1) 800 (fed day 3)[c] fed: 1 h after light breakfast	6 6 6 6 6 6 6 5	2.6 (0.5) 4.0 (0.6) 4.5 (0.6) 6.8 (1.6) 7.1 (1.3) 10 (2) 8.7 (0.8) NV	13 (2) 16 (2) 14 (4) 15 (2) 15 (1) 16 (1) 16 (2) 16 (2)	50 (12) 60 (12) 97 (28) 104 (29) 159 (29) 168 (41) 204 (33) NV	2.3 (0.3) 2.2 (0.2) 4.4 (0.7) 4.6 (1.2) 7.0 (1.5) 7.0 (1.1) 8.9 (1.0) NV	4.1 (1.0) 4.3 (0.9) 4.0 (0.8) 4.5 (1.0) 4.2 (0.5) 4.9 (0.7) 4.2 (0.2) 4.9 (0.4)	17 (3) 17 (2) 32 (8) 35 (14) 54 (11) 57 (13) 69 (9) NV
C153fa/103/ PK/US 1 USA Litka None 3 Jun 1994 Completed	The effect of age and gender on the modafinil, R-modafinil, and S-modafinil pharmacokinetic profiles after a single 200-mg dose of modafinil Open-label, parallel-group study	36 (24M/12F) Young men: 29.4 (22–37) Young women: 26.1 (19–40) Elderly men: 62.7 (53–72)	200 (fasted [young men]) 200 (fasted [young women]) 200 (fasted [elderly men]) Single doses	12 12 12	2.3 (0.44) 2.9 (0.32) 2.5 (0.41)	11.5 (2.4) 9.7 (1.7) 14.3 (2.6)	38.6 (10.4) 41.9 (7.7) 49.0 (9.2)	1.9 (0.44) 2.5 (0.39) 2.4 (0.47)	3.3 (0.6) 2.9 (0.4) 3.7 (1.0)	12.3 (3.2) 13.4 (2.0) 15.5 (2.9)
C153fa/106/ MD/US 1 USA Morgenroth None 11 Apr 1994 Completed	Safety of modafinil, and pharmacokinetics of modafinil, R-modafinil, and S-modafinil after 21-day administration of 400 mg modafinil after a single 200-mg dose Randomized, double-blind, placebo-controlled, parallel-group study	16 (8M/8F) modafinil: 28.8 (19–39) placebo: 30.8 (28–35)	400 (fed [men]) 400 (fed [women]) fed: 1 h after light breakfast 21 days of 400 mg/day, following a 200-mg single dose on day 1	6 6	5.5 (1.29) 7.2 (2.87)	14.8 (3.9) 12.5 (1.7)	82.6 (24.5) 102.2 (45)	3.9 (1.03) 4.9 (2.42)	4.5 (1.23) 3.5 (0.45)	29.3 (10.7) 35.4 (18.2)

[a] Withdrawals and abbreviations are described on the next page.

Table II.6

Table 7: Summary of Pharmacokinetic Parameters for CEP-10953, R-Modafinil Acid and Modafinil Sulfone in Healthy Young Men Administered Single Oral Doses of CEP-10953 at 100, 150, 200 or 300 mg or PROVIGIL at 200 mg (Pharmacokinetic Analysis Set)

Compound	Dose (mg)	n	C_{max} (µg/mL)	t_{max}[a] (hr)	AUC_{0-12} (µg·hr/mL)
CEP-10953	100	18	1.97 ± 0.25	5.5 [0.5-11.0]	20.1 ± 3.5
	150	18	2.99 ± 0.41	6.5 [3.0-11.0]	29.9 ± 4.6
	200	17	4.04 ± 0.69	6.0 [2.0-8.0]	42.4 ± 7.2
	300	18	6.37 ± 0.88	5.0 [3.0-12.0]	66.2 ± 8.5
R-Modafinil acid	100	18	<0.200[b]	NC	NC
	150	18	0.207 ± 0.120	6.0 [3.0-11.0]	1.3 ± 0.8[c]
	200	17	0.344 ± 0.111	6.0 [4.0-8.0]	2.7 ± 1.7[c]
	300	18	0.531 ± 0.213	6.0 [3.0-10.0]	5.3 ± 1.9[c]
Modafinil sulfone	100	18	<0.200[b]	NC	NC
	150	18	<0.200[b]	NC	NC
	200	17	0.283 ± 0.135	14.0 [13.0-14.0]	1.5 ± 0.9[c]
	300	18	0.443 ± 0.159	14.0 [11.0-14.0]	2.7 ± 1.5
PROVIGIL	200	18			
(RS)-Modafinil			4.35 ± 0.94	2.0 [0.5-6.0]	35.0 ± 6.7
(RS)-Modafinil acid			2.15 ± 0.37	4.0 [2.0-6.0]	18.2 ± 3.2
Modafinil sulfone			<0.200[b]	NC	NC

SOURCE: Pharmacokinetics Report, section 16.1.13.
[a] Median [range].
[b] Below the limit of quantitation of 0.200 µg/mL.
[c] Concentrations of the metabolite were not quantifiable over the entire 14-hr sampling interval in all subjects; the value shown is for AUC_{0-t}.
NC=Not calculable.

Table II.7

Table 7: Mean ± SD Pharmacokinetics Parameters for CEP-10953 in Healthy Young Men on the 1st, 7th, and 14th Days of Oral Administration at 50, 100, 200, 250, 300, or 400 mg Once Daily for up to 14 Consecutive Days (Pharmacokinetics Analysis Set)

Day	Dose (mg)	C_{max} (µg/mL)	AUC[a] (µg·hr/mL)	$t_{1/2}$[b] (hr)	CL/F (mL/min)	R	Median t_{max} (hr)
1	50	1.28 ± 0.20	21.3 ± 7.4	NC	43.0 ± 13.8	NA	1.3
	100	2.60 ± 0.35	41.8 ± 6.2	11.3 [10.3-12.1]	40.7 ± 6.2	NA	1.8
	200	4.54 ± 1.51	91.9 ± 33.0	15.9 [12.0-23.4]	39.4 ± 10.6	NA	1.3
	250	5.87 ± 0.68	129.2 ± 15.0	15.6 [13.6-17.4]	32.6 ± 4.0	NA	3.0
	300	6.48 ± 1.06	139.6 ± 9.5	14.6 [11.8-16.3]	36.0 ± 2.4	NA	1.5
	400	9.70 ± 1.80	200.1 ± 52.8	12.9 [9.4-19.5]	35.6 ± 11.6	NA	1.5
7	50	1.83 ± 0.23	25.4 ± 4.1	NC	33.6 ± 5.5	1.8 ± 0.2	2.0
	100	4.03 ± 0.67	54.2 ± 8.2	NC	31.4 ± 4.7	1.7 ± 0.1	0.5
	200	7.40 ± 2.17	111.8 ± 39.4	NC	32.4 ± 9.2	2.0 ± 0.2	2.0
	250	9.23 ± 0.73	148.3 ± 9.6	NC	28.2 ± 1.9	1.8 ± 0.1	3.0
	300	10.85 ± 1.27	165.4 ± 13.8	NC	30.4 ± 2.6	1.8 ± 0.2	2.3
	400[c]	13.39 ± 5.25	189.5 ± 77.8	14.7 [11.3-18.4]	41.5 ± 20.9	1.4 ± 0.5	2.3
14	50	1.78 ± 0.07	23.4 ± 3.4	14.4 [10.9-18.4]	36.2 ± 5.3	1.7 ± 0.3	1.3
	100	3.99 ± 0.88	56.2 ± 8.9	15.3 [13.8-19.6]	30.3 ± 4.8	1.8 ± 0.2	1.5
	200	7.36 ± 1.76	105.9 ± 25.0	20.2 [16.9-23.2]	33.0 ± 8.0	1.9 ± 0.2	1.8
	250	10.51 ± 2.35	136.1 ± 8.2	17.9 [14.6-22.1]	30.7 ± 1.9	1.6 ± 0.2	1.8
	300	9.99 ± 0.95	150.4 ± 12.7	15.3 [13.1-17.2]	33.4 ± 2.8	1.6 ± 0.1	2.5

SOURCE: Pharmacokinetics report, section 16.1.13.
[a] $AUC_{0-\infty}$ on day 1 and $AUC_{0-\tau}$ on days 7 and 14.
[b] Harmonic mean [range].
[c] Patients receiving the 400-mg/day dosage of CEP-10953 were discontinued on day 7 of administration.

III. TOXICOLOGY

A. Single dose oral toxicity study of optical isomers of CN-801 in rats with toxicokinetics study (Study No. B-4933; [redacted] Report Issued 1/28/03; [redacted] GLP) b(4)

1. Methods

The individual enantiomers of modafinil (CN-801) were administered once orally at doses of 0 ([redacted] vehicle), 500, 700, or 1100 mg/kg to S-D rats (5/sex/group) to compare their acute toxicity. In addition, satellite groups were included for determination of plasma concentrations of each isomer and the 2 major metabolites.

2. Results

a. Minimum Lethal Dose

Administration of S-modafinil produced no deaths in males while 2/5 females died at 1100 mg/kg. Administration of R-modafinil produced death in 1/5 males and 3/5 females at 1100 mg/kg (1 to 3 days after administration). Therefore, the minimum lethal dose was estimated to be higher than 1100 mg/kg in males and between 700 and 1100 mg/kg in females for S-modafinil, and 1100 mg/kg in males and between 700 and 1100 mg/kg in females for R-modafinil, indicating that minimum lethal dose was comparable between the 2 enantiomers.

b. Clinical Signs

Administration of either enantiomer was associated with an increase in spontaneous movement, hypersensitivity to noise, and stereotypy (repetition of the same actions such as self-biting, cage biting, and other behaviors in the cage) in all males and females at all dose levels. Prone position/lateral position and decrease in spontaneous movement were observed in males and females given the S- or R-isomer at 1100 mg/kg. In females that were given the S-isomer at 700 or 1100 mg/kg and in males and females that were given R-isomer at 700 or 1100 mg/kg, stereotypy-related changes such as swelling of hind limb, hemorrhage in nasal cavity or forelimb/hind limb, and loss of fingers in the forelimb were observed in some of the animals.

c. Pathology

In the animals that died, discoloration of the kidney (bilateral) was observed in 1 female with both the S- and R-isomer at 1100 mg/kg, and dark red foci in the glandular stomach in 1 female with the S-isomer at 1100 mg/kg, and in 1 male and 3 females with the R-isomer at 1100 mg/kg. Histopathological examination of the kidney and stomach, which was done on representative animals that died (1 female given S-isomer at 1100 mg/kg, and 1 male and 3 females given R-isomer at 1100 mg/kg), revealed vacuolation in proximal tubular epithelium or dilatation **of Henle's loop and distal tubules in the kidney and erosion in the glandular** stomach.

d. Plasma levels (**Table III.A1**)

For both S-(d-) and R-(l-) isomers, AUC increased greater than dose proportionally except in females given the S-isomer. Comparison of AUC between males and females revealed that it was higher in females than in males at all dose levels for the S-isomer, while it was comparable between males and

females at 1100 mg/kg and lower in females than in males at 500 and 700 mg/kg for R-isomer. Comparison of these values with those obtained in a previous TK study of racemic modafinil showed that the AUC of modafinil after administration of the S-isomer was comparable to that seen after racemic modafinil at all dose levels, while AUCs of the acid and sulfone metabolites after administration of the S-isomer were comparable to or higher than those seen after administration of racemic modafinil. After administration of the R-isomer, the AUC of modafinil was comparable to that seen after administration of racemic modafinil in males while it was lower in females at 500 and 700 mg/kg. For the acid and sulfone metabolites, AUCs after administration of the R-isomer was comparable to or lower than that of the racemate.

3. Conclusions

After acute oral administration of the S- and R-isomers of modafinil to rats, the minimum lethal dose was estimated to be higher than 1100 mg/kg in males and between 700 and 1100 mg/kg in females for the S-isomer, and 1100 mg/kg in males and between 700 and 1100 mg/kg in females for the R-isomer. Thus, the minimum lethal dose was comparable between the 2 isomers.

Table III.A1

Text Table 5-1. Summary of TK parameters

Sex	Male			Female		
Dose (mg/kg)	500	700	1100	500	700	1100
d-isomer of CN-801						
T_{max} (h)	1	4	4	4	4	2
C_{max} (μg/mL)	67.46	102.06	120.76	108.44	122.94	160.99
AUC_{0-24h} (μg·h/mL)	705.28	1128.48	1842.04	1459.49	1965.46	2490.06
Acid metabolite						
T_{max} (h)	1	1	1	2	2	8
C_{max} (μg/mL)	15.01	11.84	16.49	16.95	9.91	12.96
AUC_{0-24h} (μg·h/mL)	142.15	120.71	193.12	220.47	171.96	212.24
Sulfone metabolite						
T_{max} (h)	4	8	8	24	8	24
C_{max} (μg/mL)	41.07	59.72	85.65	24.07	30.42	58.94
AUC_{0-24h} (μg·h/mL)	595.34	1173.63	1540.83	468.11	575.42	918.81

Values are expressed as group mean.

Text Table 5-2. Summary of TK parameters

Sex	Male			Female		
Dose (mg/kg)	500	700	1100	500	700	1100
l-isomer of CN-801						
T_{max} (h)	1	4	8	4	4	8
C_{max} (μg/mL)	80.51	99.33	114.94	77.52	71.74	133.77
AUC_{0-24h} (μg·h/mL)	607.88	1162.29	1961.66	438.95	665.86	1922.90
Acid metabolite						
T_{max} (h)	1	4	8	4	4	8
C_{max} (μg/mL)	5.29	7.53	7.89	3.22	3.27	7.29
AUC_{0-24h} (μg·h/mL)	41.13	85.96	133.64	18.19	28.08	104.54
Sulfone metabolite						
T_{max} (h)	8	8	24	4	4	8
C_{max} (μg/mL)	17.88	28.63	50.14	5.49	4.53	20.15
AUC_{0-24h} (μg·h/mL)	249.58	597.58	994.72	34.46	47.49	283.84

Values are expressed as group mean.

B. 4-Week Oral Gavage Toxicity and Toxicokinetic Study with R-Modafinil in Rats (Study No. DS-03-027; [redacted] Study Number 6573-157; [redacted] Report Issued 11/5/04; GLP) b(4)

1. Methods

R-Modafinil was administered orally to rats (S-D) at doses of 0 (vehicle), 60, 200, or 600 mg/kg/day for 29 days. This study was designed to compare a new lot (Lot No. 03188K2a) with a [redacted] than that of the lot used in the 13-week study (Batch No. 02117K2a). Parameters included mortality, clinical observations, food consumption, body weights, clinical and anatomic pathology, and toxicokinetics. b(4)

2. Results

a. Mortality, Clinical Observations, and Body Weights

All animals survived until sacrifice on Day 30. The most prominent T-R observations were hyperactivity, pawing and/or biting of cage, and clear oral discharge at the MD or higher. Body weights were not significantly different among groups.

b. Clinical Pathology

i. Hematology
Decreases (SS) in RBCs, hemoglobin, and hematocrit; increases in reticulocytes (up to 3-fold), white blood cells, and lymphocytes at the MD and HD.

ii. Clinical Chemistry and Urinalysis
No clear T-R or toxicologically significant changes in clinical chemistry. Urine volume and pH appeared D-D increased at all doses (but NS). Increased incidences of urine occult blood were noted in HD males.

c. Toxicokinetics

Plasma was collected on Days 1 and 28 for T-K analysis; however, several samples collected on Day 28 "were not analyzed successfully during the period of established stability," so there are no data for that day. On Day 1, mean R-modafinil Cmax for LD, MD, and HD males and females were 11.86 and 29.69 ug/ml; 19.01 and 24.89 ug/ml; 33.97 and 19.49 ug/ml, respectively. Mean AUCs were 6.31 and 23.80 ug·hr/ml; 27.12 and 50.17 ug·hr/ml; 188.83 and 76.74 ug·hr/ml, respectively. These values were similar those determined at the beginning of the 13-week study at the same doses (see below).

d. Necropsy

T-R macroscopic findings were not observed. Increased liver, kidney, spleen, weights and decreased thymus weights were seen at all doses.

Microscopic findings consisted of increased incidences and/or severity of centrilobular hepatocellular hypertrophy at the HD (**Table III.B1**), increased renal tubular basophilia and proteinaceous casts at all doses (**Table III.B2**), and increased splenic extramedullary hematopoiesis at the MD and HD. Transitional cell hyperplasia and apoptosis of the urinary bladder were also seen at the MD and HD (**Table III.B3**). There was also an apparent increase in cardiomyopathy in HD females: 4/10 and 0/10 in M and F C vs 5/10 and 2/10 in M and F HD (only

C and HD examined). This was also seen in the 13-week study with both racemic and R-modafinil.

3. Conclusions

Administration of R-modafinil for 4 weeks produced CNS signs (hyperactivity and stereotypy), decreased RBCs and increased reticulocytes and WBCs, and microscopic changes in the liver (centrilobular hepatocellular hypertrophy at HD), kidney (renal tubular basophilia and proteinaceous casts at all doses), spleen (increased splenic extramedullary hematopoiesis at MD and HD), bladder (transitional cell hyperplasia and apoptosis in the urinary bladder at MD and HD) and possibly heart (cardiomyopathy at HD). The findings were generally similar to those in the 13-week rat toxicity study (below), indicating that the current lot (Lot No. 03188K2a), b(4)
, is comparable to the previous lot. There was no NOEL in this study, based on kidney histopathology at the LD, which produced exposures (AUCs) of 6.31 and 23.80 ug·hr/ml in males and females, which are approximately 1/25 and 1/6 the expected clinical exposure at the MRD of 250 mg.

Table III.B1

Incidence and Mean Severity () of Test Article-Related Microscopic Findings in the Liver - Terminal Sacrifice, Day 30

	Males				Females			
CEP-10953 (R-Modafinil)	0	60	200	600	0	60	200	600
Number Examined	10	10	10	10	10	10	10	10
Centrilobular hepatocellular hypertrophy	0 (0)	0 (0)	0 (0)	4 (0.4)	0 (0)	0 (0)	0 (0)	2 (0.2)

() = Average severity rating.

Table III.B2

Incidence and Mean Severity ()[a] of Test Article-Related Microscopic Findings in the Kidney - Terminal Sacrifice, Day 30

	Males				Females			
CEP-10953 (R-Modafinil)	0	60	200	600	0	60	200	600
Number Examined	10	10	10	10	10	10	10	10
Tubular Basophilia	5 (0.5)[a]	9 (0.9)	10 (1.2)	10 (2.6)	4 (0.4)	7 (0.7)	5 (0.5)	8 (1.1)
Tubular Proteinaceous Cast	0 (0)	2 (0.2)	2 (0.2)	8 (1.1)	0 (0)	1 (0.1)	0 (0)	4 (0.5)

a Average severity rating.

Table III.B3

Incidence and Mean Severity () of Test Article-Related Microscopic Findings in the Urinary Bladder - Terminal Sacrifice, Day 30

	Males				Females			
CEP-10953 (R-Modafinil)	0	60	200	600	0	60	200	600
Number Examined	9	10	10	10	10	10	10	10
Transitional epithelial hyperplasia	0 (0)	0 (0)	5 (0.5)	7 (0.9)	0 (0.1)	0 (0)	2 (0.2)	4 (0.5)
Transitional epithelial apoptosis	0 (0)	0 (0)	5 (0.5)	6 (0.9)	1 (0.1)	0 (0)	0 (0)	6 (0.9)

() = Average severity rating.

C. 13-Week Oral Gavage Toxicity and Toxicokinetic Study with CEP-10953 (R-modafinil) in Rats with a 4-Week Interim Sacrifice and a 4-Week Recovery Period (Reference Number DS-02-030; ——— Study Number 6573-146; conducted by ——— report dated 2/5/04; GLP) b(4)

1. Methods

Rats (S-D; 30/sex/group + 6/sex/group TK) were administered 0 (vehicle: 100 mg/kg racemic modafinil (Lot # 1538-DT1-1) or 60, 200, or 600 mg/kg R-modafinil (Batch No. 02117K2a) by oral gavage (10 ml/kg) for 4 or 13 weeks (groups 1-5). Toxicity endpoints included mortality, clinical observations, body weight, food consumption, clinical pathology, anatomic pathology, and toxicokinetic evaluations.

Doses were based on the results of a range-finding study in which oral doses of 100, 200, or 400 mg/kg were given to S-D rats for 10 days. D-R CNS signs (hyperactivity, stereotypy) were seen in all treated-groups. There was no effect of treatment on body weight gain. There was a decrease in red cell parameters at the HD and a D-R increase in the total white cell counts in all treated males, which reflected increases in neutrophils, basophils, lymphocytes and/or monocytes. Treated males and females had increased liver weights (more pronounced in males). The effects observed were similar to those observed with the racemic modafinil. Plasma concentrations of the parent and 2 metabolites tended to be lower after repeated dosing, and plasma concentrations of (R)-modafinil acid and modafinil sulfone were higher in males than in females. Based on these results, 600 mg/kg was estimated to be an MTD.

2. Results

a. Observations

Six deaths occurred during the study, 5 as a result of dosing accidents and the sixth from pylonephritis, which was not considered T-R. T-R clinical signs included hyperactivity, repeated pawing or biting of the front or the bottom of the cage, and clear oral discharge in a D-R manner at all doses of R-modafanil and in the modafanil group. All the observations resolved during the recovery period.

b. Body Weights

BW gain was statistically significantly decreased in MD and HD R-modafanil and modafinil males compared to C (BW gain D1-92 = 352, 292, 345, 311, and 275 in groups 1-5, respectively). At the end of the dosing period, BWs for males given modafinil or MD or HD R-modafinil were lower (11, 8, and 14%, respectively) than control males. There was no effect in females, however, despite higher exposures to parent (BW gain D1-92 = 135, 133, 137, 134, and 128 in groups 1-5, respectively).

c. Toxicokinetics

The results of TK analyses are shown in **Table III.C1**. Week 4 TK parameters could only be determined in the HD R-modafinil dose group due to technical problems. R-modafinil (armodafinil) exposures were generally greater in females than in males. There was no evidence of autoinduction in this study; however, in the 10-day dose range-finding study, there was some decrease in exposure over time (**Table III.C2**). WK13 AUCs for R-modafinil acid were 0.5, 4.1, and 11.7 and 0.2, 3.4, and 17.9 ug.h/ml in males and females at the LD, MD, and HD, respectively. WK13 AUCs for R-modafinil sulfone were ND, 2.8, and 25.8 and ND, 0.1, and 8.4 ug.h/ml in males and females at the LD, MD, and HD,

respectively. After racemic modafinil (CEP-1538), concentrations of CEP-1538, (RS)-modafinil acid, and modafinil sulfone were consistent with those seen previously in rats (**Table III.C3**). Unfortunately, R-modafanil was not measured after administration of the racemate, but previous rat PK data indicate that the AUC of the R-enantiomer is about 1/2 that of the S-enantiomer after administration of the racemate due to stereoselective metabolism. In rats, R- is more rapidly cleared than S-modafinil. In contrast, in dogs and humans R- has a longer half-life than S-modafinil.

Table III.C1

Table 3: Mean C_{max} and AUC of armodafinil on Day 1 and Weeks 4 and 13 of Administration in a 13-Week Oral Toxicity and Toxicokinetic Study of armodafinil in Male and Female Rats

Dose (mg/kg)	Day 1				Week 4				Week 13			
	C_{max} (µg/mL)		$AUC_{0-\infty}$ (µg•hr/mL)		C_{max} (µg/mL)		AUC_{0-t} (µg•hr/mL)		C_{max} (µg/mL)		AUC_{0-t} (µg•hr/mL)	
	M	F	M	F	M	F	M	F	M	F	M	F
60	10.14	5.67	5.6	3.1	NV	NV	NV	NV	10.99	15.04	11.3	8.5
200	17.90	16.14	30.2	19.1	NV	NV	NV	NV	40.56	48.35	48.0	67.1
600	60.75	36.42	89.6	118.6	24.90	51.26	110.2	185.8	31.02	41.81	127.0	186.8

C_{max} = maximum observed plasma concentration; AUC = area under the plasma concentration versus time curve; M = male; F = female; NV= no value

Table III.C2

Table 2: Mean C_{max}, t_{max} and AUC of armodafinil on Days 1 and 10 of Administration in a 10-Day Oral Range-Finding Toxicity/Toxicokinetic Study of CEP-10953 in Male and Female Rats

Sex	Day	Dose (mg/kg/day)	C_{max} (µg/mL)	t_{max} (hr)	$AUC_{0-\infty}$ or AUC_{0-t} (µg•hr/mL)
Male	1	100	16.94	0.5	25.8
		200	24.83	0.5	65.5
		400	35.54	0.5	119.3
	10	100	10.46	0.5	15.7
		200	12.52	0.5	27.7
		400	12.73	1.0	60.8
Female	1	100	25.67	0.5	27.9
		200	43.38	1.0	90.2
		400	56.24	0.5	145.7
	10	100	12.61	0.5	18.2
		200	21.94	0.5	56.2
		400	28.73	0.5	111.9

C_{max} = maximum observed plasma concentration; t_{max} = time of C_{max}; AUC = area under the plasma concentration versus time curve

Table III.C3

Table 1 Composite pharmacokinetic parameters for (RS)-modafinil, (RS)-modafinil acid and modafinil sulfone in male and female rats on Day 1 and during Weeks 4 and 13 of daily oral administration at 400 mg/kg/day of (RS)-modafinil

Compound	Sex	Day	Group	Dose (mg/kg/day)	C_{max} (µg/mL)	t_{max} (hr)	AUC_{0-t} (µg•hr/mL)
Modafinil	Male	D1	6	400	47.53	0.5	135.1
		WK4			NV	NV	NV
		WK13			17.65	0.5	81.1
Modafinil Acid	Male	D1	6	400	10.54	0.5	42.7
		WK4			10.10	0.5	33.6
		WK13			5.24	0.5	17.8
Modafinil Sulfone	Male	D1	6	400	7.33	8.0	38.2
		WK4			15.55	2.0	79.8
		WK13			15.00	4.0	77.5
Modafinil	Female	D1	6	400	46.82	0.5	159.3
		WK4			NV	NV	NV
		WK13			26.42	1.0	126.8
Modafinil Acid	Female	D1	6	400	9.22	0.5	47.0
		WK4			17.88	4.0	94.6
		WK13			8.03	1.0	34.6
Modafinil Sulfone	Female	D1	6	400	0.30	2.0	0.3
		WK4			9.27	4.0	47.5
		WK13			7.11	4.0	41.5

NV: No Value

d. Clinical Pathology

i. Hematology

R-modafinil (CEP-10953) treatment was associated with decreased RBCs, hemoglobin, and hematocrit and increased WBCs and lymphocytes (SS at MD and HD; **Table II.C4**). These effects were generally reversible. Modafinil (CEP-1538) produced similar effects that were generally comparable in magnitude to those observed at the MD or HD of R-modafinil.

Table III.C3 Summary of Hematology

Summary of Clinical Hematology Data

Test Article	Control	CEP-1538	CEP-10953			CEP-1538		CEP-10953	
Group	1	2	3	4	5	6	7	8	9
Level (mg/kg/day)	0	400	60	200	600	400	60	200	600

Group		RBC (E6/UL) Week 5	RBC (E6/UL) Week 14	RBC (E6/UL) Week 18	HGB (G/DL) Week 5	HGB (G/DL) Week 14	HGB (G/DL) Week 18	HCT (%) Week 5	HCT (%) Week 14	HCT (%) Week 18
1M	Mean	8.05	8.55	8.78	15.9	15.4	15.4	45.7	46.0	45.9
	SD	0.380	0.478	0.519	0.65	0.68	0.93	1.95	1.76	2.30
	N	9	20	5	9	20	5	9	20	5
2M	Mean	7.11*	7.00*	8.50	14.2*	13.6*	16.0	40.9*	40.3*	47.4
	SD	0.432	0.368	0.188	0.68	0.76	0.36	2.00	2.15	0.62
	N	10	19	5	10	19	5	10	19	5
3M	Mean	7.87	8.50	8.82	15.6	15.0	15.5	44.6	45.3	45.9
	SD	0.436	0.463	0.586	0.53	0.76	0.94	1.21	2.23	2.17
	N	10	20	5	10	20	5	10	20	5
4M	Mean	7.53*	7.99*	8.87	15.0*	14.6*	15.6	42.3*	43.6*	46.1
	SD	0.366	0.444	0.290	0.43	0.59	0.52	1.48	2.84	1.06
	N	10	19	5	10	19	5	10	19	5
5M	Mean	6.87*	6.59*	8.87	14.4*	13.4*	16.2	40.5*	39.4*	47.9
	SD	0.372	0.422	0.310	0.37	0.88	0.66	1.29	2.45	1.60
	N	10	20	5	10	20	5	10	20	5
Statistics		P	P	P	P	P	P	P	P	P

*= P ≤ 0.05
P = ANOVA (and Dunnetts, if applicable)

Group		PLT (E3/UL) Week 5	PLT (E3/UL) Week 14	PLT (E3/UL) Week 18	WBC (E3/UL) Week 5	WBC (E3/UL) Week 14	WBC (E3/UL) Week 18	N-SEG (E3/UL) Week 5	N-SEG (E3/UL) Week 14	N-SEG (E3/UL) Week 18
1M	Mean	1165	1274	1251	6.6	7.7	6.7	0.8	1.2	1.4
	SD	101.8	161.9	102.8	1.95	2.57	1.91	0.27	0.44	1.16
	N	9	20	5	9	20	5	9	20	5
2M	Mean	1272	1201	1215	14.4*	12.1*	7.5	2.1*	1.6	1.1
	SD	143.6	103.3	129.2	3.20	2.66	1.10	1.22	0.73	0.41
	N	10	19	5	10	19	5	10	19	5
3M	Mean	1262	1284	1290	8.7	9.6	10.0*	1.1	1.7	0.9
	SD	178.9	135.4	229.6	2.90	3.11	1.40	0.41	1.51	0.22
	N	10	20	5	10	20	5	10	20	5
4M	Mean	1471*	1261	1351	10.5*	10.8*	7.0	1.4*	1.8	1.1
	SD	303.0	140.1	90.5	2.13	2.85	1.38	0.51	1.82	0.19
	N	10	19	5	10	19	5	10	19	5
5M	Mean	1255	1184	1269	12.6*	12.8*	7.4	2.0*	1.9	1.2
	SD	149.4	109.6	143.1	4.76	2.61	2.11	0.88	0.56	0.48
	N	10	20	5	10	20	5	10	20	5
Statistics		P	P	P	PK	P	P	PK	P	P

Table III.C3(cont.) Summary of Hematology

Group		RBC (E6/UL) Week 5	RBC (E6/UL) Week 14	RBC (E6/UL) Week 18	HGB (G/DL) Week 5	HGB (G/DL) Week 14	HGB (G/DL) Week 18	HCT (%) Week 5	HCT (%) Week 14	HCT (%) Week 18
1F	Mean	7.73	8.10	8.39	15.7	15.3	16.0	45.0	45.4	46.8
	SD	0.447	0.302	0.212	0.60	0.47	0.42	1.69	1.47	1.09
	N	9	20	5	9	20	5	9	20	5
2F	Mean	6.59*	6.40*	8.39	14.0*	13.6*	16.1	39.9*	40.2*	47.1
	SD	0.349	0.322	0.436	0.71	0.76	0.49	2.01	2.05	1.20
	N	9	20	5	9	20	5	9	20	5
3F	Mean	7.72	7.91	8.15	15.6	15.1	15.6	44.6	44.7	45.7
	SD	0.302	0.279	0.340	0.69	0.53	0.66	1.54	1.84	1.86
	N	9	20	5	9	20	5	9	20	5
4F	Mean	7.56	7.50*	8.11	15.2	14.7*	15.8	43.9	43.7*	46.0
	SD	0.342	0.322	0.282	0.43	0.45	0.48	1.46	1.48	1.41
	N	10	20	5	10	20	5	10	20	5
5F	Mean	6.77*	6.76*	8.26	14.3*	14.0*	16.5	41.3*	41.3*	48.0
	SD	0.376	0.436	0.536	0.55	0.63	0.36	1.99	2.03	1.23
	N	10	20	5	10	20	5	10	20	5
Statistics		P	P	P	P	PK	P	P	P	P

Group		PLT (E3/UL) Week 5	PLT (E3/UL) Week 14	PLT (E3/UL) Week 18	WBC (E3/UL) Week 5	WBC (E3/UL) Week 14	WBC (E3/UL) Week 18	N-SEG (E3/UL) Week 5	N-SEG (E3/UL) Week 14	N-SEG (E3/UL) Week 18
1F	Mean	1169	1234	1195	5.5	6.3	6.3	0.7	1.7	0.6
	SD	205.3	112.4	122.9	0.84	2.02	1.43	0.32	1.74	0.26
	N	9	20	5	9	20	5	9	20	5
2F	Mean	1304	1113*	1262	9.2*	6.8	6.0	1.0	0.9	0.7
	SD	159.2	116.2	148.2	1.34	1.42	1.00	0.38	0.40	0.36
	N	9	20	5	9	20	5	9	20	5
3F	Mean	1155	1202	1217	6.2	5.4	5.9	0.7	0.6*	0.4
	SD	95.5	115.8	97.9	1.68	1.89	1.21	0.27	0.24	0.09
	N	9	20	5	9	20	5	9	20	5
4F	Mean	1144	1182	1192	6.5	6.3	6.3	0.8	0.8	0.8
	SD	328.5	151.9	167.2	1.85	1.86	0.45	0.80	0.66	0.25
	N	10	20	5	10	20	5	10	20	5
5F	Mean	1122	1076*	1168	10.6*	7.4	6.3	1.1	1.1	0.6
	SD	288.5	220.5	79.0	2.16	1.74	0.47	0.46	0.82	0.24
	N	10	20	5	10	20	5	10	20	5
Statistics		P	P	P	P	P	P	P	PK	P

ii. Clinical Chemistry

Cholesterol, protein, bilirubin, I PHOS, CA and GGT were increased in R-modafinil (all doses) and racemic modafinil groups.

e. Necropsy

i. Organ Weights

Treatment-related increases in liver, kidney, and spleen weights were seen at all doses of R-modafanil and in the modafanil group (**Table III.C5**). These increases correlated with microscopic changes in these organs.

Table III.C5

Summary of Organ Weight Data (g)

Terminal Sacrifice

Test Article	Control	CEP-1538	CEP-10953		CEP-1538		CEP-10953	
Group	1	2	3	4	5	6	7	8	9
Level (mg/kg/day)	0	400	60	200	600	400	60	200	600

Organ		Group 1M	Group 2M	Group 3M	Group 4M	Group 5M	Statistic
to BR	Mean	6.58322	9.89575*	7.16230	7.31935	8.89570*	P
Ratio	SD	0.880295	0.958972	0.645872	0.663222	0.815136	
	N	15	14	15	14	15	
KIDNEY	Mean	3.5194	4.6164*	3.7329	3.8775	4.6896*	P
	SD	0.52465	0.48106	0.35957	0.36330	0.50649	
	N	15	14	15	14	15	
to TBW	Mean	0.64562	0.95233*	0.72772*	0.79367*	1.08302*	P
(%)	SD	0.048984	0.082415	0.060439	0.082964	0.096068	
	N	15	14	15	14	15	
to BR	Mean	1.61673	2.09166*	1.73512	1.76874	2.14163*	P
Ratio	SD	0.184827	0.226095	0.163614	0.131025	0.224790	
	N	15	14	15	14	15	
SPLEEN	Mean	0.8908	1.3986*	0.9329	0.9313	1.4363*	P
	SD	0.22917	0.19167	0.12344	0.23681	0.26304	
	N	15	14	15	14	15	
to TBW	Mean	0.16234	0.30821*	0.18240	0.19008	0.32208*	PK
(%)	SD	0.029771	0.035420	0.027468	0.042794	0.059600	
	N	15	14	15	14	15	

*= P < 0.05
K = rank-transformed data
P = ANCOVA (and Dunnetts, if applicable)

Organ		Group 1F	Group 2F	Group 3F	Group 4F	Group 5F	Statistic
to BR	Mean	3.96527	5.88435*	4.10185	4.17361*	5.34939*	PK
Ratio	SD	0.360301	0.723870	0.261568	0.273978	0.542451	
	N	15	15	15	15	15	
KIDNEY	Mean	1.9854	2.4132*	1.9235	2.1067	2.3312*	PK
	SD	0.14021	0.26770	0.16735	0.23013	0.19618	
	N	15	15	15	15	15	
to TBW	Mean	0.72223	0.91254*	0.67219	0.77092	0.90891*	P
(%)	SD	0.040369	0.114632	0.042239	0.067991	0.085801	
	N	15	15	15	15	15	
to BR	Mean	1.00647	1.19328*	0.95920	1.04314	1.16138*	PK
Ratio	SD	0.067076	0.133872	0.066736	0.103717	0.089039	
	N	15	15	15	15	15	
SPLEEN	Mean	0.5395	0.9036*	0.5834	0.6323	0.7881*	P
	SD	0.08753	0.19686	0.08516	0.08947	0.13464	
	N	15	15	15	15	15	
to TBW	Mean	0.19628	0.34618*	0.20481	0.23102*	0.30339*	P
(%)	SD	0.031628	0.033747	0.028500	0.028198	0.040136	
	N	15	15	15	15	15	

* P < 0.05

ii. Gross Pathology

No T-R macroscopic changes were reported.

iii. Microscopic Pathology

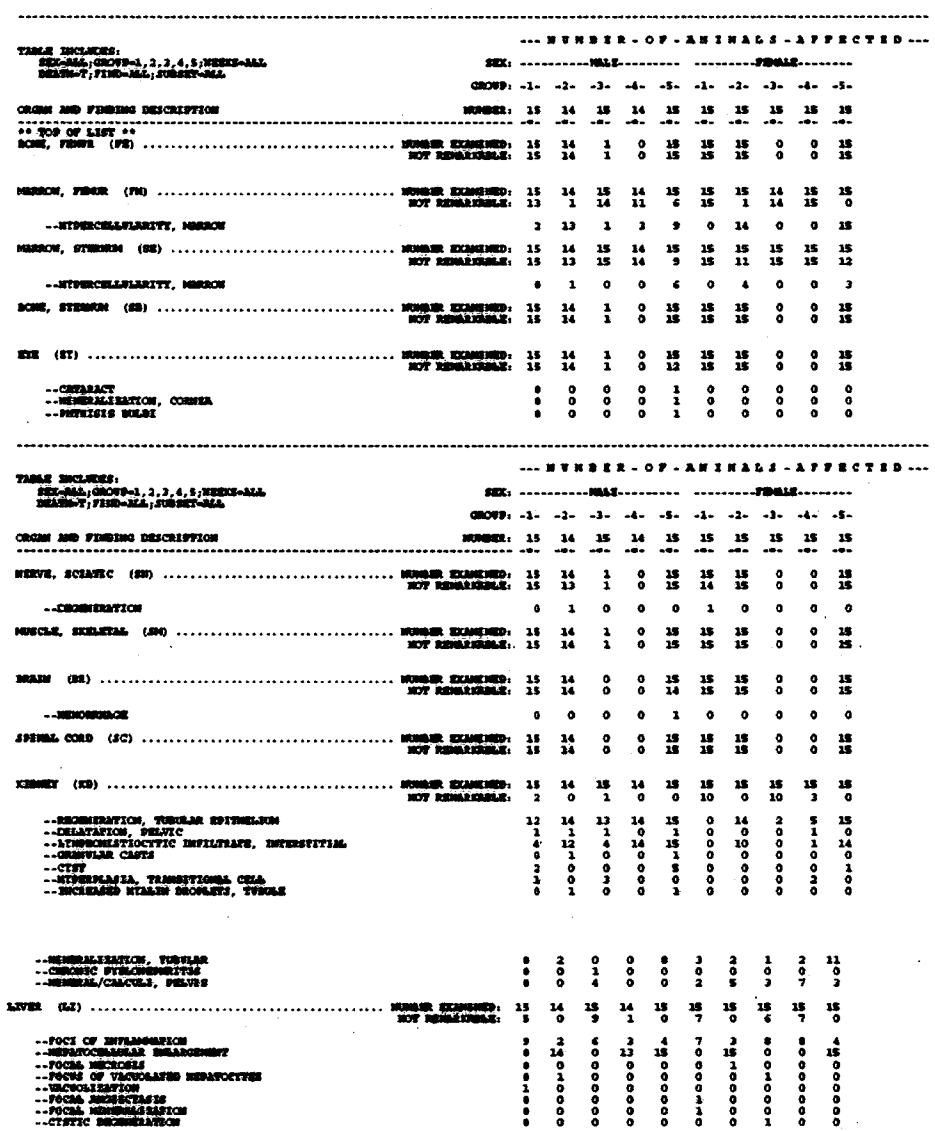
T-R microscopic findings observed at the interim sacrifice consisted of increased cellularity of bone marrow in the racemate and HD R-modafinil groups; hepatocellular hypertrophy and focal necrosis in the racemate and MD and HD R-modafinil groups; and increased splenic hematopoiesis and pigment, increased nephropathy (tubular regeneration, chronic inflammation), and hyperplasia and increased apoptosis of the urinary bladder urothelium in the racemate and all R-modafinil groups.

Similar changes were seen at terminal sacrifice (**Table III.C6**): increased cellularity of bone marrow and hypertrophy of thyroid follicular epithelium in the racemate and HD R-modafinil groups; hepatocellular hypertrophy, and increased splenic hematopoiesis and pigment in racemate and MD and HD R-modafinil groups; and increased renal tubular regeneration

and mineralization and hyperplasia and increased apoptosis of the urinary bladder urothelium in racemate and all R-modafinil groups. There also appeared to be an increased incidence of cardiomyopathy in racemate and HD R-modafinil animals at termination, and this was still seen after recovery (**Table III.C7**). Kidney and bladder changes were still somewhat increased in incidence and severity in treated animals, particularly females, after the recovery period.

Table III.C6

Incidence of Microscopic Observations - Terminal Sacrifice



PAGE: 1

TABLE INCLUDES: SEX=ALL;GROUP=1,2,3,4,5;WEEK=ALL DEATH=T;FIND=ALL;SUBSET=ALL		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE---------				
ORGAN AND FINDING DESCRIPTION	GROUP: / NUMBER:	-1- / 15	-2- / 14	-3- / 15	-4- / 14	-5- / 15	-1- / 15	-2- / 15	-3- / 15	-4- / 15	-5- / 15
** TOP OF LIST **											
BONE, FEMUR (FE)	NUMBER EXAMINED:	15	14	1	0	15	15	15	0	0	15
	NOT REMARKABLE:	15	14	1	0	15	15	15	0	0	15
MARROW, FEMUR (FM)	NUMBER EXAMINED:	15	14	15	14	15	15	15	14	15	15
	NOT REMARKABLE:	13	1	14	11	6	15	1	14	15	0
--HYPERCELLULARITY, MARROW		2	13	1	3	9	0	14	0	0	15
MARROW, STERNUM (SE)	NUMBER EXAMINED:	15	14	15	14	15	15	15	15	15	15
	NOT REMARKABLE:	15	13	15	14	9	15	11	15	15	12
--HYPERCELLULARITY, MARROW		0	1	0	0	6	0	4	0	0	3
BONE, STERNUM (SB)	NUMBER EXAMINED:	15	14	1	0	15	15	15	0	0	15
	NOT REMARKABLE:	15	14	1	0	15	15	15	0	0	15
EYE (ET)	NUMBER EXAMINED:	15	14	1	0	15	15	15	0	0	15
	NOT REMARKABLE:	15	14	1	0	12	15	15	0	0	15
--CATARACT		0	0	0	0	1	0	0	0	0	0
--MINERALIZATION, CORNEA		0	0	0	0	1	0	0	0	0	0
--PHTHISIS BULBI		0	0	0	0	1	0	0	0	0	0

TABLE INCLUDES: SEX=ALL;GROUP=1,2,3,4,5;WEEK=ALL DEATH=T;FIND=ALL;SUBSET=ALL		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE---------				
ORGAN AND FINDING DESCRIPTION	GROUP: / NUMBER:	-1- / 15	-2- / 14	-3- / 15	-4- / 14	-5- / 15	-1- / 15	-2- / 15	-3- / 15	-4- / 15	-5- / 15
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	15	14	1	0	15	15	15	0	0	15
	NOT REMARKABLE:	15	13	1	0	15	14	15	0	0	15
--DEGENERATION		0	1	0	0	0	1	0	0	0	0
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	15	14	1	0	15	15	15	0	0	15
	NOT REMARKABLE:	15	14	1	0	15	15	15	0	0	15
BRAIN (BR)	NUMBER EXAMINED:	15	14	0	0	15	15	15	0	0	15
	NOT REMARKABLE:	15	14	0	0	14	15	15	0	0	15
--HEMORRHAGE		0	0	0	0	1	0	0	0	0	0
SPINAL CORD (SC)	NUMBER EXAMINED:	15	14	0	0	15	15	15	0	0	15
	NOT REMARKABLE:	15	14	0	0	15	15	15	0	0	15
KIDNEY (KI)	NUMBER EXAMINED:	15	14	15	14	15	15	15	15	15	15
	NOT REMARKABLE:	2	0	1	0	0	10	0	10	3	0
--DEGENERATION, TUBULAR EPITHELIUM		12	14	13	14	15	0	14	2	5	15
--DILATATION, PELVIC		1	1	1	0	1	0	0	0	1	0
--LYMPHOCYTIC INFILTRATE, INTERSTITIAL		4	12	4	14	15	0	10	0	1	14
--GRANULAR CASTS		0	1	0	0	1	0	0	0	0	0
--CYST		2	0	0	0	5	0	0	0	0	1
--HYPERPLASIA, TRANSITIONAL CELL		1	0	3	0	0	0	0	0	2	0
--INCREASED HYALIN DROPLETS, TUBULE		0	1	0	0	1	0	0	0	0	0
--MINERALIZATION, TUBULAR		0	2	0	0	0	3	2	1	2	11
--CHRONIC PYELONEPHRITIS		0	0	1	0	0	0	0	0	0	0
--MINERAL/CASTS, PELVIS		0	0	4	0	0	2	5	3	7	3
LIVER (LI)	NUMBER EXAMINED:	15	14	15	14	15	15	15	15	15	15
	NOT REMARKABLE:	5	0	9	1	0	7	0	6	7	0
--FOCI OF INFLAMMATION		9	2	6	3	4	7	2	8	8	4
--HEPATOCELLULAR ENLARGEMENT		0	14	0	13	15	0	15	0	0	15
--FOCAL NECROSIS		0	0	0	0	0	0	1	0	0	0
--FOCUS OF VACUOLATED HEPATOCYTES		0	1	0	0	0	0	0	1	0	0
--VACUOLIZATION		1	0	0	0	0	0	0	0	0	0
--FOCAL INFARCTION		0	0	0	0	0	1	0	0	0	0
--FOCAL MINERALIZATION		0	0	0	0	0	1	0	0	0	0
--CYSTIC DEGENERATION		0	0	0	0	0	0	0	1	0	0

TABLE INCLUDES: SEX=MAL;GROUP=1,2,3,4,5;WEEKS=ALL DEATH=T;FIND=ALL;SUBSET=ALL		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	15	14	15	14	15	15	15	15	15	15
ESOPHAGUS (ES)	NUMBER EXAMINED:	15	14	0	0	15	15	15	0	0	15
	NOT REMARKABLE:	15	14	0	0	15	15	15	0	0	15
THYROID (TT)	NUMBER EXAMINED:	15	14	15	14	15	15	15	15	15	15
	NOT REMARKABLE:	15	9	15	14	8	15	8	15	15	7
--HYPERTROPHY,FOLLICULAR CELL		0	5	0	0	7	0	7	0	0	8
PARATHYROID (PT)	NUMBER EXAMINED:	7	11	0	0	12	12	14	0	0	12
	NOT REMARKABLE:	7	11	0	0	12	12	14	0	0	12
HEART (HT)	NUMBER EXAMINED:	15	14	0	0	15	15	15	1	0	15
	NOT REMARKABLE:	13	11	0	0	9	14	13	0	0	14
--CHRONIC CARDIOMYOPATHY		2	3	0	0	5	1	1	0	0	1
--CHRONIC INFLAMMATION, EPICARDIUM		0	0	0	0	1	0	0	0	0	0
--NECROSIS		0	0	0	0	0	0	1	0	0	0
--GRANULOMA SARCOID		0	0	0	0	0	0	0	1	0	0
TONGUE (TO)	NUMBER EXAMINED:	15	14	0	0	15	15	14	0	0	15
	NOT REMARKABLE:	11	6	0	0	11	6	10	0	0	10
--HEMORRHAGE		4	8	0	0	4	9	4	0	0	5
--INFLAMMATION, ACUTE		0	0	0	0	0	1	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	15	13	15	14	15	15	15	15	15	15
	NOT REMARKABLE:	15	2	5	1	1	15	3	11	3	0
--HYPERPLASIA, DIFFUSE, UROTHELIUM		0	7	8	13	14	0	12	3	12	15
--APOPTOSIS, INCREASED, UROTHELIUM		0	8	3	13	12	0	1	1	3	6
--INFILTRATE, LYMPHOHISTIOCYTIC		0	1	1	0	1	0	0	0	0	0
--EPITHELIAL HYPERPLASIA, UROTHELIUM		0	0	1	0	0	0	0	0	0	0
--CALCULI		0	0	1	0	0	0	0	0	0	0

Table III.C7

Recovery Sacrifice

TABLE INCLUDES: SEX=MAL;GROUP=1,2,3,4,5;WEEKS=ALL DEATH=F;FIND=ALL;SUBSET=ALL		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	5	5	5	5	5	5	5	5	5	5
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	5	5	0	0	5	5	5	0	0	5
	NOT REMARKABLE:	5	5	0	0	5	5	5	0	0	5
BRAIN (BR)	NUMBER EXAMINED:	5	5	0	0	5	5	5	0	0	5
	NOT REMARKABLE:	5	5	0	0	5	5	5	0	0	5
SPINAL CORD (SC)	NUMBER EXAMINED:	5	5	0	0	5	5	5	0	0	5
	NOT REMARKABLE:	5	5	0	0	5	5	5	0	0	5
KIDNEY (KD)	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5	5
	NOT REMARKABLE:	0	0	2	0	0	2	1	4	2	0
--REGENERATION, TUBULAR EPITHELIUM		5	5	3	5	5	0	2	1	1	5
--LYMPHOHISTIOCYTIC INFILTRATE, INTERSTITIAL		2	4	0	2	4	0	1	0	1	1
--CYST		1	0	0	0	0	1	0	0	0	0
--HYPERPLASIA, TRANSITIONAL CELL		1	0	0	0	0	1	0	0	0	0
--MINERALIZATION, TUBULAR		0	1	0	0	3	2	0	0	0	1
--CHRONIC PYELONEPHRITIS		1	0	0	0	0	0	0	0	0	0
--MINERAL/CALCULI, PELVIS		0	0	0	0	0	2	3	0	2	2
LIVER (LI)	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5	5
	NOT REMARKABLE:	1	2	2	3	0	4	2	5	2	4
--FOCI OF INFLAMMATION		3	3	3	2	5	1	3	0	3	1
--FOCAL NECROSIS		0	0	1	0	0	0	0	0	0	0

TABLE INCLUDES: SEX=MAL;GROUP=1,2,3,4,5;WEEKS=ALL DEATH=T;FIND=ALL;SUBSET=ALL		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	5	5	5	5	5	5	5	5	5	5
HEART (HT)	NUMBER EXAMINED:	5	5	0	0	5	5	5	0	0	5
	NOT REMARKABLE:	5	4	0	0	3	5	4	0	0	5
--CHRONIC CARDIOMYOPATHY		0	1	0	0	2	0	1	0	0	0
TONGUE (TO)	NUMBER EXAMINED:	5	5	0	0	5	5	5	0	0	5
	NOT REMARKABLE:	5	3	0	0	5	5	5	0	0	4
--HEMORRHAGE		0	2	0	0	0	0	0	0	0	1
SPLEEN (SP)	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5	5
	NOT REMARKABLE:	3	0	1	1	0	0	0	0	0	0
--HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED		1	0	0	0	0	0	0	0	0	0
--INCREASED PIGMENT		2	5	4	4	5	5	5	5	5	5
URINARY BLADDER (UB)	NUMBER EXAMINED:	5	5	5	5	5	5	5	5	5	5
	NOT REMARKABLE:	4	5	5	3	5	5	2	4	3	1
--HYPERPLASIA, DIFFUSE, UROTHELIUM		0	0	0	2	0	0	3	1	2	4
--APOPTOSIS, INCREASED, UROTHELIUM		0	0	0	0	0	0	0	0	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC		1	0	0	0	0	0	0	0	0	0
--EPITHELIAL HYPERPLASIA, UROTHELIUM		3	0	0	0	0	0	0	0	0	0

3. Conclusions

R-modafinil administration to rats for 3 months produced clinical signs, including stereotypy, decreased RBC parameters, and microscopic changes in the bone marrow, spleen, thyroid, liver, kidney, and urinary bladder. All of these effects have been seen in previous oral repeat dose studies in rats with racemic modafinil and were seen in the current study in the comparator control group. Urothelial hyperplasia/apoptosis had not been recognized as an effect of modafanil previously, but had been seen in previous repeat dose studies with racemic modafinil. Although the effects were qualitatively similar, it appeared that the R-enantiomer may have been somewhat more potent than the racemate in producing some effects on the kidney (tubular mineralization) and particularly on the bladder. Based on the PK data from the 10-day range-finding study, it appears that plasma exposures to parent are similar between R- and racemic modafinil at the same dose, ie, 400 mg/kg. Microscopic findings in the kidney and bladder were seen at the LD of 60 mg/kg, which was associated with exposures <1/10 those expected clinically. Findings in the kidney and urinary bladder were not completely reversed after 4 weeks.

D. 13-Week Oral Gavage Toxicity and Toxicokinetic Study with CEP-10953 (R-modafinil) in Dogs with a 4-Week Interim Sacrifice and a 4-Week Recovery Period (Cephalon Study Number: DS-02-031; [redacted] Study Number 6573-145; conducted by [redacted], Report Issued 05 February 2004; GLP) b(4)

1. Methods

Dogs (beagle; 6-8/sex/group) were treated with 0 (vehicle: [redacted]; Group 1), 75 → 60 mg/kg racemic modafinil (Lot # 1538-DT1-1; Group 2) or 7.5, 20 or 50 mg/kg/day R-modafanil (Batch No. 02117K2a; Groups 3-5) by oral gavage (2.5 ml/kg) for 4 or 13 weeks. Three/sex/group were sacrificed after 4 weeks, 3/sex/group after 13 weeks; and 2/sex in Groups 1, 2, and 5 after 4 weeks of recovery. Assessment of toxicity was based on mortality, clinical observations, body weight and food consumption data, electrocardiography (prior to treatment, 15 to 75 min after dosing during Wks 4 and 13, and at the end of Wk 17), ophthalmology, clinical pathology, toxicokinetics, and anatomic pathology.

Doses were based on a range-finding study in which oral doses of 12.5, 25, or 50 mg/kg were given to dogs for 10 days. CNS signs were seen in all treated-groups. There was a dose-related decrease in BW gain. There were no changes in hematological parameters, and the only clinical chemistry finding was a D-R increase in alkaline phosphatase at the MD and HD. The effects were similar to those observed in dogs with the racemic modafinil. Based on these results 50 mg/kg was thought to be the approximate MTD.

2. Results

a. Mortality

Due to what were considered T-R clinical signs and body weight loss, 1 female in the racemic modafinil group (Grp 2, No. H00328) was sacrificed on Day 9. Clinical pathology findings in this dog were said to be consistent with inflammation, dehydration, severe cholestasis, electrolyte depletion, and stress (markedly increased neutrophils, cholesterol, bilirubin, alkaline phosphatase, and gamma GT; moderately increased hematocrit, APTT, glucose, and BUN; markedly decreased sodium, potassium, and chloride; and moderately decreased lymphocytes). A transmural duodenal ulcer and inflammation and the occurrence of mucosal necrosis and ulceration in the esophagus were present. This animal also had slight myeloid hyperplasia in the femur and sternum bone marrow and moderate bile stasis with bile accumulation in bile ducts as well as bile canaliculi, minimal atrophy of centrilobular hepatocytes, and moderate thymic involution/lymphocytic depletion.

b. Observations

Throughout the study, several animals in both R- and racemic modafinil groups received veterinary treatment for clinical signs, body weight loss, and poor appetite. As a result, several animals (3 males and 4 females in racemate group, 2 MD R-modafinil males) were suspended from dosing for varying periods. Because of the poor condition of animals given racemic modafinil, the dose for this group was reduced from 75 to 60 mg/kg on D13.

Clinical signs included D-R stereotypy in all treatment groups. Behavioral observations were generally seen 1 to 2 hours after dosing and persisted for several hours. These included circling, hypoactivity, hyperactivity, and repetitive movements (side to side motion, head bobbing, pacing, general movements, and jumping on and off the perch). The incidence of the behavioral observations

generally decreased as the study progressed, although several of the repetitive observations were still noted towards the end of the treatment period, particularly for animals given the racemate or HD R-isomer. Generally, clinical signs were similar in the HD R-modafinil and racemate groups.

c. Body Weights

During the first 1-2 weeks of dosing treated groups exhibited a decrease in food consumption and a concomitant body weight loss (Day 8 BWs 10 - 15% lower than Day 1 for racemate or HD R-modafinil group males and females and MD R-modafinil males). However, after approximately 2 weeks of dosing, the BW gains were similar among groups.

d. Ophthalmology

No T-R effects noted.

e. ECG

No T-R effects observed.

f. Clinical Pathology

Decreased RBC parameters (**Table III.D1**) and increased cholesterol and alkaline phosphatase (**Table III.D2**) were observed in all R-modafanil and racemic modafinil groups. These changes did not appear to get worse over time, and were reversible for the most part (RBCs in males not completely reversed after 4 weeks). The effects on alkaline phosphatase were consistent with bile stasis observed microscopically. Similar effects have been observed in repeat-dose toxicity studies in dogs with R,S-modafinil (NDA 20-717). There were no effects on urinalysis parameters.

Table III.D1

Summary of Clinical Hematology Data

Test Article	Control	CEP-1538		CEP-10953	
Group	1	2	3	4	5
Level (mg/kg/day)	0	75/60	7.5	20	50

Group		RBC (E6/UL) Week -2	RBC (E6/UL) Week -1	RBC (E6/UL) Week 5	RBC (E6/UL) Week 14	RBC (E6/UL) Week 18
1M	Mean	7.15	7.18	6.64	7.02	7.22
	SD	0.426	0.288	0.491	0.332	0.799
	N	8	8	8	5	2
2M	Mean	7.05	7.03	5.32*	5.46*	6.77
	SD	0.468	0.464	0.288	0.498	0.509
	N	8	8	8	5	2
3M	Mean	6.95	7.01	6.35	6.39	
	SD	0.322	0.534	0.322	0.342	
	N	6	6	6	3	
4M	Mean	7.54	7.61	6.31	6.12*	
	SD	0.455	0.234	0.595	0.368	
	N	6	6	6	3	
5M	Mean	7.18	7.10	5.48*	5.29*	6.71
	SD	0.480	0.549	0.475	0.389	0.750
	N	8	8	8	5	2
Statistics		D	D	D	D	X

*= D < or =0.05
D = ANOVA (and Dunnett's, if applicable)
X = not analyzed

Group		RBC (E6/UL) Week -2	RBC (E6/UL) Week -1	RBC (E6/UL) Week 5	RBC (E6/UL) Week 14	RBC (E6/UL) Week 18
1F	Mean	7.16	7.12	6.90	6.59	6.91
	SD	0.364	0.365	0.505	0.401	0.276
	N	8	8	8	5	2
2F	Mean	6.81	6.93	5.45*	5.45*	6.98
	SD	0.331	0.321	0.184	0.468	0.410
	N	8	8	7	5	2
3F	Mean	6.77	6.83	6.14	6.03	
	SD	0.414	0.216	0.668	0.158	
	N	6	6	6	3	
4F	Mean	6.96	7.05	5.74*	6.29	
	SD	0.400	0.455	0.396	0.745	
	N	6	6	6	3	
5F	Mean	7.43	7.44	5.89*	5.79	6.68
	SD	0.437	0.283	0.739	0.738	0.431
	N	8	8	8	5	2
Statistics		P	P	PK	P	X

Table III.D2

Summary of Clinical Chemistry Data

Test Article Control CEP-1538 CEP-10953
Group 1 2 3 4 5
Level (mg/kg/day) 0 75/60 7.5 20 50

Group		ALK PHOS (IU/L) Week -2	ALK PHOS (IU/L) Week -1	ALK PHOS (IU/L) Week 5	ALK PHOS (IU/L) Week 14	ALK PHOS (IU/L) Week 18
1M	Mean	60	58	54	49	46
	SD	17.0	15.0	14.0	11.4	4.2
	N	8	8	8	5	2
2M	Mean	50	48	185*	146*	46
	SD	20.8	16.9	88.2	40.6	2.1
	N	8	8	8	5	2
3M	Mean	53	51	81	84	
	SD	15.2	15.7	34.3	37.6	
	N	6	6	6	3	
4M	Mean	48	45	120*	90	
	SD	12.5	10.2	37.2	25.5	
	N	6	6	6	3	
5M	Mean	47	44	229*	137*	52
	SD	11.1	12.5	151.1	59.9	6.4
	N	8	8	8	5	2
Statistics		P	P	PK	P	X

*= P < or =0.05
X = rank-transformed data
P = ANOVA (and Dunnett's, if applicable)
X = not analyzed

Group		ALK PHOS (IU/L) Week -2	ALK PHOS (IU/L) Week -1	ALK PHOS (IU/L) Week 5	ALK PHOS (IU/L) Week 14	ALK PHOS (IU/L) Week 18
1F	Mean	51	45	41	33	38
	SD	13.3	10.6	11.8	9.0	2.1
	N	8	8	8	5	2
2F	Mean	46	44	143*	215*	46
	SD	10.4	11.3	36.8	123.3	0.7
	N	8	8	7	5	2
3F	Mean	54	50	60	88	
	SD	17.5	16.5	11.2	27.6	
	N	6	6	6	3	
4F	Mean	57	51	113*	99*	
	SD	23.6	17.0	49.8	27.4	
	N	6	6	6	3	
5F	Mean	61	56	173*	201*	59
	SD	27.6	26.6	57.6	117.7	6.4
	N	8	8	8	5	2
Statistics		PK	PK	PK	PK	X

g. Plasma Levels

Results of TK determinations are shown in **Table III.D3** and **III.D4**. Plasma exposures to R-modafinil and the racemate were markedly lower after repeated dosing. WK13 AUCs for R-modafinil acid were 0.0, 1.5, and 5.5 and 0.0, 2.0, and 6.3 ug.h/ml in males and females at the LD, MD, and HD, respectively. WK13 AUCs for R-modafinil sulfone were 12.8, 24.3, and 77.4 and 8.6, 25.6, and 78.8 ug.h/ml in males and females at the LD, MD, and HD, respectively. Plasma levels of racemic modafinil were consistent with those seen previously in dogs. R-modafanil was not measured after administration of the racemate, but previous dog PK data indicate that the AUC of the R-enantiomer is about 2X that of the S-enantiomer after administration of the racemate due to stereoselective metabolism. After a 30-mg/kg oral dose, the AUC was greater and the t1/2 longer for R- compared to S-modafinil: AUCs for R- and S-modafinil were 70.0 and 38.1 µg·hr/ml, respectively, and t1/2s were 5.01 and 3.52 hr.

Table III.D3

Text Table 1: Mean ± SD pharmacokinetic parameters for (R)-modafinil in male and female beagle dogs on Day 1 and during Weeks 4 and 13 of daily oral administration at 7.5, 20 or 50 mg/kg/day of (R)-modafinil

Sex	Sampling Period	Gp	Dose (mg/kg/day)	n	C_{max} (µg/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ or AUC_{0-t}[a] (µg·hr/mL)
Male	Day 1	3	7.5	6	5.45 ± 1.12	1.0 ± 0.0	1.9 ± 0.7	23.4 ± 6.5
		4	20	6	15.20 ± 3.57	1.2 ± 0.4	3.5 ± 1.0	96.5 ± 34.1
		5	50	8	38.91 ± 9.51	1.4 ± 0.5	4.4 ± 1.9	396.0 ± 100.1
	Week 4	3	7.5	6	4.33 ± 1.03	1.0 ± 0.0	1.3 ± 0.3	11.2 ± 4.2
		4	20	6	13.69 ± 2.85	1.0 ± 0.0	1.2 ± 0.2	32.9 ± 5.4
		5	50	8	37.33 ± 5.81	1.0 ± 0.0	1.1 ± 0.1	71.5 ± 16.2
	Week 13	3	7.5	3	5.12 ± 0.90	1.0 ± 0.0	1.4 ± 0.3	14.0 ± 4.3
		4	20	3	12.28 ± 1.05	1.0 ± 0.0	1.2 ± 0.2	30.1 ± 4.8
		5	50	5	30.49 ± 6.17	1.2 ± 0.4	1.0 ± 0.2	93.8 ± 14.2
Female	Day 1	3	7.5	6	3.90 ± 0.97	1.3 ± 0.5	2.6 ± 1.1	21.3 ± 6.8
		4	20	6	12.69 ± 2.46	1.8 ± 1.3	2.7 ± 0.8	72.1 ± 17.4
		5	50	8	32.87 ± 6.58	2.1 ± 0.8	5.8 ± 1.7	333.6 ± 82.0
	Week 4	3	7.5	6	4.83 ± 1.13	1.0 ± 0.0	1.3 ± 0.4	12.6 ± 3.9
		4	20	6	10.24 ± 2.71	1.0 ± 0.0	1.3 ± 0.2	25.1 ± 6.3
		5	50	8	28.12 ± 4.06	1.0 ± 0.0	1.2 ± 0.1	81.3 ± 9.3
	Week 13	3	7.5	3	4.57 ± 0.17	1.3 ± 0.6	1.3 ± 0.4	12.4 ± 4.4
		4	20	3	14.98 ± 2.33	1.0 ± 0.0	1.1 ± 0.1	34.1 ± 4.5
		5	50	5	34.51 ± 3.98	1.0 ± 0.0	1.1 ± 0.2	97.8 ± 12.6

a $AUC_{0-\infty}$ for Day 1 and AUC_{0-t} for Weeks 4 and 13.

Table III.D4

Table 1 Mean ± SD pharmacokinetic parameters for modafinil, modafinil acid and modafinil sulfone in male and female beagle dogs on Day 1 and during Weeks 4 and 13 of daily oral administration at 75→60 mg/kg/day of racemic modafinil

Compound	Sex	Sampling Period	Group	Dose (mg/kg/day)	n	C_{max} (µg/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ or AUC_{0-t}[b] (µg·hr/mL)
Modafinil	Male	Day 1	2	75→60[a]	8	40.66 ± 5.65	1.9 ± 1.0	4.1 ± 1.1	363.9 ± 62.7
		Week 4			8	22.53 ± 5.81	1.1 ± 0.4	1.2 ± 0.3	64.3 ± 15.3
		Week 13			5	23.40 ± 6.61	1.0 ± 0.0	1.2 ± 0.3	62.5 ± 11.6
Modafinil Acid	Male	Day 1	2	75→60[a]	8	19.44 ± 5.15	2.3 ± 0.7	3.7 ± 1.5	131.4 ± 33.6
		Week 4			8	13.50 ± 2.67	1.5 ± 0.5	1.3 ± 0.4	49.1 ± 12.5
		Week 13			5	17.73 ± 4.13	1.4 ± 0.5	1.3 ± 0.3	63.3 ± 20.0
Modafinil Sulfone	Male	Day 1	2	75→60[a]	8	14.40 ± 2.12	6.5 ± 2.1	NC	191.0 ± 47.7[c]
		Week 4			8	11.86 ± 2.39	1.9 ± 0.4	1.7 ± 0.7	57.5 ± 15.3
		Week 13			5	12.64 ± 3.31	2.0 ± 0.0	1.6 ± 0.2	55.8 ± 12.6
Modafinil	Female	Day 1	2	75→60[a]	8	33.28 ± 5.62	1.5 ± 0.5	3.6 ± 0.4	262.8 ± 51.1
		Week 4			6	22.50 ± 3.15	1.2 ± 0.4	1.5 ± 0.3	65.9 ± 8.8
		Week 13			4	25.87 ± 4.72	1.0 ± 0.0	1.2 ± 0.2	66.7 ± 9.0
Modafinil Acid	Female	Day 1	2	75→60[a]	8	24.33 ± 3.43	3.0 ± 1.1	3.3 ± 1.1	185.7 ± 30.2
		Week 4			6	17.85 ± 2.88	1.7 ± 0.5	1.5 ± 0.3	71.7 ± 15.8
		Week 13			4	19.38 ± 5.59	1.3 ± 0.5	1.2 ± 0.3	68.1 ± 23.5
Modafinil Sulfone	Female	Day 1	2	75→60[a]	8	13.60 ± 2.81	6.0 ± 2.1	NC	112.3 ± 70.6[c]
		Week 4			6	11.28 ± 1.28	1.8 ± 0.4	1.6 ± 0.4	52.4 ± 5.7
		Week 13			4	12.98 ± 2.38	1.8 ± 0.5	1.4 ± 0.2	57.0 ± 7.6

[a] The dogs were administered 75 mg/kg/day of racemic modafinil on Days 1-12 and 60 mg/kg/day on Day 13 through sacrifice.
[b] $AUC_{0-\infty}$ for Day 1 and AUC_{0-t} for Weeks 4 and 13.
[c] $AUC_{0-\infty}$ could not be calculated; the results presented are for AUC_{0-t}.
NC: Not Calculable

h. Necropsy

i. Organ Weights

At the 4- and 13-week sacrifices, there were D-R increases in liver/gallbladder weights in R- and R,S-modafinil groups (up to 200%; **Table III.D5**). Kidney weights were D-D increased in R- and R,S-modafinil group males at terminal sacrifice.

Table III.D5

Summary of Organ Weight Data (g) - Terminal Sacrifice

Test Article Control CEP-1530 CEP-10953
Group 1 2 3 4 5
Level (mg/kg/day) 0 75/60 7.5 20 50

Organ		Group 1M	Group 2M	Group 3M	Group 4M	Group 5M	Statistic
TBW	Mean	10192	9645.0	9233.3	9775.0	9276.7	P
	SD	746.53	535.38	641.80	624.05	223.07	
	N	3	3	3	3	3	
BRAIN	Mean	80.0003	82.4307	74.1323	79.7373	80.3677	P
	SD	3.68467	8.39871	1.93812	3.18365	5.16117	
	N	3	3	3	3	3	
to TBW	Mean	0.78742	0.91237	0.80526	0.81891	0.86632	P
(%)	SD	0.061937	0.090287	0.055965	0.074895	0.050417	
	N	3	3	3	3	3	
to BR	Mean	1.00000	1.00000	1.00000	1.00000	1.00000	X
Ratio	SD	0.000000	0.000000	0.000000	0.000000	0.000000	
	N	3	3	3	3	3	
KIDNEY	Mean	45.1893	56.7907	46.9623	55.5527	54.3997	PK
	SD	2.73386	10.25744	4.27113	0.48106	1.33166	
	N	3	3	3	3	3	
to TBW	Mean	0.44418	0.62468*	0.50958	0.56976*	0.58538*	P
(%)	SD	0.027536	0.079012	0.060328	0.031398	0.000664	
	N	3	3	3	3	3	

*= P < or =0.05
K = rank-transformed data
P = ANOVA (and Dunnett's, if applicable)
X = not analyzed

Organ		Group 1M	Group 2M	Group 3M	Group 4M	Group 5M	Statistic
THYROID/-	Mean	0.8497	0.6737	0.7747	0.7680	0.8967	P
PARATHYR	SD	0.14833	0.08130	0.20543	0.15690	0.11547	
	N	3	3	3	3	3	
to TBW	Mean	0.00838	0.00748	0.00833	0.00794	0.00965	P
(%)	SD	0.000817	0.001178	0.001738	0.002116	0.001032	
	N	3	3	3	3	3	
to BR	Mean	0.01063	0.00829	0.01047	0.00960	0.01115	P
Ratio	SD	0.001879	0.001730	0.002031	0.001703	0.001384	
	N	3	3	3	3	3	
EPIDIDYMIS	Mean	3.4477	3.1017	3.4247	2.8783	2.8930	P
	SD	0.27974	0.52513	0.04946	0.43416	0.46852	
	N	3	3	3	3	3	
to TBW	Mean	0.03383	0.03421	0.03683	0.02957	0.03119	P
(%)	SD	0.001212	0.004404	0.007183	0.005385	0.005028	
	N	3	3	3	3	3	
to BR	Mean	0.04210	0.03806	0.04628	0.03616	0.03587	P
Ratio	SD	0.002954	0.008724	0.011890	0.005857	0.003621	
	N	3	3	3	3	3	
LIVER/	Mean	223.1477	447.4993*	252.7770	302.5990*	445.9847*	PK
GALLBLAD	SD	11.07750	80.03760	33.30512	29.09953	78.25314	
	N	3	3	3	3	3	
to TBW	Mean	2.19136	4.92387*	2.73609	3.09584*	4.79958*	PK
(%)	SD	0.053460	0.634775	0.169540	0.207213	0.774882	
	N	3	3	3	3	3	
to BR	Mean	2.79207	5.43275*	3.41101	3.79762	5.52605*	P
Ratio	SD	0.159237	0.986449	0.449108	0.389619	0.679379	
	N	3	3	3	3	3	

Terminal Sacrifice

Test Article	Control	CEP-1538	CEP-10953		
Group	1	2	3	4	5
Level (mg/kg/day)	0	75/60	7.5	20	50

Organ		Group 1F	Group 2F	Group 3F	Group 4F	Group 5F	Statistic
to BR Ratio	Mean	0.01360	0.01618	0.01493	0.01288	0.01601	P
	SD	0.002676	0.002925	0.002994	0.000213	0.002846	
	N	3	3	3	3	3	
THYROID/-PARATHYR	Mean	0.8690	0.7537	0.5670	0.5853	0.6023	P
	SD	0.25687	0.13126	0.13337	0.10985	0.03958	
	N	3	3	3	3	3	
to TBW (%)	Mean	0.00919	0.00953	0.00786	0.00825	0.00811	P
	SD	0.001497	0.001149	0.001737	0.001544	0.000511	
	N	3	3	3	3	3	
to BR Ratio	Mean	0.01107	0.00994	0.00794	0.00798	0.00814	P
	SD	0.003332	0.001071	0.002098	0.001604	0.001270	
	N	3	3	3	3	3	
LIVER/ CALARIAD	Mean	205.1647	312.5503*	219.0147	236.8197	255.6720*	PK
	SD	26.53322	74.83639	9.85792	10.53132	30.56898	
	N	3	3	3	3	3	
to TBW (%)	Mean	2.22484	3.36244*	3.041187*	3.34815*	3.44078*	P
	SD	0.290837	0.174326	0.058000	0.399402	0.405112	
	N	3	3	3	3	3	

ii. Gross Pathology

No T-R changes noted at interim or terminal sacrifice.

iii. Microscopic Pathology

Bile stasis (primarily centrilobular) was seen in the MD and HD R-modafinil and racemate groups at the 4- and 13-week sacrifices, and periportal-midzonal hepatocellular hypertrophy was observed in these groups at 13 weeks (**Tables III.D6** and **III.D7**). There appeared to be an increased incidences in kidney findings (tubular regeneration and mineralization) in R- and R,S-modafinil-treated females at termination, but since tubular mineralization was seen in practically all animals including controls at the interim and recovery sacrifices, the incidence in C females at termination may have been too low. Thymic involution/lymphocytic depletion seen in R- and R,S-modafinil-treated animals at 4- and 13-weeks was considered to be stress-related. Thymus and liver changes appeared reversible based on findings in the 4-week recovery group (**Table III.D7**).

Table III.D6

Incidence of Microscopic Observations

Interim Sacrifice

PAGE: 3

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=I;FIND=ALL;SUBSET=ALL		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	3	3	3	3	3	3	2	3	3	3
LIVER (LI)	NUMBER EXAMINED:	3	3	3	3	3	3	2	3	3	3
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--ATROPHY, HEPATOCYTES, CENTRILOBULAR		0	0	0	1	1	0	0	0	0	2
--CONGESTION		1	0	0	0	0	1	0	0	0	0
--DEGENERATION/NECROSIS, HEPATOCELLULAR, CENTRILOBULAR		0	0	0	0	1	0	0	0	1	0
--FIBROSIS, CAPSULAR/SUBCAPSULAR		1	0	0	0	0	1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		2	2	3	3	1	3	2	3	3	3
--INFLAMMATION, SUBACUTE-CHRONIC, CENTRILOBULAR		0	0	0	0	1	1	0	0	0	0
--INFLAMMATION, SUBACUTE, PORTAL		0	0	0	0	0	0	0	1	0	0
--NECROSIS, INDIVIDUAL HEPATOCYTE		0	2	0	1	0	2	0	1	0	1
--PIGMENT, KUPFFER CELL		0	1	0	0	2	2	1	2	2	2
--STASIS, BILE PRIMARILY CENTRILOBULAR		0	1	0	2	1	0	0	0	0	1
GALLBLADDER (GB)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	3	3	3	3	3	2	3	3	3
HEART (HT)	NUMBER EXAMINED:	3	3	3	3	3	3	2	3	3	3
	NOT REMARKABLE:	3	3	2	3	2	3	2	3	2	2
--HEMATOCYST, VALVULAR		0	0	1	0	0	0	0	0	0	0
--MINERALIZATION, VASCULAR		0	0	0	0	1	0	0	0	0	0
--MYXOMATOUS CHANGE, VASCULAR		0	0	0	0	0	0	0	0	1	1
KIDNEY (KD)	NUMBER EXAMINED:	3	3	3	3	3	3	2	3	3	3
	NOT REMARKABLE:	1	0	0	0	0	0	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	1	1	0	0	0	0	0	1
--MINERALIZATION, TUBULAR		2	3	3	3	3	3	2	3	3	2
--REGENERATION, TUBULAR EPITHELIUM		0	0	0	1	1	0	0	0	0	1

Table III.D7

Incidence of Microscopic Observations

Terminal Sacrifice

PAGE: 2

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=T;FIND=ALL;SUBSET=ALL		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	3	3	3	3	3	3	3	3	3	3
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	3	3	3	3	3	3	3	3	2
--EDEMA		0	0	0	0	0	0	0	0	0	1
BRAIN (BR)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	3	3	3	3	3	3	3	3	3
LUNG (LU)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	1	0	0	2	0	1	1	1	0
--FIBROSIS, INTERSTITIAL		0	1	0	0	0	0	0	0	0	1
--FIBROSIS, PLEURAL/SUBPLEURAL		0	1	0	0	0	0	0	0	0	0
--HYPERPLASIA/HYPERTROPHY, BRONCHIOLAR/ALVEOLAR EPITHELIUM		0	1	1	0	0	1	0	0	0	2
--INFILTRATE, LYMPHOHISTIOCYTIC		0	1	1	0	0	1	0	2	2	1
--INFILTRATE, MACROPHAGE, ALVEOLAR		0	1	2	2	1	1	1	0	0	1
--INFILTRATE, MACROPHAGE, INTRACYTOPLASMIC FOREIGN MATERIAL, ALVEO		0	0	0	0	0	0	1	0	0	0
--INFLAMMATION, CHRONIC		0	0	0	0	0	0	1	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	0	0	0	0	0	1	2
--INFLAMMATION, GRANULOMATOUS		0	0	0	0	0	0	0	0	0	1
--THROMBUS		0	0	0	0	0	1	0	0	0	0
KIDNEY (KD)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	0	0	2	0	0	3	0	0	1	0
--DEGENERATION, TUBULAR		0	0	1	0	0	0	0	0	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC		0	1	1	0	0	0	0	0	0	1
--MINERALIZATION, TUBULAR		2	2	1	2	3	0	3	2	2	3
LIVER (LI)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	0	0	0	0	0	0	0	0	0
--CONGESTION		0	2	0	1	2	0	0	0	0	0
--DEGENERATION/NECROSIS, HEPATOCELLULAR, CENTRILOBULAR		0	0	0	0	1	0	0	0	0	0
--GLYCOGEN, HEPATOCELLULAR, INCREASED		0	0	0	0	2	0	0	0	0	0
--HYPERTROPHY, HEPATOCELLULAR, PERIPORTAL-MIDZONAL CYTOPLASM OF AFFECTED CELLS OFTEN HAS INCREASED EOSINOPHILIC STAINING		0	2	0	3	3	0	3	0	1	3
--INFILTRATE, LYMPHOHISTIOCYTIC		2	2	3	2	2	3	1	2	3	3
--INFLAMMATION, ACUTE		0	0	0	0	0	0	1	0	0	0
--INFLAMMATION, SUBACUTE-CHRONIC, CENTRILOBULAR		0	1	0	0	0	0	0	0	0	0
--INFLAMMATION, SUBACUTE, PORTAL		0	0	0	0	1	0	0	0	0	2
--NECROSIS, INDIVIDUAL HEPATOCYTE		0	0	0	1	0	0	0	0	0	0
--PIGMENT, KUPFFER CELL		0	1	1	0	1	1	0	2	2	2
--STASIS, BILE PRIMARILY CENTRILOBULAR		0	1	0	0	1	0	1	0	0	1
GALLBLADDER (GB)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	3	3	3	3	3	3	3	3	3

HEART (HT)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	3	2	3	3	3	2	3	3
--HEMATOCYST, VALVULAR		0	0	1	0	0	0	0	0	0
--MINERALIZATION, VASCULAR		0	0	0	0	0	0	1	0	0	0
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	3	3	3	3	3	3	3	3
TONGUE (TO)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	3	3	3	3	3	3	3	3
SPLEEN (SP)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	3	3	3	3	2	3	3	3
--FIBROSIS, CAPSULAR		0	0	0	0	0	1	0	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	3	3	3	3	3	3	2	3	3	3
	NOT REMARKABLE:	3	2	2	1	2	3	1	3	2	0
--INVOLUTION/DEPLETION, LYMPHOCYTIC		0	1	1	2	1	0	1	0	1	3
LN, MESENTERIC (MS)	NUMBER EXAMINED:	3	3	3	3	3	3	3	3	3	3
	NOT REMARKABLE:	3	3	3	3	3	3	3	3	3	3

Table III.D8

Incidence of Microscopic Observations

Recovery Sacrifice

TABLE INCLUDES:
SEX=ALL;GROUP=1,2,5;WEEKS=ALL
DEATH=U;FIND=ALL;SUBSET=ALL

		--- NUMBER-OF-ANIM					
	SEX:	-----MALE----			----FEMALE---		
	GROUP:	-1-	-2-	-5-	-1-	-2-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	2	2	2	2	2	2
** FROM PREVIOUS PAGE **							
KIDNEY (KD)	NUMBER EXAMINED:	2	2	2	2	2	2
	NOT REMARKABLE:	0	0	1	1	0	0
--LIPIDOSIS, GLOMERULAR		0	0	0	0	1	0
--MINERALIZATION, TUBULAR		2	2	1	1	2	2
--REGENERATION, TUBULAR EPITHELIUM		0	0	0	0	0	1
LIVER (LI)	NUMBER EXAMINED:	2	2	2	2	2	2
	NOT REMARKABLE:	0	1	1	0	0	2
--INFILTRATE, LYMPHOHISTIOCYTIC		2	1	1	0	2	0
--PIGMENT, KUPFFER CELL		0	1	0	1	0	0
--VACUOLATION, HEPATOCELLULAR, CENTRILOBULAR		0	0	0	2	0	0
GALLBLADDER (GB)	NUMBER EXAMINED:	2	2	2	2	2	2
	NOT REMARKABLE:	2	2	2	2	2	2
HEART (HT)	NUMBER EXAMINED:	2	2	2	2	2	2
	NOT REMARKABLE:	2	2	2	2	2	2
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	2	2	2	2	2	2
	NOT REMARKABLE:	2	2	2	2	2	2

3. Conclusions

Oral administration of R-modafinil (7.5, 20 or 50 mg/kg) or modafinil (75 →60 mg/kg) to dogs for 4 or 13 weeks produced typical clinical signs (stereotypy), transient BW gain reduction, hematology and clinical chemistry changes (↓RBCs, ↑Alk Phos), liver weight increases, and microscopic evidence of hepatocellular hypertrophy and bile stasis as well as thymic involution/lymphocytic depletion. The findings at the HD of R-modafinil were generally similar to those observed with racemic modafinil. Thymus and liver changes appeared reversible. Based on thymic involution/lymphocytic infiltration at the LD, there was no NOEL. The exposure at this dose was about 1/10 that expected clinically.

IV. CARCINOGENICITY

R-modafinil was not evaluated for carcinogenic potential. Modafinil was evaluated in a two year oral carcinogenicity study in Sprague-Dawley rats and a 78-week oral carcinogenicity study in CD-1 mice (NDA 20-717). These studies have been reviewed previously. "Because the mouse study used an inadequate high dose that was not representative of a maximum tolerated dose," modafinil was subsequently evaluated in a 26-week dermal Tg.AC transgenic mouse bioassay as part of an FDA Phase 4 commitment. The rat study was also considered inadequate by the pharmacology reviewer, but was ultimately accepted after CAC consultation.

A. 26-Week Dermal Carcinogenicity Study in Tg.AC Mice (Cephalon study no. DS-03-015; [redacted] Study No. AA52YL.7D82.BTL; conducted by [redacted] completed 3/29/04; GLP) b(4)

1. Methods

Tg.AC transgenic mice (20/sex/group) were treated with modafinil (Lot # 1538-DT1-1) at doses of 62.5, 125, and 250 mg/kg (Groups 3, 4 and 5) given dermally twice daily (6 hr apart) for 26 weeks (total daily doses of 125, 250, and 500 mg/kg). The vehicle control group (20/sex; Group 1) was treated twice daily with methanol. A positive control group (20/sex; Group 2) was treated with 1.25 ug tetradecanoyl phorbol acetate (TPA) in 0.1 ml methanol 3 times per week. The doses used in this study were based on the results of a 4-week dose range-finding study (TK data shown in **Table IV.A1)** and were approved by the CAC (minutes dated 3/4/03). The HD was thought to represents the maximum feasible dose based on the limit of solubility of modafinil in methanol and the maximum application volume (200 ul). The exec-CAC also noted that "there is merit to using a Tg.AC topical assay even though this is an orally administered drug." All animals were observed for mortality and clinical signs and were weighed weekly. A detailed examination for non-skin tumor clinical signs, including signs of toxicity and dermal irritation, was performed on Day 1 and weekly thereafter. A separate evaluation of the animals' skin was performed weekly (for 27 weeks, including once prior to study start) for evidence of tumors at the site of application (SOA) and non-SOA. A skin tumor was designated "latent" after reaching a size of 2 mm in diameter and protruding from the surface of the skin. A skin tumor was designated "actual" if remaining countable for three consecutive weeks. Positive control mice with a count of ≥20 actual skin tumors at the SOA were sacrificed without necropsy. Surviving positive controls were sacrificed without necropsy on D182 (females) or D183 (males). At termination (D183-184), all surviving animals were sacrificed, weighed, and necropsied. Organ weights were taken and specified tissues were preserved for histopathological evaluation. Except for the positive control animals, representative sections of non-lesioned skin at the SOA, and skin at a non-SOA site were evaluated microscopically from all animals found dead, sacrificed moribund, and surviving to scheduled sacrifice. All other specified non-skin tissues and non-skin gross lesions found in those same animals (excluding Group 2) were also evaluated microscopically in the HD and C groups. In addition, a total of 10% of all the skin tumors per animal (with a minimum of 1 and maximum of 5, or the only tumor meeting the requirements per tumor-bearing animal) identified during the in-life phase of the study, located in the shaved site of application and found at necropsy, were processed for histopathological evaluation.

2. Results

There was no effect of treatment on mortality (0/20, 1/20, 2/20, 1/20, and 3/20 male mice; and 2/20, 2/20, 3/20, 2/20, and 0/20 female mice from Groups 1-5, respectively). 15/20 male mice and 11/20 female mice from the positive control group were sacrificed

according to protocol after 20 actual skin tumors were found at the SOA. Drug treatment did not produce any notable dermal irritation. Dermal irritation at the SOA seen in all positive control males and females was attributed to the known irritant properties of TPA. There were no treatment-related clinical signs and no effects on male body weights. Female body weights were D-D increased (SS) in drug treated groups compared to C beginning at Day 15, but there were no significant effects on overall body weight gain in either sex.

Statistical analysis (by sponsor and FDA statistician) of numbers of tumor bearing animals at Week 27 did not indicate any significant differences in any of the drug treatment groups compared to the vehicle control (VC) group. Incidences of mice with skin tumors (latent or actual papillomas) at the site of application (SOA) were 1/20, 20/20, 0/18, 1/19, and 0/17 males; and 0/18, 20/20, 2/20, 2/20, and 0/20 females in Groups 1-5, respectively. Incidences of mice with skin tumors at a non-site of application (NSOA) were 1/20, 0/20, 0/18, 0/19, and 1/17 males; and 0/18, 0/20, 0/20, 5/20, and 2/20 females in Groups 1-5, respectively. So, there was a non-dose-related (and NS) increase in skin tumors in treated females (**Table IV.A2**). Most of the increase was in NSOA latent papillomas in MD females (5/20). Incidences of animals with SOA tumors were statistically significantly increased in positive control males and females compared to VC.

There were no T-R gross necropsy findings. Liver weights were increased in drug-treated animals at all doses in both sexes; heart, brain, and spleen weights were increased in MD and HD females; and thymus weights were increased in LD males and HD females. Centrilobular hepatocellular hypertrophy was found microscopically in all HD females and 18/20 HD males. Malignant lymphoma was found in 1 HD male, and erythroleukemia was seen in 2 HD males and 3 LD females, but these were not considered to be T-R.

3. Conclusion

Dermal administration of modafinil to Tg.AC mice at doses of 125, 250 and 500 mg/kg for 26 weeks did not produce a clear increase in the incidence of dermal tumors or in incidences of neoplastic changes in other tissues that were examined microscopically. The positive control (TPA) produced the expected significant increase in dermal tumors.

Table IV.A1

Table 6: Mean Plasma Concentrations of Modafinil, Modafinil Acid, and Modafinil Sulfone in Male and Female FVB/N Mice after Twice-Daily Dermal Administration of 125 or 250 mg/kg for up to 26 Consecutive Days

	Males				Females			
	125 mg/kg bid		250 mg/kg bid		125 mg/kg bid		250 mg/kg bid	
	Day 1	Day 26	Day 1	Day 26	Day 1	Day 26	Day 1	Day 26
Modafinil								
C_{max}[a] (µg/mL)	23.48	9.62	47.25	6.54	15.97	6.67	30.65	2.23
AUC_{0-t} (µg·hr/mL)	48.1	26.5	130.6	26.9	47.2	21.5	128.4	9.8
Modafinil Acid								
C_{max}[a] (µg/mL)	3.00	1.05	5.4	0.00	2.28	0.99	4.17	0.66
AUC_{0-t} (µg·hr/mL)	7.5	1.7	20.4	0.00	5.2	2.9	19.8	1.7
Modafinil Sulfone								
C_{max}[a] (µg/mL)	1.70	2.43	8.92	3.54	2.57	0.94	7.57	0.62
AUC_{0-t} (µg·hr/mL)	5.9	8.1	35.4	10.0	8.4	3.8	32.6	0.9

[a] Values shown are for the first daily dosing; below the limit of quantitation (<0.5 µg/mL); C_{max} = maximum observed plasma concentration; AUC = area under the plasma concentration versus time curve; bid = twice a day

5.2.3 Conclusions

Table IV.A2 Summary incidence of animals with papillomas- Study week 27

CEPHALON STUDY AA52YL.7D82.BTL -- PAPILLOMA DATA

L=Latent papilloma not yet observed for 3 weekly obs

A=Maximum Actual Papilloma observed for 3 Weekly Obs

AD=Maximum Actual Papillomas observed for 3 Weekly Obs but Subsequently Disappeared

SOA= Site of Application

NSOA=Non-SOA

AC=Maximum Actual Carcinomas observed for 3 Weekly Obs

ACD=Maximum Actual Carcinomas observed for 3 Weekly Obs but Subsequently Disappeared

LC=Latent Carcinoma not yet observed for 3 Weekly Obs

STUDY WEEK 27

Group #	Sex (M or F)	Incidence (Latent) Animals bearing at least one latent pap or Ca per effective # of Animals (% incidence) SOA	NSOA	Anywhere	Burden (Latent) Latent papillomas/latent papilloma bearing animal SOA only
1	M	0/20 (0)	1/20 (5)	1/20 (5)	0.0
1	F	0/18 (0)	0/18 (0)	0/18 (0)	0.0
2	M	17/20 (85)	0/20 (0)	17/20 (85)	8.2*
2	F	17/20 (85)	0/20 (0)	17/20 (85)	6.5*
3	M	0/18 (0)	0/18 (0)	0/18 (0)	0.0
3	F	0/20 (0)	0/20 (0)	0/20 (0)	0.0
4	M	0/19 (0)	0/19 (0)	0/19 (0)	0.0
4	F	1/20 (5)	5/20 (25)	5/20 (25)	1.0
5	M	0/17 (0)	0/17 (0)	0/17 (0)	0.0
5	F	0/20 (0)	2/20 (10)	2/20 (10)	0.0

Incidence (Actual) Animals bearing at least one actual pap or Ca per effective # of Animals (% incidence) SOA	NSOA	Anywhere	Burden (Actual) Actual papillomas/actual papilloma bearing animal SOA only
1/20 (5)	0/20 (0)	1/20 (5)	1.0
0/18 (0)	0/18 (0)	0/18 (0)	0.0
20/20 (100)	0/20 (0)	20/20 (100)	19.8*
20/20 (100)	0/20 (0)	20/20 (100)	14.9*
0/18 (0)	0/18 (0)	0/18 (0)	0.0
2/20 (10)	0/20 (0)	2/20 (10)	1.0
1/19 (5)	0/19 (0)	1/19 (5)	1.0
1/20 (5)	2/20 (10)	3/20 (15)	1.0
0/17 (0)	1/17 (6)	1/17 (6)	0.0
0/20 (0)	1/20 (5)	1/20 (5)	0.0

Incidence (All) Animals bearing at least one latent or actual pap or Ca per effective # of Animals (% incidence) SOA	NSOA	Anywhere	Burden (All papo) All papillomas/papilloma bearing animal SOA only
1/20 (5)	1/20 (5)	2/20 (10)	1.0
0/18 (0)	0/18 (0)	0/18 (0)	0.0
20/20 (100)	0/20 (0)	20/20 (100)	26.7*
20/20 (100)	0/20 (0)	20/20 (100)	20.5*
0/18 (0)	0/18 (0)	0/18 (0)	0.0
2/20 (10)	0/20 (0)	2/20 (10)	1.0
1/19 (5)	0/19 (0)	1/19 (5)	1.0
2/20 (10)	5/20 (25)	8/20 (30)	1.0
0/17 (0)	1/17 (6)	1/17 (6)	1.0
0/20 (0)	2/20 (10)	2/20 (10)	0.0

* For positive control animals, tumor burden reflects burden at time of death, scheduled sacrifice, or terminal sacrifice.

B. Bacterial Reverse Mutation Assay ('[redacted]. Study Number AA85HZ.503.BTL; Cephalon Project Number DS-03-036; performed by [redacted]; report dated 8/04; GLP) b(4)

1. Methods

R-modafinil (Lot No. 03188K2a) was tested in the Bacterial Reverse Mutation (Ames) Assay using Salmonella typhimurium tester strains TA98, TA100, TA1535 and TA1537 and Escherichia coli tester strain WP2 uvrA in the presence and absence of Aroclor-induced rat liver S9. The assay was performed in two phases, using the plate incorporation method. The first phase, the initial toxicity-mutation assay, was used to establish the dose-range for the confirmatory mutagenicity assay and to provide a preliminary mutagenicity evaluation. The second phase, the confirmatory mutagenicity assay, was used to evaluate and confirm the mutagenic potential of the test article.

2. Results

In the initial toxicity-mutation assay, the concentrations tested were 2.5, 7.5, 25, 75, 200, 600, 1800 and 5000 ug per plate. No positive mutagenic response was observed. Neither precipitate nor appreciable toxicity was observed. Based on these findings, the maximum concentration tested in the confirmatory mutagenicity assay was 5000 ug per plate.

In the confirmatory mutagenicity assay, no positive mutagenic response was observed at concentrations of 75, 200, 600, 1800 and 5000 ug per plate (**Table IV.B1**). Neither precipitate nor appreciable toxicity was observed.

Table IV.B1.

Bacterial Mutation Assay
Summary of Results - Confirmatory Mutagenicity Assay

Table 22

Test Article Id : CEP-10953 Lot No. 03188K2a
Study Number : AA85HZ.503.BTL Experiment Nos : B2, B3 and B4

Average Revertants Per Plate ± Standard Deviation
Liver Microsomes: None

Dose (µg/plate)	TA98[a]	TA100	TA1535	TA1537	WP2 uvrA
Vehicle	28 ± 3	229 ± 8	21 ± 4	8 ± 2	15 ± 3
75	26 ± 6	209 ± 16	17 ± 5	4 ± 2	11 ± 2
200	26 ± 8	234 ± 7	24 ± 3	9 ± 1	14 ± 1
600	22 ± 4	223 ± 25	28 ± 2	6 ± 2	12 ± 4
1800	33 ± 2	239 ± 2	30 ± 3	8 ± 1	12 ± 2
5000	23 ± 3	234 ± 8	28 ± 6	8 ± 1	8 ± 1
Positive	146 ± 14	718 ± 99	295 ± 30	676 ± 33	111 ± 3

Liver Microsomes: Rat liver S9

Dose (µg/plate)	TA98[a]	TA100[b]	TA1535	TA1537	WP2 uvrA
Vehicle	43 ± 5	173 ± 17	15 ± 5	5 ± 2	13 ± 2
75	34 ± 3	172 ± 2	18 ± 1	8 ± 1	14 ± 2
200	44 ± 6	157 ± 10	16 ± 2	8 ± 1	15 ± 1
600	35 ± 4	156 ± 7	18 ± 1	6 ± 1	13 ± 1
1800	36 ± 6	153 ± 4	14 ± 4	8 ± 3	14 ± 1
5000	38 ± 11	157 ± 26	11 ± 2	7 ± 1	10 ± 1
Positive	1335 ± 94	969 ± 147	137 ± 25	161 ± 20	842 ± 34

Vehicle = Vehicle Control
Positive = Positive Control (50 µL plating aliquot)
Plating aliquot: 50 µL
a = Data from Experiment B3
b = Data from Experiment B4

3. Conclusions

R-modafinil was negative in the Ames test under the conditions employed.

C. In vitro mammalian chromosome aberration test (Cephalon Study Number: DS-03-015; [redacted], Study Number AA52YL.7D82.BTL; conducted by [redacted] Completed 3/29/04; GLP) b(4)

1. Methods

R-modafinil (Lot No. 03188K2a), was tested in the in vitro mammalian chromosome aberration test using human peripheral blood lymphocytes (HPBL) in both the absence and presence of an Aroclor-induced S9 activation system. A preliminary toxicity test was performed to establish the dose range for testing in the cytogenetic test. The chromosome aberration assay was used to evaluate clastogenic potential. In the preliminary assay, the maximum dose tested was 2730 ug/ml. Human peripheral blood lymphocytes were treated in the absence and presence of an Aroclor-induced S9 activation system for 4 hours and continuously for 20 hours in the absence of S9 activation.

2. Results (**Table IV.C.1**)

Visible precipitate was observed at 2730 ug/ml. Concentrations < 819 ug/ml were soluble. Substantial toxicity (i.e., ≥50% reduction in mitotic index relative to solvent control) was observed at 2730 ug/ml in both the non-activated and S9 activated 4 hr exposure groups, and at dose levels > 273 ug/ml in the non-activated 20 hr exposure group. Based on the results of the preliminary test, doses selected for testing in the chrom ab assay ranged from 125 to 2000 ug/ml for both the non-activated and the S9 activated 4 hr exposure groups, and from 25 to 500 ug/ml for the non-activated 20 hr exposure group.

In the cytogenetic analysis of the non-activated 4 hr exposure group, mitotic inhibition was 53%, relative to control, at the highest test concentration evaluated microscopically for chromosome aberrations, 1750 ug/ml. The doses selected for analysis of chrom abs were 500, 1000 and 1750 ug/ml. The percentage of cells with structural or numerical aberrations was not significantly increased above that of the solvent control at any dose level. The percentage of structurally damaged cells in the MMC (positive control) group was statistically significant (13.0%).

In the cytogenetic analysis of the S9 activated group, mitotic inhibition was 53%, relative to C, at the highest concentration evaluated for chrom abs, 2000 ug/ml. The doses selected for analysis of chrom abs were 500, 1000 and 2000 ug/ml. The percentage of cells with structural or numerical aberrations was not significantly increased above that of the solvent control at any dose. The percentage of structurally damaged cells in the CP (positive control) group was statistically significant (15.0%).

In the cytogenetic analysis of the non-activated 20 hr exposure group, mitotic inhibition was 55%, relative to C, at the highest concentration evaluated for chrom abs, 250 ug/ml. The doses selected for analysis of chrom abs were 50, 150 and 250 ug/ml. The percentage of cells with structural or numerical aberrations was not significantly increased above that of the solvent control at any dose level. The percentage of structurally damaged cells in the MMC (positive control) group was statistically significant (16.0%).

Table IV.C1

SUMMARY

Treatment (µg/mL)	S9 Activation	Treatment Time	Mean Mitotic Index	Cells Scored	Aberrations Per Cell (Mean +/- SD)		Cells With Aberrations Numerical (%)	Structural (%)
DMSO	-	4	6.4	200	0.010	±0.100	0.0	1.0
CEP-10953 (Lot No. 03188K2a)								
500	-	4	6.9	200	0.000	±0.000	0.0	0.0
1000	-	4	5.7	200	0.000	±0.000	0.0	0.0
1750	-	4	3.0	200	0.010	±0.100	0.5	1.0
MMC, 0.6	-	4	5.2	200	0.140	±0.376	0.0	13.0**
DMSO	+	4	7.5	200	0.000	±0.000	1.0	0.0
CEP-10953 (Lot No. 03188K2a)								
500	+	4	6.2	200	0.000	±0.000	0.0	0.0
1000	+	4	6.1	200	0.000	±0.000	1.0	0.0
2000	+	4	3.5	200	0.020	±0.140	0.5	2.0
CP, 20	+	4	3.4	100‡	0.180	±0.458	0.0	15.0**
DMSO	-	20	7.3	200	0.000	±0.000	0.0	0.0
CEP-10953 (Lot No. 03188K2a)								
50	-	20	6.5	200	0.000	±0.000	0.0	0.0
150	-	20	6.0	200	0.000	±0.000	0.0	0.0
250	-	20	3.3	200	0.000	±0.000	0.5	0.0
MMC, 0.3	-	20	5.5	100‡	0.170	±0.403	0.0	16.0**

‡ Numerical aberrations are out of 200 cells scored.
Treatment: Cells from all treatment conditions were harvested at 20 hours after the initiation of the treatments.
Aberrations per Cell: Severely damaged cells were counted as 10 aberrations.
Percent Aberrant Cells: *, p≤0.05; **, p≤0.01; using the Fisher's exact test.

3. Conclusions

R-modafinil (Lot No. 03188K2a) was negative for the induction of structural and numerical chromosome aberrations in the non-activated and S9 activated test systems in the in vitro mammalian chromosome aberration test using human peripheral lymphocytes.

V. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

A fertility and general reproductive performance study was not conducted using R-modafinil. However, because the original fertility and reproductive performance and rabbit embryofetal development studies for modafinil (NDA 20-717) were not thought to have evaluated MTDs (and fertility study was not conducted according to current GLP regulations), repeat studies were conducted as part of a Phase 4 commitment and are included here. A rat embryofetal development study was conducted with R-modafinil.

A. ORAL (GAVAGE) FERTILITY AND GENERAL REPRODUCTION TOXICITY STUDY OF MODAFINIL (CEP-1538) IN RATS (Study # DS-99-002; Protocol 1503-005; report dated 9/28/99; conducted by [redacted] GLP) b(4)

1. Methods

Rats (Sprague-Dawley; 25/sex/grp + 6/sex/grp TK) received 0 (Vehicle), 100, 240, or 480 mg/kg modafanil orally (via gavage) either beginning 28 days before cohabitation (maximum 21 days) and continuing through the day before sacrifice (males) or beginning 15 days before cohabitation and continuing through Day 7 of presumed gestation (females). (According to the report, a mix-up during the first week of dosing males resulted in the dosing solutions for the MD and HD groups being switched, but because of the data collection system employed, the group numbers could not be changed. Therefore, groups III and IV received the HD and MD, respectively, and groups are not in the usual order in the Tables. Since dosing was consistent throughout the study, it would not appear to be compromised.) Body weights and food consumption were recorded during the dosing and postdosing periods. After cohabitation, males were sacrificed, and a gross necropsy was performed, and the liver, testes, epididymides, seminal vesicles, and prostate were weighed. Sperm concentration and motility were evaluated. Females were sacrificed and C-sectioned on GD 20. Fetuses were examined for gross external alterations only. Blood samples were collected from satellite rats for plasma level determinations.

Strain: [redacted] CDBR VAF/Plus b(4)
Drug lot: 1538-DT1-1

2. Results

a. Mortality and Clinical Observations

Two HD males were found dead on Days 7 and 30. These deaths were considered trmt-related due to the presence of exaggerated pharmacological observations prior to death. One LD male found dead on D12 was attributed to intubation error. No trmt-related female deaths occurred (1 C female found dead on D14 and 1 MD female sacrificed on D15 due to a broken limb not T-R).

D-D increases in observations of repetitive sniffing and chewing, repetitive licking, and hyperactivity occurred at all doses; increases in excess salivation and repetitive scratching were seen at the MD and HD; and localized alopecia on the underside, swollen limbs and swollen snout were seen at the HD.

b. Body Weight

Body weight gains for the entire dosage period (Days 1 to 70 and Days 1 to termination) were significantly reduced in MD (11 and 9%) and HD males (27 and 24%) compared to C. In females, significantly reduced BW gain occurred during the first week of dosing at the HD, resulting in significantly decreased body

weight gain for the entire precohabitation period (D1-15: 50% below C) and significantly decreased BWs on Days 8 and 15 of this period. BW gains were significantly reduced on GDs 0-8 in MD (14%) and HD (23%) females. BW gains were increased compared to C for the rest of the gestation period in these groups, resulting in increased BW gains for the entire postdosage period (GDs 8-20). BW gains for the entire gestation period (GDs 0-20) were comparable.

c. Plasma drug levels

Male TK data are shown below. In females, modafinil AUCs were 23.1, 168.1, and 317.9 ug.h/ml on Day 1 of dosing; 22.2, 121.3, and 111.8 ug.h/ml on Day 13; and 36.8, 72.4, and 155 ug.h/ml on GD 7 in the LD, MD, and HD groups, respectively. Thus, concentrations of modafinil decreased markedly with repeated dosing at the MD and HD. There were similar but less pronounced decreases in levels of modafinil acid and modafinil sulfone.

Table V.A1

Pharmacokinetic Parameters for Modafinil, Modafinil Acid and Modafinil Sulfone in Male Rats after Oral Administration of 100, 240 or 480 mg/kg/day

Modafinil						
	Day 1[a]			Day 27[a]		
Dose (mg/kg/day)	AUC_{0-t}[b] (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hour)	AUC_{0-t}[b] (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hour)
100	28.9	12.39	1	26.9	10.65	1
240	100.7	36.71	1	59.0	10.40	2
480	446.1	47.98	1	101.7	13.41	4
Modafinil Acid						
	Day 1[a]			Day 27[a]		
Dose (mg/kg/day)	AUC_{0-t}[b] (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hour)	AUC_{0-t}[b] (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hour)
100	7.5	3.39	1	8.4	3.60	1
240	24.8	7.50	1	19.7	4.15	2
480	95.0	6.24	1	35.7	6.35	2
Modafinil Sulfone						
	Day 1[a]			Day 27[a]		
Dose (mg/kg/day)	AUC_{0-t}[b] (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hour)	AUC_{0-t}[b] (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hour)
100	3.2	2.43	2	2.1	2.05	2
240	20.8	4.35	1	27.7	5.39	4
480	124.9	10.54	4	90.3	16.37	8

[a] Day of Administration

[b] AUC_{0-t}, where t is the time of the last sample with quantifiable concentrations.

d. Male and female Reproductive Indices

There were no clear effects on estrous cycling or fertility parameters. (**Tables V.A2** and **V.A3**). However, while all rats mated, there was a D-R increase in the time to mate in treated males and females (SS at HD). There were no apparent effects of treatment on caudal epididymal sperm motility, total sperm count and density.

Table V.A2

TABLE B6 (PAGE 1): MATING AND FERTILITY - SUMMARY - Fo GENERATION MALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)		I 0 (VEHICLE)	II 100	III 480	IV 240
RATS IN COHABITATION	N	24	24	23a	24
INCLUDED IN ANALYSES	N	23b	23b	23	24
DAYS IN COHABITATION c	MEAN+S.D.	1.7 + 1.0	2.6 + 2.4	2.8 + 1.6**	2.4 + 2.7
RATS THAT MATED d	N(%)	23(100.0)	23(100.0)	23(100.0)	24(100.0)
FERTILITY INDEX e,f	N/N (%)	22/23 (95.6)	23/23 (100.0)	23/23 (100.0)	24/24 (100.0)
RATS WITH CONFIRMED MATING DATES g	N	23	23	23	23
RATS MATING h DAYS 1-7 DAYS 8-14	N(%) N(%)	23(100.0) 0(0.0)	22(95.6) 1(4.3)	23(100.0) 0(0.0)	23(95.8) 0(0.0)
RATS PREGNANT/RATS IN COHABITATION g	N/N (%)	22/23 (95.6)	23/23 (100.0)	23/23 (100.0)	23/24 (95.8)

a. Includes values for rat 2564, which was found dead on day 30 of study (day 2 of cohabitation).
b. Includes values for rats that had abnormal testes and epididymides; see the individual necropsy observations table (Table B15).
c. Restricted to rats with a confirmed mating date on days 1 to 14 of cohabitation and rats that did not mate.
d. Includes only one mating for each male rat.
e. Number of pregnancies/number of rats that mated.
f. Includes only one pregnancy for each rat that impregnated more than one female rat.
g. Includes only one confirmed mating for each male rat.
h. Restricted to rats with a confirmed mating date on days 1 to 14 of cohabitation.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

Table V.A3

TABLE C16 (PAGE 2): ESTROUS CYCLING, MATING AND FERTILITY - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 100	III 480	IV 240
RATS IN COHABITATION	N	24b	25	25	24b
INCLUDED IN ANALYSES	N	23c	24d	25	24
DAYS IN COHABITATION e	MEAN+S.D.	1.7 + 1.0	2.0 + 1.0	2.9 + 1.6** [24]f	2.8 + 4.8
RATS THAT MATED	N(%)	23(100.0)	24(100.0)	25(100.0)	24(100.0)
FERTILITY INDEX g	N/N (%)	22/23 (95.6)	23/24 (95.8)	25/25 (100.0)	24/24 (100.0)
RATS WITH CONFIRMED MATING DATES	N	23	24	24	23
MATED BY FIRST MALE h DAYS 1-7 DAYS 8-14	N(%) N(%)	23(100.0) 0(0.0)	24(100.0) 0(0.0)	24(100.0) 0(0.0)	23(100.0) 0(0.0)
MATED BY SECOND MALE h DAYS 15-21	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
RATS PREGNANT/RATS IN COHABITATION	N/N (%)	22/23 (95.6)	23/24 (95.8)	25/25 (100.0)	24/24 (100.0)

[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on day 1 of study through day 17 of presumed gestation.
b. Includes values for rats that died or were moribund sacrificed during the precohabitation period.
c. Includes values for rat 2608; male rat 2588 had small, purple and flaccid testes and small epididymides
d. Includes values for rat 2626; male rat 2526 had small epididymides and testes.
e. Restricted to rats with a confirmed mating date and rats that did not mate.
f. Includes values for rat 2664, male rat was found dead on day 30 of study (day 2 of cohabitation)
g. Number of pregnancies/number of rats that mated.
h. Restricted to rats with a confirmed mating date.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

e. Maternal term sacrifice parameters

No treatment effects on C-sectioning or litter parameters were apparent (**Tables V.A4** and **V.A5**). No T-R increases in external fetal abnormalities were apparent: there was 1 malformed fetus in each of the C, MD, and HD groups.

Table V.A4

TABLE C14 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 100	III 480	IV 240
RATS TESTED	N	24b	25	25	24b
PREGNANT	N(%)	22(91.7)	23(92.0)	25(100.0)	24(100.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 20 OF GESTATION	N	22	23	25	24c
CORPORA LUTEA	MEAN±S.D.	18.3 ± 2.7	18.4 ± 2.8	18.0 ± 2.4	18.4 ± 3.6
IMPLANTATIONS	MEAN±S.D.	15.7 ± 2.5	16.0 ± 2.3	15.8 ± 1.7	15.2 ± 3.2
LITTER SIZES	MEAN±S.D.	14.9 ± 3.5	15.6 ± 2.2	15.2 ± 1.6	14.4 ± 3.4
LIVE FETUSES	N	327	360	381	345
	MEAN±S.D.	14.9 ± 3.5	15.6 ± 2.2	15.2 ± 1.6	14.4 ± 3.4
DEAD FETUSES	N	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.9 ± 2.2	0.3 ± 0.6	0.6 ± 0.8	0.8 ± 1.2
EARLY RESORPTIONS	N	19	7	15	19
	MEAN±S.D.	0.9 ± 2.2	0.3 ± 0.6	0.6 ± 0.8	0.8 ± 1.2
LATE RESORPTIONS	N	0	0	0	0
DAMS WITH ANY RESORPTIONS	N(%)	6(27.3)	6(26.1)	11(44.0)	10(41.7)
DAMS WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH VIABLE FETUSES	N(%)	22(100.0)	23(100.0)	25(100.0)	24(100.0)
PLACENTAE APPEARED NORMAL	N(%)	22(100.0)	22(95.6)	25(100.0)	24(100.0)
PLACENTAE: FUSED	N(%)	0(0.0)	1(4.3)	0(0.0)	0(0.0)

a. Dosage occurred on day 1 of study through day 7 of gestation.
b. Includes values for rats that died or were moribund sacrificed during the precohabitation period
c. Includes values for dam 2690, which did not have a confirmed mating date and was sacrificed on day 37 of study (an estimated day 21 of gestation).

Table V.A5

TABLE C15 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY - F1 GENERATION LITTERS

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 100	III 480	IV 240
LITTERS WITH ONE OR MORE LIVE FETUSES	N	22	23	25	24
IMPLANTATIONS	MEAN±S.D.	15.7 ± 2.5	16.0 ± 2.3	15.8 ± 1.7	15.2 ± 3.2
LIVE FETUSES	N	327	360	381	345
	MEAN±S.D.	14.9 ± 3.5	15.6 ± 2.2	15.2 ± 1.6	14.4 ± 3.4
LIVE MALE FETUSES	N	171	186	191	193
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	52.7 ± 21.4	51.4 ± 15.0	49.5 ± 14.0	44.5 ± 13.0
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	3.39 ± 0.39	3.53 ± 0.28	3.57 ± 0.36	3.56 ± 0.47 [23]b
MALE FETUSES	MEAN±S.D.	3.51 ± 0.39	3.62 ± 0.28	3.67 ± 0.39	3.65 ± 0.56 [23]b
FEMALE FETUSES	MEAN±S.D.	3.26 ± 0.39	3.43 ± 0.29	3.48 ± 0.37	3.48 ± 0.44 [23]b
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	6.8 ± 15.1	1.9 ± 3.4	3.6 ± 4.9	5.4 ± 9.3

[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on day 1 of study through day 7 of gestation.
b. Excludes values for dam 2690, which did not have a confirmed mating date and was sacrificed on day 37 of study (an estimated day 21 of gestation).

f. Necropsy

In males, liver weights were increased (SS) at all doses, and increases in the ratios of the weights of the testes, seminal vesicles, and epididymides were seen at the HD (thought to reflect the reduced terminal BWs in this group). Female liver and ovarian weights and ratios were increased at the MD and HD.

3. Conclusions

Two T-R deaths occurred in HD males. Clinical signs were observed at all doses (100, 240, and 480 mg/kg), and decreased BW gain and increased reproductive organ weights were seen at the MD and HD. There was an effect on time to mating in treated animals (SS at HD), but no other effects on fertility or on C-sectioning and litter parameters.

B. ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF CEP-10953 (R-MODAFINIL) IN RATS (Protocol 1503-010, Study # DS-03-011, report dated 2/11/03, conducted by [redacted], GLP) b(4)

1. Methods

Female rats (S-D; 25/group + 6/grp TK) were treated with 0 (vehicle), 60, 200, or 600 mg/kg R-modafinil by oral gavage (10 ml/kg) once daily on gestational days (GDs) 7 through 17. All rats were examined for clinical observations, abortions, premature deliveries and deaths before and approximately 90 minutes after dosing. Body weights and food consumption were recorded. Main study animals were euthanized on GD 21 and C-sectioned. Fetuses were weighed and examined for external, soft tissue, and/or skeletal alterations (1/2 Wilson's sectioned/ 1/2 stained). Doses were based on a dose range-finding study at doses of 200, 400, and 800 mg/kg, in which the HD was associated with excessive maternal toxicity (deaths), increased resorption, and decreased fetal BWs.

Strain: [redacted]CD(SD)IGS BR VAF/Plus b(4)
Drug lot #: 02117K2a

2. Results

a. Effects on the dam

No T-R deaths occurred. One C rat delivered and was sacrificed on GD 21. All other rats survived until scheduled euthanasia. Increased numbers of rats with localized alopecia, excess salivation, hyperactivity, hyperreactivity and repetitive chewing were seen at the HD. There was a statistically significant increase in liver weights at the MD and HD. Terminal body weights, ovarian weights and ratios of ovary weight to terminal body weight were similar among the groups.

HD dams lost weight on GDs 7 to 10 and had decreased body weight gain and food consumption for the overall dosing period (GDs 7-18: 27% below C; **Figure V.B1**). TK data are shown in **Table V.B1** below. Exposure to R-modafinil was lower (40%) on Day 17 compared to Day 7 at the HD. At the LD, levels were below the limit of detections in most cases.

b. Fetal evaluations

i. There was a slight increase in resorption (early) at the HD (**Table V.B2**).
ii. Fetal body weights were reduced (SS) in the HD group (**Table V.B3**) .
iii. There were increases in the number of fetuses and litters with any alteration observed at all doses (SS at MD and HD; **Table V.B4**). This increase was primarily due to increased numbers of fetuses with visceral and skeletal variations (eg, dilation of the renal pelvis and decreased ossification of sternal centra; **Table V.B5-7**).

3. Conclusions

R-modafinil should be considered a (selective) developmental toxicant based on increased incidences of visceral and skeletal variations at the MD and HD and decreased fetal BW at the HD, which also produced minimal maternal toxicity. The NOEL (60 mg/kg) was associated with very low plasma exposures to R-modafanil compared to clinical (AUC approximately 0.03 times expected clinical exposures at 250 mg).

Figure V.B1

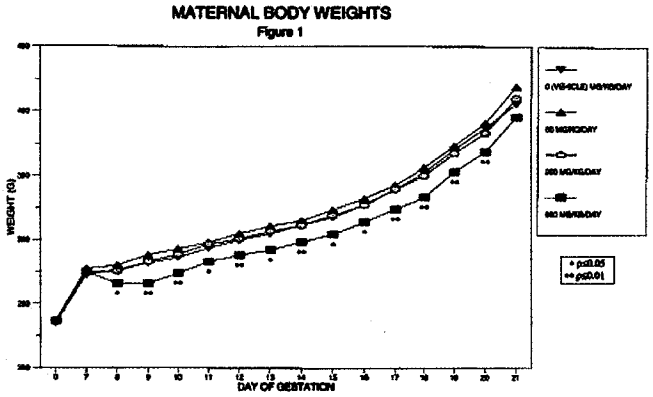


Table V.B1

Table A **Composite mean plasma concentrations (μg/mL) of R-modafinil, modafinil sulfone and R-modafinil acid in presumed pregnant female rats after oral doses of 60, 200 or 600 mg/kg/day for 11 days of CEP-10953 (R-modafinil) during Cephalon Study No. DS-03-011**

DAY 7	Group 2: 60 mg/kg/day			Group 3: 200 mg/kg/day			Group 4: 600 mg/kg/day		
Time (hr)	*R-M*	*R-MA*	*MS*	*R-M*	*R-MA*	*MS*	*R-M*	*R-MA*	*MS*
Predose	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]
1	4.08	BLQ[a]	BLQ[a]	24.85	2.06	BLQ[a]	57.27	2.61	0.47
2	BLQ[a]	BLQ[a]	BLQ[a]	6.97	BLQ[a]	BLQ[a]	38.91	2.09	0.59
4	BLQ[a]	BLQ[a]	BLQ[a]	1.69	0.35	BLQ[a]	7.35	BLQ[a]	BLQ[a]
8	BLQ[a]	BLQ[a]	BLQ[a]	0.81	BLQ[a]	BLQ[a]	6.14	0.33	BLQ[a]
24	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	7.43	BLQ[a]	BLQ[a]
C_{max}, μg/mL	4.08	BLQ	BLQ	24.85	2.06	BLQ	57.27	2.61	0.59
t_{max}, hr	1.0	-	-	1.0	1.0	-	1.0	1.0	2.0
AUC_{0-t}, μg·hr/mL	2.0	0.0	0.0	42.0	2.4	0.0	258.5	6.4	0.8
DAY 17	**Group 2: 60 mg/kg/day**			**Group 3: 200 mg/kg/day**			**Group 4: 600 mg/kg/day**		
Time (hr)	*R-M*	*R-MA*	*MS*	*R-M*	*R-MA*	*MS*	*R-M*	*R-MA*	*MS*
Predose	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	0.21	0.83	BLQ[a]	BLQ[a]
1	4.24	0.32	BLQ[a]	15.82	1.63	BLQ[a]	23.79	2.48	0.32
2	1.60	BLQ[a]	BLQ[a]	8.38	0.85	BLQ[a]	25.58	2.19	0.78
4	BLQ[a]	BLQ[a]	BLQ[a]	7.51	1.10	BLQ[a]	19.21	1.90	0.24
8	BLQ[a]	BLQ[a]	BLQ[a]	1.00	BLQ[a]	BLQ[a]	14.44	1.22	0.63
24	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]	BLQ[a]
C_{max}, μg/mL	4.24	0.32	BLQ	15.82	1.63	BLQ	25.58	2.48	0.78
t_{max}, hr	1.0	1.0	-	1.0	1.0	-	2.0	1.0	2.0
AUC_{0-t}, μg·hr/mL	5.0	0.2	0.0	52.9	4.0	NC	149.1	13.9	3.5

R-M – R-modafinil; ***R-MA*** – R-modafinil acid; ***MS*** – modafinil sulfone;

[a] BLQ – below the limit of quantitation (Although the assay limit of quantitation was 0.20 μg/mL, the effective lower limit for these samples was 0.40 μg/mL, due to the low sample volume and the resultant need for a minimal 2-fold dilution.)

Appears This Way
On Original

Table V.B2

TABLE 8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 60	III 200	IV 600
RATS TESTED	N	25	25	25	25
PREGNANT	N(%)	22(88.0)	23(92.0)	23(92.0)	24(96.0)
DELIVERED AND SACRIFICED	N(%)	1(4.5)	0(0.0)	0(0.0)	0(0.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 21 OF GESTATION	N	21	23	23	24
INCLUDED IN ANALYSES	N	20b	21b	23	24
CORPORA LUTEA	MEAN±S.D.	15.2 ± 1.8	16.5 ± 2.0	16.2 ± 2.0	16.2 ± 2.3
IMPLANTATIONS	MEAN±S.D.	13.9 ± 2.3	14.7 ± 1.7	14.1 ± 2.3	13.9 ± 2.0
LITTER SIZES	MEAN±S.D.	13.4 ± 2.3	14.2 ± 1.6	13.4 ± 2.5	13.1 ± 2.0
LIVE FETUSES	N	267	299	308	315
	MEAN±S.D.	13.4 ± 2.3	14.2 ± 1.6	13.4 ± 2.5	13.1 ± 2.0
DEAD FETUSES	N	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.6 ± 0.6	0.4 ± 0.8	0.7 ± 1.3	0.8 ± 0.9
EARLY RESORPTIONS	N	10	9	15	18
	MEAN±S.D.	0.5 ± 0.6	0.4 ± 0.8	0.6 ± 1.3	0.8 ± 0.9
LATE RESORPTIONS	N	1	0	1	1
	MEAN±S.D.	0.0 ± 0.2	0.0 ± 0.0	0.0 ± 0.2	0.0 ± 0.2
DAMS WITH ANY RESORPTIONS	N(%)	10(50.0)	6(28.6)	7(30.4)	12(50.0)
DAMS WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH VIABLE FETUSES	N(%)	20(100.0)	21(100.0)	23(100.0)	24(100.0)
PLACENTAE APPEARED NORMAL	N(%)	20(100.0)	21(100.0)	23(100.0)	24(100.0)

a. Dosage occurred on days 7 through 17 of gestation.
b. Excludes values for litters that consisted of two or less fetuses or all early resorptions.

Table V.B3

TABLE 9 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 60	III 200	IV 600
LITTERS WITH ONE OR MORE LIVE FETUSES	N	21	22	23	24
INCLUDED IN ANALYSES	N	20b	21b	23	24
IMPLANTATIONS	MEAN±S.D.	13.9 ± 2.3	14.7 ± 1.7	14.1 ± 2.3	13.9 ± 2.0
LIVE FETUSES	N	267	299	308	315
	MEAN±S.D.	13.4 ± 2.3	14.2 ± 1.6	13.4 ± 2.5	13.1 ± 2.0
LIVE MALE FETUSES	N	138	152	148	151
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	52.1 ± 15.3	51.0 ± 16.0	47.9 ± 16.8	47.8 ± 16.6
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	5.50 ± 0.21	5.47 ± 0.26	5.46 ± 0.26	5.29 ± 0.20**
MALE FETUSES	MEAN±S.D.	5.63 ± 0.24	5.65 ± 0.22	5.66 ± 0.24	5.40 ± 0.21**
FEMALE FETUSES	MEAN±S.D.	5.35 ± 0.24	5.28 ± 0.30	5.26 ± 0.23	5.18 ± 0.22
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	3.8 ± 4.2	2.7 ± 5.1	5.0 ± 9.6	5.5 ± 6.2

a. Dosage occurred on days 7 through 17 of gestation.
b. Excludes values for litters that consisted of two or less fetuses or all early resorptions.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

Table V.B4

TABLE 10 (PAGE 1): FETAL ALTERATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 60	III 200	IV 600
LITTERS EVALUATED	N	21	22	23	24
FETUSES EVALUATED	N	269	300	308	315
LIVE	N	269	300	308	315
LITTERS WITH FETUSES WITH ANY ALTERATION OBSERVED	N(%)	4(19.0)	7(31.8)	11(47.8)	11(45.8)
FETUSES WITH ANY ALTERATION OBSERVED	N(%)	4(1.5)	8(2.7)	16(5.2)**	18(5.7)**
% FETUSES WITH ANY ALTERATION/LITTER	MEAN±S.D.	1.5 ± 3.1	6.8 ± 21.2	5.0 ± 6.4	5.4 ± 7.2

a. Dosage occurred on days 7 through 17 of gestation.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

Table V.B5

TABLE 11 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 60	III 200	IV 600
LITTERS EVALUATED	N	21	22	23	24
FETUSES EVALUATED	N	269	300	308	315
LIVE	N	269	300	308	315
HINDLIMBS: ROTATED MEDIALLY					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.3)	0(0.0)
BODY: EDEMA					
LITTER INCIDENCE	N(%)	0(0.0)	2(9.1)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	2(0.7)b	1(0.3)	0(0.0)
TONGUE: PROTRUDED					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.3)b	0(0.0)	0(0.0)
JAW: MICROGNATHIA					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.3)b	0(0.0)	0(0.0)
BODY: ELONGATED					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.3)b	0(0.0)	0(0.0)

a. Dosage occurred on days 7 through 17 of gestation.
b. Fetus 10041-1 had other gross external alterations.

Table V.B6

TABLE 12 (PAGE 1): FETAL SOFT TISSUE ALTERATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 60	III 200	IV 600
LITTERS EVALUATED	N	21	21	23	24
FETUSES EVALUATED	N	129	144	147	151
LIVE	N	129	144	147	151
EYES: MICROPHTHALMIA					
LITTER INCIDENCE	N(%)	1(4.8)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.8)	0(0.0)	0(0.0)	0(0.0)
EYES: RETINA, FOLDED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
HEART: PERICARDIAL SAC, LARGE					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.7)b	0(0.0)
VESSELS: UMBILICAL ARTERY DESCENDED TO THE LEFT OF URINARY BLADDER					
LITTER INCIDENCE	N(%)	0(0.0)	2(9.5)	3(13.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	2(1.4)	3(2.0)b	1(0.7)
LUNGS: LEFT, LOBE ABSENT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
KIDNEYS: PELVIS, SLIGHT DILATION					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(8.3)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	3(2.0)**
KIDNEYS: PELVIS, MODERATE DILATION					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)

a. Dosage occurred on days 7 through 17 of gestation.
b. Fetus 10061-4 had other soft tissue alterations.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

Table V.B7

TABLE 13 (PAGE 1): FETAL SKELETAL ALTERATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	60	200	600
LITTERS EVALUATED	N	21	22	23	24
FETUSES EVALUATED	N	140	156	161	164
LIVE	N	140	156	161	164
SKULL: MANDIBLES, SHORT					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA					
LITTER INCIDENCE	N(%)	1(4.8)	1(4.5)	3(13.0)	1(4.2)
FETAL INCIDENCE	N(%)	1(0.7)	1(0.6)	5(3.1)c,d	1(0.6)
CERVICAL VERTEBRAE: ARCH, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	2(8.7)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	2(1.2)c	0(0.0)
THORACIC VERTEBRAE: CENTRUM, BIFID					
LITTER INCIDENCE	N(%)	1(4.8)	3(13.6)	3(13.0)	1(4.2)
FETAL INCIDENCE	N(%)	1(0.7)	3(1.9)b	4(2.5)	1(0.6)
RIBS: SHORT					
LITTER INCIDENCE	N(%)	1(4.8)	0(0.0)	1(4.3)	2(8.3)
FETAL INCIDENCE	N(%)	1(0.7)	0(0.0)	3(1.9)c,d	2(1.2)
STERNAL CENTRA: INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	2(9.1)	1(4.3)	5(20.8)
FETAL INCIDENCE	N(%)	0(0.0)	2(1.3)b	2(1.2)	7(4.3)e**
STERNAL CENTRA: ASYMMETRIC					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.6)e

a. Dosage occurred on days 7 through 17 of gestation.
b. Fetus 10044-5 had other skeletal alterations.
c. Fetus 10056-3 had other skeletal alterations.
d. Fetuses 10056-5 and 10056-7 had other skeletal alterations.
e. Fetus 10096-7 had other skeletal alterations.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

C. ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF CEP-1538 (CN-801) IN RABBITS (Protocol 1503-007, Study No. DS-01-018; report dated 7/17/02, conducted by [redacted], GLP) b(4)

1. Methods

Timed-mated female rabbits (New Zealand White; 20/grp + 4/grp TK) were treated with 0 (vehicle), 45, 90, or 180 mg/kg racemic modafinil by oral gavage on gestation days (GDs) 6 through 18. Does were observed for viability, clinical signs, premature deliveries and deaths before and approximately 90 minutes after dose administration. Body weights and food consumption were recorded during the dosing and postdosing period. Blood samples for TK determinations were collected at 0.5, 1, 2, 4, 8 and 24 hours after dosing on GDs 6 and 18 and predosing on GD 18. Main study does were sacrificed on GD 29 and C-sectioned. Numbers of corpora lutea were recorded and uteri excised and examined for pregnancy, number and distribution of implantation sites, early and late resorptions and live and dead fetuses. All fetuses were examined for gross, soft tissue, and skeletal alterations.

Strain: New Zealand White [redacted](NZW)SPF)
Drug lot #: lot 1538-DT1-1

2. Results

a. Maternal effects

Two LD does died on GDs 15 and 16, but these were not considered T-R. Two MD and 1 HD doe aborted on GDs 26, 27, and 20, respectively. It is not clear whether these were T-R. The fetuses from the MD does were said to be normal

for gestational age, while HD doe had 10 resorptions (5 early, 5 late). Clinical observations included: excessive sniffing, chewing, licking and grooming at all doses. As a result of the excessive chewing, licking and grooming, a significantly increased number of HD does had ulceration on the neck or paws and scabbing on the paws, nose, neck and back. There were no T-R necropsy observations.

BW gain was significantly decreased during the overall treatment period in the HD group (mean change GDs 6-19: 0.03±0.24 vs 0.28±0.11 in C; **Figure V.C1**). Food consumption values were also significantly reduced in this group.

TK data from satellite animals are shown in **Table V.C1** below. Unlike the situation in rats, there was not much decline in parent levels over time. But exposures at the HD were still only a little higher than typical clinical exposures.

Table V.C1

Table A Estimated Mean Pharmacokinetic Parameters (± SD) for Modafinil, Modafinil Acid and Modafinil Sulfone after Oral Administration of 45, 90 or 180 mg/kg/day of Modafinil to Rabbits on Days 6 through 18 of Presumed Gestation

Dose	45 mg/kg/day		90 mg/kg/day		180 mg/kg/day	
	Modafinil					
Parameter	Day 6*	Day 18*	Day 6	Day 18	Day 6	Day 18
C_{max} µg/mL	9.66 ± 5.12	13.39 ± 4.56	22.09 ± 5.53	19.77 ± 7.15	36.82 ± 10.62	37.82 ± 10.23
t_{max} hr	2.0 ± 1.4	1.0 ± 0.7	3.1 ± 1.8	2.3 ± 1.3	4.5 ± 2.5	2.5 ± 1.7
AUC_{0-t} µg•hr/mL	39.0 ± 16.2	42.4 ± 15.3	90.5 ± 34.4	77.9 ± 34.6	219.0 ± 68.7	203.3 ± 45.4
	Modafinil Acid					
Parameter	Day 6	Day 18	Day 6	Day 18	Day 6	Day 18
C_{max} µg/mL	4.75 ± 2.22	5.30 ± 2.60	13.94 ± 5.75	7.71 ± 2.16	12.42 ± 0.96	12.60 ± 3.09
t_{max} hr	1.9 ± 1.5	1.0 ± 0.7	3.1 ± 1.8	1.9 ± 1.5	3.3 ± 1.5	1.5 ± 1.7
AUC_{0-t} µg•hr/mL	13.6 ± 3.5	10.1 ± 3.3	44.0 ± 14.4	23.8 ± 5.6	72.5 ± 12.4	46.2 ± 9.2
	Modafinil Sulfone					
Parameter	Day 6	Day 18	Day 6	Day 18	Day 6	Day 18
C_{max} µg/mL	1.86 + 0.75	2.05 ± 0.38	3.64 ± 1.03	2.77 ± 1.15	5.97 ± 3.42	5.38 ± 0.77
t_{max} hr	4.5 ± 2.5	1.5 ± 0.6	3.5 ± 1.0	3.0 ± 1.2	5.5 ± 3.0	4.0 ± 0.0
AUC_{0-t} µg•hr/mL	5.4 ± 1.5	5.5 ± 2.5	16.0 ± 9.0	12.1 ± 6.5	32.0 ± 17.0	31.4 ± 8.6

*Day 6 of gestation = Day 1 of dosing; Day 18 of gestation = Day 13 of Dosing

b. Developmental effects

i. Resorptions were increased and live fetuses reduced in the HD group (**Table V.C1**).

ii. There appeared to be a slight decrease (NS) in fetal BWs at the MD and HD (**Table V.C2**). The failure to see a strict dose-relationship was probably due to the increase in early resorptions at the HD.

iii. Numbers of fetuses and litters with any alterations were increased at the HD (**Table V.C3**). The majority of fetal alterations occurred in 1 C litter (7110; 7 malformed fetuses) and 1 HD litter (7168; 10 malformed fetuses), each with several fetuses with multiple malformations of the type typically seen spontaneously. Litter 7110 had 6 fetuses with cleft palate and 7 with flat ribs. Litter 7168 had 9 fetuses with open eyelids and fore and hindlimbs rotated medially, and 7 with fused digits on the fore and/or hindlimbs. However, when these two litters were excluded or the number of litters with malformations and the number and severity of malformations were considered, skeletal malformations and some skeletal variations appeared to be increased slightly at the HD (**Table V.C4-6**).

Fetuses with skeletal malformations consisted of 9 C fetuses from 3/20 litters (7110-3, -4, -6, -7, -8, -9, -10 with bilateral flat ribs and skull malformations; 7109-7 and 7114-4 with misaligned vertebrae); 3 LD fetuses from 3/17 litters (7129-7, 7138-4, 7140-5 with misaligned vertebrae); 2 MD fetus from 2/17 litters (7158-10 with fused thoracic centra and ribs, 7151-1 with misaligned vertebrae); and 13 HD fetuses from 4/17 litters (7166-10 with hemivertebra, fused and split ribs, and 11 total ribs; 7171-2 with hemivertebra, small thoracic arch, fused vertebral centra, small rib, fused and split ribs, 11 total ribs, and fused lumbar arches; 7167-3 with a bilateral flat vertebral arch; 7168-6 with hemivertebra; 7168-1, -2, -3, -4, -5, -7, -8, -9, -10 with fused phalanges and/or short/small tibial bones).

The variations fusion of the manubrium to the 1st sternal centra and/or fusion of the sternal centra occurred in 1, 4, 0 and 13 fetuses from 1/20, 3/17, 0/17 and 4/17 litters in the four respective dosage groups. 10 of these HD fetuses were from litter 7168.

3. Conclusions

Resorptions were increased in the HD (180 mg/kg) group, resulting in a reduced number of live fetuses, and there appeared to be a slight decrease (NS) in fetal BWs at the MD and HD. An increased incidence of fetal alterations (malformations and variations) was found in the HD group. This was attributed by the sponsor to 1 litter with similar alterations which were considered congenital and not T-R. One litter also contributed most of the alterations in the Control group. However, when these two litters were excluded or the number of litters with alterations or the number and severity of malformations were considered, skeletal malformations and some skeletal variations appeared to be increased somewhat at the HD. The HD was minimally maternally toxic, reducing maternal body weight gain somewhat over the dosage period, but not excessively. Therefore, based on these data, modafanil should be identified as a developmental toxicant, primarily based on lethality, which could have masked a more obvious teratogenic effect. The MD (90 mg/kg) can be considered a NOEL for adverse effects on embryo-fetal development.

Figure V.C1

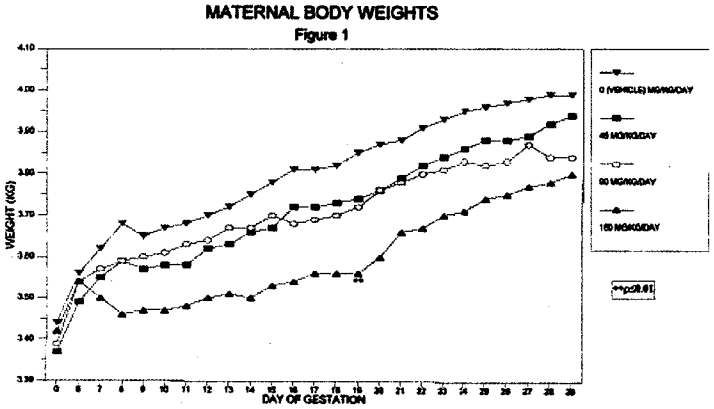


Table V.C1

TABLE 8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 45	III 90	IV 180
RABBITS TESTED	N	20	20	20	20
PREGNANT	N(%)	20(100.0)	19(95.0)	19(95.0)	18(90.0)
FOUND DEAD	N(%)	0(0.0)	2(10.5)	0(0.0)	0(0.0)
ABORTED AND SACRIFICED	N(%)	0(0.0)	0(0.0)	2(10.5)	1(5.6)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	20	17	17	17
CORPORA LUTEA	MEAN±S.D.	9.6 ± 2.1	10.5 ± 2.3	9.9 ± 1.4	9.9 ± 1.5
IMPLANTATIONS	MEAN±S.D.	9.0 ± 1.9	9.6 ± 2.1	8.9 ± 1.6	8.8 ± 1.6
LITTER SIZES	MEAN±S.D.	8.5 ± 2.0	9.0 ± 2.0	8.5 ± 1.5	7.6 ± 2.4
LIVE FETUSES	N	170	153	144	130
	MEAN±S.D.	8.5 ± 2.0	9.0 ± 2.0	8.5 ± 1.5	7.6 ± 2.4
DEAD FETUSES	N	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.5 ± 0.9	0.6 ± 0.9	0.6 ± 0.8	1.2 ± 2.1
EARLY RESORPTIONS	N	3	8	5	15
	MEAN±S.D.	0.2 ± 0.4	0.5 ± 0.9	0.3 ± 0.8	0.9 ± 2.0
LATE RESORPTIONS	N	7	3	2	5
	MEAN±S.D.	0.4 ± 0.9	0.2 ± 0.4	0.1 ± 0.3	0.3 ± 0.7
DOES WITH ANY RESORPTIONS	N(%)	6(30.0)	7(41.2)	7(41.2)	8(47.0)
DOES WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DOES WITH VIABLE FETUSES	N(%)	20(100.0)	17(100.0)	17(100.0)	17(100.0)
PLACENTAE APPEARED NORMAL	N(%)	20(100.0)	17(100.0)	17(100.0)	17(100.0)

a. Dosage occurred on days 6 through 18 of gestation.

Table V.C2

TABLE 9 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 45	III 90	IV 180
LITTERS WITH ONE OR MORE LIVE FETUSES	N	20	17	17	17
IMPLANTATIONS	MEAN±S.D.	9.0 ± 1.9	9.6 ± 2.1	8.9 ± 1.6	8.8 ± 1.6
LIVE FETUSES	N	170	153	144	130
	MEAN±S.D.	8.5 ± 2.0	9.0 ± 2.0	8.5 ± 1.5	7.6 ± 2.4
LIVE MALE FETUSES	N	87	80	70	73
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	52.8 ± 15.7	51.0 ± 16.0	47.4 ± 17.0	57.1 ± 10.9
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	40.36 ± 4.62	41.38 ± 5.03	38.77 ± 5.49	39.35 ± 5.05
MALE FETUSES	MEAN±S.D.	41.70 ± 5.13	41.64 ± 5.17	39.54 ± 5.76	39.74 ± 5.18
FEMALE FETUSES	MEAN±S.D.	38.90 ± 4.73	40.74 ± 5.27	37.56 ± 5.50	38.77 ± 5.38
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	5.6 ± 10.2	6.3 ± 8.7	4.4 ± 5.5	13.2 ± 21.0

a. Dosage occurred on days 6 through 18 of gestation.

Table V.C3

TABLE 10 (PAGE 1): FETAL ALTERATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 45	III 90	IV 180
LITTERS EVALUATED	N	20	17	17	17
FETUSES EVALUATED	N	170	153	144	130
LIVE	N	170	153	144	130
LITTERS WITH FETUSES WITH ANY ALTERATION OBSERVED	N(%)	10(50.0)	8(47.1)	9(52.9)	12(70.5)
FETUSES WITH ANY ALTERATION OBSERVED	N(%)	21(12.4)	13(8.5)	10(6.9)	27(20.8)**
% FETUSES WITH ANY ALTERATION/LITTER	MEAN±S.D.	11.5 ± 19.1	9.1 ± 12.2	7.1 ± 7.3	21.9 ± 27.3

a. Dosage occurred on days 6 through 18 of gestation.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

Table V.C4

TABLE 11 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE)	II 45	III 90	IV 180
LITTERS EVALUATED	N	20	17	17	17
FETUSES EVALUATED	N	170	153	144	130
LIVE	N	170	153	144	130
EYES: LIDS OPEN					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	9(6.9)**h-o
FORE AND/OR HINDLIMBS: FUSED DIGITS					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	7(5.4)**h-j,l-o
FORE AND/OR HINDLIMBS: ROTATED MEDIALLY					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	3(1.8)d-f	0(0.0)	0(0.0)	9(6.9)**h-o
PALATE: CLEFT					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	6(3.5)b,c-g	0(0.0)	0(0.0)	0(0.0)
TONGUE: SMALL					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	7(4.1)b-g	0(0.0)	0(0.0)	0(0.0)
TONGUE: IRREGULAR SHAPE					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	4(2.4)b,d-f	0(0.0)	0(0.0)	0(0.0)
FORE AND/OR HINDLIMBS: FLEXED DOWNWARD					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	3(1.8)d-f	0(0.0)	0(0.0)	0(0.0)
HEAD: DOMED					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	2(1.2)e,f	0(0.0)	0(0.0)	0(0.0)

a. Dosage occurred on days 6 through 18 of gestation.
b. Fetus 7110-3 had other gross external alterations.
c. Fetus 7110-6 had other gross external alterations.
d. Fetus 7110-7 had other gross external alterations.
e. Fetus 7110-8 had other gross external alterations.
f. Fetus 7110-9 had other gross external alterations.
g. Fetus 7110-10 had other gross external alterations.
h. Fetus 7168-1 had other gross external alterations.
i. Fetus 7168-2 had other gross external alterations.
j. Fetus 7168-3 had other gross external alterations.
k. Fetus 7168-4 had other gross external alterations.
l. Fetus 7168-5 had other gross external alterations.
m. Fetus 7168-7 had other gross external alterations.
n. Fetus 7168-8 had other gross external alterations.
o. Fetus 7168-9 had other gross external alterations.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

Table V.C5

TABLE 13 (PAGE 1): FETAL SKELETAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)	45	90	180
LITTERS EVALUATED	N	20	17	17	17
FETUSES EVALUATED	N	170	153	144	130
LIVE	N	170	153	144	130
SKULL - IRREGULAR OSSIFICATION:b (SUMMARIZATION OF ALL IRREGULAR OSSIFICATION OF THE SKULL c; INDIVIDUAL SUBCATEGORIES CITED BELOW)					
LITTER INCIDENCE	N(%)	6(30.0)	3(17.6)	1(5.9)	4(23.5)
FETAL INCIDENCE	N(%)	7(4.1)	3(2.0)	1(0.7)	5(3.8)
SKULL: NASALS, IRREGULAR OSSIFICATION (SUMMARIZATION OF MIDLINE SUTURE DISPLACED; INTRANASAL; FUSED; INTERNASAL; NASAL-FRONTAL, IRREGULAR SUTURE)					
LITTER INCIDENCE	N(%)	4(20.0)	1(5.9)	1(5.9)	2(11.8)
FETAL INCIDENCE	N(%)	5(2.9)	1(0.6)	1(0.7)	3(2.3)
SKULL: NASALS, MIDLINE SUTURE DISPLACED					
LITTER INCIDENCE	N(%)	2(10.0)	0(0.0)	0(0.0)	2(11.8)
FETAL INCIDENCE	N(%)	2(1.2)	0(0.0)	0(0.0)	3(2.3)
SKULL: NASAL, CONTAINED AN INTRANASAL					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
SKULL: NASALS, FUSED					
LITTER INCIDENCE	N(%)	1(5.0)	1(5.9)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.6)	1(0.6)	0(0.0)	0(0.0)
SKULL: NASALS, CONTAINED AN INTERNASAL					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.9)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.7)	0(0.0)
SKULL: NASAL - FRONTAL, IRREGULAR SUTURE					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
SKULL: FRONTALS, IRREGULAR OSSIFICATION (SUMMARIZATION OF INTRAFRONTAL; INTERFRONTAL)					
LITTER INCIDENCE	N(%)	1(5.0)	2(11.8)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	1(0.6)	2(1.3)	0(0.0)	1(0.8)
SKULL: FRONTAL, CONTAINED AN INTRAFRONTAL					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.9)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
SKULL: FRONTALS, CONTAINED AN INTERFRONTAL					
LITTER INCIDENCE	N(%)	1(5.0)	1(5.9)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	1(0.6)	1(0.6)	0(0.0)	1(0.8)m
SKULL: PARIETAL, CONTAINED A HOLE					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	1(0.6)g	0(0.0)	0(0.0)	1(0.8)w
SKULL: PALATE, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	6(3.5)d-i	0(0.0)	0(0.0)	0(0.0)
SKULL: ANTERIOR FONTANELLE, LARGE					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	2(1.2)g,h	0(0.0)	0(0.0)	0(0.0)
SKULL: EYE SOCKET, SMALL					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.6)h	0(0.0)	0(0.0)	0(0.0)
HYOID: ALA, ANGULATED					
LITTER INCIDENCE	N(%)	2(10.0)	1(5.9)	2(11.8)	2(11.8)
FETAL INCIDENCE	N(%)	2(1.2)	1(0.6)	2(1.4)	3(2.3)
THORACIC VERTEBRAE: HEMIVERTEBRA					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(11.8)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(1.5)n,x
THORACIC VERTEBRAE: ARCH, SMALL					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.8)x
THORACIC VERTEBRAE: CENTRA, FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.9)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.7)1	1(0.8)x

Table V.C5 (cont.)

LUMBAR VERTEBRAE: ARCHES, FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.8)s
LUMBAR VERTEBRAE: ARCH, FLAT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.8)o
LUMBAR VERTEBRAE: HEMIVERTEBRA					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.8)u
CAUDAL VERTEBRAE: MISALIGNED					
LITTER INCIDENCE	N(%)	2(10.0)	3(17.6)	1(5.9)	1(5.9)
FETAL INCIDENCE	N(%)	2(1.2)	3(2.0)k	1(0.7)	1(0.8)
RIBS: FLAT					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	7(4.1)d-i	0(0.0)	0(0.0)	0(0.0)
RIBS: SMALL					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.8)s
RIBS: FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.9)	2(11.8)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.7)l	2(1.5)n,s
RIBS: SPLIT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(11.8)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(1.5)n,s
RIBS: 11 PRESENT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(11.8)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(1.5)n,s
RIBS: THICKENED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.8)m
MANUBRIUM: FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	4(3.1)p,q** u,y
STERNAL CENTRA: FUSED					
LITTER INCIDENCE	N(%)	1(5.0)	3(17.6)	0(0.0)	4(23.5)
FETAL INCIDENCE	N(%)	1(0.6)	4(2.8)	0(0.0)	13(10.0)o-q** r-x,z
STERNAL CENTRA: ASYMMETRIC					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.9)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)j	0(0.0)	0(0.0)
STERNAL CENTRA: INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	2(11.8)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	2(1.3)j,k	0(0.0)	1(0.8)
PELVIS: PUBES, NOT OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.9)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.7)	0(0.0)
HINDLIMB: TIBIA, SHORT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	7(5.4)p-s,** v,w,y
HINDLIMB: PHALANGES, FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(1.5)p,q
HINDLIMB: TIBIA, SMALL					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	3(2.3)q,t,x**
HINDLIMB: TIBIA, NOT OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.8)t

FOOTNOTES:

a. Dosage occurred on days 6 through 19 of gestation.
b. Fetuses with alterations of the skull and/or hyoid are not separately identified in this summarization, except when alterations of other ossification sites were also present.
c. Includes all alterations noted for the skull except hyoid, ala(e), angulated; anterior fontanelle, large; palate, incompletely ossified; eye socket, small. These categories are excluded because these alterations do not result from irregular ossification.
d. Fetus 7110-3 had other skeletal alterations.
e. Fetus 7110-6 had other skeletal alterations.
f. Fetus 7110-7 had other skeletal alterations.
g. Fetus 7110-8 had other skeletal alterations.
h. Fetus 7110-9 had other skeletal alterations.
i. Fetus 7110-10 had other skeletal alterations.
j. Fetus 7138-6 had other skeletal alterations.
k. Fetus 7138-4 had other skeletal alterations.
l. Fetus 7158-10 had other skeletal alterations.
m. Fetus 7163-7 had other skeletal alterations.
n. Fetus 7166-10 had other skeletal alterations.
o. Fetus 7167-3 had other skeletal alterations.
p. Fetus 7168-1 had other skeletal alterations.
q. Fetus 7168-2 had other skeletal alterations.
r. Fetus 7168-3 had other skeletal alterations.
s. Fetus 7168-4 had other skeletal alterations.
t. Fetus 7168-5 had other skeletal alterations.
u. Fetus 7168-6 had other skeletal alterations.
v. Fetus 7168-7 had other skeletal alterations.
w. Fetus 7168-8 had other skeletal alterations.
x. Fetus 7168-9 had other skeletal alterations.
y. Fetus 7168-10 had other skeletal alterations.
z. Fetus 7171-2 had other skeletal alterations.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

VI. Summary and Evaluation

Armodafinil (R-modafinil) is the R-(levorotary) enantiomer of modafinil, a racemic compound previously approved for the treatment of narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder in adults (NDA 20-717). The agreed-upon (pre-NDA meeting 10/22/04) bridging studies for this application consisted of safety pharmacology, 13-week repeat dose toxicity studies in rats and dogs, and an embryofetal developmental toxicity study in rats. [redacted] some qualification studies (4-week general toxicity, in vitro gentox) were performed with a lot (03188K2a) considered representative of the clinical drug substance batches. b(4)

In pharmacology studies in which the enantiomers were compared to each other and the racemate, there were no obvious differences aside from some differences in potency (eg, the S-enantiomer was more potent in increasing locomotor activity; Table I.2). Similar stimulant-like behavioral effects were observed in mice and rats; like the racemate, S- and R-modafinil both produced increased spontaneous activity, hypersensitivity to noise, and stereotypy (repetition of the same actions such as self-biting, cage biting, and other behaviors in the cage) in rats. However, in rats following pretreatment with an inhibitor of hepatic metabolism (proadifen) which lowered the dose at which stereotypy was seen, the extent and duration of stereotypies were greater (up to 2X) for R-modafinil than for S-modafinil or racemic modafinil. Studies of the wake-promoting activity of modafinil and its enantiomers in rats showed them to be similar. When waking activity was evaluated in the rat by recording EEG/EMG activity, all 3 compounds produced a significant wake-enhancing effect at 100 mg/kg ip in rats, but S-modafinil showed significantly greater activity than either the R-enantiomer or racemate. The difference in pharmacological activity between the enantiomers was thought be at least partly due to PK differences, ie, increased clearance of R- compared to S-modafinil in rats.

No competitive ligand binding inhibition was found when R-modafinil was tested against a panel of receptors and transporters, including adenosine, benzodiazepine, dopamine, galanin, melanocortin, melatonin, and serotonin, at concentrations of up to 10 uM. However, in rat striatal preparations, the R-enantiomer, like the racemate, bound to the dopamine transporter (IC50 = 4.1 uM). There were no significant differences in the affinities of the isomers or racemate for the dopamine transporter site.

R-modafinil was well-absorbed and eliminated mainly by metabolism (hydrolytic and oxidative) in the animals species tested. Metabolism appears to be enantioselective, and enantioselectivity species-specific. S-modafinil was more rapidly cleared than R-modafinil in mice, dogs and humans, while the opposite was true in rats. Like racemic modafinil, R-modafinil induced hepatic enzyme activity in vivo in rats, mice, and dogs. During studies in rats and dogs, exposure to the parent generally decreased with repeated dosing, sometimes markedly, indicating autoinduction. At high doses in rats and dogs, there is evidence of saturability of elimination pathways. There was no evidence for interconversion of the enantiomers.

Safety pharmacology studies did not reveal any new risks for R-modafinil. The cardiovascular safety evaluation included an in vivo study in conscious dogs and an in vitro study with dog Purkinje fibers. Effects included possible increases in HR and decreases in the RR, QT, and QTcF intervals at oral doses of 20 mg/kg or greater, and a decrease in action potential duration at concentrations of 50 μM or greater. These results did not indicate that R-modafinil is likely to induce QT prolongation in vivo. Behavioral effects in the Irwin study included hyperactivity and stereotypic behavior at ≥100 mg/kg po.

In an acute toxicity study of the isomers in rats, R- and S-modafinil were given once at oral doses of 0 (Ora-Plus vehicle), 500, 700, or 1100 mg/kg. Administration of the S-isomer produced

mortality in 0/5 males and 2/5 females at the HD. The R-isomer produced mortality in 1/5 males and 3/5 females at the HD. Both isomers produced hyperactivity and stereotypy at all doses. In animals that died, histopathological examination of the kidney and stomach revealed vacuolation in the proximal tubular epithelium, dilation of the distal tubules in the kidney, and erosion in the glandular stomach. Exposure increased in a greater than dose-proportional manner for males and females given the R-isomer and males given the S-isomer. Based on the results of this study, the minimum lethal dose and production of clinical signs were considered to be comparable between the two optical isomers.

In repeated-dose oral toxicity studies in rats and dogs of up to 13-weeks duration, typical stimulant-like CNS signs (hyperactivity and stereotypic behavior), and clinical pathology and histopathology changes indicative of effects on the RBCs, kidney (rats), bladder (rats), liver, and possibly heart (rat) were observed with both the racemate and R-enantiomer. As previously observed with modafinil, R-modafinil did not produce a clear increase in malformations in rats but was developmentally toxic at doses that were minimally maternally toxic. There was no clear evidence of mutagenic or carcinogenic potential in studies of either R-modafinil (gentox) or modafinil (Tg.AC). However, in all the of toxicology studies of R- and racemic modafinil, the highest doses evaluated were associated with plasma exposure to parent that were very low in comparison to clinical exposures. This has often been a problem with stimulants, due to the sensitivity of animals to the pharmacological effects of these agents (including hyperactivity, stereotypy, and anorexia), and is exacerbated in this case by the apparent autoinduction of metabolism seen in all animal species.

In the 13-week rat study, at oral doses of 0 ——— vehicle), 60, 200, or 600 mg/kg of R-modafinil or 400 mg/kg racemic modafinil, dose-related clinical signs (including stereotypic behavior at all doses), decreased BW gain in males (SS in MD and HD R-modafinil and modafinil), clinical pathology changes (decreased RBC parameters and increased WBCs at MD and HD R-modafinil and modafinil), and microscopic findings in the bone marrow (increased cellularity), spleen (increased splenic hematopoiesis and pigment), thyroid (hypertrophy of follicular epithelium at HD R-modafinil or modafinil), liver (hepatocellular hypertrophy and focal necrosis at MD and HD R-modafinil and modafinil), kidney and urinary bladder (renal tubular regeneration and chronic inflammation and hyperplasia and increased apoptosis of bladder urothelium at all doses of R-modafinil and modafinil), and possibly heart (chronic cardiomyopathy in HD R-modafinil and racemate) were seen with both R-modafinil and modafinil. Bone marrow hypercellularity and splenic extramedullary hematopoiesis were consistent with a regenerative response to the anemia produced. Hepatocellular hypertrophy was considered to be due to enzyme induction, and follicular cell hypertrophy in the thyroid was thought but not proven to be secondary to increased metabolism of circulating thyroid hormones. Although not demonstrated in these studies, urothelial hyperplasia in rats was thought to be due to alterations in urinary pH by modafinil as has been shown with other drugs. All effects were at least partially reversible. TK data showed that exposures to parent were generally greater in females than in males. While autoinduction was seen in other rat studies, AUCs did not decrease over time in this study. Plasma exposures to parent at the highest dose of R-modafinil tested (600 mg/kg) were about equal to those expected in humans at the maximum recommended dose of 250 mg (~150 ug.h/ml). Based on nephropathy and urothelial hyperplasia/apoptosis of the bladder epithelium, the LOAEL of R-modafinil was 60 mg/kg/day, which was associated with AUCs <1/10 those expected clinically. (Exposure comparisons are somewhat problematic due to species differences in metabolite formation.) The relevance of these findings is unclear, given species differences in the metabolism of modafinil and since they have not been seen in dogs or reported in clinical experience with the racemate. Although the bladder findings were apparently not noted in previous subchronic or chronic rat studies with the racemate, which were conducted at oral doses of up to 400 mg/kg, they were seen with comparable incidence and severity in racemic and R-modafinil groups, at similar total modafinil exposures, in the current study. Renal histopathology observed in the current rat studies after administration of R- or R,S-modafinil has been reported

b(4)

previously in subchronic or chronic studies of modafinil (NDA 20-717). Although the pathology descriptions are somewhat different, this was considered to result from an exacerbation of the chronic progressive nephropathy commonly seen in aging rats.

In the 13-week dog study, at oral doses of 0 —— ; vehicle), 7.5, 20, or 50 mg/kg R-modafinil or 75→60 mg/kg racemic modafinil (1 T-R death; dose lowered on D13), CNS signs, including hyperactivity and stereotypy (all doses R-modafinil and racemate), transient body weight loss (MD and HD R-modafinil and racemate), decreased RBC parameters (up to 25% below C; all doses R-modafinil and racemate), increased alkaline phosphatase and cholesterol (up to 4-fold; all trmt groups), increased liver/gallbladder and kidney (males) weights (all trmt groups), and microscopic changes in the liver (hepatocellular hypertrophy and bile stasis at MD and HD R-modafinil and racemate), thymus (thymic involution/lymphocytic depletion at all doses), and possibly kidney were observed in both R-modafinil and racemic modafinil groups. There was evidence of reversibility for the liver and thymus effects in the 4-week recovery group. Toxicokinetic data indicated no sex difference in exposures, which decreased markedly between D1 and Wk4. At the HD of 50 mg/kg, exposures to R-modafinil were only about 2/3 those expected clinically at the MRD of 250 mg. b(4)

Result of genotoxicity results submitted with NDA 20-717 did not indicate that racemic modafinil was mutagenic or clastogenic [redacted] an Ames test and chromosome aberration assay in human lymphocytes were conducted with R-modafinil (Lot 03188K2a). The results in both cases were negative. b(4)

Carcinogenicity studies were not performed with R-modafinil, rather the studies conducted with the racemate were relied upon (NDA 20-717). However, the original mouse carcinogenicity study of racemic modafinil was deemed inadequate because the HD (60 mg/kg) evaluated was not considered to be an MTD, and the drug was approved with the stipulation that another mouse study be performed Phase 4. In order to fulfill this requirement, modafinil was evaluated in a 26-week Tg.AC transgenic mouse bioassay, which was approved by the CAC. In this study (previously reviewed; review dated 6/1/04), racemic modafinil was applied dermally twice a day to groups of Tg.AC mice (20 sex/group) at daily doses of 0 (methanol vehicle), 125, 250, and 500 mg/kg for 26 weeks. Doses were based on the results of a 28-day dermal toxicity study in the parent FVB/N mouse strain and were agreed upon by the CAC (previously reviewed; minutes dated 3/4/03). The HD of 500 mg/kg was considered to represent the maximum feasible dose based on volume of application and vehicle (methanol) solubility limitations. The positive control was treated with tetradecanoyl phorbol acetate (TPA). There were no statistically significant increases in incidences of dermal tumors at the site of application or in incidences of neoplastic changes in other tissues examined. However, there was an apparent non-dose-related increase in skin tumors in treated females: incidences of mice with skin tumors (latent and actual) at all sites (SOA and NSOA) were 2/20, 20/20, 0/18, 1/19, and 1/17 males; and 0/18, 20/20, 2/20, 6/20, and 2/20 females in vehicle control, positive control, and LD, MD, and HD modafinil groups, respectively (**Table IV.A2)**. Most of the increase was in NSOA latent papillomas in MD females (5/20). The positive control only increased tumors at the SOA. The significance of an increase in NSOA tumors without an increase at the SOA is uncertain. It could reflect a requirement for metabolic activation. In validation studies for the Tg.AC model, topical applications of the known human carcinogens melphalan and cyclophosphamide increased NSOA papillomas without increasing skin tumors at the SOA (Toxicol Pathol 29 (Suppl 1):60-80, 2001). These were considered equivocal responses in the literature report. TK data collected in the 4-week range-finding study for modafinil indicate that exposures were very low compared to human therapeutic levels, apparently due to autoinduction (although metabolite levels decreased too; see **Table IV.A1**). Interestingly, at the end of the 4-week treatment period, exposures at 125 mg/kg bid were higher than those at 250 mg/kg bid in females. However, it is not known how plasma concentrations relate to dermal exposure, which would presumably be the relevant measure in this study. In addition, since there are no TK data from the 26-week study to confirm the non-

linearity, and the increase in papillomas was neither D-R nor SS, the results cannot be considered conclusively positive. Another question relates to the model itself. While the topical Tg.AC assay was apparently considered appropriate for evaluation of an oral drug at the time it was accepted (by full CAC, 10/97), it is not now (personal communications from D. Jacobson-Kram and Abby Jacobs). This has to do in part with the inability of the dermal model to adequately assess the carcinogenic potential of metabolites, of which there are two major ones for modafanil.

In the two-year rat carcinogenicity study of racemic modafinil, doses of 0, 6, 30, or 60 mg/kg/day were administered in the diet. There were no clinical signs or BW effects indicative of dose-limiting toxicity, but mortality was increased somewhat in HD males compared to C. This was attributed to a treatment-related increase (or exacerbation) in the severity of chronic progressive nephropathy. At the end of treatment, hepatocellular carcinoma was observed in 2 of 28 surviving HD females, but was not considered T-R. The adequacy of this rat study is questionable. Limited plasma level data indicated that concentrations were well below those seen clinically (see previous reviews). The pharm/tox reviewer (Aisar Atrakchi) considered the study inadequate based on failure to evaluate an MTD (original NDA review dated 3/31/97), but the exec-CAC disagreed and concluded that an MTD had been reached based on mortality and transient BW reduction seen at the HD (minutes dated 3/11/97). The study was ultimately accepted, but it must be viewed as marginal at best and, in combination with the 2 less-than-adequate mouse carcinogenicity studies, does not inspire much confidence in the assessment of carcinogenic potential for modafinil or, by extension, armodafinil.

As a condition for approval of NDA 20-717 for racemic modafinil, an oral fertility and general reproductive performance study was to be conducted Phase 4. The original study was not thought to have evaluated an MTD and was not conducted according to current GLP. In the Phase 4 study submitted with the current application, in which male and female rats were given oral doses of 0 (vehicle), 100, 240, or 480 mg/kg prior to and during mating and early gestation, clinical signs (stereotypy) and mortality (2 males) were observed at the HD and decreased BW gain was seen at the MD and HD. There were no effects on fertility, sperm, estrous cycling, or C-sectioning parameters, but there was a D-R increase in time to mate (days in cohabitation) in males and females (SS at HD). The reproductive NOAEL of 240 mg/kg was associated with a plasma exposure to parent that is about equal to that in humans at the recommended dose of 200 mg.

The effects of R-modafinil on embryo/fetal development were examined in rats. In this study, dams were given oral doses of 0 (vehicle), 60, 200 or 600 mg/kg from GD7 to 17. Clinical signs (hyperactivity, hyperreactivity and repetitive chewing) and decreased BW gain at the HD indicated an appropriate level of maternal toxicity. In the C-section and fetal evaluations, there was a slight increase in resorption (early) and fetal body weights were reduced (SS) in the HD group. There was an increase in the number of fetuses with any alteration observed at all doses (SS at MD and HD). This increase was primarily due to increased numbers of fetuses with common visceral and skeletal variations (eg, dilation of the renal pelvis and decreased ossification of sternal centra). The sponsor did not consider these T-R because there was no clear dose relationship for any one specific type of alteration; however, the combined incidence is generally considered an index of developmental toxicity, and some of the skeletal variations were related. Based on the individual data, it appeared that incidences of variations were increased at the MD and HD. Therefore, R-modafinil should be labeled as a developmental toxicant, based on increased incidences of visceral and/or skeletal variations at the MD and HD and decreased fetal BW at the HD. The developmental NOEL was associated with maternal plasma levels that were below the detection limit in most cases. The LOEL produced an AUC that is about 1/5 that in humans at the clinical MRD. The results of this study appear to be in agreement with those in the first modafinil embryofetal study, in which resorptions and visceral and skeletal variations were increased at the HD of 200 mg/kg. A subsequent rat embryofetal development study at doses of up to 480 mg/kg

did not find any developmental effects, but there was some question about the conduct of the study based on the variability of maternal blood levels (see review dated 7/2/01).

In a rabbit embryo/fetal development study of modafinil conducted as part of the Phase 4 commitment, does were given oral doses of 0 (vehicle), 45, 90, or 180 mg/kg from GD 6 through 18. Clinical signs and decreased BW gain indicated sufficient but not excessive maternal toxicity at the HD. Resorptions were increased in the HD group (~2X), resulting in a reduced number of live fetuses, and there appeared to be a slight decrease (NS) in fetal BWs at the MD and HD. An increased incidence of fetal alterations was found in the HD group. This was attributed by the sponsor to 1 litter with similar alterations which were not considered T-R. One litter also contributed most of the alterations in the control group. However, when these two litters were excluded or the number of litters with alterations or the number and severity of malformations were considered, skeletal malformations and some skeletal variations appeared to be increased somewhat at the HD. Therefore, based on these data, modafanil should be identified as a developmental toxicant, based primarily on embryolethality, which could have masked a more obvious teratogenic effect. The MD, which can be considered a NOEL for adverse effects on embryo-fetal development, was associated with maternal plasma exposures to parent approximately equal to those expected clinically.

Although the pre- and postnatal development studies of modafinil were accepted for NDA 20-717, they were non-standard in that neurobehavioral assessments were not conducted on offspring exposed for the currently recommended period of development, ie, implantation through weaning (see NDA review). This does not provide a complete assessment for a neuroactive compound, given the protracted critical period for brain development.

The studies of R-modafinil submitted, which can be considered adequate with respect to conduct **and "fitness for purpose" (ie, bridging to modafinil studies), indicate that that there is no significant** difference in toxicity between R-modafinil and racemic modafinil at comparable exposures (total parent) in studies of up to 3 months duration. But since the bridging strategy rests on the premise that the toxic potential of modafinil is understood, questions about the adequacy of the toxicity evaluation of modafinil are raised. This is of course primarily important for reproductive/developmental toxicity and carcinogenicity assessments, which the clinical experience with modafinil would not address. It appears that when the bridging strategy for R-modafinil was accepted by the Division, it was assumed that the deficiencies in the original modafinil non-clinical studies had been or would be corrected postapproval. But the carcinogenicity assessment remains problematic (see above). It is recommended that this be addressed in a carcinogenicity study of R-modafinil, which could be conducted Phase 4. In light of the poor (or non-existent) exposure margins achieved in the animal studies of both modafinil and R-modafinil, the use of R-modafinil for this study can be justified by its lower capacity to induce its own metabolism in rodents compared to the racemate as well as by the absence of chronic studies with the R-enantiomer (exposure in mouse studies of modafinil is unknown). In addition, while the Phase 4 reproductive and embryofetal development studies are adequate, the pre- and postnatal developmental toxicity evaluation of modafinil is incomplete and should be repeated according to current standards with armodafinil.

VII. Recommendations

The NDA is approvable with respect to the pharmacology/toxicology portion on the condition that a carcinogenicity assessment [redacted] be conducted Phase 4. Recommendations concerning the proposed labeling are made below.

b(4)

cc:
NDA (21-875)
Div File
HFD-120/EFisher/LFreed/CCalder

J.E. Fisher, Ph.D.

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Fisher
4/28/2006 04:18:27 PM
PHARMACOLOGIST

Lois Freed
4/30/2006 12:38:17 PM
PHARMACOLOGIST
Please see comments in separate memo.

Appears This Way
On Original