Study C10953a/102/PK/UK

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Pharmacokinetics, Safety, and Tolerability of Multiple Ascending Oral Doses of CEP-10953 in Healthy Young Men

Principal Investigator: Stephen Freestone
Study Center: Inveresk Research, Tranent, EH33 2NE, Scotland, U.K.
Study Period: June 3, 2003 – September 2, 2003

Objectives:
Primary:
- To determine the pharmacokinetic profile of ascending oral doses of CEP-10953 (14 days treatment) in healthy young adult men

Secondary:
- To assess the safety and tolerability of multiple ascending oral doses of CEP-10953 (14 days treatment)

Drug Products:
Test formulation: CEP-10953, 50-mg capsules, Lot #: 03011K5a (Cephalon, Inc.)
Matching Placebo: matching placebo capsules, Lot #: 03010K5a (Cephalon, Inc.)

Study Design:
This was a randomized, double-blind, placebo-controlled, parallel-group design of multiple rising oral doses of CEP-10953 in 49 healthy young adult male subjects. To be enrolled, all subjects must be of any ethnic origin aged 21~40 years, a Body Mass Index (BMI) $\leq$30 kg/m^2, who met the inclusion and exclusion criteria. Prescription or OTC medication (with the exception of paracetamol) was not allowed during the study. Alcohol, antiseptic mouthwash, or grapefruit juice were prohibited within 48 hours before dosing.

A total of 6 doses were studied in 6 panels. All 6 panels were well matched regarding age, race, height, weight, and BMI. Forty fasted subjects (8/panel in 6:2 ratio) on Day 1 were randomized to receive 1 of 5 doses of CEP-10953 (50, 100, 200, 300, and 400 mg QD) or matching placebo capsules in sequential manner for 14 consecutive days. An intermediate 250-mg dose (9/panel in 7:2 ratio) was later added as an additional panel (after the 400-mg dose) in an attempt to further elucidate the tolerability profile. There were 7-day period between 2 panels. Study drug was taken in the morning, with no standard fasting required except for pharmacokinetics characterization on Days 1, 7, and 14. Subjects were discharged from the clinic on Days 8 and 15, and returned on Days 16-18, with a follow-up on Day 21.

Safety Assessments:
Safety assessments were conducted at screening, baseline, and during the study, including continuous adverse events monitoring throughout the study, clinical laboratory test results (hematology, serum chemistry, and urinalysis), physical examination, vital signs, and electrocardiography (ECG). The ECG monitoring was carried out at screening and

baseline, throughout Days 1, 7, and 14 (before each blood sampling time point), predose on Days 2, 4, and 8, and on Day 13 at check-in; and on Days 15-18.

Pharmacokinetics Assessments:
Blood samples were collected on Day 1, 7, and 14 from each subject for pharmacokinetic profiling of CEP-10953 and metabolites modafinil sulfone and R-modafinil acid at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 13, and 16 hours postdose. Additional blood samples were collected predose on Days 2, 5, 6, 8, 12, and 13 and on post-treatment Days 15-18. Plasma samples were stored frozen at - 20°C until assayed.

Plasma concentrations of CEP-10953, modafinil sulfone, and R-modafinil acid were analyzed by a validated HPLC method performed at Cephalon, Inc. (West Chester, PA).

Table 1. Assay validation for Study C10953a/102/PK/UK

			R-modafinil (CEP-10953)	R-modafinil acid	Modafinil sulfone
Method:			HPLC	HPLC	HPLC
Standard curve					
	Range:		0.20~50.00 µg/mL	0.20~50.00 µg/mL	0.20~50.00 µg/mL
		Precision:	0.0~8.0 %	0.0~8.0 %	0.0~8.0 %
		Accuracy:	98.2~102 %	98.2~102 %	97.8~103 %
	Linearity:		$r^2 = 0.9971$	$r^2 = 0.9968$	$r^2 = 0.9963$
LOQ					
	LLOQ:		0.20 µg/mL	0.20 µg/mL	0.20 µg/mL
QC					
	Low:		0.60 µg/mL	0.60 µg/mL	0.60 µg/mL
		Precision:	6.6 %	8.6 %	6.8 %
		Accuracy:	102 %	96.7 %	98.3 %
	Med:		20.00 µg/mL	20.00 µg/mL	20.00 µg/mL
		Precision:	6.3 %	7.5 %	6.5 %
		Accuracy:	97.4 %	94.8 %	95.3 %
	High:		50.00 µg/mL	50.00 µg/mL	50.00 µg/mL
		Precision:	11.2 %	9.9 %	10.8 %
		Accuracy:	96.7 %	94.2 %	94.6 %

b(4)

Pharmacokinetic Analysis:
The following pharmacokinetic parameters for CEP-10953, modafinil sulfone and R-modafinil acid were calculated by standard non-compartmental methods: C_{max}, t_{max}, AUC_{0-t} (Days 7 and 14), $AUC_{0-\infty}$ (Day 1 only), K_{el}, $t_{1/2}$, R, CL/F, and V/F.

Statistical Analysis:
All pharmacokinetic data available from each sampling time point were included in the pharmacokinetic analyses. All pharmacokinetics parameters were summarized using descriptive statistics to include mean, standard deviation, median, minimum, and maximum values for each dose group receiving CEP-10953. All data listings, summaries, and statistical analyses were generated using Statistical Analysis Software (SAS®) Version 8.2.

RESULTS

Demographics of Subjects:
A total of 49 male subjects were enrolled in study and received at least 1 dose of study drug, while 36 (73%) subjects completed the study and 13 (27%) withdrew from the study. All subjects received at least 1 dose of CEP-10943. Most of the subjects (45 of 49, 92%) were white, 3 (6%) were black, and 1 (2%) was Asian. The mean age, weight, height, and BMI were 27.1 years (20-39 years of age), 77.8 kg (59.4-98.9 kg), 179.9 cm (163-194 cm), and 24.0 kg/m^2 (17.5-29.3 kg/m^2), respectively. Data from all subjects who received study drug were included in the pharmacokinetics analyses.

Pharmacokinetic Summary:
The mean plasma concentration-profiles and pharmacokinetic parameters of CEP-10953, R-modafinil acid, and modafinial sulfone following multiple rising oral doses of 50, 100, 200, 250, 300, and 400 mg QD are shown in Figures 1-8. The summary of pharmacokinetic parameters and statistics are shown in Tables 2-4.

Figure 1. Mean CEP-10953 plasma concentration-time profiles following multiple oral doses of CEP-10953 in healthy male volunteers on Day 1

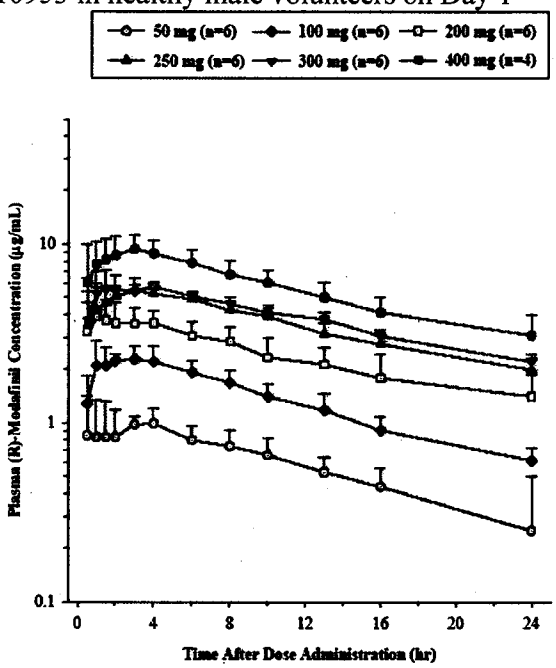


Figure 2. Mean CEP-10953 plasma concentration-time profiles following multiple oral doses of CEP-10953 in healthy male volunteers on Day 7

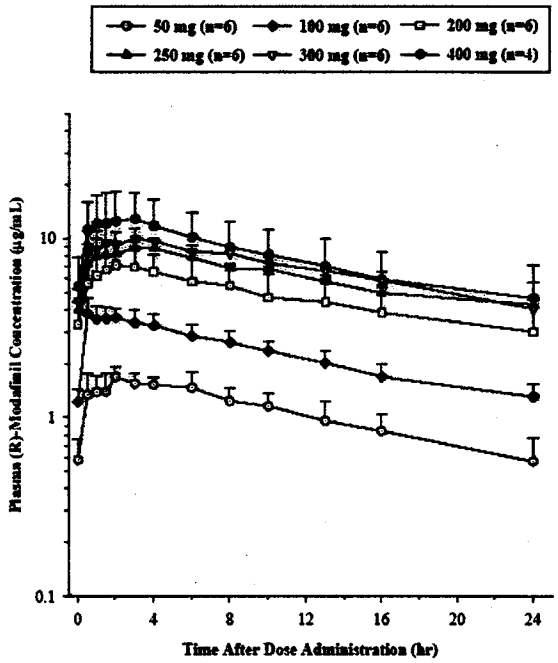


Figure 3. Mean CEP-10953 plasma concentration-time profiles following multiple oral doses of CEP-10953 in healthy male volunteers on Day 14

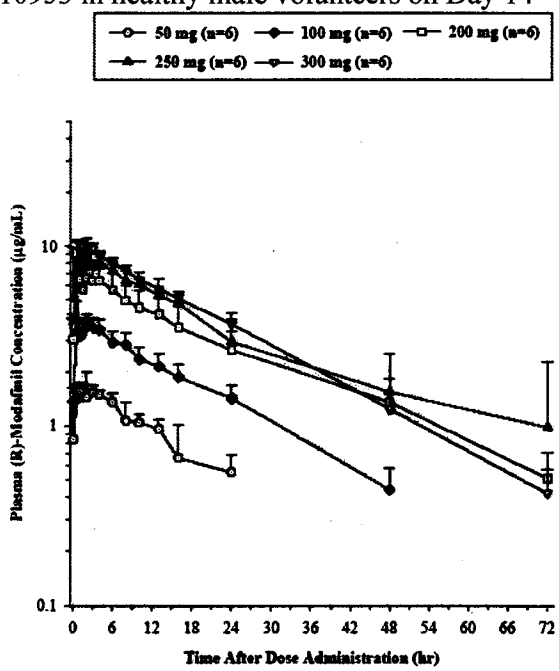
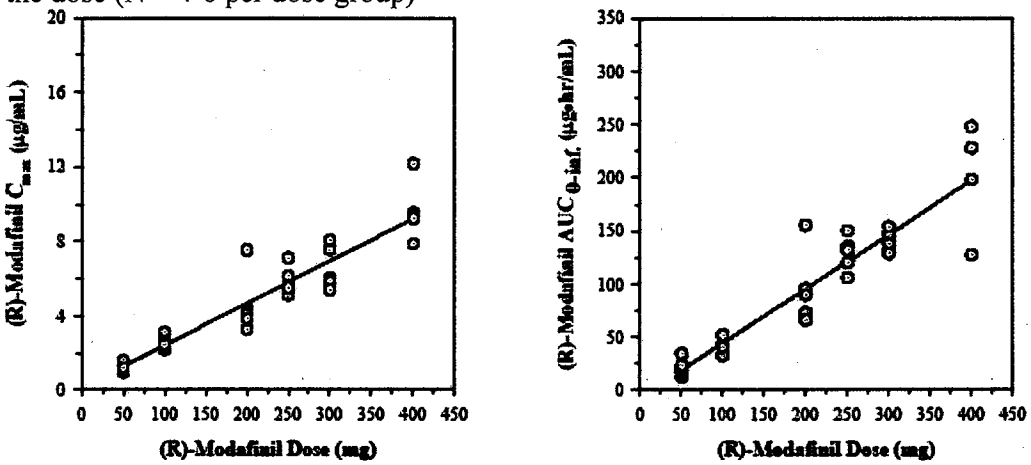


Table 2. Summary of pharmacokinetic results (mean ± SD) for CEP-10953 in healthy male volunteers following multiple oral doses of CEP-10953 on Days 1, 7, and 14

Day	Dose (mg)	C_{max} (µg/mL)	AUC[a] (µg·hr/mL)	$t_{½}$[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

Figure 4. Individual C_{max} and $AUC_{0-\infty}$ values of CEP-10953 on Day 1 as a function of the dose (N = 4-6 per dose group)



Note: The lines shown represent the best fit of the data and were obtained by unweighted linear regression analysis of the 50-400-mg dose data for C_{max} and $AUC_{0-\infty}$.

Figure 5. Individual C_{max} and $AUC_{0-\infty}$ values of CEP-10953 on Day 7 as a function of the dose (N = 4-6 per dose group)

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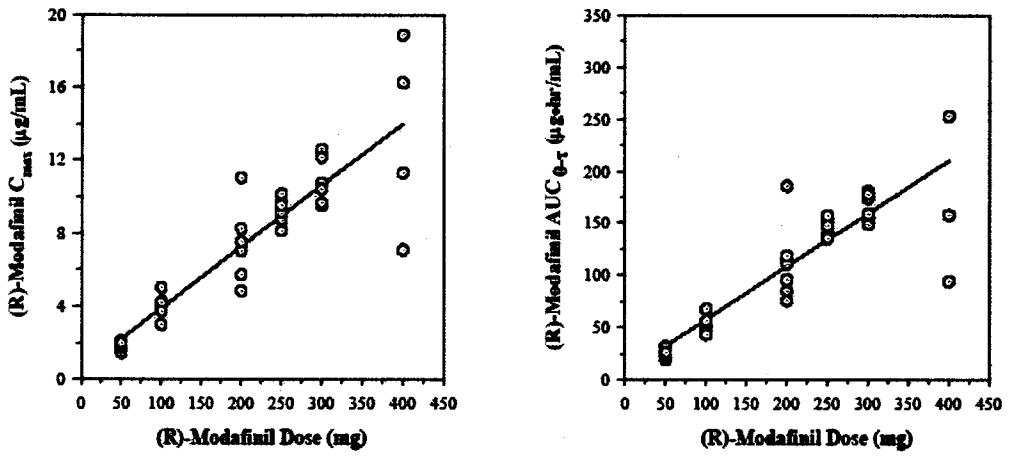
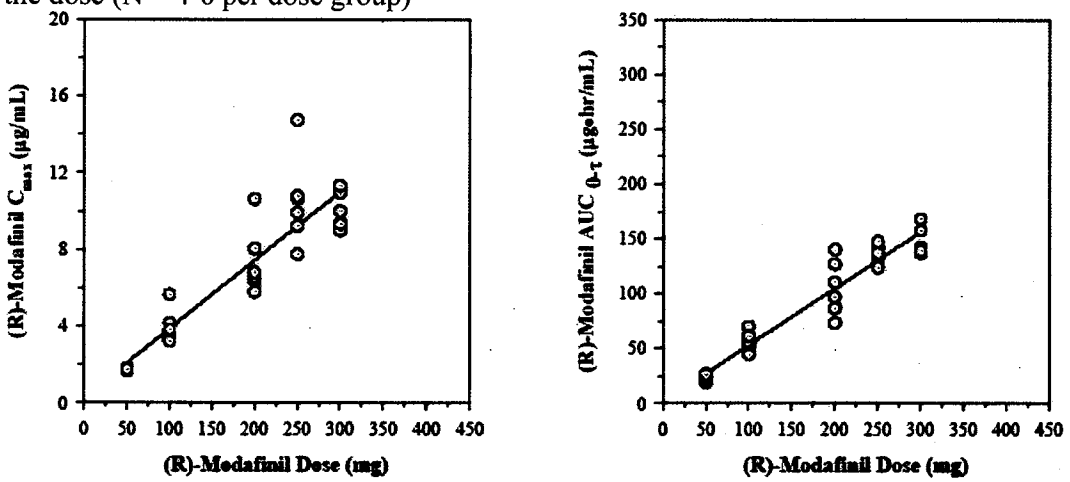


Note: The lines shown represent the best fit of the data and were obtained by unweighted linear regression analysis of the 50-400-mg dose data for C_{max} and $AUC_{0-\tau}$.

Figure 6. Individual C_{max} and $AUC_{0-\infty}$ values of CEP-10953 on Day 14 as a function of the dose (N = 4-6 per dose group)



Note: The lines shown represent the best fit of the data and were obtained by unweighted linear regression analysis of the 50-300-mg dose data for C_{max} and $AUC_{0-\tau}$.

Figure 7. Mean R-modafinil acid plasma concentration-time profiles following multiple oral doses of CEP-10953 in healthy male volunteers on (A) Day 1, (B) Day 7, and (C) Day 14

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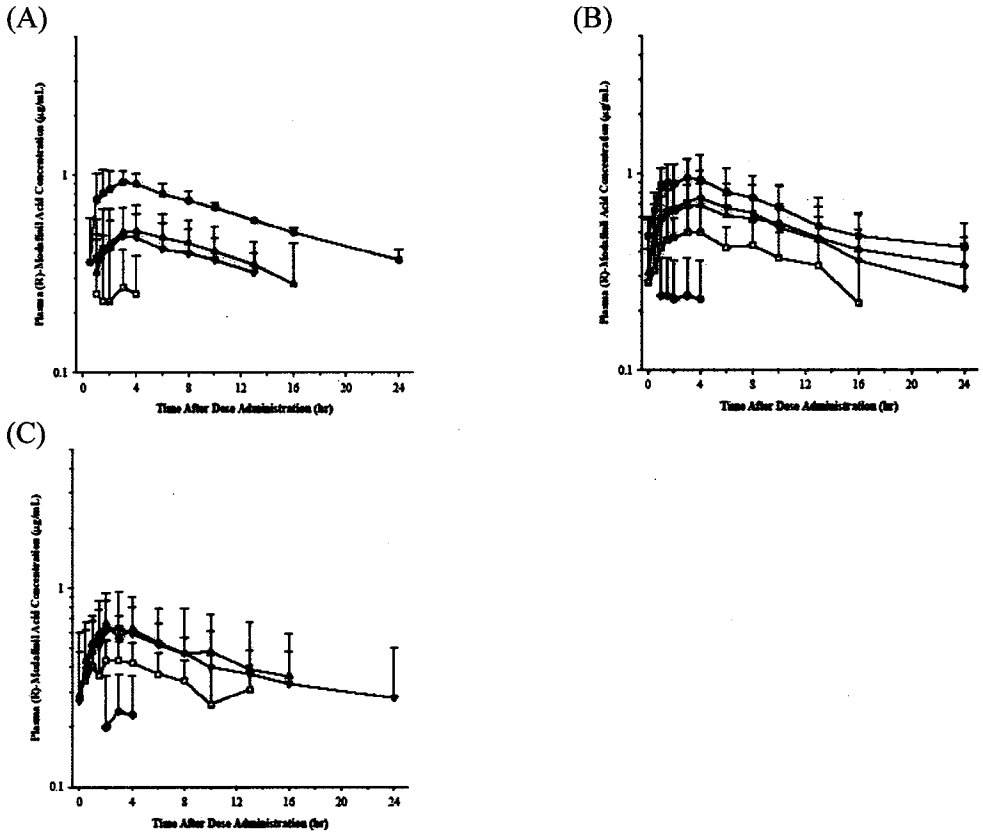

Table 3. Summary of pharmacokinetic results (mean ± SD) for R-modafinil acid in healthy male volunteers following multiple oral doses of CEP-10953 on Days 1, 7, and 14

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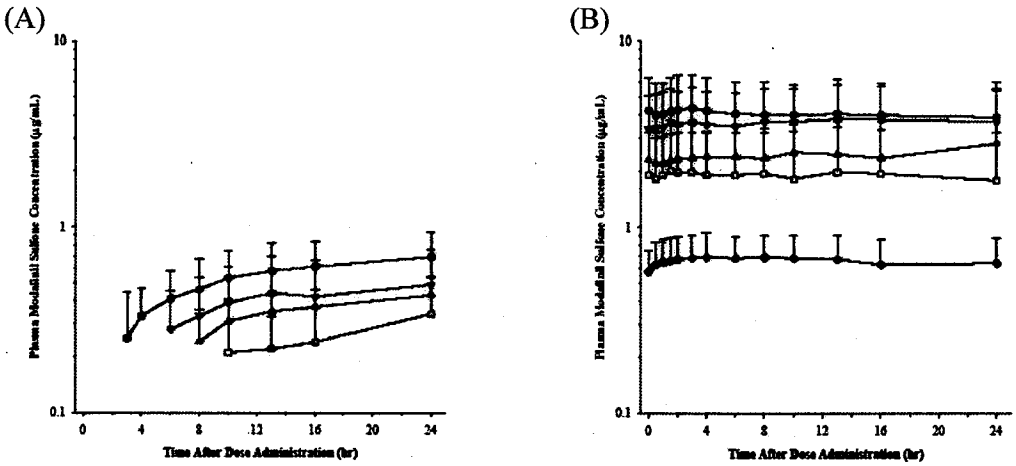
Day	Dose (mg)	n	C_{max} (µg/mL)	t_{max}[a] (hr)	AUC[b] (µg•hr/mL)	$t_{1/2}$[c] (hr)
1	50	6	BLQ	NC	NC	NC
	100	6	BLQ	NC	NC	NC
	200	6	0.31 ± 0.18	1.5 [1.0-3.0]	2.9 ± 2.7[d]	NC
	250	6	0.53 ± 0.16	4.0 [1.5-6.0]	13.4 ± 5.2	14.7 [8.1-22.0]
	300	6	0.52 ± 0.16	3.0 [1.0-4.0]	13.0 ± 3.6	16.6 [13.1-29.9]
	400	4	0.93 ± 0.13	3.0 [2.0-3.0]	24.1 ± 3.5	15.8 [11.6-24.7]
7	50	6	BLQ	NC	NC	NC
	100	6	0.25 ± 0.14	1.0 [1.0-3.0]	2.6 ± 1.9[f]	NC
	200	6	0.54 ± 0.19	2.0 [0.0-24.0]	8.2 ± 2.7	NC
	250	6	0.70 ± 0.20	3.0 [1.5-4.0]	11.9 ± 3.1	NC
	300	6	0.79 ± 0.27	3.0 [1.5-4.0]	12.1 ± 5.0	NC
	400[e]	4	1.00 ± 0.27	2.3 [1.0-4.0]	15.0 ± 4.0	16.3 [12.0-25.0]
14	50	6	BLQ	NC	NC	NC
	100	6	0.25 ± 0.14	2.0 [2.0-3.0]	2.5 ± 2.0[f]	NC
	200	6	0.46 ± 0.11	2.0 [1.0-3.0]	7.1 ± 2.3	20.0 [15.2-33.2]
	250	6	0.74 ± 0.17	2.0 [0.0-4.0]	10.1 ± 2.7	17.1 [15.7-19.1]
	300	6	0.65 ± 0.34	2.0 [1.5-3.0]	10.6 ± 5.4	18.2 [11.6-48.3]

Figure 8. Mean modafinal sulfone plasma concentration-time profiles following multiple oral doses of CEP-10953 in healthy male volunteers on (A) Day 1, (B) Day 7, and (C) Day 14



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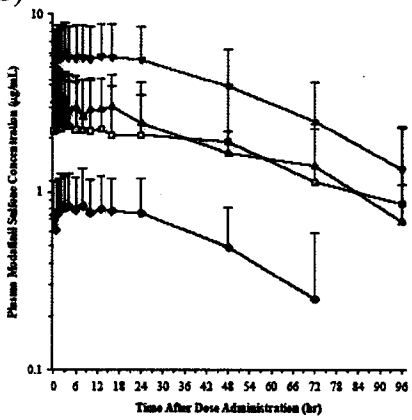

Table 4. Summary of pharmacokinetic results (mean ± SD) for modafinil sulfone in healthy male volunteers following multiple oral doses of CEP-10953 on Days 1, 7, and 14

Day	Dose (mg)	n	C_{max} (µg/mL)	t_{max}[a] (hr)	AUC[b] (µg•hr/mL)	$t_{1/2}$[c] (hr)
1	50	6	BLQ	NC	NC	NC
	100	6	BLQ	NC	NC	NC
	200	6	0.37 ± 0.21	24.0 [10.0-24.0]	4.9 ± 0.9[d]	NC
	250	6	0.43 ± 0.10	24.0 [24.0 for all]	6.7 ± 1.8[d]	NC
	300	6	0.50 ± 0.27	24.0 [13.0-24.0]	9.9 ± 3.0[d]	NC
	400	4	0.71 ± 0.24	24.0 [16.0-24.0]	11.9 ± 4.8[d]	NC
7	50	6	BLQ	NC	NC	NC
	100	6	0.72 ± 0.22	7.0 [4.0-24.0]	15.8 ± 5.4	NC
	200	6	2.18 ± 1.63	2.0 [0.0-24.0]	45.6 ± 37.4	NC
	250	6	3.19 ± 2.40	10.0 [1.5-24.0]	58.9 ± 28.2	NC
	300	6	3.94 ± 2.02	14.5 [8.0-24.0]	88.1 ± 44.8	NC
	400[e]	4	4.45 ± 2.20	3.0 [2.0-16.0]	96.9 ± 48.7	28.4 [20.6-40.9]
14	50	6	BLQ	NC	NC	NC
	100	6	0.88 ± 0.50	3.5 [0.5-8.0]	18.9 ± 10.4	39.2 [30.3-53.1]
	200	6	2.49 ± 2.30	2.5 [0.0-16.0]	52.5 ± 49.0	34.5 [22.8-104.8]
	250	6	3.79 ± 2.52	5.0 [0.0-16.0]	67.4 ± 33.3	38.1 [30.2-52.8]
	300	6	6.14 ± 3.25	2.5 [1.0-16.0]	135.5 ± 72.1	29.2 [21.9-39.1]

Safety Summary:

No deaths or other serious adverse events, with most adverse events reported as mild at doses less than 300 mg and were treatment- and dose-related. Among the 13 subjects withdrawn from the study, 2 subjects (#001038 and 001040) receiving 400 mg QD doses withdrew due to adverse events (i.e., insomnia), 5 subjects withdrew for reasons not related to adverse events, and 6 subjects withdrew because the sponsor discontinued treatment with 400 mg due to a high number of adverse events experienced within the dose group. Otherwise, no subjects withdrew at doses up to 300 mg QD. Among the 37 subjects who receive all doses of CEP-10953, the most frequently occurred adverse

events were in nervous and gastrointestinal systems, including headache (43%), palpitation (32%), and nausea (22%). The frequency of palpitation and anxiety at 300-400 mg doses increased to 83% and 50%, respectively, with insomnia and paresthesia seen at 400 mg doses. No clinically meaningful abnormal laboratory values, vital signs, physical examination findings, or ECG findings were reported. The 400 mg treatment was not well tolerated and was terminated after 7 days. The 300-mg QD dose was reported to be the maximum tolerated dose (MTD), while 200 mg QD and 250 mg QD were well tolerated.

CONCLUSION:

- Pharmacokinetics of CEP-10953 was characterized as linear and dose-proportional, with respect to mean C_{max} and $AUC_{0-\infty}$, following the oral doses of 50 to 400 mg in fasted young men on day 1 and at steady state.

- Steady-state plasma levels were achieved at approximately 7 days, with no consistent difference of $t_{1/2}$ values reported between Day 1 and at steady-state. The steady-state plasma levels were slightly increased, compared to that of single doses, as CL/F values were decreased. The accumulation ratio (R) ranged 1.4-1.9, similar to the predicted value (R_{ss}=1.2) based on single dose PK.

- Consistent PK results to studies with single doses for the 2 circulating metabolites were also observed

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Study C10953a/103/PK/MN

A Double-Blind, Randomized, Placebo-Controlled and Active-Controlled (PROVIGIL), Parallel-Group Study to Evaluate the Pharmacokinetic Profile and the Pharmacokinetic/Pharmacodynamic Relationship of Single Doses of CEP-10953 (100, 150, 200, and 300 mg) in Subjects Undergoing Acute Sleep Deprivation

Principal Investigator: Jean-Paul Macher, MD; Prof Antony N. Nicholson
Study Center: (1) Forenap Pharma, Centre Hospitalier de Rouffach,
BP27 – 27 Rue du 4 RSM, 68250 Rouffach, France
(2) QinetiQ, Cody Technology Park,
Building A50, Ively Road, Farnborough, Hampshire, GU14 0LX, United Kingdom.
Study Period: June 26, 2003 – September 2, 2003

Objectives:
Primary:
- To evaluate the pharmacodynamic profile over time of single doses of CEP-10953 (100, 150, 200, or 300 mg) in healthy young men undergoing acute sleep deprivation, measured using the Maintenance of Wakefulness Test (MWT).

Secondary:
- To assess the pharmacodynamic profile over time of single doses of CEP-10953 with subjective sleepiness measured by the Karolinska Sleepiness Scale (KSS), attention and working memory measured by the Cognitive Drug Research (CDR) system, and behavioral attention measured by the Psychomotor Vigilance Task (PVT)
- To assess the pharmacokinetic profile of single doses of CEP-10953 up to 14 hours postdose
- To assess the pharmacokinetic/pharmacodynamic relationship over time of single doses of CEP-10953
- To compare the pharmacodynamic profile of single doses of CEP-10953 with that of 200 mg of PROVIGIL and that of a placebo
- To compare the pharmacodynamic profile, at various time points, across the doses of CEP-10953
- To evaluate the safety profile of CEP-10953

Drug Products:
Test formulation: CEP-10953, 50-mg capsules, Lot #: 03011K5a (Cephalon, Inc.)
Active control: PROVIGIL (100 mg tablets), Lot #: 02047B5a (Cephalon, Inc.)
Matching Placebo: matching placebo capsules for CEP-10953, Lot #: 03010K5a (Cephalon, Inc.);
matching placebo tablets for PROVIGIL, Lot #: 02049B5a (Cephalon, Inc.)

Study Design:

This was a double-blind, randomized, placebo-controlled and active-controlled (PROVIGIL), parallel-group study of single oral doses of CEP-10953 in subjects undergoing acute sleep deprivation. The total duration of the study was 3 weeks, including 1 day of active treatment and sleep deprivation. To be enrolled, all subjects must be of any ethnic origin aged 18~40 years, a Body Mass Index (BMI) $\leq$30 kg/m^2, who agreed to a stable sleep/wake schedule (8 hours in bed) beginning 1 week prior to dosing and met all the inclusion and exclusion criteria. Subjects must obstain from nicotine, caffeine, and alcohol during the inpatient study period.

The study drugs include single doses of CEP-10953 of 100, 150, 200, and 300 mg, a placebo, and the active control PROVIGIL of 200 mg. A total of 107 subjects were randomly assigned to 1 of the 6 treatment groups (well matched in regard to demographic characteristics), with 18 subjects per group.

Following the screening procedures of at least 1 week, eligible subjects reported to the **clinic on day –1 for the inpatient phase of the study, and were to sleep from 2300 of day –** 1 until 0700 of day 1, during which period they will undergo polysomnography. Subjects will be permitted to lie down only for sleep periods/polysomnography and while undergoing the MWT. After waking, subjects will begin KSS testing at 1-hour intervals, testing for attention and working memory using the CDR system, and PVT testing at 2-hour intervals. Single doses of study drug were administered at 1925 (7:25 PM) followed immediately by a standard meal.

Pharmacokinetic blood samples were collected postdose for up to 14 hours. The primary (MWT) and secondary (KSS, CDR system, PVT) pharmacodynamic variables and endpoints were assessed starting during the night of Day 1, the sleep deprivation period, followed by PSG (Polysomnography) during a sleep period (1100-1900). Subjects were discharged from the clinic on evening of Day 2 after the final assessments. A follow-up was conducted 7 days after the discharge.

Safety Assessments:
Safety assessments were conducted at screening and during the study, including adverse events monitoring, clinical laboratory test results (hematology, serum chemistry, and urinalysis), physical examination, vital signs, and electrocardiography (ECG). The 12-lead ECG monitoring was carried out at screening and on Days 1 and 2 of the study. In addition, concomitant medications were recorded and nocturnal PSG was conducted to assess effect of treatment on sleep efficiency.

Pharmacodynamics Assessments:
As the primary assessment of pharmacodynamic profile over time for each dosing group, a Maintenance of Wakefulness Test (MWT) was performed every 2 hours during a sleep deprivation period starting 2200 of Day 1 until the sleep period on Day 2. The MWT sleep latency in minutes (ie, time to 3 epochs of stage 1 sleep or 1 epoch of stages 2, 3, 4 or REM sleep) and latency to 10 seconds of sleep were analyzed in order to measure the ability of a subject to remain awake.

Other secondary pharmacodynamic variables and endpoints were assessed during Days 1 and 2 (except during sleep periods) as follows:

- The Karolinska Sleepiness Scale (KSS) at 1-hour intervals to measure sleepiness
- The Cognitive Drug Research (CDR) system at 2-hour intervals to test attention and working memory,
- The Psychomotor Vigilance Task (PVT) at 2-hour intervals to test for behavioral alertness.

Pharmacokinetics Assessments:

Blood samples were collected from each subject for pharmacokinetic profiling of (R)-modafinil and metabolites modafinil sulfone and (R)-modafinil acid at predose, 0.5 hour, and then at 1-hour intervals for up to 14 hours postdose. Plasma samples were stored **frozen at –20°C until assayed. Plasma concentrations of (R)-modafinil, modafinil sulfone,** and (R)-modafinil acid following CEP-10953 or PROVIGIL administration were analyzed by a validated HPLC- method performed at the b(4)

Table 1. Assay validation for Study C10953a/103/PK/MN

			R-modafinil (CEP-10953)	R-modafinil acid	Modafinil sulfone
Method:			HPLC	HPLC	HPLC
Standard curve					
	Range:		0.20~50.00 µg/mL	0.20~50.00 µg/mL	0.20~50.00 µg/mL
		Precision:	1.8~4.6 %	2.2~4 %	1.4~3.5 %
		Accuracy:	-1~0.6 %	-9.5~5.8 %	-0.4~0.4 %
	Linearity:		$r^2 = 0.9996$	$r^2 = 0.9993$	$r^2 = 0.9997$
LOQ	LLOQ:		0.20 µg/mL	0.20 µg/mL	0.20 µg/mL
QC	Low:		0.600 µg/mL	0.600 µg/mL	0.600 µg/mL
		Precision:	3.3 %	4.5 %	2.8 %
		Accuracy:	4.3 %	3.7 %	3.8 %
	Med:		20.0 µg/mL	20.0 µg/mL	20.0 µg/mL
		Precision:	4.3 %	5.0 %	3.6 %
		Accuracy:	3.0 %	7.5 %	2.5 %
	High:		40.0 µg/mL	40.0 µg/mL	40.0 µg/mL
		Precision:	3.6 %	3.6 %	2.8 %
		Accuracy:	1.8 %	2.0 %	1.5 %

Pharmacokinetic Analysis:

The following pharmacokinetic parameters for CEP-10953, (R)- and (RS)-modafinil sulfone, and (R)- and (RS)-modafinil acid were calculated: C_{max}, t_{max}, and AUC_{0-t}. All pharmacokinetic data available from each sampling time point were included in the pharmacokinetic analyses. All plasma concentrations and pharmacokinetics parameters were summarized using descriptive statistics to include mean, standard deviation, median, minimum, and maximum values for each dose group. All data listings, summaries, and statistical analyses were generated using WinNonlin® software, Version 4.1.

Pharmacodynamic Analysis:

The following pharmacodynamic parameters were obtained: sleepiness-related parameters (MWT, KSS), attention-related parameters (CDR, PVT), and working-memory–related parameter (CDR). All pharmacodynamic variables were analyzed at each time point and were summarized using descriptive statistics.

Analysis for Pharmacokinetic/Pharmacodynamic Relationship:
Pharmacokinetic/pharmacodynamic profiles were described by the plots of each mean pharmacodynamic variable overlaid with the mean plasma concentration-time profiles for each treatment group. The pharmacokinetic analysis set was used in assessing all exploratory pharmacokinetic/pharmacodynamic correlations utilizing ANOVA and pairwise comparisons. Only MWT sleep latency, KSS, PVT variables, and CDR system variables (speed from tests of attention and power of attention) were used for the assessments. Correlations between the pharmacodynamic parameters and the corresponding plasma drug concentrations were determined for each treatment group. Modeling of the pharmacokinetic/pharmacodynamic data was performed by external experts.

RESULTS

Demographics of Subjects:
A total of 107 male subjects were enrolled and completed the study, 71 received CEP-10953, 18 received PROVIGIL, and 18 received a placebo. The mean age, weight, height, and BMI were 27.1 years (18-40 years of age), 75.7 kg (57.0-101.5 kg), 178.2 cm (167-193 cm), and 23.8 kg/m^2 (18-30 kg/m^2), respectively. There were no statistically significant differences among the treatment groups with respect to demographic characteristics. Race of the subjects was not reported. Data from all subjects who received study drug were included in the pharmacokinetics/pharmacodynamics analyses.

Pharmacokinetic Summary:
The mean plasma concentration-profiles and pharmacokinetic parameters of CEP-10953, (R)- and (RS)-modafinil acid, and (R)- and (RS)-modafinil sulfone following single oral CEP-10953 doses of 100, 150, 200, and 300 mg and oral PROVIGIL dose of 200 mg are shown in Figures 1-4. The summary of corresponding pharmacokinetic parameters and statistics are shown in Table 2.

Figure 1. Mean CEP-10953 plasma concentration-time profiles following single oral doses of CEP-10953 ranging from 100 to 300 mg in healthy male volunteers

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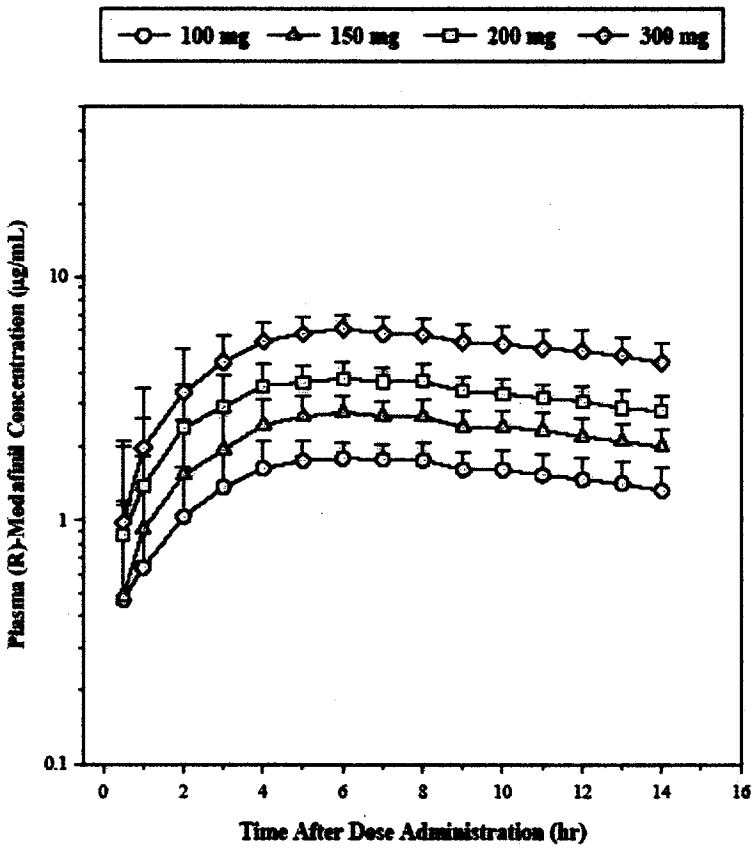
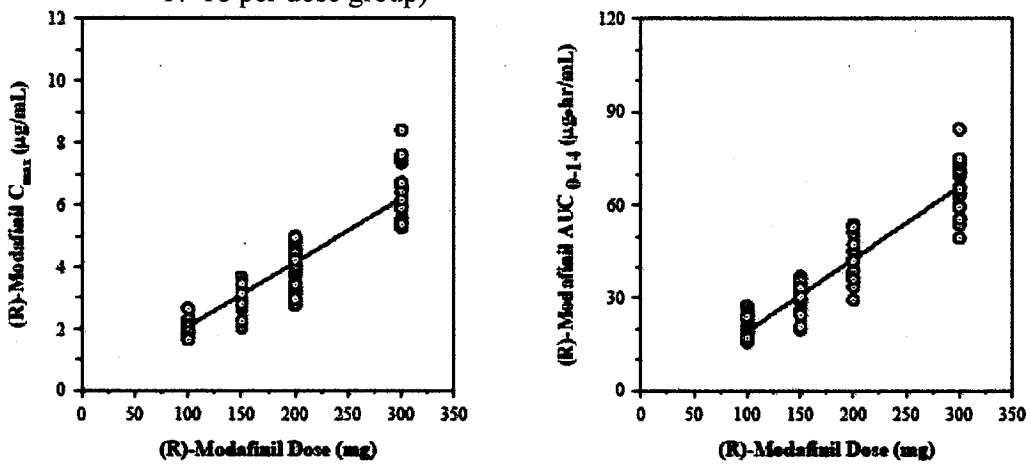


Figure 2. Individual C_{max} and AUC_{0-14} values of CEP-10953 as a function of the dose (N = 17-18 per dose group)



Note: The lines shown represent the best fit of the data and were obtained by unweighted linear regression analysis of the 100-300-mg dose data for C_{max} and AUC_{0-14}.

Figure 3. Mean plasma concentration-time profiles of (R)-modafinil acid and (R)-modafinil sulfone following single oral doses of CEP-10953

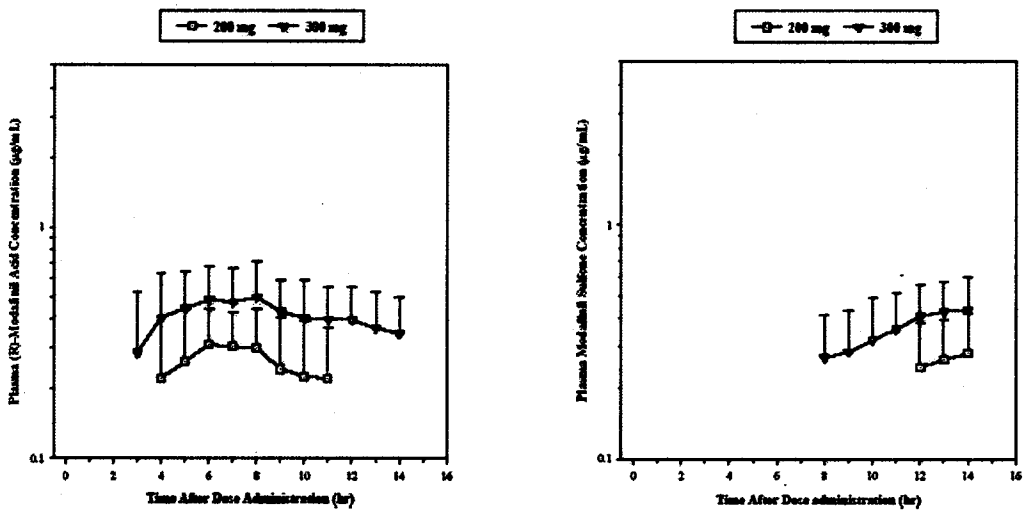


Table 2. Summary of pharmacokinetic results (mean ± SD) for CEP-10953 in healthy male volunteers following single oral doses of CEP-10953 or PROVIGIL

Compound	Dose (mg)	n	C_{max} (µg/mL)	t_{max}[a] (hr)	AUC_{0-14} (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.

Figure 4. Mean plasma concentration-time profiles of (RS)-modafinil and (RS)-modafinil acid following single oral PROVIGIL of 200 mg

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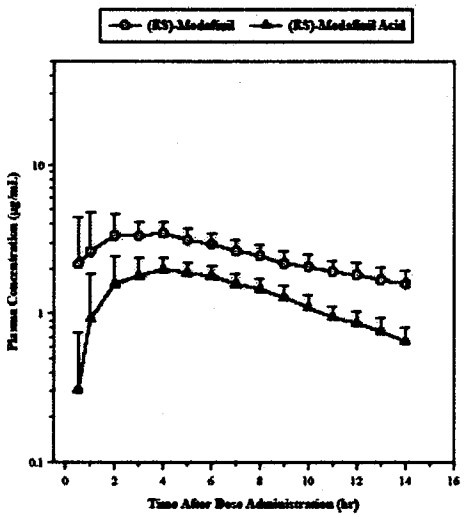


Pharmacodynamic Summary:

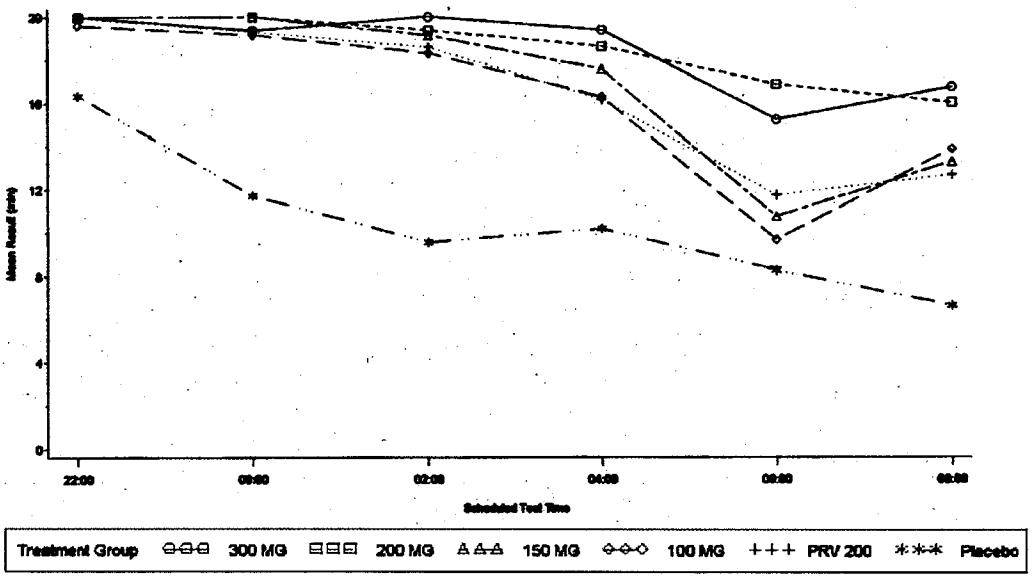
I. MWT:

Table 3. Maintenance of Wakefulness Test sleep latency over time by treatment group

Treatment group	Scheduled test time 22:00	00:00	02:00	04:00	06:00	08:00
Placebo	16.4 (5.93)	11.7 (7.32)	9.6 (7.95)	10.2 (7.10)	8.3 (6.49)	6.6 (7.56)
(N=18)	18 B	18 B	18 B	18 B	18 B	18 B
CEP-10953 100 MG	19.6 (1.65)	19.2 (2.87)	18.3 (4.08)	16.3 (5.65)	9.7 (7.98)	13.9 (7.46)
(N=18)	18 A	18 A	18 A	18 A	18 B	18 A
CEP-10953 150 MG	20.0 (0.00)	20.0 (0.00)	19.1 (2.54)	17.6 (5.03)	10.8 (6.83)	13.3 (7.32)
(N=18)	18 A	18 A	18 A	18 A	18 B	18 A
CEP-10953 200 MG	20.0 (0.00)	20.0 (0.00)	19.4 (2.50)	18.6 (3.69)	16.9 (6.23)	16.0 (6.21)
(N=17)	17 A	17 A	16 A	17 A	17 A	16 A
CEP-10953 300 MG	20.0 (0.00)	19.4 (2.59)	20.0 (0.00)	19.4 (2.15)	15.2 (6.11)	16.7 (5.16)
(N=18)	18 A	18 A	18 A	18 A	18 A	18 A
PROVIGIL 200 MG	20.0 (0.00)	19.3 (2.95)	18.6 (3.51)	16.2 (6.52)	11.7 (7.71)	12.7 (7.12)
(N=18)	18 A	18 A	18 A	18 A	18 B	18 A
Overall trt p-value^	<0.0001	<0.0001	<0.0001	<0.0001	0.0023	0.0005
Linear trend p-value#	0.0002	<0.0001	<0.0001	<0.0001	0.0002	<0.0001
Quadratic trend p-value@	0.0057	<0.0001	<0.0001	0.0158	0.7263	0.0834

Note: Variable: Sleep latency (min)
Summary statistics are mean (sd) in the first row and n and letter representing the statistical order of the treatment groups in the second row.
^P-value for the overall treatment comparison is from an analysis of variance (ANOVA) with treatment and center as factors.
#P-value for the linear trend test is from an ANOVA with treatment and center as factors on the CEP doses and placebo (using a contrast 0.67, 0.22, 0, -0.22, -0.67).
@P-value for the quad. trend test is from an ANOVA with trt. and center as factors on the CEP doses and placebo (using a contrast 0.55, -0.33, -0.44, -0.33, 0.55).

Figure 5. Maintenance of Wakefulness Test sleep latency over time by treatment group



II. KSS:

- There was no evidence of a consistent treatment effect among the treatment groups throughout the night demonstrated with this measure.
- There were statistically significant differences at 0150 and 0550 in favor of all doses of CEP-10953 and PROVIGIL compared to placebo.
- In addition, in the early morning (0550 and 0750) there were statistically significant differences in favor of the higher doses of CEP-10953 (200 and 300 mg) and PROVIGIL compared to placebo.

III. CDR System Testing:

- For simple reaction time (speed in msec): There were statistically significant differences in favor of all CEP-10953 doses and PROVIGIL compared to the placebo at 0055 through 0655, as shown in Figure 6.
- Similar statistically significant differences were observed for the digit vigilance tast, choice reaction time, numeric working memory, and analyses of composit factors (such as power of attention) for all CEP-10953 doses and PROVIGIL compared to the placebo. (Figure 7-9)
- There were no statistically significant differences between any of the CEP-10953 doses.

Figure 6. Cognitive Drug Research System results for simple reaction time (speed) over time by treatment group

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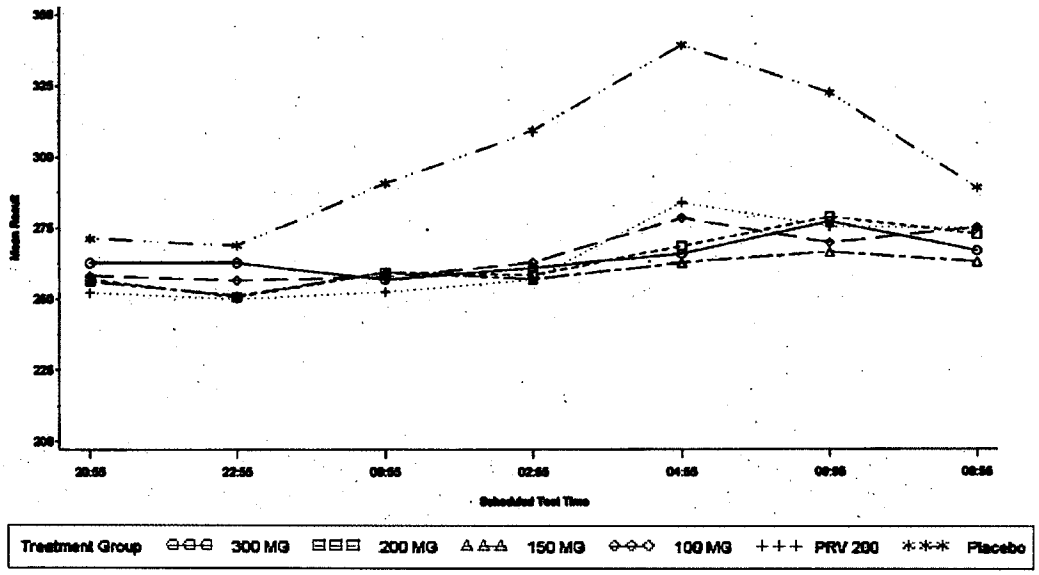

Figure 7. Cognitive Drug Research System results for digital vigilance (speed of detection) over time by treatment group

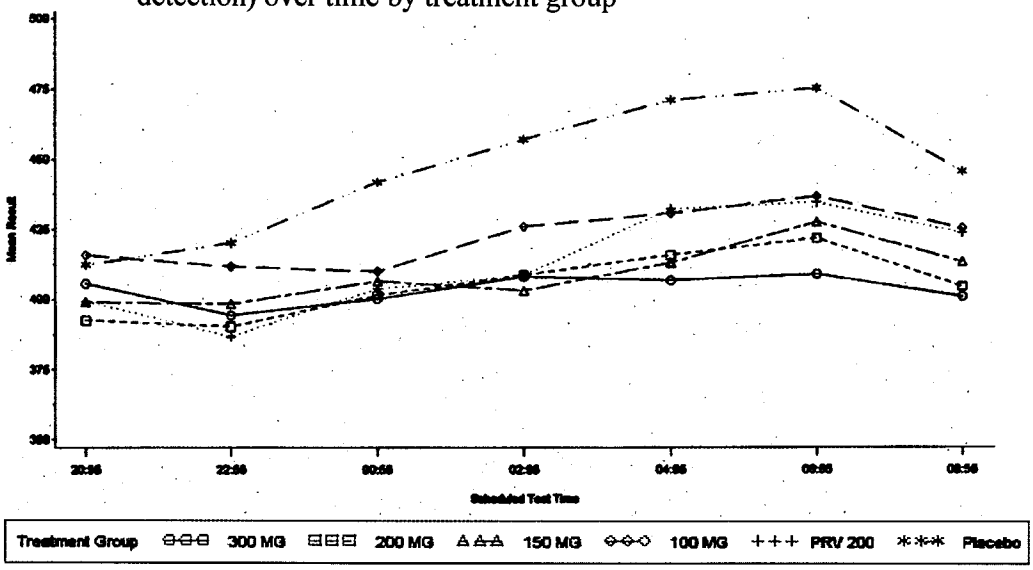

Figure 8. Cognitive Drug Research System results for choice reaction time (speed) over time by treatment group

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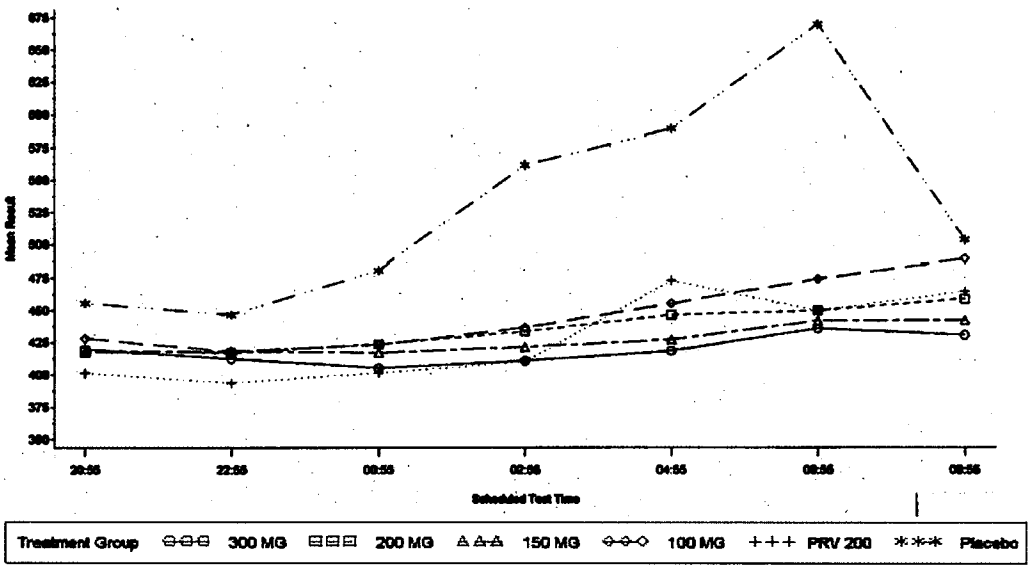
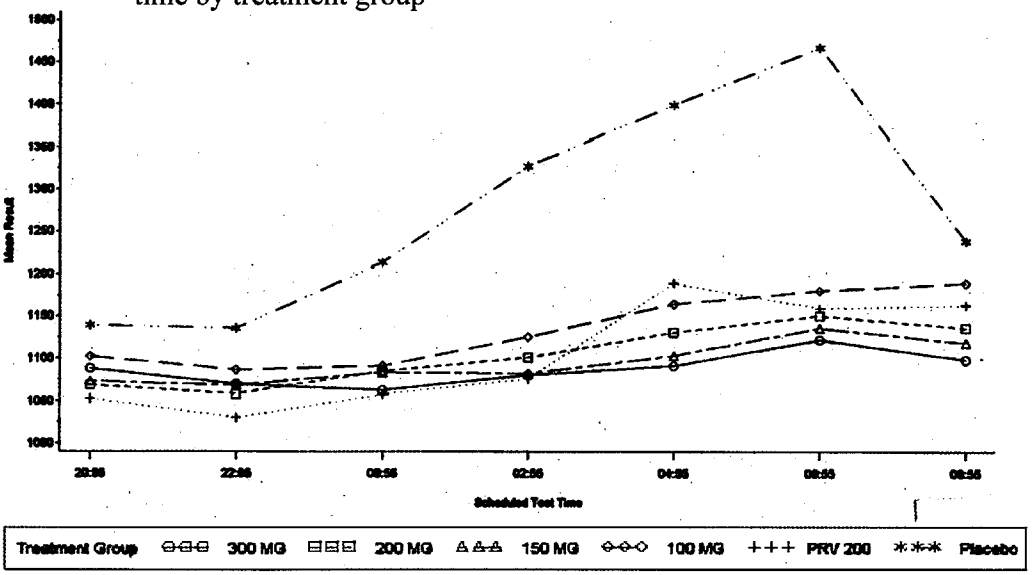


Figure 9. Cognitive Drug Research System results for power of attention (msec) over time by treatment group



IV. PVT:

- There were no statistically significant differences in PVT median reaction time between any of the treatment groups at 2110.
- At 2310 there were statistically significant differences in favor of CEP-10953 doses of 150, 200, and 300 mg and PROVIGIL compared to placebo.
- For all other time points (0110, 0310, 0510, 0710, and 0910), there were statistically significant differences in favor of all doses of CEP-10953 and PROVIGIL compared to placebo, as shown in Figure 10.
- Similar results were seen for number of lapses, as shown in Figure 11.

- There was evidence of a statistically significant linear trend starting at 2310 and lasting throughout the night in median reaction time and number of lapses.

Figure 10. Cognitive Drug Research System results for power of attention (msec) over time by treatment group

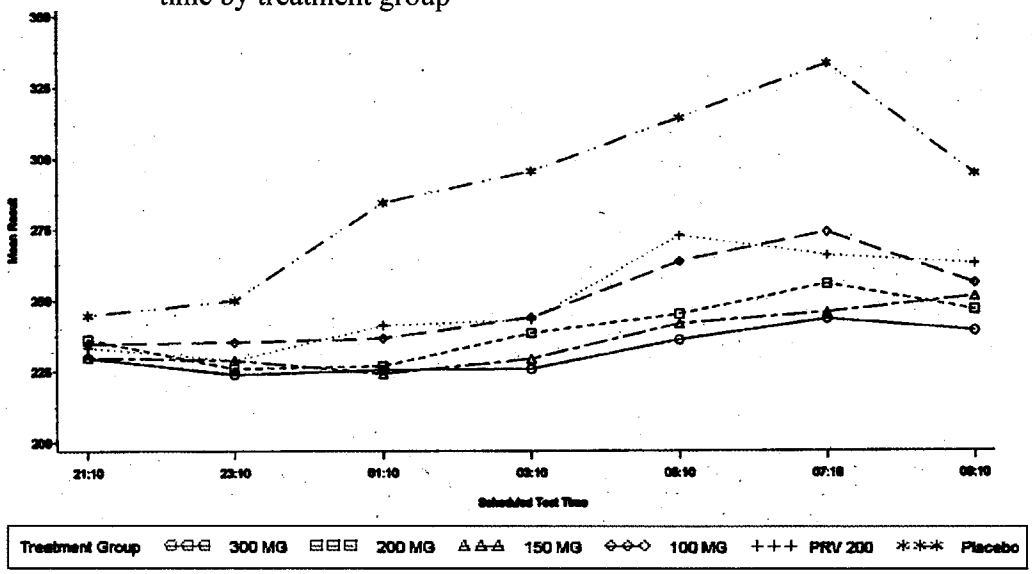
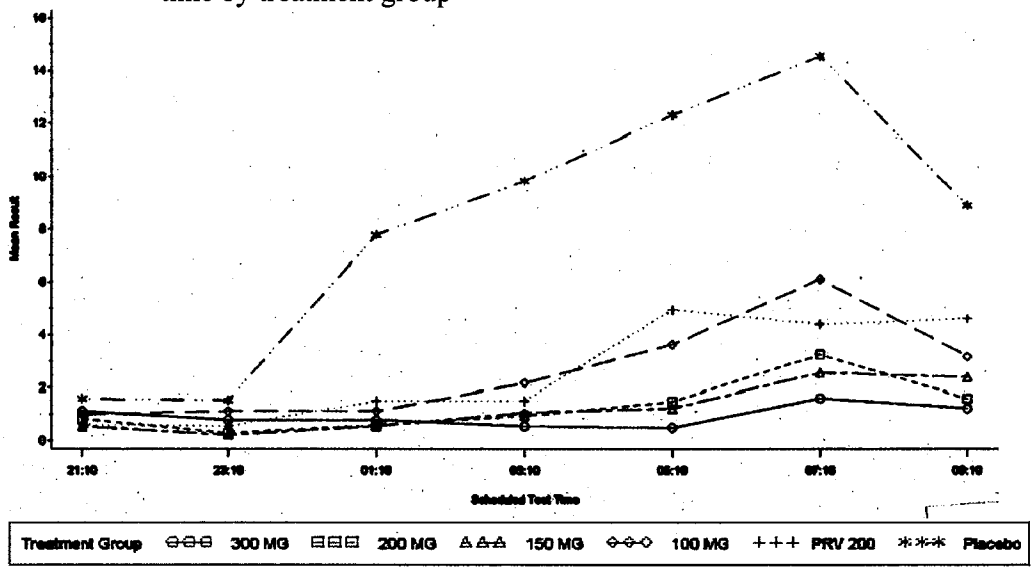


Figure 11. Cognitive Drug Research System results for power of attention (msec) over time by treatment group



Pharmacokinetic/Pharmacodynamic Summary:

- There were statistically significant correlations between all the pharmacodynamic variables and their corresponding plasma drug concentrations only for the PROVIGIL (200 mg) treatment group. (For example, see Figure 12)

- Although no statistically significant correlations (measuring the strength of linear relationship) between plasma concentrations and pharmacodynamic variables were seen for any of the CEP-10953 doses, there is a suggestion of a relationship upon visual inspection of the graphs. Specifically, as the plasma concentration decreases, there appear to be decreases in MWT sleep latency; increases in median reaction time and number of lapses from the PVT; slowing of simple reaction time, speed of detections on digit vigilance task, and choice reaction time from the CDR system testing; and worsening of the power of attention. (For example, see Figure 13)

Figure 12. Relationship between Maintenance of Wakefulness Test sleep latency and plasma concentrations over time following Provigil 200 mg

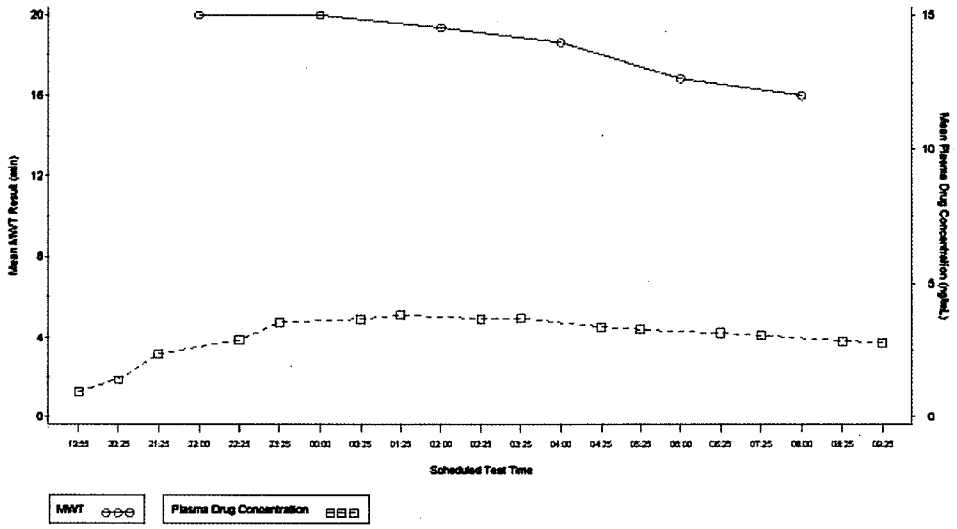
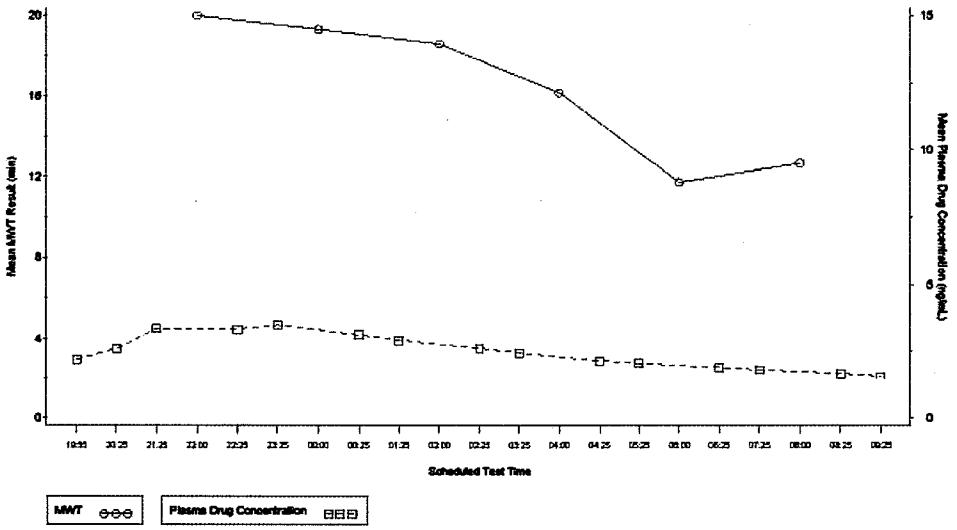


Figure 13. Relationship between Maintenance of Wakefulness Test sleep latency and plasma concentrations over time following Nuvigil 200 mg



Safety Summary:
No deaths or withdrawals due to adverse events were reported. Two serious adverse events were reported – one (tachycardia and ventricular extrasystoles) occurred in 1 subject receiving 150 mg of CEP-10953, and another (bigeminy) occurred in 1 subject receiving a placebo. Adverse events occurred more frequently in CEP-10953 treatment groups than in PROVIGIL and placebo groups. Among the 71 subjects who receive all combined doses of CEP-10953, the most frequently occurred adverse events were abdominal pain (13%), nausea (13%), headache (8%), dizziness (7%), palpitation (7%), insomnia (7%), and urinary frequency (7%), and tachycardia (6%). Headache and nausea appeared to be dose-related. No clinically meaningful abnormal laboratory values, vital signs, physical examination findings, or ECG findings were reported, except small increases in systolic blood pressure at the highest 300 mg dose and in diastolic blood pressure and pulse related to doses. An inverse relationship between CEP-10953 doses and daytime sleep efficiency was reported, with daytime sleep efficiency been lowered by ~ 20% with higher doses. Overall, single doses of CEP-10953 were well tolerated in these healthy sleep-deprived subjects.

CONCLUSION:

- Exposure to CEP-10953 was dose-proportional over the dose range evaluated and was consistent with that obtained in a previous pharmacokinetics study of CEP-10953 in healthy young men.

- The objective measures (MWT, PVT, and CDR) were in favor of all the CEP-10953 doses (especially at 200 and 300 mg) and of PROVIGIL compared to the placebo with statistically significantly differences in MWT, PVT, and CDR compared to placebo.

- Although there was no consistent statistically significant difference between CEP-10953 and PROVIGIL for approximately the first 8.5 hours postdose, higher doses (200 and 300 mg) of CEP-10953 appeared to maintain positive PD effects better than lower doses of CEP-10953 and 200-mg PROVIGIL at later time points.

- Though suggestive, no statistically significant PK and PD correlations were observed for CEP-10953.

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Study C10953/1023/BE/US

A Randomized, Open-Label Crossover Study to Evaluate the Bioequivalence of EP-10953 Tablets (Five 50-mg Tablets Versus One 250-mg Tablet) in Healthy Subjects

Principal Investigator: Dennis Swearingen, MD
Study Center: MDS Pharma Services,
4747 E Beautiful Lane, Phoenix, Arizona 85044.
Study Period: July 10, 2004 – July 22, 2004

Objectives:
Primary:
- To assess whether five 50-mg tablets of CEP-10953 are bioequivalent to one 250-mg tablet of CEP-10953 in healthy men and women

Secondary:
- To assess the safety of CEP-10953 administered as a single oral dose of five 50-mg tablets or as a single oral dose of one 250-mg tablet

Drug Products:
Reference formulation: CEP-10953, 50 mg Tablets, Lot #: 04053K5a (Cephalon, Inc)
Test formulation: CEP-10953, 250 mg Tablets, Lot #: 04092K5a (Cephalon, Inc),
Batch size: ——— b(4)

Study Design:
This was a randomized, open-label, single-center, two-way crossover pharmacokinetic and safety study in healthy, non-smoking male and female subjects under fasting conditions. A total of 30 subjects within an age range of 18 to 45 years and a Body Mass Index (BMI) ≤ 30 kg/m^2, who met the inclusion and exclusion criteria, were enrolled in the study.

The study consisted of an initial screening period of up to 21 days and 12-day duration for treatment, with a minimum 7-day washout between 2 treatments. Following an overnight fast of at least 10 hours, all subjects were randomized to one of the two treatment sequences (A→B or B→A) in the morning:
Treatment A: single oral dose of 5 x 50-mg tablets of CEP-10953 on Day 1 or 9
Treatment B: single oral dose of 1 x 250-mg tablets of CEP-10953 on Day 1 or 9

Study drug was taken with 8 ounces of water, and all subjects remained fasted for at least 4 hours post-dose. Water was provided *ad libitum* until 1 hour pre-dose and after 1 hour post-dose. Subjects remained in the clinic for the duration of the study. PK blood sampling was conducted for 72 hours postdose in each treatment and safety monitoring was conducted during the study.

Safety Assessments:

Safety assessments were conducted at screening and during the study, including monitoring of adverse events, physical examination and vital signs (blood pressure, pulse, body temperature), 12-lead electrocardiograms (ECG), and clinical laboratory tests (biochemistry, hematology, urinalysis), and pregnancy tests on female subjects. The 12-lead ECG monitoring was carried out at screening and at discharge on Day 12.

Pharmacokinetics Assessments:
A total of 17 blood samples were collected from each subject for determination of plasma CEP-10953 and its metabolites (modafinil sulfone and R-modafinil acid) concentrations at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 13, 16, 24, 36, 48, 60, and 72 hours post-dose. Plasma samples were stored frozen at - 20°C until assayed.

Plasma concentrations of CEP-10953, modafinil sulfone, and R-modafinil acid were analyzed by a validated HPLC method performed at

Table 1. Assay validation for Study C10953/1023/BE/US

			R-modafinil (CEP-10953)	R-modafinil acid	Modafinil sulfone
Method:			HPLC	HPLC	HPLC
Standard curve					
	Range:		0.20~50.00 µg/mL	0.20~50.00 µg/mL	0.20~50.00 µg/mL
		Precision:	9.77 %	4.07~7.55 %	2.89~7.84 %
		Accuracy:	0.83 %	-2.32~3.82 %	-2.54~1.47 %
	Linearity:		$r^2 = 0.9983$	$r^2 = 0.9985$	$r^2 = 0.9988$
LOQ	LLOQ:		0.20 µg/mL	0.20 µg/mL	0.20 µg/mL
QC	Low:		0.60 µg/mL	0.60 µg/mL	0.60 µg/mL
		Precision:	19.84 %	15.87 %	16.59 %
		Accuracy:	7.92 %	9.73 %	6.99 %
	Med:		20.00 µg/mL	20.00 µg/mL	20.00 µg/mL
		Precision:	9.49 %	10.48 %	6.44 %
		Accuracy:	-3.31 %	-0.76 %	-4.74 %
	High:		50.00 µg/mL	50.00 µg/mL	50.00 µg/mL
		Precision:	6.00 %	5.00 %	3.75 %
		Accuracy:	-3.19 %	-2.15 %	-5.64 %

b(4)

Pharmacokinetic Analysis:
The following PK parameters for CEP-10953 and its metabolites from both treatment groups were calculated using standard non-compartmental methods: C_{max}, $AUC_{0-\infty}$, AUC_{0-t}, t_{max}, $t_{1/2}$, λ_Z, CL/F, and V/F.

Statistical Analysis:
Descriptive statistics were provided on the plasma concentrations and all PK parameters of CEP-10953 and its metabolites for each formulation or treatment. The ANOVA was performed on PK parameters and included treatment, sequence, and period as fixed effects and subject (nested within sequence) as a random effect. For the bioequivalence determination, the 90% confidence intervals (CI) were calculated based on geometric mean ratios (between treatments) of the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} for the

parent drug CEP-10953. The BE limits were set at 80~125%. For t_{max} and $t_{1/2}$, a Wilcoxon Signed Rank Test of the median of the paired treatment differences was used.

RESULTS

Demographics of Subjects:

A total of 30 subjects (18 men and 12 women) were enrolled in study, received at least 1 dose, and were evaluable for safety, and 27 subjects completed the study. Three subjects (# 4, 5, and 6) withdrew during the study due to treatment-unrelated reasons and thus were not included in PK analyses. The subjects consisted of 37% Caucasians, 7% black, and 57% Hispanic, and 60% of subjects were male. The mean age, weight, height and BMI were 29.3 years (18-44 years of age), 72.3 kg (56.5-91.2 kg), 168.3 cm (150.4-180.6 cm), and 25.5 kg/m^2 (21.1-32.4 kg/m^2), respectively. Final pharmacokinetic analysis and bioequivalence evaluation were performed on 25 subjects after excluding 2 additional subjects (#28 and 30) who showed quantifiable (and >5% C_{max}) predose plasma CEP-10953 levels.

Pharmacokinetic Summary:

Mean CEP-10953 plasma concentration-time profiles following oral doses of 5 x 50 mg (treatment A) and of 1 x 250 mg (treatment B) are shown in Figures 1-4. The summary of pharmacokinetic parameters and statistical analysis of each pharmacokinetic parameter are shown in Tables 2-6.

Figure 1. Mean CEP-10953 plasma concentration-time profiles following single oral doses of 5 x 50 mg reference (Treatment A) and 1 x 250 mg test (Treatment B) formulations (N = 25)

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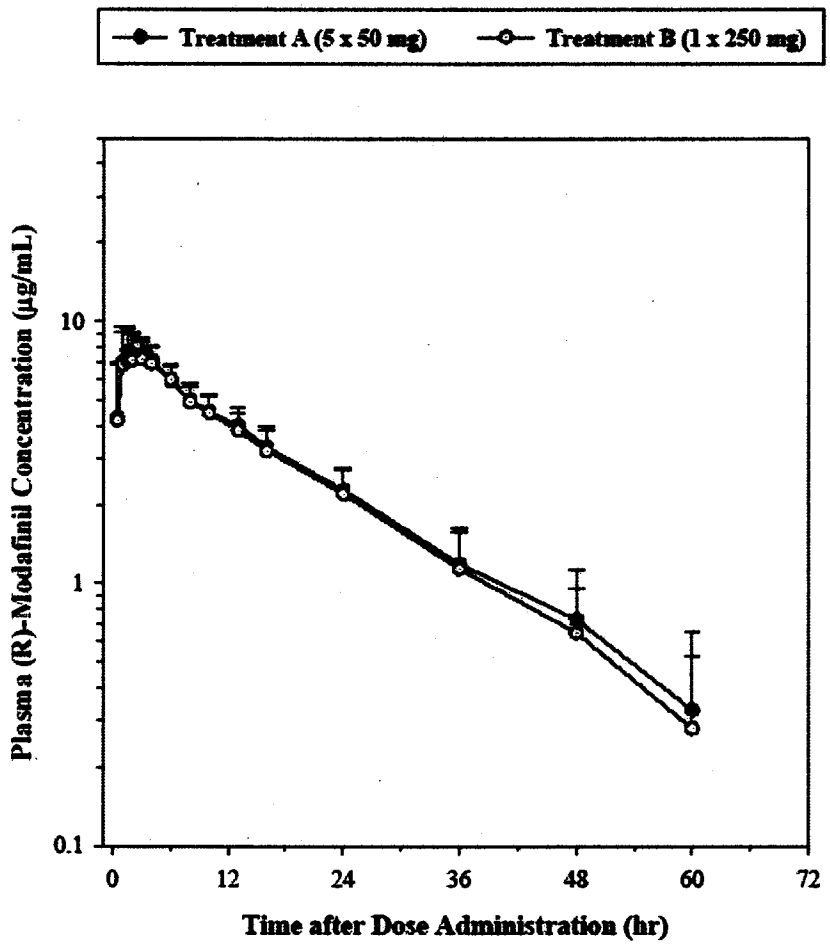

Table 2. Summary of pharmacokinetic results and statistical analysis for CEP-10953 following single oral doses of 5 x 50 mg reference (Treatment A) and 1 x 250 mg test (Treatment B) formulations

Pharmacokinetic parameters	Plasma CEP-10953 Treatment B (N=25)	Treatment A (N=25)	90% CI[a]	% Mean Ratio[a]
C_{max} (µg/mL)	8.45±1.72	8.54±1.30	93.43, 103.9	98.5
AUC_{0-t} (µg•hr/mL)	138.3±24.73	141.9±22.73	94.27, 99.03	96.6
$AUC_{0-\infty}$ (µg•hr/mL)	144.7±26.31	148.6±24.25	94.25, 99.02	96.6
t_{max} (hr)	2.3±1.5	1.8±1.0	NA	NA
%Extrapolation	4.4120±1.8797	4.4757±1.8234	NA	NA
$t_{1/2}$ (hr)	12.8±2.84	13.0±3.07	NA	NA
λ_z (1/hr)	0.0566±0.0132	0.0558±0.0121	NA	NA
CL/F (mL/min)	29.8±5.71	28.8±4.97	NA	NA
V_z/F (L)	32.2±5.67	31.8±5.98	NA	NA

Table 3. Statistical comparison for T_{max} and $t_{1/2}$ of plasma CEP-10953

Pharmacokinetic Parameter	Median		Difference B–A		p-value
	Treatment B	Treatment A	Median[a]	95% CI	
$t_{1/2}$	12.5	12.9	–0.25	–0.70, 0.30	0.3066
t_{max}	2.0	1.5	0.25	–0.25, 1.00	0.3797

Per DSI report and recommendation, plasma data of CEP-10953 from 4 additional subjects (#10-13) were excluded from the PK and BE analysis. Results of mean CEP-10953 plasma concentration-time profiles following oral doses of Treatment A and Treatment B and summary of each of the PK parameters and statistical analysis are shown in the following figure and table.

Figure 2. Mean CEP-10953 plasma concentration-time profiles following single oral doses of 5 x 50 mg reference (Treatment A) and 1 x 250 mg test (Treatment B) formulations (N = 21)

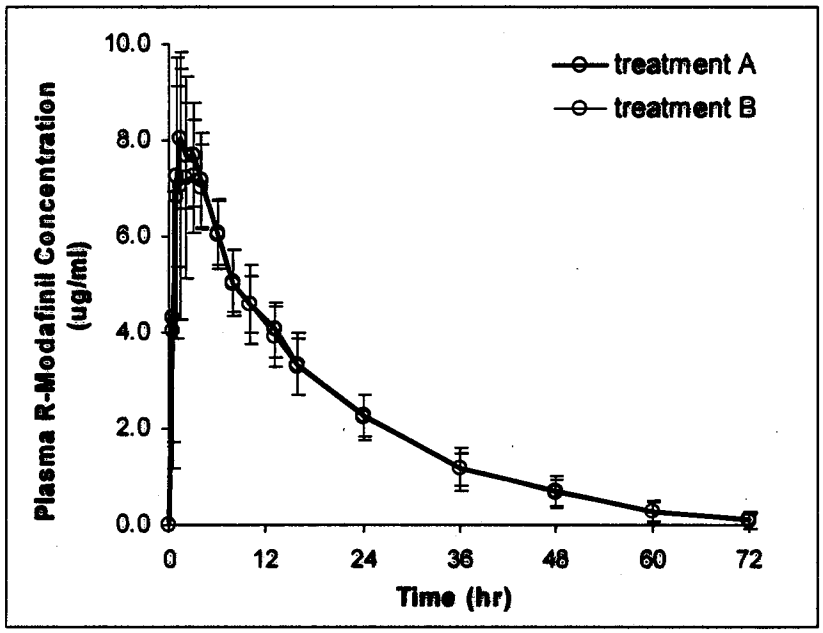

Table 4. Summary of pharmacokinetic results and statistical analysis for CEP-10953 following single oral doses of 5 x 50 mg reference (Treatment A) and 1 x 250 mg test (Treatment B) formulations

Pharmacokinetic parameters	Plasma CEP-10953		90% CI[a]	% Mean Ratio[a]
	Treatment B (N=21)	Treatment A (N=21)		
Cmax (μg/mL)	8.48±1.21	8.61±1.15	92.6-105.1	98.7
AUC_{0-t} (μg·hr/mL)	139.9±1.189	144.3±1.155	94.2-99.3	96.7
$AUC_{0-\infty}$	146.4±1.188	151.0±1.157	94.2-99.4	96.7

(μg·hr/mL)				
Tmax (hr)	2.06±1.79	1.53±1.67	NA	NA
$T_{1/2}$ (hr)	12.6±1.23	12.8±1.23	NA	NA
λ_Z (hr-1)	0.0551±0.0123	0.0540±0.0123	NA	NA
CL/F (mL/min)	28.5±1.19	27.6±1.16	NA	NA
V_Z/F (L)	31.0±1.5	30.6±1.18	NA	NA

[a] Analysis based on ln-transformed data.
Treatment A=single oral dose of five 50-mg CEP-10953 tablets.
Treatment B=single oral dose of one 250-mg CEP-10953 tablet.

Mean metabolites (R-modafinil acid and modafinil sulfone) plasma concentration-time profiles following oral doses of 5 x 50 mg (treatment A) and of 1 x 250 mg (treatment B) are shown in following figures. The summary of pharmacokinetic parameters is shown in following tables.

Figure 3. Mean R-modafinil acid plasma concentration-time profiles following single oral doses of 5 x 50 mg reference (Treatment A) and 1 x 250 mg test (Treatment B) formulations (N = 25)

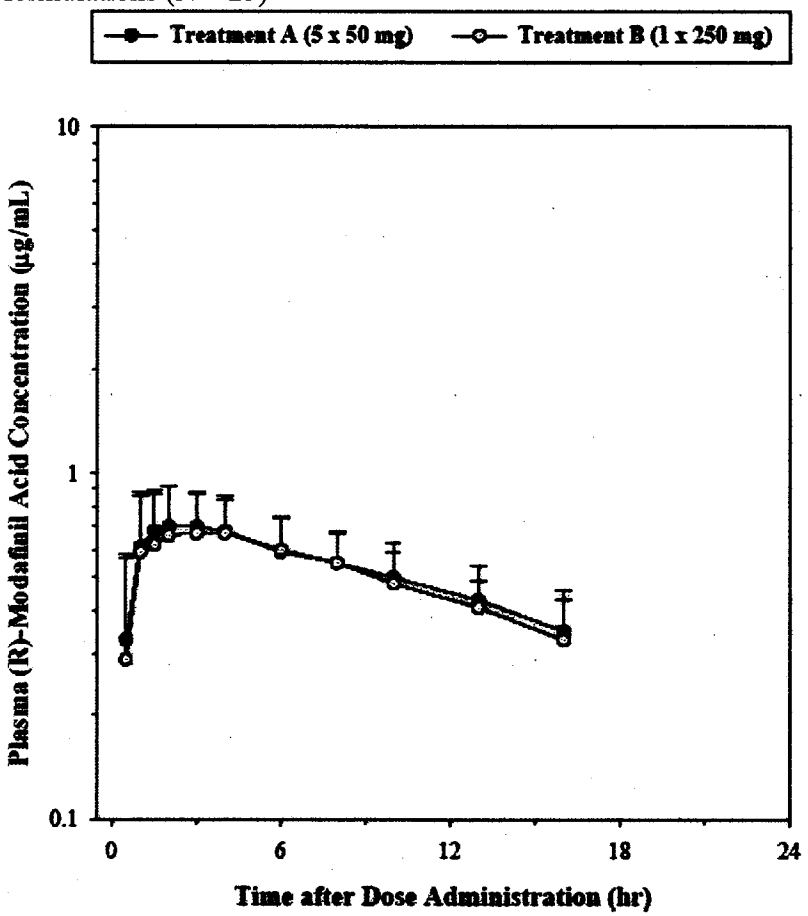

Table 5. Summary of pharmacokinetic results for R-modafinil acid following single oral doses of 5 x 50 mg reference (Treatment A) and 1 x 250 mg test (Treatment B) formulations:

Pharmacokinetic parameters	Plasma R-modafinil acid Treatment B (N=25)	Treatment A (N=25)
C_{max} (µg/mL)	0.77±0.20	0.78±0.20
t_{max} (hr)	2.2±1.2	2.0±0.99
AUC_{0-t} (µg•hr/mL)	10.1±3.06	10.7±3.37
$AUC_{0-\infty}$ (µg•hr/mL)	15.5±5.42	15.6±3.85
%Extrapolation	34.3091±10.3588	32.4909±8.55852
$t_{1/2}$ (hr)	13.8±5.85	13.4±3.26
λ_z (1/hr)	0.0557±0.0146	0.0550±0.0139

Figure 4. Mean modafinil sulfone plasma concentration-time profiles following single oral doses of 5 x 50 mg reference (Treatment A) and 1 x 250 mg test (Treatment B) formulations (N = 25)

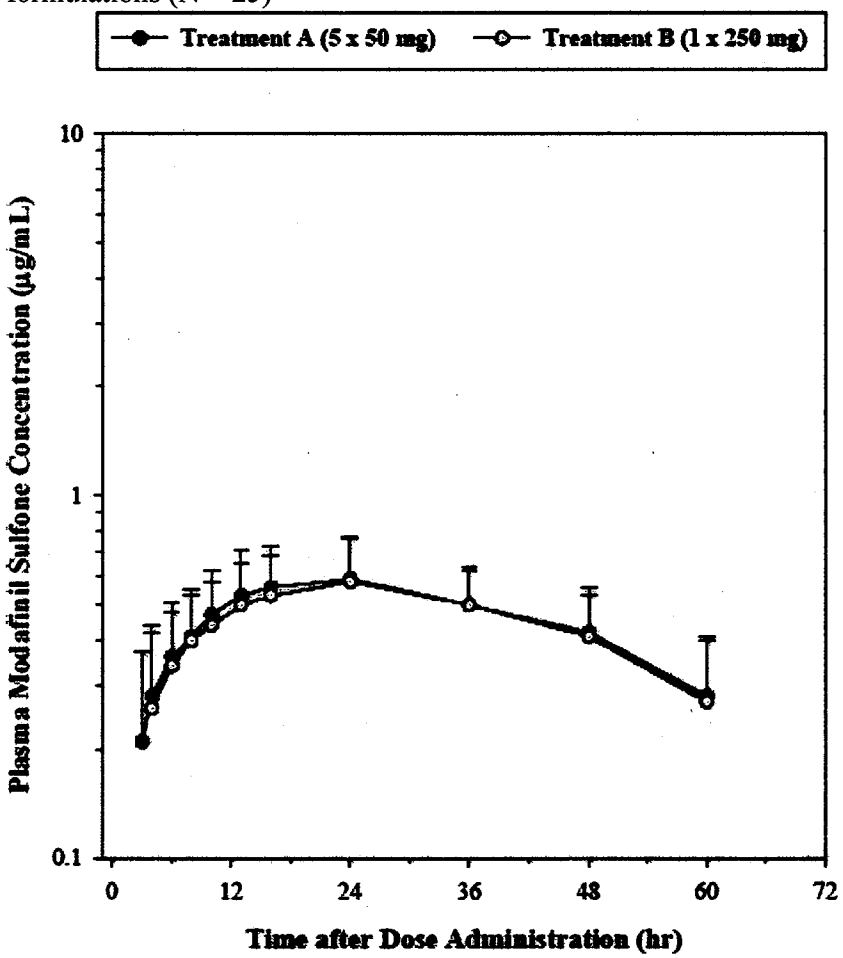

Table 6. Summary of pharmacokinetic results for modafinil sulfone following single oral doses of 5 x 50 mg reference (Treatment A) and 1 x 250 mg test (Treatment B) formulations:

	Plasma modafinil sulfone	
Pharmacokinetic parameters	**Treatment B (N=25)**	**Treatment A (N=25)**
C_{max} (µg/mL)	0.58±0.18	0.61±0.17
t_{max} (hr)	23±7.8	22±7.7
AUC_{0-t} (µg•hr/mL)	27.4±9.34	28.9±8.56
$AUC_{0-\infty}$ (µg•hr/mL)	41.6±14.8	42.0±9.49
%Extrapolation	33.1690±14.9413	31.5639±12.6112
$t_{1/2}$ (hr)	36.2±16.5	34.0±11.5
λ_z (1/hr)	0.0224±0.00796	0.0228±0.00789

Safety Summary:

No death and 1 (4%) withdrawal (due to non-active treatment-related adverse event) were reported during the study. Twenty-five (89%) subjects following treatment A and 21 (72%) subjects following treatment B experienced adverse events. A total of 156 (98%) adverse events were mild in intensity, 1 was moderate and 2 were severe, with 136 (86%) of them considered to be possibly active treatment-related. Adverse events were similar to the previous studies. Mild headache was the most commonly reported adverse event, others included dizziness, nausea, anxiety, insomnia, abdominal pain, and mild and reversible increases in heart rate. Otherwise, no clinically meaningful abnormal laboratory values, vital signs, physical examination findings, or ECG findings were reported. Single oral doses of 250 mg CEP-10953 were reported to be generally well tolerated in healthy subjects.

CONCLUSION:

- As shown, CEP-10953 exhibited similar pharmacokinetic profiles following single-dose oral administration of reference (5 x 50 mg) or test (1 x 250 mg) tablet formulation under fasting conditions. Similar results were observed with its metabolites, modafinil sulfone and R-modafinil acid.

- The rate and extent of absorption of CEP-10953 from two treatments were similar. The ratios of geometric means of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for CEP-10953 were 98.7% (92.6-105.1%), 96.7% (94.2-99.3%), and 96.7% (94.2-99.4%), respectively. The 90% CI of the geometric mean ratios of these exposure measures for the parent moiety, CEP-10953, were within the BE limits of 80-125%.

- Results demonstrate that the highest strength (1 x 250 mg) of the TBM uncoated tablets are BE to the multiples of the lowest strength (5 x 50 mg) of the clinical film-coated tablets.

Reviewer's comment:

- In the DSI report issued on November 29, 2005, Dr. Sriram Subramaniam, recommended further exclusion of the CEP-10953 concentration data for Subjects 10,

11, 12, and 13 from the BE estimation, with reason being the lack of accuracy assurance in certain analytical runs. The sample size (N=21) is still sufficient to provide >80% power at α=0.05 level for the statistical analysis. The above BE results in the Conclusion are reported based on **reviewer's own re-analysis per DSI** recommendation. No re-analysis is necessary for both metabolites since BE decision was made based on the active moiety only, i.e., the parent drug CEP-10953. Even with exclusion of these subjects, BE was demonstrated.

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Study C10953/1021/PK/US

An Open-Label, Crossover Pharmacokinetics and Safety Study to Evaluate the Effect of CEP-10953 on CYP2C19 Activity in Healthy Subjects Using Omeprazole as a Probe Substrate

Principal Investigator: Jerry Herron, MD
Study Center: Arkansas Research Medical Testing, LLC,
1207 Rebsamen Park Rd, Little Rock Arkansas, 72202.

Study Period: May 12, 2004 – May 20, 2004

Objectives:

Primary:

- To evaluate the effects of coadministration of CEP-10953 on the plasma pharmacokinetics of omeprazole, a standard probe substrate of CYP2C19, and of its 5'-hydroxy metabolite when CEP-10953 and omeprazole were given to healthy men and women

Secondary:

- To assess the safety of the coadministration of CEP-10953 and omeprazole as assessed by monitoring the occurrence of adverse events, clinical laboratory results, vital signs measurements, and electrocardiography and physical examination findings
- To measure plasma concentrations of CEP-10953 and its 2 circulating metabolites in order to document the concentrations that are associated with the effects, if any, on CYP2C19 activity that were observed

Drug Products:

Test formulation: CEP-10953, 50-mg tablets, Lot #: 04053K5a (Cephalon, Inc.)
Probe Substrate: Omeprazole 40-mg capsules, Lot #: N1986 (supplied by the study center)

Study Design:

This study was an open-label, single center, 2-way crossover pharmacokinetics and safety study in healthy adults (male and female) subjects to assess the potential PK interaction of CEP-10953 and omeprazole (a CYP2C19 substrate) under fasting condition. A total of 24 healthy adult male and female subjects (possible equal number) of any ethnic origin aged 18~45 years, inclusive, with a Body Mass Index (BMI) $\leq$30 kg/m^2, who met the inclusion and exclusion criteria were enrolled. At least 18 subjects who were CYP2C19 extensive metabolizers were expected to complete the study. Prescription or OTC medication (with the exception of acetaminophen or ibuprofen) were not allowed during the study. Alcohol, antiseptic mouthwash, or grapefruit juice were prohibited within 48 hours before dosing.

Eligible subjects reported to the study center on the evening of day -1 and remained in the clinic throughout the study. Duration of the study was 9 days. After an overnight fasting, subjects were randomized on a 1:1 basis to receive one of the 2 treatment sequences (A→B or B→A), with a 7-day washout period between treatments. Omeprazole or CEP-10953 was administered in the morning of days 1 and 8 with 8 ounces of non-mineral water.

Treatment A: 40 mg of omeprazole (1 oral capsule)

Treatment B: 400 mg of CEP-10953 (8 oral tablets) followed in 2 hours by 40 mg of omeprazole

The PK samples for analysis of omeprazole and its 5′-hydroxy metabolite were collected from Treatment A and B and the PK samples for analysis of CEP-10953 were collected from Treatment B. Safety was assessed at screening and during the study. No efficacy assessment was performed in this study.

Safety Assessments:

Safety assessments were conducted at screening, baseline, and during the study, by monitoring the occurrence of adverse events, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital signs (blood pressure, pulse), concomitant medication usage, electrocardiograms, and physical examination findings. The 12-lead ECG monitoring was carried out at screening and at discharge on Day 9.

Pharmacokinetics Assessments:

A total of 16 blood samples were collected from each subject for the determination of omeprazole and its 5′-hydroxy metabolite from Treatment A and B on Days 1 and 8 at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours postdose. A total of 19 blood samples were collected from each subject for the determination of CEP-10953 and its 2 metabolites from Treatment B on Days 1 and 8 at -2 (pre-CEP-10953-dose), -1.5, -1, 0 (pre-omeprazole-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours postdose. Plasma samples were stored frozen at - 20°C until assayed.

Plasma concentrations of omeprazole and its 5′-hydroxy metabolite were analyzed using a HPLC with tandem mass spectrometric detection (LC-MS/MS) method performed at [redacted] Plasma concentrations of CEP-10953, modafinil sulfone, and R-modafinil acid were analyzed by a validated HPLC method.

Table 1. Assay validation for Study C10953/1021/PK/US

			R-modafinil (CEP-10953)	R-modafinil acid	Modafinil sulfone	Omeprazole	5-Hydroxy-omeprazole
Method:			HPLC	HPLC	HPLC	LC/MS/MS	LC/MS/MS
Standard curve	Range:		0.20~50.00 µg/mL	0.20~50.00 µg/mL	0.20~50.00 µg/mL	1.00-1000 ng/mL	1.00-1000 ng/mL
		Precision:	2.39~4.98%	2.58~4.24%	2.50~3.81%	1.3~4.2%	6.1~8.9%
		Accuracy:	-2.55~1.42%	-3.73~1.38%	-4.75~1.76%	-6.2~2.6%	-2.6~2.3%
	Linearity:		$r^2 = 0.9994$	$r^2 = 0.9992$	$r^2 = 0.9995$	$r^2 = 0.9992$	$r^2 = 0.9961$
LOQ	LLOQ:		0.20 µg/mL	0.20 µg/mL	0.20 µg/mL	1.00 ng/mL	1.00 ng/mL

QC	Low:		0.60 μg/mL	0.60 μg/mL	0.60 μg/mL	3.0 ng/mL	3.0 ng/mL
		Precision:	5.41 %	5.79 %	5.60 %	2.7 %	7.0 %
		Accuracy:	-0.11 %	0.17 %	1.12 %	4.6 %	6.6 %
	Med:		20.00 μg/mL	20.00 μg/mL	20.00 μg/mL	30.0 ng/mL	30.0 ng/mL
		Precision:	3.59 %	4.13 %	3.35 %	2.4 %	5.4 %
		Accuracy:	-3.71 %	-4.13 %	-3.91 %	4.1 %	4.8 %
	High:		50.00 μg/mL	50.00 μg/mL	50.00 μg/mL	750.0 ng/mL	750.0 ng/mL
		Precision:	3.38 %	3.85 %	3.33 %	1.6 %	6.7 %
		Accuracy:	-5.67 %	-5.62 %	-5.08 %	-3.5 %	0.3 %

Pharmacokinetic Analysis:
The following PK parameters for omeprazole and 5′-hydroxyomeprazole (when possible) from each treatment were calculated: C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, λ_Z, $t_{1/2}$, CL/F, V/F, the P/M (Parent/Metabolite) ratio for AUC_{0-8}, and omeprazole serum hydroxylation index ([HI] or plasma P/M concentration ratio) at 2 hours postdose for phenotyping. The following PK parameters for CEP-10953 and its 2 metabolites from treatment B were calculated: C_{max}, t_{max}, and AUC_{0-t} (with $AUC_{0-\infty}$, λ_Z, and $t_{1/2}$ estimated when possible). The CYP2C19 activity was assessed by the ratios of plasma concentrations at 2 hours and of AUC_{0-8} for omeprazole and 5′-hydroxyomeprazole.

Statistical Analysis:
Subjects were phenotyped for CYP2C19 status by the omeprazole/5′-hydroxyomeprazole (P/M) ratio at 2 hours post-omeprazole-dose during treatment A. Only those data from CYP2C19 extensive metabolizers (with log P/M <1) were included in this analysis for the purpose of avoiding diluting any effect of CEP-10953 on CYP2C19 activity.

The primary PK parameters were summarized by treatment group using descriptive statistics, including the geometric mean, coefficient of variation, and geometric mean ratio. To assess the effect of CEP-10953 on omeprazole in the 2 treatment sequences as described, the 90% confidence intervals (CI) were calculated based on the difference in **means (treatment B – treatment A) of the log-transformed** $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for omeprazole. The secondary PK parameters were also summarized using descriptive statistics. The treatment effects on secondary PK parameters (t_{max}, $t_{1/2}$, CL/F, V/F) were evaluated using nonparametric Wilcoxon Signed Rank Test.

RESULTS

Demographics of Subjects:
A total of 24 subjects were enrolled in study, and all subjects received drug and completed the study. All the enrolled subjects were identified as CYP2C19 extensive metabolizers, with a median log ratio of omeprazole-to-5′-hydroxyomeprazole plasma concentration at 2 hours postdose <0.19 (ranged -0.22 ~ 0.90). Therefore, final Pharmacokinetics and safety analyses were performed on all 24 subjects who were extensive metabolizers and completed both periods of the study. The subjects consisted of 37.5% Caucasians and 62.5% black, and 67% of subjects were men. The mean age, weight, height and BMI were 38 years (19-44 years of age), 78.0 kg (60-100 kg), 174.1 cm (160-193 cm), and 25.8 kg/m^2 (19.4-29.9 kg/m^2), respectively.

Pharmacokinetic Summary:

Data were obtained from 24 subjects who were evaluable for pharmacokinetic analysis in the 2 periods of the study. The mean omeprazole and 5′-hydroxyomeprazole plasma concentration-time profiles, pharmacokinetic parameters and statistical analysis for omeprazole of 40 mg oral doses either administered alone (Day 1) or following pretreatment with CEP-10953 (Day 8) are shown in Figures 1-2 and Tables 2-4.

Figure 1. Comparative mean (SD) omeprazole plasma concentration-time profiles following single oral doses

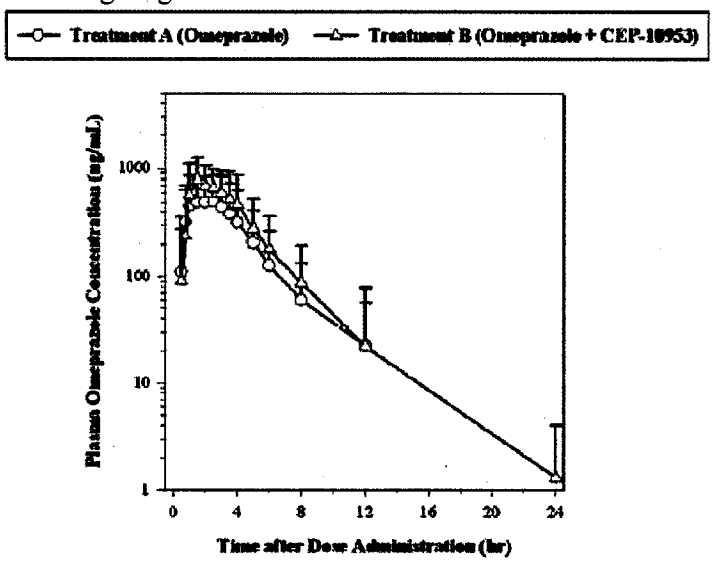

Table 2. Primary pharmacokinetic parameters of omeprazole and statistical analysis by treatment group

PK parameter	N	Omeprazole[a]	Omeprazole + CEP-10953[a]	Geometric mean ratio (omeprazole + CEP-10953/omeprazole)	90% CI for geometric mean ratio
$AUC_{0-\infty}$ (ng·hr/mL)	23[b]	2401.1±1606.09	3268.4±2062.48	1.42	1.29, 1.57
AUC_{0-t} (ng·hr/mL)	24	2420.8±1569.67	3263.2±2008.47	1.43	1.30, 1.57
C_{max} (ng/mL)	24	800.6±354.50	1051.7±404.26	1.36	1.17, 1.59

Table 3. Secondary pharmacokinetic parameters of omeprazole and statistical analysis by treatment group

PK parameter	N	Omeprazole[a]	Omeprazole + CEP-10953[a]	p-value
t_{max} (hr)	24	1.5 (0.5, 12.0)	1.5 (0.8, 4.0)	0.9774
$t_{½}$ (hr)	23[b]	1.7±0.83	1.9±0.79	0.2840
V/F (L)	23[b]	54.8±32.44	39.0±16.67	0.0227
CL/F (L/hr)	23[b]	26.4±19.57	16.7±8.86	0.0003

Figure2 . Comparative mean (SD) 5′-hydroxyomeprazole e plasma concentration-time profiles following single oral doses

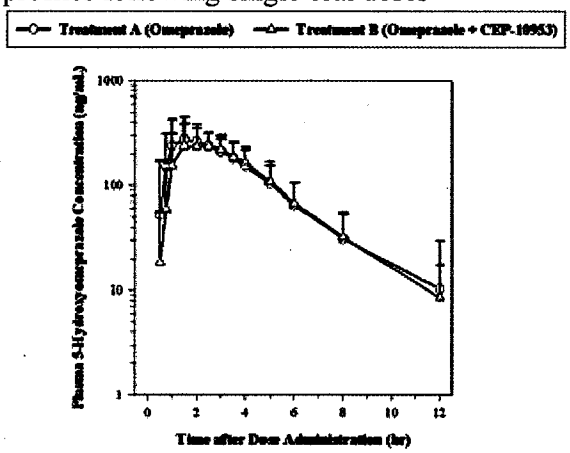

Table 4. Pharmacokinetic parameters of 5′-hydroxyomeprazole by treatment group

Pharmacokinetic parameter	n	Omeprazole[a] (N=24)	Omeprazole + CEP 10953[a] (N=24)
$AUC_{0-\infty}$ (ng•hr/mL)	23[b]	1207.8±233.47	1134.1±305.48
AUC_{0-t} (ng•hr/mL)	24	1201.4±227.18	1119.8±298.86
C_{max} (ng/mL)	24	366.4±133.02	311.3±103.10
t_{max} (hr)	24	1.5 (0.5, 12.0)	1.5 (0.8, 4.0)
$t_{½}$ (hr)	23[b]	2.0±0.94	2.0±0.88
Serum omeprazole hydroxylation index[c]	24	0.19 (-0.22, 0.90)	0.42 (0.11, 0.99)
Parent:metabolite (AUC_{0-8}) ratio	24	2.1±1.41	3.0±1.76

The mean plasma concentration-time profiles and pharmacokinetic parameters of CEP-10953, R-modafinil acid, and modafinil sulfone following concomitant CEP-10953 and omeprazole on Day 8 are shown in following figure and table.

Figure 3. Mean (SD) plasma concentration-time profiles of CEP-10953 and its metabolites following concomitant CEP-10953 and omeprazole

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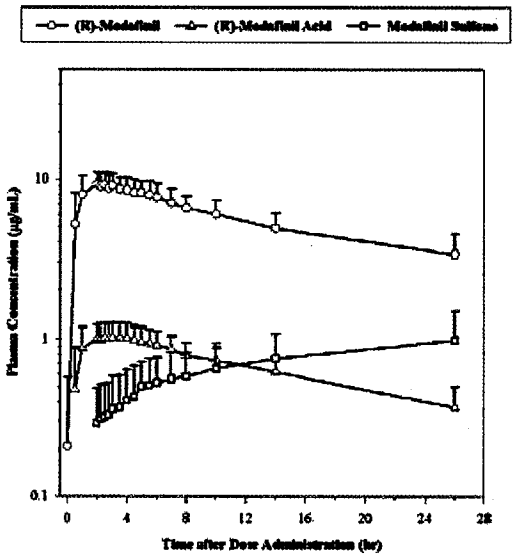

Table 5. Pharmacokinetic parameters of CEP-10953, R-modafinil acid, and modafinil sulfone

Pharmacokinetic parameter	n	CEP-10953[a] (N=24)	R-Modafinil acid[a] (N=24)	Modafinil sulfone[a] (N=24)
AUC_{0-t} (µg·hr/mL)	24	145.4±31.22	17.1±3.60	17.5±7.76
C_{max} (µg/mL)	24	9.7±1.85	1.1±0.22	1.0±0.48
t_{max} (hr)	24	2.3 (0.5, 5.0)	2.6 (1.0, 5.5)	26.0 (1.0, 26.0)

Safety Summary:

No deaths or other serious adverse events, or withdrawals due to adverse events were reported during the study. Adverse events occurred more frequently with concomitant treatment (79%) than with omeprazole alone (8%, somnolence). However, it was not clear whether the increased incidences of adverse events were due to CEP-10953 or to the increased omeprazole exposure. Headache was the most frequently reported adverse event with 1 incidence considered severe, followed by insomnia, psychomotor hyperactivity, and dry mouth, attributing to treatment with CEP-10953. No clinically meaningful abnormal laboratory values, vital signs, physical examination findings, or ECG findings were reported. Coadministration of CEP-10953 of 400 mg and omeprazole of 40 mg was reported to be generally well tolerated.

CONCLUSION:

- Coadministration of CEP-10953 and omeprazole (2 hours apart) resulted in an approximate 40% increase in exposure measures ($AUC_{0-\infty}$, AUC_{0-t}, and C_{max}) of omeprazole as compared to administration of omeprazole alone. The increases in exposure were reflected by the significant decreases of 29-37% in V/F and CL/F.

- The mean AUC_{0-8} ratio (parent/metabolite) was increased by approximately 40% and the mean serum hydroxylation index [HI] was increased by more than 2 folds, indicating inhibition by CEP-10953 of omeprazole metabolism via the CYP2C19 pathway.

- The 90% CI of the geometric mean difference for the log transformed exposure measurements between two treatments fell outside the BE limits of 80-125%, suggesting the interaction between CEP-10953 and omeprazole (through CYP2C19).

- The PK profiles of CEP-10953 and its two circulating metabolites when coadministered with omeprazole were similar to that previously reported for this single dose of CEP-10953. For example, the mean Cmax following this single 400-mg dose was within 10% of the targeted value, i.e., the mean Cmax at steady-state at a dosage of 250 mg/day.

- It can be concluded that treatment with CEP-10953 causes partial inhibition of CYP2C19 activity in humans in vivo, and the comedications that are substrates for CYP2C19 may require dosage reduction.

Reviewer's comment:

- The accumulation of modafinil sulfone has been observed following multiple dosing. The inhibition potential on CYP2C19 by sulfone metabolite has been reported (according to the Provigil label). Therefore, the inhibitory effect of armodafinil on CYP2C19 following chronic doses may potentially be greater than what was observed in this study.

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Study C10953/1022/PK/US

An Open-Label Pharmacokinetics and Safety Study to Evaluate the Effect of Repeated Administration of CEP-10953 on CYP3A4 Activity in Healthy Subjects Using Midazolam (Intravenous and Oral) as the Probe Substrate

Principal Investigator: Jerry Herron, MD
Study Center: Arkansas Research Medical Testing, LLC,
1207 Rebsamen Park Rd, Little Rock Arkansas, 72202.
Study Period: June 6, 2004 – July 12, 2004

Objectives:
Primary:

- To evaluate the effect of repeated daily administration of CEP-10953 on CYP3A4 activity in healthy subjects, using the plasma concentration versus time profiles of midazolam following intravenous and oral administration before and after 4 weeks of CEP-10953 administration.

Secondary:

- To assess the relative contributions of intestinal and hepatic CYP3A4 induction to any interaction between the prototypic CYP3A4 substrate, midazolam, and CEP-10953
- To assess safety by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, and electrocardiography and physical examination findings

Drug Products:

Test formulation: CEP-10953, 50-mg tablets, Lot #: 04053K5a (Cephalon, Inc.)
Probe Substrate: Midazolam, IV 2 mg (1.0 mg midazolam HCl/mL), Lot #: 342163 and 342315 (supplied by the study center)
Midazolam, oral syrup 5 mg (2.0 mg midazolam HCl/mL), Lot #: 456131A (supplied by the study center)

Study Design:

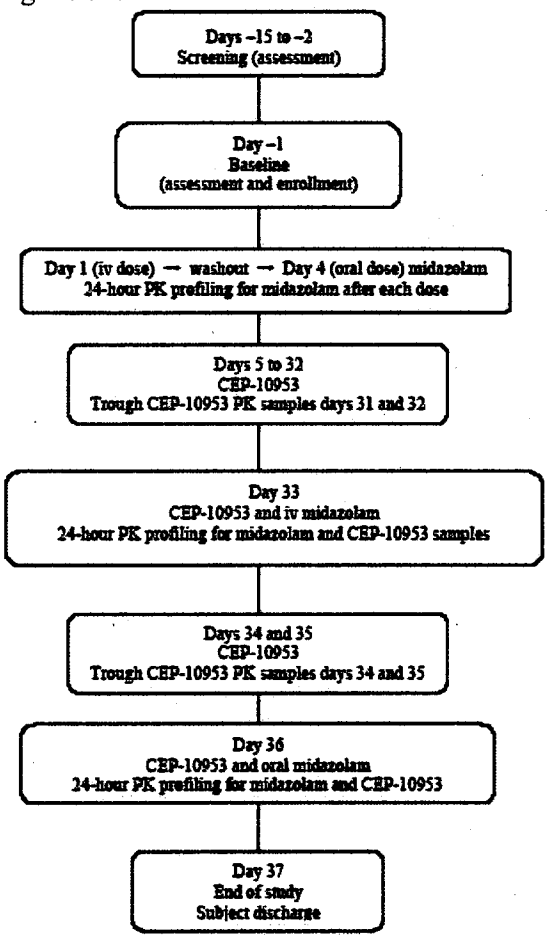
This study was an open-label, single center, nonrandomized pharmacokinetics and safety study in healthy adult male and female subjects to assess the potential PK interaction of CEP-10953 with intravenous and oral midazolam (a CYP3A4 substrate) under fasting condition. No control group was employed in this study. A total of 24 healthy adult male and female subjects (possible equal number) of any ethnic origin aged 18~45 years, inclusive, with a Body Mass Index (BMI) ≤ 30 kg/m^2, who met the inclusion and exclusion criteria were evaluated. Prescription or OTC medication (with the exception of acetaminophen, ibuprofen, and non-oral contraceptives) were not allowed during the study. Alcohol, antiseptic mouthwash, or grapefruit juice were prohibited within 48 hours before dosing.

Eligible subjects reported to the study center on the evening of days -1 and 30, and remained at study center for 5 days postdose. Oral and IV midazolam and CEP-10953 doses were administered in the morning after an overnight fasting.

CEP-10953: Oral doses were administered to all subjects beginning at 100 mg/day on Day 5, titrated in 50-mg increments every 2 days until 250 mg/day was reached on Day 11 and thereafter.

Midazolam: Single IV midazolam doses (2 mg) were administered to all subjects on Days 1 and 33 and single oral midazolam doses (5 mg) were administered on Days 4 and 36.

The overall study design is shown as follows:



PK=pharmacokinetics.
Intravenous (iv) midazolam=2-mg total dose administered as an iv injection, over 5 minutes.
Oral midazolam=5-mg total dose, administered in syrup form.
CEP-10953=100-mg starting dose titrated upwards at 50 mg/day every 2 days to 250 mg/day.

The PK samples were collected for the analysis of midazolam and its metabolite, 1′-hydroxymidazolam, and trough levels of CEP-10953. Safety was assessed at screening and during the study. No efficacy assessment was performed in this study.

Safety Assessments:

Safety assessments were conducted at screening, baseline, and throughout the study by monitoring the occurrence of adverse events, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital signs (blood pressure, pulse), concomitant medication usage, electrocardiograms, and physical examination findings. The 12-lead ECG monitoring was carried out at screening and at discharge on Day 37.

Pharmacokinetics Assessments:
A total of 15 blood samples were collected from each subject for the determination of **midazolam and 1'-hydroxymidazolam at pre**dose, 10, 20, 30, and 45 minutes, and at 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 24 hours post each IV and oral midazolam dose. The trough CEP-10953 plasma concentrations were collected on Days 31~36, and samples collected on Days 33 and 36 were also analyzed for CEP-10953 and its metabolites. Plasma samples were stored frozen at - 20°C until assayed.

Plasma concentrations of midazolam and **1'-hydroxymidazolam were analyzed using a** HPLC [redacted] method performed at [redacted]. Plasma concentrations of CEP-10953, modafinil sulfone, and R-modafinil acid were analyzed by a validated HPLC method. b(4)

Table 1. Assay validation for Study C10953/1022/PK/US

			R-modafinil (CEP-10953)	R-modafinil acid	Modafinil sulfone	Midazolam	1-Hydroxy-midazolam
Method:			HPLC [redacted]	HPLC [redacted]	HPLC [redacted]	LC/MS/MS	LC/MS/MS
Standard curve	Range:		0.20~50.00 µg/mL	0.20~50.00 µg/mL	0.20~50.00 µg/mL	0.10-100 ng/mL	0.10-100 ng/mL
		Precision:	3.29~7.97%	2.50~7.30%	3.23~8.39%	1.60~4.94%	2.05~6.72%
		Accuracy:	-1.37~1.58%	-2.75~2.53%	-2.09~2.28%	-0.56~0.66%	-4.64~3.60%
	Linearity:		$r^2 = 0.9992$	$r^2 = 0.9995$	$r^2 = 0.9989$	$r^2 = 0.9999$	$r^2 = 0.9999$
LOQ	LLOQ:		0.20 µg/mL	0.20 µg/mL	0.20 µg/mL	0.10 ng/mL	0.10 ng/mL
QC	Low:		0.60 µg/mL	0.60 µg/mL	0.60 µg/mL	0.3 ng/mL	0.3 ng/mL
		Precision:	9.26 %	9.80 %	8.33 %	5.31 %	5.99 %
		Accuracy:	4.32 %	7.28 %	5.72 %	-6.25 %	-5.93 %
	Med:		20.00 µg/mL	20.00 µg/mL	20.00 µg/mL	3.00 ng/mL	3.00 ng/mL
		Precision:	8.21 %	5.18 %	4.85 %	5.65 %	5.98 %
		Accuracy:	0.49 %	-0.17 %	-1.60 %	-2.52 %	-3.34 %
	High:		50.00 µg/mL	50.00 µg/mL	50.00 µg/mL	75.00 ng/mL	75.00 ng/mL
		Precision:	5.94 %	4.67 %	5.79 %	4.14 %	3.67 %
		Accuracy:	-2.02 %	-1.47 %	-3.94 %	-0.97 %	-4.18 %

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Pharmacokinetic Analysis:
The following PK parameters for CEP-10953, midazolam and 1'-hydroxymidazolam were calculated for each subject: C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, λ_Z, $t_{1/2}$, AUC_{0-24} for CEP-10953 and its metabolites after 1st dose, CL and V for IV dosing, and CL/F and V/F for oral dosing. Additional PK parameters for midazolam, such as F_H, F_G, and F_{oral}, were determined.

Statistical Analysis:

The primary PK parameters were summarized using descriptive statistics, including the geometric mean, coefficient of variation, and geometric mean ratio. To assess the effect of CEP-10953 on IV and oral midazolam, the 90% confidence intervals (CI) were calculated based on the difference in means of the log-transformed $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for midazolam before and after repeated doses of CEP-10953. The acceptance criteria for 90% CI was set at 80-125%.

The secondary PK parameters (t_{max}, volume of distribution, clearance, and $t_{½}$) were also summarized using descriptive statistics. The treatment effects were evaluated using nonparametric Wilcoxon Signed Rank Test and 95% CI of the changes of pharmacokinetic parameters were provided. The F_{oral}, F_H, and F_G of midazolam before and after repeated doses of CEP-10953 were summarized and a 90% CI for these values was provided.

RESULTS

Demographics of Subjects:

A total of 24 subjects were enrolled in study and received treatment, 22 subjects completed the study, and 2 subjects (#2212 and 2214) discontinued prior to coadministration of CEP-10953 and midazolam due to the withdrawal consent and the failure to follow up. The subjects consisted of 33% Caucasians and 67 % black, and 71% of subjects were men. The mean age, weight, height and BMI were 38 years (26-45 years of age), 82.1 kg (64.4-100.2 kg), 174.9 cm (162.6-185.4 cm), and 26.8 kg/m^2 (20.6-30.0 kg/m^2), respectively. Therefore, final safety analysis was performed on 24 subjects, excluding 2 in the safety analysis data set for concomitant CEP-10953 and midazolam. Final pharmacokinetic analyses for CEP-10953 and midazolam were performed on all 17 subjects, excluding 2 discontinuation and 5 (#2205, 2206, 2217, 2219, and 2220) due to noncompliance with CEP-10953 dosing regimen.

Pharmacokinetic Summary:

The mean midazolam and 1′-hydroxymidazolam plasma concentration-time profiles for midazolam IV and oral doses either administered alone or following pretreatment with CEP-10953 are shown in Figures 1-2. The summary of pharmacokinetic parameters and statistical analysis of each pharmacokinetic parameter are shown in Tables 2-6.

Table 2. Pharmacokinetic profiles of IV and oral midazolam administered alone

$AUC_{0-\infty}$ (ng•hr/mL) (N=17)	AUC_{0-t} (ng•hr/mL) (N=17)	C_{max} (ng/mL) (N=17)	t_{max} (hr) (N=17)	$t_{½}$ (hr) (N=17)	Vol dist (L) (N=17)	Clearance (mL/min) (N=17)	F_{oral}
Intravenous[a]							
76.9±16.47	74.8±15.92	NA	NA	5.0±1.49	196.4±71.89	27.1±5.53	NA
Oral[b]							
53.8±19.53	51.6±18.03	18.7±6.29	0.5 (0.3, 2.5)	4.7±1.75	669.6±217.02	103.1±31.75	0.3

Figure 1. Comparative mean (SD) midazolam and 1′-hydroxymidazolam plasma concentration-time profiles following single IV doses

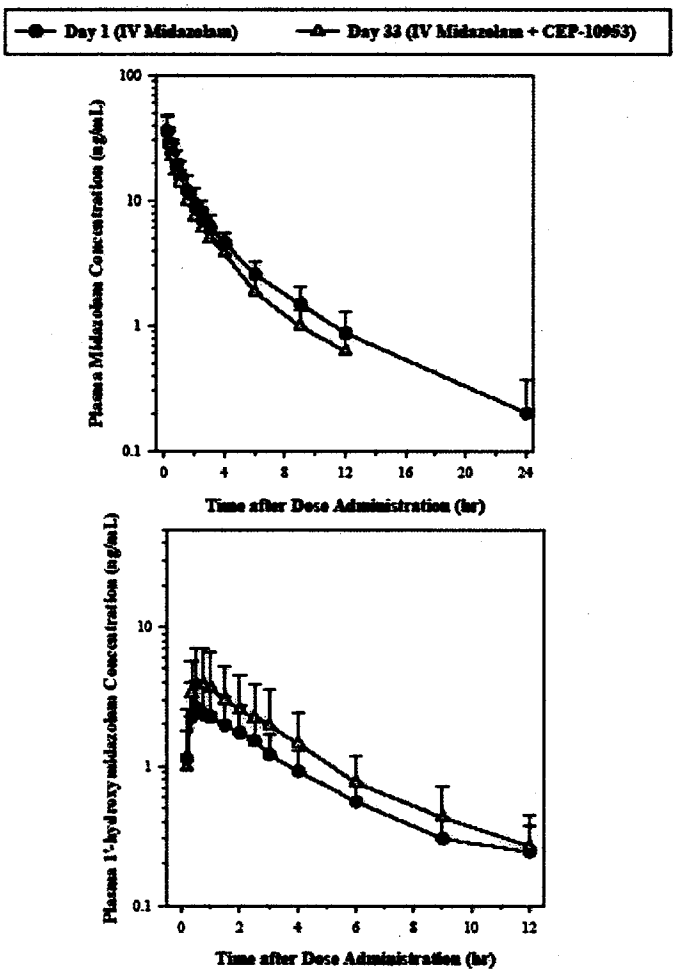

Figure 2. Comparative mean (SD) midazolam and 1′-hydroxymidazolam plasma concentration-time profiles following single oral doses

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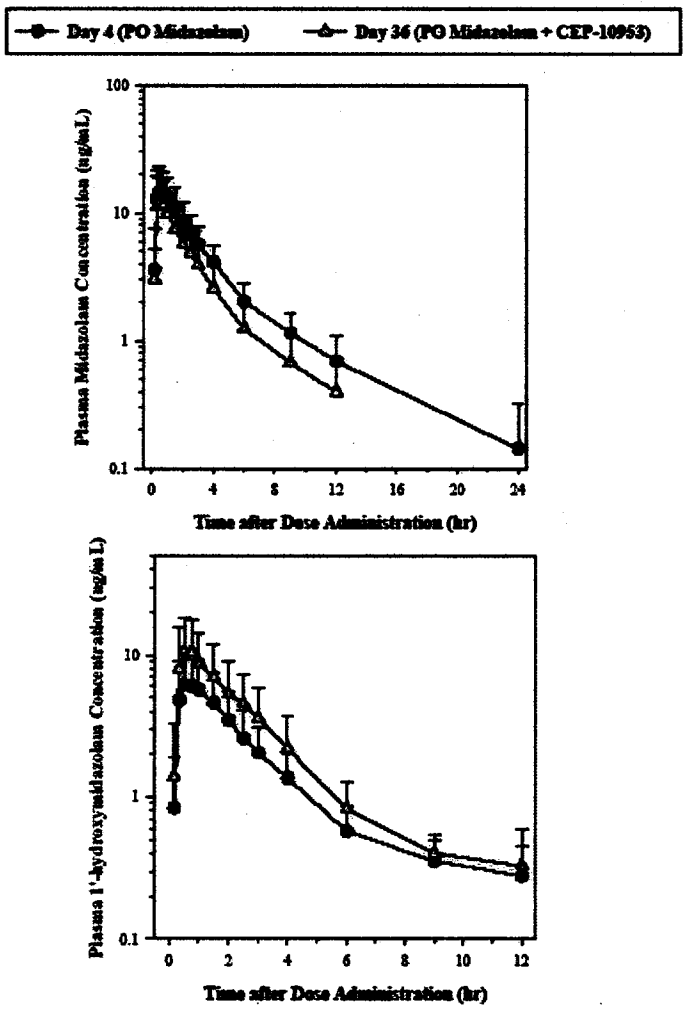

Table 3. Primary pharmacokinetic parameters of midazolam and statistical analysis by treatment group

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PK parameter	N	Midazolam[a] (Geomean)	Midazolam + CEP-10953[a,b] (Geomean)	Geometric mean ratio (with/without CEP-10953)	90% CI for mean ratio
Intravenous					
$AUC_{0-\infty}$ (ng•hr/mL)	17	76.9±16.47 (75.3)	63.5±11.97 (62.5)	0.83	0.78, 0.89
AUC_{0-t} (ng•hr/mL)	17	74.8±15.92 (73.3)	61.8±11.88 (60.7)	0.83	0.77, 0.89
C_{max} (ng/mL)	17	NA	NA	NA	NA
Oral					
$AUC_{0-\infty}$ (ng•hr/mL)	17	53.8±19.53 (51.0)	36.5±16.85 (33.6)	0.66	0.58, 0.74
AUC_{0-t} (ng•hr/mL)	17	51.6±18.03 (49.0)	34.9±16.37 (32.1)	0.65	0.58, 0.74
C_{max} (ng/mL)	17	18.7±6.29 (17.6)	15.2±7.22 (14.0)	0.79	0.68, 0.93

Table 4. Secondary pharmacokinetic parameters of midazolam and statistical analysis by treatment group

PK parameter	N	Midazolam[a]	Midazolam + CEP-10953[a,b]	P-Value	95% CI for median difference
Intravenous					
t_{max} (hr)	17	NA	NA	NA	NA
$t_{½}$ (hr)	17	5.0±1.49	4.2±1.32	0.0128	-1.4, -0.2
V (L)	17	196.4±71.89	196.8±68.62	0.7819	-25.8, 31.9
CL (mL/min)	17	27.1±5.53	32.5±6.07	0.0003	3.2, 8.0
Oral					
t_{max} (hr)	17	0.5 (0.3, 2.5)	0.5 (0.3, 2.5)	0.9070	-0.4, 0.3
$t_{½}$ (hr)	17	4.7±1.75	4.4±1.76	0.2199	-0.9, 0.3
V/F (L)	17	669.6±217.02	936.2±320.92	<0.0001	168.0, 351.1
CL/F (mL/min)	17	103.1±31.75	159.4±54.71	<0.0001	34.6, 77.7

Table 5. Fractions of bioavailability of midazolam and statistical analysis by treatment group

PK parameter	N	Midazolam[a] (Geomean)	Midazolam + CEP-10953[a,b] (Geomean)	Geometric mean ratio (with/without CEP-10953)	90% CI for mean ratio
F_{Oral}	17	0.28±0.063 (0.272)	0.23±0.079 (0.215)	0.791	0.697, 0.897
F_G	17	0.45±0.100 (0.439)	0.42±0.134 (0.401)	0.915	0.788, 1.063
F_H	17	0.62±0.073 (0.618)	0.54±0.089 (0.537)	0.868	0.822, 0.915

Table 6. Pharmacokinetic parameters of 1′-hydroxymidazolam by treatment group

PK parameter	n	Midazolam[a]	Midazolam + CEP 10953[a]
Intravenous			
$AUC_{0-\infty}$ (ng•hr/mL)	17	12.1±5.27	16.9±11.93
AUC_{0-t} (ng•hr/mL)	17	10.5±4.82	15.7±11.67
C_{max} (ng/mL)	17	2.8±1.61	4.3±3.12
t_{max} (hr)	17	0.5 (0.2, 2.0)	0.5 (0.3, 1.5)
$t_{½}$ (hr)	17	5.2±1.88	4.1±1.44
Oral			
$AUC_{0-\infty}$ (ng•hr/mL)	17	20.1±9.80	30.2±18.47
AUC_{0-t} (ng•hr/mL)	17	18.6±9.73	28.6±18.49
C_{max} (ng/mL)	17	8.1±3.82	12.7±6.55
t_{max} (hr)	17	0.5 (0.3, 2.5)	0.8 (0.3, 2.5)
$t_{½}$ (hr)	17	5.7±1.91	4.8±2.07

The mean plasma concentration-time profiles and pharmacokinetic parameters of CEP-10953, R-modafinil acid, and modafinil sulfone following concomitant multiple CEP-10953 doses and midazolam are shown in the following figure and tables .

Figure 3. Mean (SD) plasma concentration-time profiles of CEP-10953 and its metabolites following concomitant doses with IV (left) and Oral (right) midazolam on Days 33 and 36, respectively

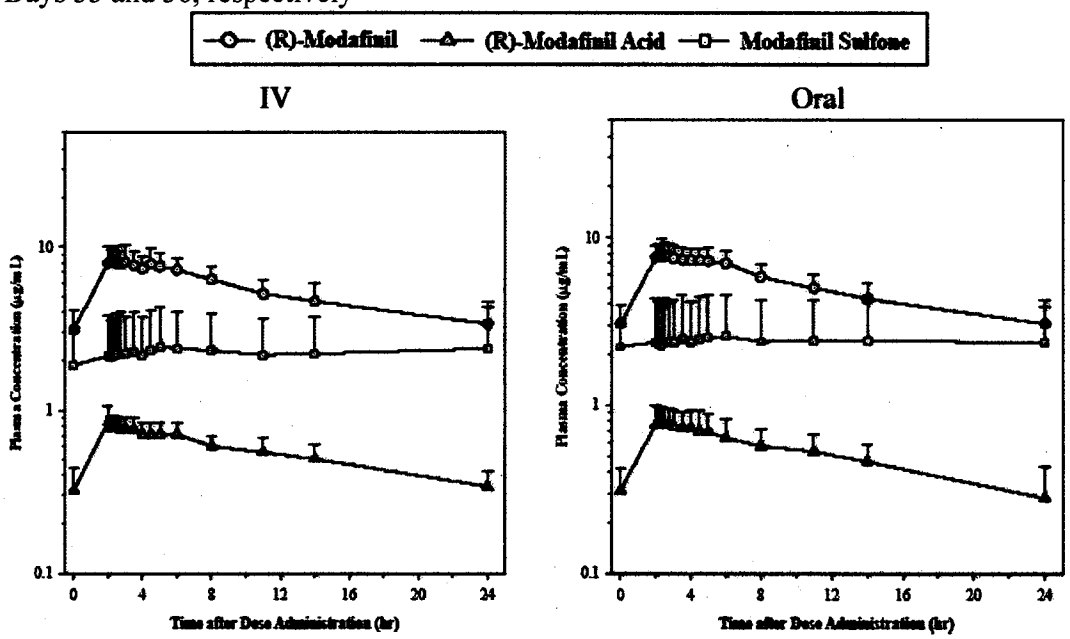

Table 7. Pharmacokinetic parameters of CEP-10953, R-modafinil acid, and modafinil sulfone

PK parameter	CEP10953[a] (N=17)		R-Modafinil acid[a] (N=17)		Modafinil sulfone[a] (N=17)	
	Day 33[b]	Day 36[b]	Day 33[b]	Day 36[b]	Day 33[b]	Day 36[b]
$AUC_{0-\tau}$ (ng•hr/mL)	127.2±30.81	119.9±24.47	12.9±2.25	12.5±2.97	54.1±38.70	57.6±45.13
AUC_{0-t} (ng•hr/mL)	127.2±30.81	119.9±24.47	12.9±2.25	12.0±3.78	54.1±38.70	57.6±45.13
C_{max} (ng/mL)	8.8±2.13	8.6±1.59	0.9±0.21	0.8±0.20	2.7±2.08	2.7±2.08
t_{max} (hr)	2.2 (2.0, 4.5)	2.5 (2.0, 4.5)	2.0 (2.0, 3.5)	2.3 (2.0, 4.5)	6.0 (2.0, 24.0)	6.0 (0.0, 14.0)

Table 8. Mean (SD) trough plasma concentrations of CEP-10953 on Days 31~37

Study day	n	CEP-10953 concentration[a] (μg/mL)
Day 31	17	3.4±1.20
Day 32	17	3.4±1.27
Day 33	17	3.1±0.97
Day 34	17	3.4±1.24
Day 35	17	3.3±0.82
Day 36	17	3.1±0.89
Day 37	17	3.1±0.84

Safety Summary:

No deaths or other serious adverse events, or withdrawals due to adverse events were reported during the study. One subject in each of 3 treatments reported severe headache, and similar adverse event profiles were reported for all treatments. Most adverse events were mild or moderate in severity. The most common adverse events reported in subjects treated with CEP-10953 were headache, insomnia, psychomotor hyperactivity (ie, hyperactivity, intermittent hyperactivity), and nausea. No clinically meaningful abnormal laboratory values, vital signs, physical examination findings, or ECG findings were reported. Coadministration of CEP-10953 and midazolam at the doses tested was reported to be generally well tolerated.

CONCLUSION:

- Coadministration of armodafinil resulted in approximate 17% and 32% reductions in systemic exposure for intravenous and oral midazolam, respectively, with corresponding 40% and 50%increases in **exposure of 1'-hydroxymidazolam** metabolite.

- The 90% confidence intervals of the geometric mean ratios difference for ln-transformed exposure between two treatments fell outside the boundary of 80~125%, supporting interaction between armodafinil and midazolam. The moderate CYP3A4 inducing ability of armodafinil may result in reduced efficacy of drugs that are substrates for CYP3A4.

- Results suggest that armodafinil modestly induced both hepatic and intestinal CYP3A4 activity. The overall oral bioavailability was approximately 28%, with a larger contribution to the first-pass effect from the intestine (F_G ~0.45) than from the liver (F_H ~0.62).

Reviewer's comment:

- Results of this study suggest that dosage adjustment may be needed for co-medications that are substrates for CYP3A4, such as cyclosporine.

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Study C10953/1025/PK/US

An Open-Label Pharmacokinetics and Safety Study to Evaluate the Effect of Repeated Administration of CEP-10953 on CYP1A2 Activity in Healthy Subjects Using Caffeine as the Probe Substrate

Principal Investigator: Jon L. Ruckle, MD
Study Center: Radiant Research, 401 Kamakee Street, Honolulu, Hawaii, 96814.
Study Period: October 23, 2004 – December 7, 2004

Objectives:
Primary:

- To evaluate the effect of repeated daily administration of CEP-10953 on CYP1A2 activity in healthy subjects, using the plasma concentration versus time profile of caffeine following single oral dose administration alone and after 4 weeks of CEP-10953 administration.

Secondary:

- To measure plasma concentrations of CEP-10953 and its 2 circulating metabolites (modafinil sulfone and R-modafinil acid) and caffeine and its metabolite (paraxanthine) for the determination of their respective pharmacokinetic profiles
- To assess safety by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, and electrocardiography and physical examination findings

Drug Products:
Test formulation: CEP-10953, 50-mg tablets, Lot #: 04053K5a (Cephalon, Inc.)
Probe Substrate: Caffeine 200-mg capsules, Lot #: 4D12 (supplied by the study center)

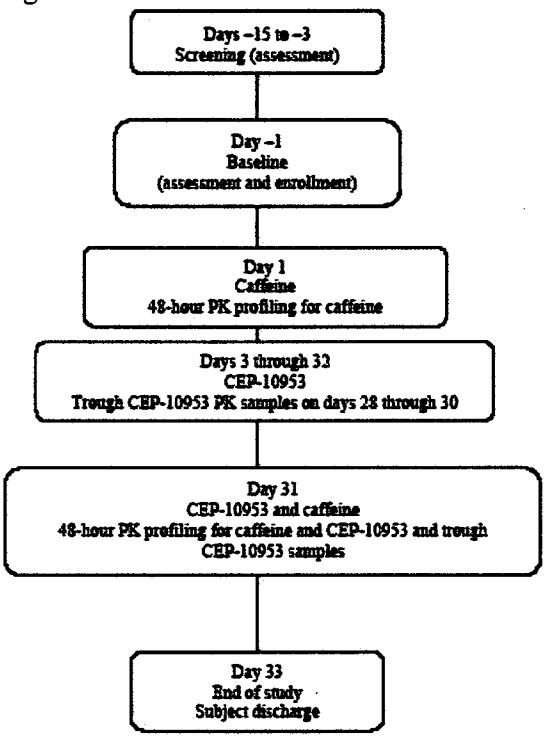
Study Design:
This study was an open-label, single center, nonrandomized pharmacokinetics and safety study in healthy, non-smoking, adult (male and female) subjects to assess the potential PK interaction of CEP-10953 and oral caffeine (a CYP1A2 substrate) under fasting condition. A total of 29 healthy adult male and female subjects (possible equal number) of any ethnic origin aged 18~45 years, inclusive, with a Body Mass Index (BMI) $\leq$30 kg/m^2, who met the inclusion and exclusion criteria were enrolled. In addition, subjects must abstain from caffeine- and xanthine-containing products for at least 48 hours prior to the treatment and throughout the study. Prescription or OTC medications (with the exception of paracetamol) were not allowed. Alcohol, antiseptic mouthwash, or grapefruit juice were prohibited within 48 hours before dosing.

After the initial screening, eligible subjects reported to and stayed at the study center on Days -3~3 and on Days 27~33, while on Days 4~27 subjects reported to the center on an outpatient basis. Oral caffeine and CEP-10953 were administered in the morning, after an overnight fasting, with 8 ounces of non-mineral water.

CEP-10953: Oral doses were administered to all subjects beginning at 100 mg/day on Day 3 titrated in 50-mg increments every 2 days until 250 mg/day was reached on Day 9 and through Day 32.

Caffeine: Single oral caffeine doses (200 mg) were administered to all subjects on Days 1 and 31.

The overall study design is shown as follows:



PK=pharmacokinetic.
Caffeine: 200-mg tablet.
CEP-10953: 100-mg starting dose titrated upwards at 50 mg/day every 2 days to 250 mg/day.

The PK samples were collected over a 48-hour period after the caffeine administration for the analyses of caffeine, paraxanthine, CEP-10953 and its metabolites, as well as trough levels of CEP-10953 from Days 28 to 30. Safety was assessed at screening and throughout the study. No efficacy assessment was performed in this study.

Safety Assessments:

Safety assessments were conducted at screening, baseline, and throughout the study, by monitoring the occurrence of adverse events, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital signs (blood pressure, pulse), concomitant medication usage, electrocardiograms, and physical examination findings. The 12-lead ECG monitoring was carried out at screening and at discharge on Day 33.

Pharmacokinetics Assessments:

On days 1 and 31, a total of 15 blood samples were collected from each subject for the determination of caffeine, paraxanthine, CEP-10953 and its metabolites (modafinil sulfone and R-modafinil acid) at predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 18, 24, 36, and 48 hours post-caffeine-doses. Plasma samples were stored frozen at - 20°C until assayed.

Plasma concentrations of caffeine and paraxanthine were analyzed using a HPLC with [redacted] method performed at [redacted]. Plasma concentrations of CEP-10953, modafinil sulfone, and R-modafinil acid were analyzed by a validated HPLC [redacted] method.

b(4)

Table 1. Assay validation for Study C10953/1025/PK/US

			R-modafinil (CEP-10953)	R-modafinil acid	Modafinil sulfone	Caffeine	Para-xanthine
Method:			HPLC [redacted]	HPLC [redacted]	HPLC- [redacted]	LC/MS/MS	LC/MS/MS
Standard curve	Range:		0.20~50.00 µg/mL	0.20~50.00 µg/mL	0.20~50.00 µg/mL	25.0~25000 ng/mL	25.0~25000 ng/mL
		Precision:	2.69~6.13%	5.57~8.21%	4.27~7.19%	2~7%	1~4%
		Accuracy:	-1.69~2.92%	-1.05~3.24%	-1.65~1.33%	-2~1%	-3~2%
	Linearity:		$r^2 = 0.9989$	$r^2 = 0.9978$	$r^2 = 0.9985$	$r^2 = 0.9993$	$r^2 = 0.9996$
LOQ	LLOQ:		0.20 µg/mL	0.20 µg/mL	0.20 µg/mL	25.0 ng/mL	25.0 ng/mL
QC	Low:		0.60 µg/mL	0.60 µg/mL	0.60 µg/mL	50 ng/mL	50 ng/mL
		Precision:	7.92 %	5.05 %	6.63 %	11 %	10 %
		Accuracy:	-3.46 %	-0.84 %	2.80 %	3 %	5 %
	Med:		20.00 µg/mL	20.00 µg/mL	20.00 µg/mL	750 ng/mL	750 ng/mL
		Precision:	10.75 %	5.78 %	6.15 %	5 %	3 %
		Accuracy:	-1.96 %	-3.12 %	0.62 %	-2 %	0 %
	High:		50.00 µg/mL	50.00 µg/mL	50.00 µg/mL	15000 ng/mL	15000ng/mL
		Precision:	5.37 %	5.89 %	7.05 %	3 %	2 %
		Accuracy:	-4.79 %	-4.46 %	-1.42 %	-1 %	-1 %

Pharmacokinetic Analysis:
The following PK parameters for caffeine and paraxanthine were calculated: C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, λ_Z, CL/F, and V/F, and ratio of caffeine to paraxanthine based on plasma concentration at the 3-hour time point. In addition, C_{max}, t_{max}, $AUC_{0-\tau}$, and trough concentration on Days 28~30 for CEP-10953 and its metabolites were determined.

Statistical Analysis:
The primary PK parameters were summarized by treatment group using descriptive statistics, including the geometric mean, coefficient of variation, and geometric mean ratio. To assess the effect of CEP-10953 on caffeine, the 90% confidence intervals (CI) were calculated based on the difference in geometric means (between caffeine alone and in combination with CEP-10953) of the log-transformed $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for caffeine. The secondary PK parameters were also summarized using a descriptive statistics. The treatment effects on secondary PK parameters (t_{max}, $t_{1/2}$, CL/F, V/F) for caffeine were evaluated using nonparametric methods, such as Wilcoxon Signed Rank Test and Hodges-Lehman estimates.

RESULTS

Demographics of Subjects:
A total of 29 subjects were enrolled in study and were evaluable for safety following each treatment alone, with 25 subjects completing the study. Four subjects (#1020, 1021, 1022, and 1024) withdrew prior to the concomitant treatment and thus were not included in final PK analyses. The subjects consisted of 55% Caucasians, 3% black, 21%Asian, and 14% others, and 62% of subjects were men. The mean age, weight, height and BMI were 28.4 years (18-45 years of age), 74.1 kg (48.6-98.8 kg), 173.6 cm (158.4-195.4 cm), and 24.6 kg/m^2 (17.6-30.4 kg/m^2), respectively. Final pharmacokinetics analysis was performed on 24 subjects after excluding additional 1 subject (#1014) who showed appreciably higher caffeine and paraxanthine levels prior to the concomitant treatment.

Pharmacokinetic Summary:
Data were obtained from 24 subjects who were evaluable for pharmacokinetic analysis in the 2 phases of the study. The mean plasma concentration-time profiles, pharmacokinetic parameters and statistical analysis for caffeine of 200 mg oral doses either administered alone (Day 1) or following pretreatment with CEP-10953 (Day 31) are shown in Figure 1 and Tables 2-3.

Figure 1. Comparative mean (SD) caffeine plasma concentration-time profiles following single oral doses

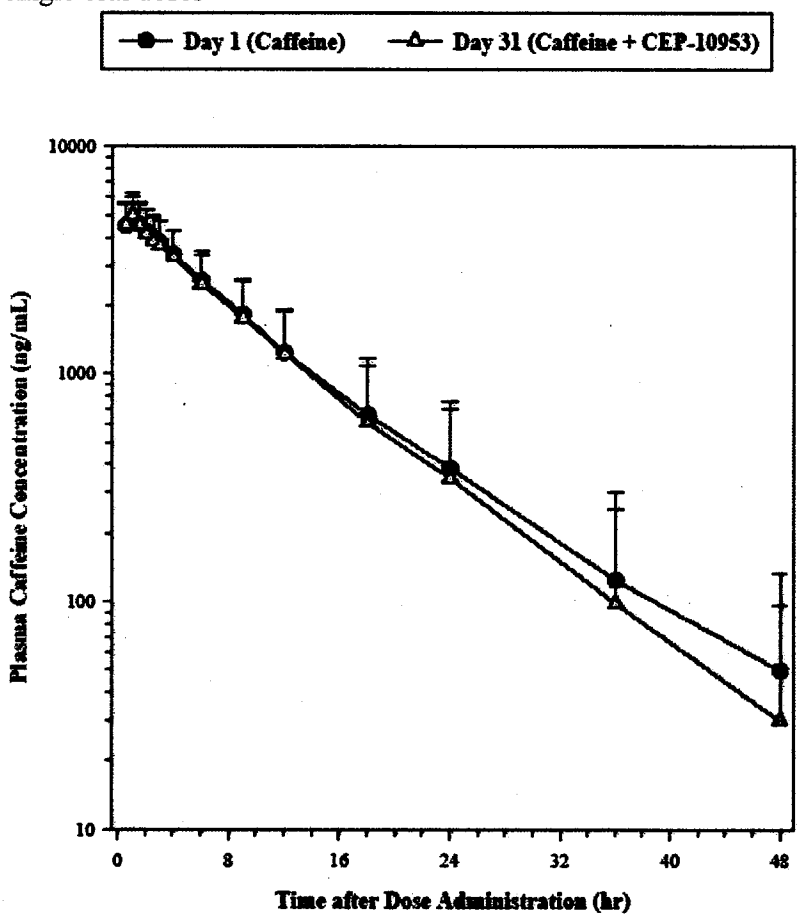


Table 2. Primary pharmacokinetic parameters of caffeine and statistical analysis by treatment group

Pharmacokinetic parameter	n	Caffeine[a] (Geomean) (N=24)	n	Caffeine + CEP-10953[a,b] (Geomean) (N=24)	Geometric mean ratio (caffeine + CEP-10953)	90% CI for mean ratio
$AUC_{0-\infty}$ (ng•hr/mL)	23	47338±20374.1 (43309)	24	44291±19302.7 (40148)	95.32	90.88, 99.97
AUC_{0-t} (ng•hr/mL)	24	45307±19677.6 (41337.0)	24	43523±18769.3 (39479)	95.51	91.10, 100.12
C_{max} (ng/mL)	24	5006±1160.7 (4878)	24	5193±1128.4 (5074)	104.03	100.47, 107.72

Table 3. Secondary pharmacokinetic parameters of caffeine and statistical analysis by treatment group

Pharmacokinetic parameter	n	Caffeine[a] (N=24)	n	Caffeine + CEP-10953[a,b] (N=24)	P-Value	95% CI for difference
t_{max} (hr)	24	0.8 (0.5, 1.5)	24	1.0 (0.5, 1.0)	>0.9999	0.00, 0.25
$t_{½}$ (hr)	23	5.3 (2.8, 11.8)	24	5.1 (2.7, 9.7)	0.0002	−1.05, −0.30
V_z/F (L)	23	39.5 (25.8, 66.1)	24	38.1 (23.2, 62.6)	0.0171	−4.89, −0.46
CL/F (mL/min)	23	77.3 (37.4, 175.3)	24	76.4 (39.5, 232.0)	0.2198	−1.80, 9.20
Caffeine/paraxanthine ratio (3 hours)	24	4.0 (2.0, 9.7)	24	4.2 (1.9, 9.6)	0.6796	−0.20, 0.35
λ_z (hr^{-1})	23	0.1 (0.1, 0.2)	24	0.1 (0.1, 0.3)	0.0014	0.00, 0.02

The mean plasma concentration-time profiles and pharmacokinetic parameters of paraxanthine are shown in Figure 2 and Tables 4-5.

Figure 2. Comparative mean (SD) paraxanthine plasma concentration-time profiles following single oral doses of caffeine

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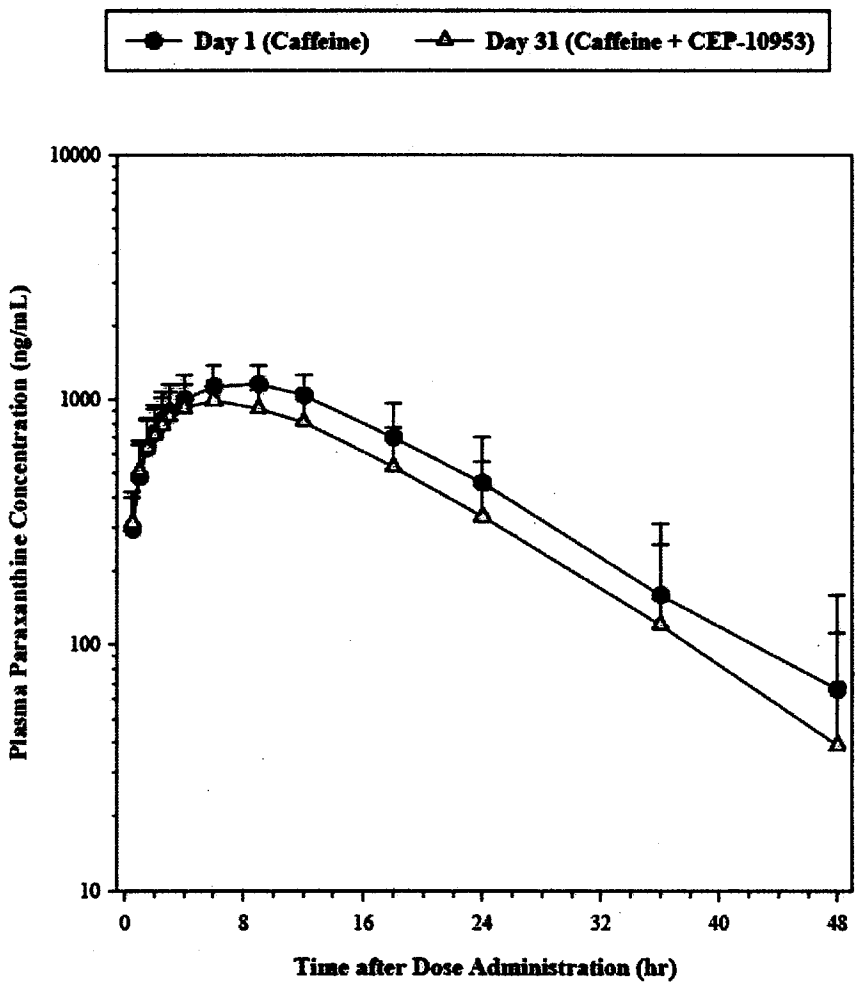

Table 4. Primary pharmacokinetic parameters of paraxanthine and statistical analysis by treatment group

Pharmacokinetic parameter	n	Caffeine[a] (N=24)	n	Caffeine + CEP 10953[a] (N=24)
$AUC_{0-\infty}$ (ng•hr/mL)	24	26472±8029.8	24	21074±6845.3
AUC_{0-t} (ng•hr/mL)	24	25204±6588.4	24	20055±5966.1
C_{max} (ng/mL)	24	1227±216.8	24	1044±191.2
t_{max} (hr)	24	9.0 (4.0, 18.0)	24	6.0 (1.0, 12.0)
$t_{½}$ (hr)	24	6.8 (4.0, 17.2)	24	6.4 (3.7, 17.9)
λ_z (hr^{-1})	24	0.1 (0.0, 0.2)	24	0.1 (0.0, 0.2)

Table 5. Mean (SD) trough plasma concentrations of CEP-10953 on Days 28~30

Study day	n	CEP-10953 concentration* (µg/mL) (N=24)
28	24	2.7±0.75
29	24	2.8±0.76
30	24	2.6±0.67

The mean plasma concentration-time profiles and pharmacokinetic parameters of CEP-10953, R-modafinil acid, and modafinil sulfone following concomitant CEP-10953 and caffeine on Day 31 are shown in Figure 3 and Table 6.

Figure 3. Mean (SD) plasma concentration-time profiles of CEP-10953 and its metabolites following concomitant CEP-10953 and caffeine

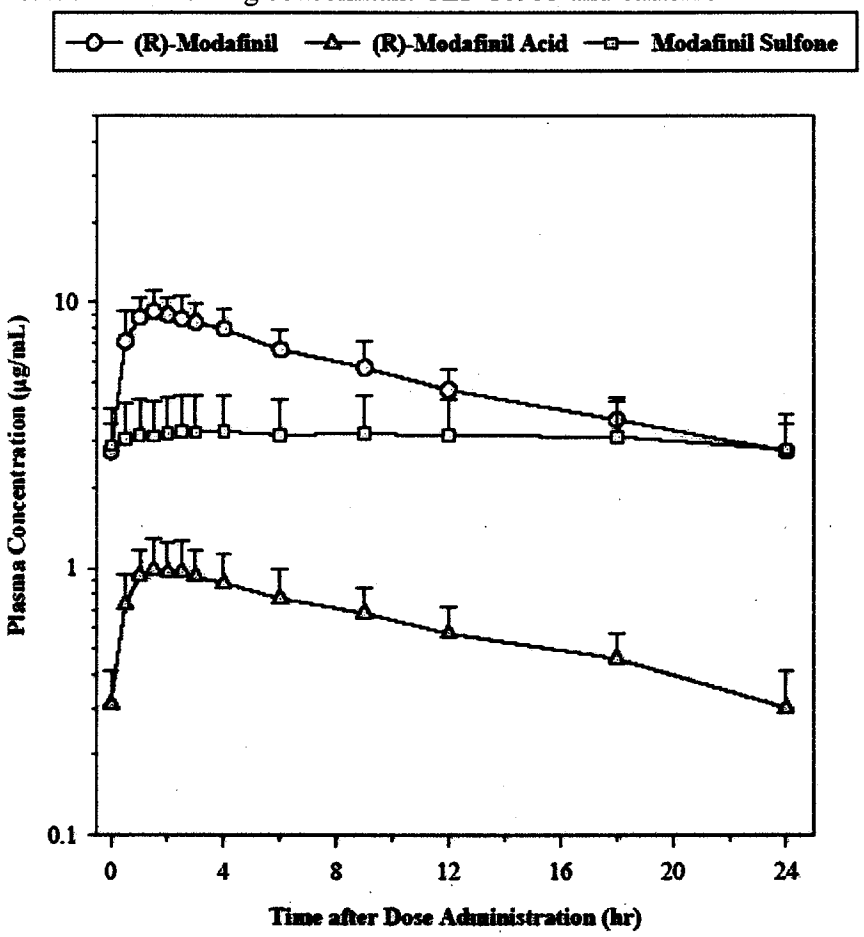

Table 6. Pharmacokinetic parameters of CEP-10953, R-modafinil acid, and modafinil sulfone

Pharmacokinetic parameter	n	CEP10953[a] (N=24)	R-Modafinil acid[a] (N=24)	Modafinil sulfone[a] (N=24)
AUC_{0-t} (µg•hr/mL)	24	124.7±22.68	14.5±3.72	74.8±27.03
$AUC_{0-\tau}$ (µg•hr/mL)	24	124.7±22.68	14.6±3.56	74.8±27.03
C_{max} (µg/mL)	24	9.9±1.57	1.0±0.29	3.5±1.24
t_{max} (hr)	24	1.5 (0.5, 3.0)	1.5 (0.5, 3.0)	3.0 (0.5, 18.0)
λ_z (hr^{-1})	24	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	NC
$t_{½}$ (hr)	24	17.0 (9.5, 26.2)	14.9 (10.4, 23.6)	NC
CL/F	24	35.1 (24.0, 45.5)	NC	NC

Safety Summary:
No deaths or other serious adverse events, or withdrawals due to adverse events were reported during the study. Subjects (# 1020, 1021, 1022, and 1024) were discontinued from the study as the result of missing multiple CEP-10953 doses. Most of the adverse events were mild or moderate in severity. Adverse events occurred more frequently with CEP-10953 treatment alone (93%), compared to caffeine treatment alone (48%) or with concomitant CEP-10953 and caffeine (80%). Headache was the most frequently reported adverse event and appeared to be attributed to treatment with CEP-10953. Among the common adverse events associated with caffeine alone, tremor was increased following coadministration of CEP-10953 and caffeine. No clinically meaningful abnormal laboratory values, vital signs, physical examination findings, or ECG findings were reported. Coadministration of CEP-10953 of 250 mg/day and caffeine of 200 mg was reported to be generally well tolerated.

CONCLUSION:

- Coadminstration with CEP-10953 did not alter the pharmacokinetic profile and exposure measurements ($AUC_{0-\infty}$, $AUC_{0-\infty}$, and C_{max}) of caffeine. The caffeine/paraxanthine ratios at 3 hours remained similar.

- The 90% CI of the geometric mean ratios for exposure ($AUC_{0-\infty}$, $AUC_{0-\infty}$, and C_{max}) between two treatments fell within the BE limits of 80-125%, suggesting the lack of effect of CEP-10953 on caffeine via CYP1A2. No recommendation for dose adjustment is necessary for comedications that are substrates for CYP1A2.

- The sponsor noticed an increased incidence of caffeine-related events (i.e., tremor) when coadministered with CEP-10953 but concluded that "treatment with CEP-10953 had no clinically meaningful effect on either the profile or the severity of events reported following the administration of caffeine alone". The potential impact from caffeine intake >200 mg (multiple or bigger cups of coffee) is not clear.

4.3 Pharmacometric Consult Review

Office of Clinical Pharmacology and Biopharmaceutics

Pharmacometrics Review

NDA :	**21-875**
Compound:	**NUVIGIL™ , Armodafinil (CEP-10953)**
Submission Dates:	**03/31/2005** **06/10/2005** **06/13/2005** **06/24/2005** **08/12/2005** **09/27/2005** **09/29/2005** **10/31/2005**
Sponsor:	**Cephalon, Inc**
Pharmacometrics Reviewers:	**Rajanikanth Madabushi Ph.D.** **Venkatesh Atul Bhattaram Ph.D**

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Summary

Cephalon, Inc is seeking the approval of NUVIGIL™ (armodafinil) Tablets (hereafter referred to as Nuvigil) for treatment of excessive sleepiness associated with shift work sleep disorder (SWSD), obstructive sleep apnea/hypoapnea syndrome (OSAHS), and narcolepsy.

It was theorized by the sponsor that because of longer half-life and lower maximum plasma concentration (Cmax) compared to the approved PROVIGIL™ (modafinil), Nuvigil, may result in better tolerability and improved wake promotion at later times. The present review focuses on time course of the effect of Nuvigil, characterized by baseline corrected mean sleep latency assessed by Maintenance of Wakefulness Test (MWT) or Multiple Sleep Latency Test (MSLT). MWT was the test administered in the narcolepsy and OSAHS studies while MSLT was the test used in SWSD study. The other aspect of review pertains to relationship between effectiveness and the occurrence of headache, which is the most commonly reported adverse event. A brief summary of the pharmacometric findings are outlined below:

1) Narcolepsy (Study 3020): Following the administration of armodafinil (150 or 250 mg/day) to patients with Narcolepsy, increased mean sleep latency from baseline compared to placebo was maintained from 09:00 hrs to 15:00 hrs over weeks 4, 8 and 12 respectively. No relationship could be found between the change in mean sleep latency and proportion of patients experiencing headache for the placebo and Nuvigil groups. However, 250 mg/day Nuvigil group showed a trend towards increased proportion of patients experiencing headache with increase in MWT from baseline.
2) OSAHS (Studies 3021 and 3025): In the two pivotal trials, administration of Nuvigil (150 or 250 mg/day) increased the mean sleep latency, from baseline compared to placebo. This effect maintained from 09:00 hrs to 15:00 hrs over weeks 4, 8 and 12 respectively. For 250 mg/day the proportion of patients experiencing headache increased with increase in sleep latency from baseline. Furthermore, the proportion of patients experiencing headache for all the groups was higher for patients with change in mean sleep latency corresponding to 3rd and 4th quartiles.
3) SWSD (Study 3022): In adults with excessive sleepiness associated with chronic SWSD, Nuvigil (150 mg/day) resulted in increase of sleep latency, from baseline compared to placebo. The effect was maintained from 24:00 hrs to 08:00 hrs (next day) at weeks 4, 8 and 12 respectively. No relationship could be found between the change in mean sleep latency and proportion of patients experiencing headache for the placebo and Nuvigil groups.

Background

Armodafinil (R-modafinil), the active ingredient of Nuvigil, is a levorotatory enantiomer of racemic compound modafinil, a wakefulness promoting agent. In the United States, PROVIGIL™ Tablets (modafinil or RS-modafinil) are currently approved for the treatment of patients with excessive sleepiness associated with excessive

sleepiness associated with shift work sleep disorder (SWSD), obstructive sleep apnea/hypoapnea syndrome (OSAHS), and narcolepsy. The recommended dose of PROVIGIL is 200 mg given once a day. For patients with narcolepsy and OSAHS, PROVIGIL™ should be taken as a single dose in the morning. For patients with SWSD, PROVIGIL™ should be taken approximately 1 hour prior to start of their shift work. The precise mechanism(s) through which armodafinil or modafinil promote wakefulness is unknown. However, both armodafinil and modafinil have shown essentially similar pharmacological properties in nonclinical animal and *in vitro* studies.

Data

Four pivotal trials - 1 study in narcolepsy (study C10953/3020/NA/MN or **Study 3020**), 2 studies in OSAHS (studies C10953/3021/AP/MN or **Study 3021** and C10953/3025/AP/MN or **Study 3025**) and 1 study in SWSD (study C10953/3022/CM/MN or **Study 3022**), were conducted by the sponsor to demonstrate effectiveness and safety of Nuvigil. The trials were double-blind, placebo-controlled, parallel-group studies. The duration of double-blind treatment was 12 weeks. The details of the studies contributing to the efficacy data are listed in the table below (per sponsors report: 2.7.3 Summary of Clinical Efficacy page#1):

Table 1: Phase 3 Double-Blind, Placebo-Controlled Studies of Armodafinil

Sleep disorder	Number of efficacy-evaluable patients (full analysis set)*			
	Armodafinil			
Study number	250 mg/day	150 mg/day	Total	Placebo
OSAHS				
Study 3021	121	120	241	124
Study 3025	—	116	116	120
SWSD				
Study 3022	—	112	112	104
Narcolepsy				
Study 3020	60	58	118	58

*The full analysis set includes patients who received at least 1 dose of study drug, had a baseline and at least 1 postbaseline Maintenance of Wakefulness Test assessment (narcolepsy and OSAHS) or Multiple Sleep Latency Test assessment (SWSD), and at least 1 postbaseline Clinical Global Impression of Change assessment.
OSAHS=obstructive sleep apnea/hypopnea syndrome; SWSD=sleep work shift disorder.

For all the four studies the effectiveness analyses included two primary variables as follows:

1) The change from baseline to endpoint (last post baseline observation) in average sleep latency. This was obtained from the Maintenance of Wakefulness Test **(MWT – average of 4 tests at 09:00,** 11:00, 13:00 and 15:00) for the narcolepsy and OSAHS studies. The MWT test was administered for 20 min in narcolepsy trial and for 30 min in the OSAHS studies. For SWSD study, the average change in sleep latency from baseline was obtained by administering **MSLT test (MSLT –** average of 4 naps at 0200, 04:00, 06:00, and 08:00).

2) The proportion of patients with at least minimal improvement of Clinical Global Impression of Change (CGI-C) rating at endpoint.

For both primary effectiveness variables, the change from baseline to endpoint in sleep latency as assessed by MWT or MSLT for the respective indications and the proportion of patients with at least minimal improvement in CGI-C rating at endpoint, statistically significant differences from placebo in favor of Nuvigil were observed. For statistical details, please refer to **statistician's review.**

Based upon the above summarized results, the sponsor is seeking approval of Nuvigil under 21 CFR, parts 314 and 601, which is application to market a new drug, biologic, or an antibiotic drug for human use.

Sponsor's Analysis

Pharmacokinetic/pharmacodynamic (PK/PD) modeling and clinical trial simulation were performed by the sponsor to guide the dose selection and study design for the pivotal trials. Population pharmacokinetic (PPK) modeling of pooled data from Nuvigil and PROVIGIL™ Phase 1 studies was performed to characterize the pharmacokinetic profiles of R- and S-modafinil. The R-and S-modafinil pharmacokinetics was adequately described by a linear 1-compartment model with first-order absorption. The clearance of S-modafinil was found to be 3 times faster than R-modafinil. No effect of age or gender was observed on any of the pharmacokinetic parameters. However, the effect of age was not fully characterized due to the limited range of the covariates. Only bodyweight was found to have a linear relationship with volume of distribution (V/F). The analysis did not reveal any significant covariates which could potentially lead to dosing adjustment. The PPK model thus developed was used to simulate concentration-time profiles using different treatment regimens of Provigil and Nuvigil for use in PK/PD modeling and simulation as shown in the figure **below (per sponsor's report # CP-05-001 page #22).**

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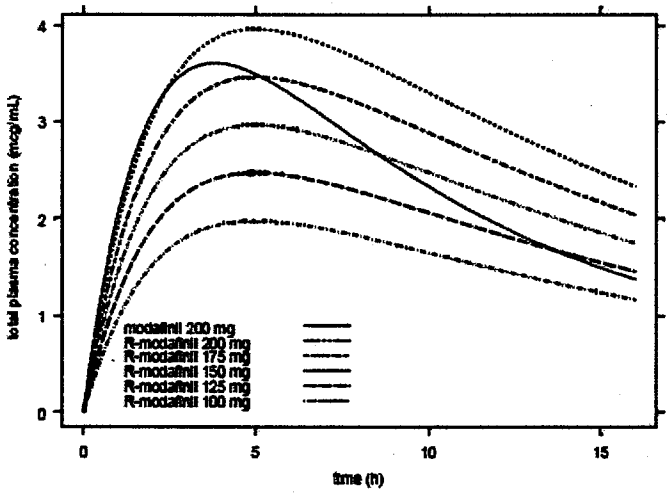
Figure1: Predicted Mean Total Drug Concentration (Single-Dose)



A multicomponent PK/PD model in sleep-deprived healthy subjects was developed. The pharmacodynamic measure of MWT was obtained following administration of Nuvigil **(100 – 300 mg), Provigil (200 mg) and placebo**. The corresponding drug concentrations were simulated using the PPK model. A linear model described the hazard of falling asleep as a function of clock time of the MWT in the placebo-treated subjects, while inhibitory Emax model described the drug effect on the hazard. This multicomponent PK/PD model showed a clear decline in the hazard with the increase in drug concentrations and also established the equipotency of both the enantiomers.

The PK/PD model developed was applied to patients in each of the three indications obtained from Provigil Phase 3 studies. A nonlinear model described the hazard for falling asleep in placebo-treated patients while the inhibitory Emax model described the drug effect. The estimated EC50 in patients for the target populations was significantly higher compared to healthy subjects indicating that patient population required higher drug levels compared to healthy subjects. Further simulations again indicated a dose of 150 mg Nuvigil was likely to achieve a comparable MWT to that of 200 mg dose of Provigil at early times and a potentially superior MWT at later times. A typical simulation results of placebo, armodafinil and modafinil are summarized in the figure **below (per sponsor's report # CP-05-001, page#58).**

Figure 2: A typical plot comparing simulated medians and 90% confidence intervals of population mean MWT for Placebo/Nuvigil with PROVIGIL™ (200 mg).

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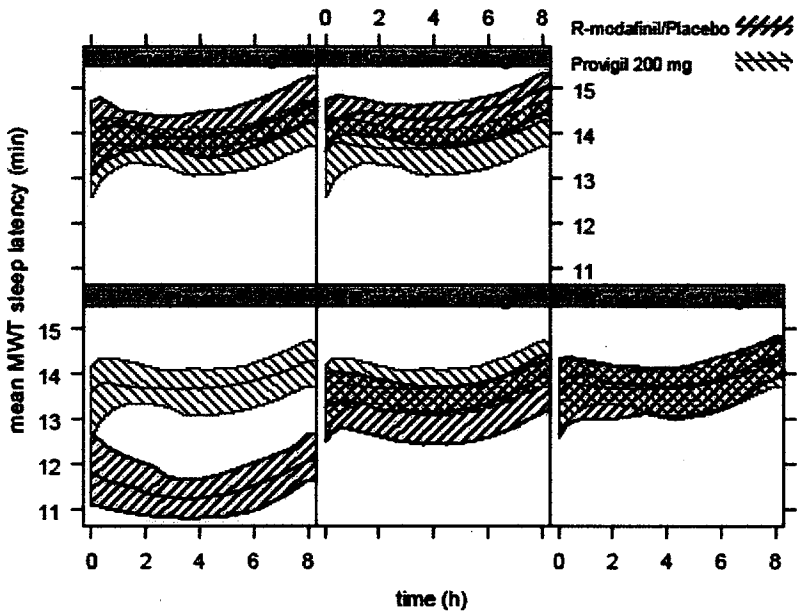

Based on the above analysis the sponsors chose doses of 150 and 250 mg/day of Nuvigil for the pivotal trials.

Sponsor's efficacy analyses did not involve any modeling of the data. However, all the studies used a 2-tailed test at the 0.05 level of significance. For a study to be positive, the results of both primary measures (MWT/MSLT and CGI-C) were required to be statistically significant at a 0.05 significance level. For the studies with multiple armodafinil dosage groups (study 3021 [OSAHS] and study 3020 [narcolepsy]), the primary comparison in each was between the combined armodafinil groups and the placebo group, and the individual dosage comparisons were performed only if this primary comparison was statistically significant at a 0.05 level.

Reviewer's comments and analysis

PROVIGIL™ (racemic modafinil) currently approved for treatment of patients with excessive sleepiness associated with OSAHS, SWSD or narcolepsy has been reported to have diminished effectiveness for some patients later in the day. This is an important factor to consider for patients who experience excessive sleepiness later in the work day or during commute home from work. Therefore it was desirable to have a product that could provide wake promotion throughout the work hours of the day. The sponsors developed Nuvigil (R-modafinil) with this purpose as it was found to have a **half-life of 15 hours. The sponsor's effectiv**eness analysis involved comparisons of the change in sleep latency from baseline averaged across clusters of time-points following dosing (early and late). Such an analysis will not be able to accurately describe wake promotion over the entire day. In contrast, our analysis aims at graphically describing the

time course of effect over different weeks compared with placebo. Further the review attempts to explore the relationship between headache which is the most common adverse event and the wake promotion effect of Nuvigil.
The review attempts at answering the following questions:

1. What is the time course of effect across the indications sought for approval?
2. Is there a relationship between the effect and headache?

What is the time course of effect across the indications?

The primary objective measure in the trials was change from baseline to endpoint (last post-baseline observation) in average sleep latency , which was obtained from MWT (average of 4 tests at 0900, 1100, 1300 and 1500 hrs) for narcolepsy and OSAHS and from MSLT (average of 4 naps at 0200, 0400, 0600 and 0800 hrs) for the SWSD study. One of the secondary efficacy measures was sleep latency assessed at later time points of MWT (average of naps at 1500, 1700 and 1900 hrs). However, this average change in the sleep latency does not provide insight into the time course of drug effect. Moreover, averages across different time points, discard the underlying time component and thus decrease the value of the information provided by the data. Effect-time plots reveal entire time course of effect and should be used to show the effect over given time period.
Narcolepsy:

The time course of change in time matched mean sleep latency from baseline over the 6 naps at weeks 4, 8 and 12 for placebo and Nuvigil (150 and 250 mg/day) groups is shown in the figure (Figure 3) below. Either doses of Nuvigil consistently increase the sleep latency to a similar extent from baseline and maintained **till 15:00 – 17:00 hrs at** weeks 4, 8 and 12 respectively. However, the intensity of the effect begins to decline by 15:00 hrs and is more pronounced with 250 mg/day dosing regimen. The loss of drug effect by 19:00 hrs is more evident by 12th week compared to weeks 4 and 8.

Figure 3: Time course of effect in patients with Narcolepsy (Study 3020)

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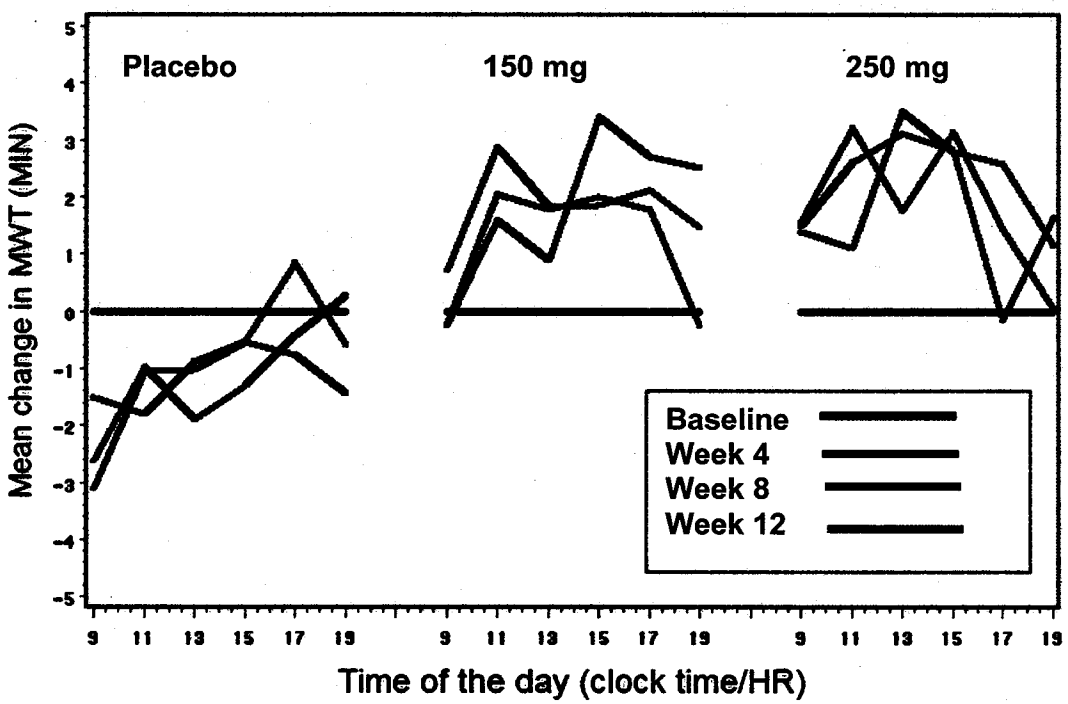

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OSAHS:

The time course of baseline corrected change in time-matched mean sleep latency over 6 naps at weeks 4, 8 and 12 for placebo and Nuvigil (150 and 250 mg/day) groups is shown in the figures (Figures 4 & 5) below. It can be seen from the effect-time plots, Nuvigil increases the sleep latency compared **to placebo and maintains till 17:00 – 19:00** hrs. However, the effect of Nuvigil starts to decline by 15:00 hrs with 150 mg/day and by 13:00 hrs for 250 mg/day regimen. This decline is comparatively more pronounced at weeks 8 and 12.

Figure 4: Time course of effect in patients with OSAHS (Study 3021).

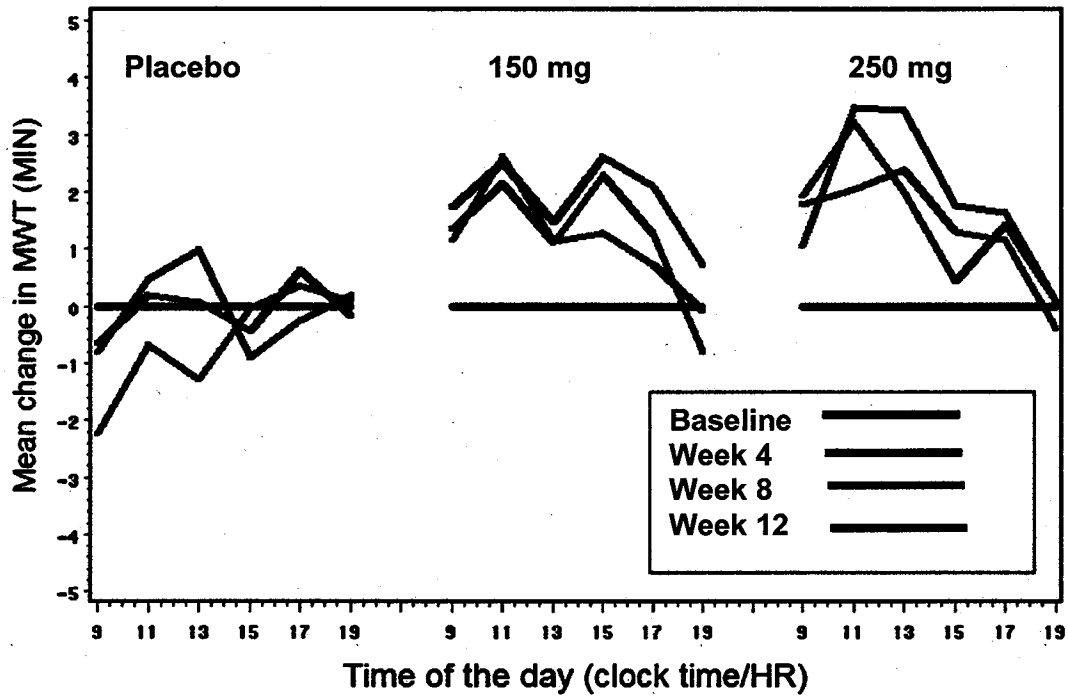

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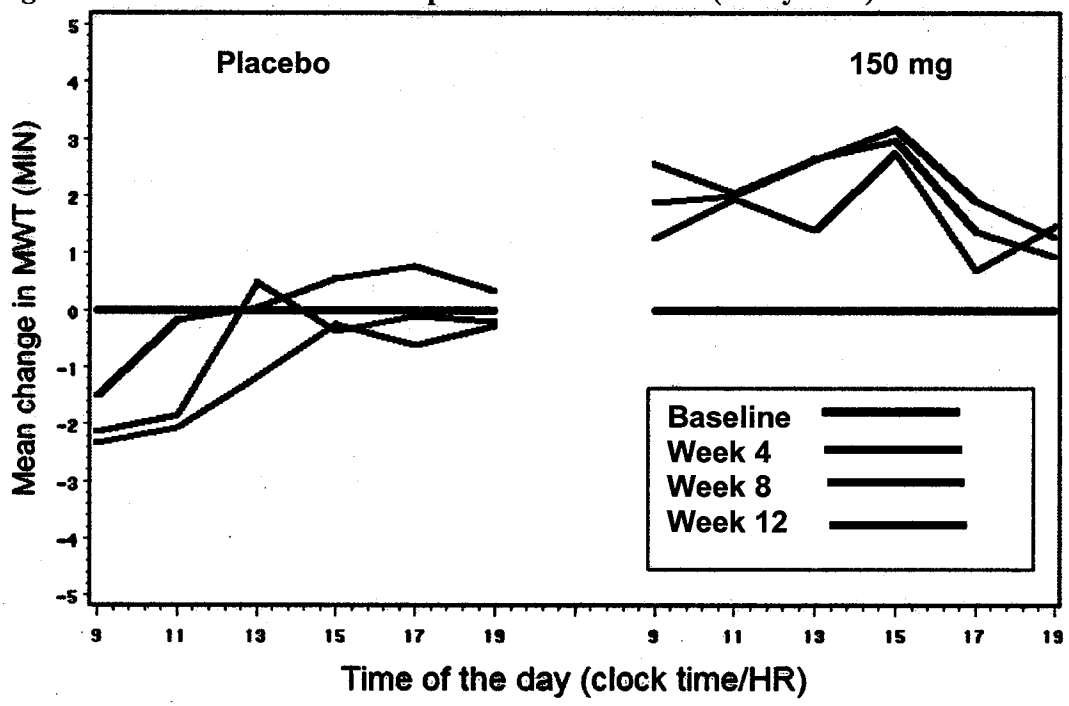
Figure 5: Time course of effect in patients with OSAHS (Study 3025).



SWSD:

The time course of change in sleep latency as assessed from MSLT from baseline over 5 naps at weeks 4, 8 and 12 for placebo and Nuvigil (150 mg/day) groups is shown in the figure (Figure 6) below. Nuvigil increases the sleep latency by 24:00 hrs and maintains wakefulness consistently above the baseline levels till 08:00 hrs. The maximum increase from baseline was seen at 02:00 hrs which increased with every visit.

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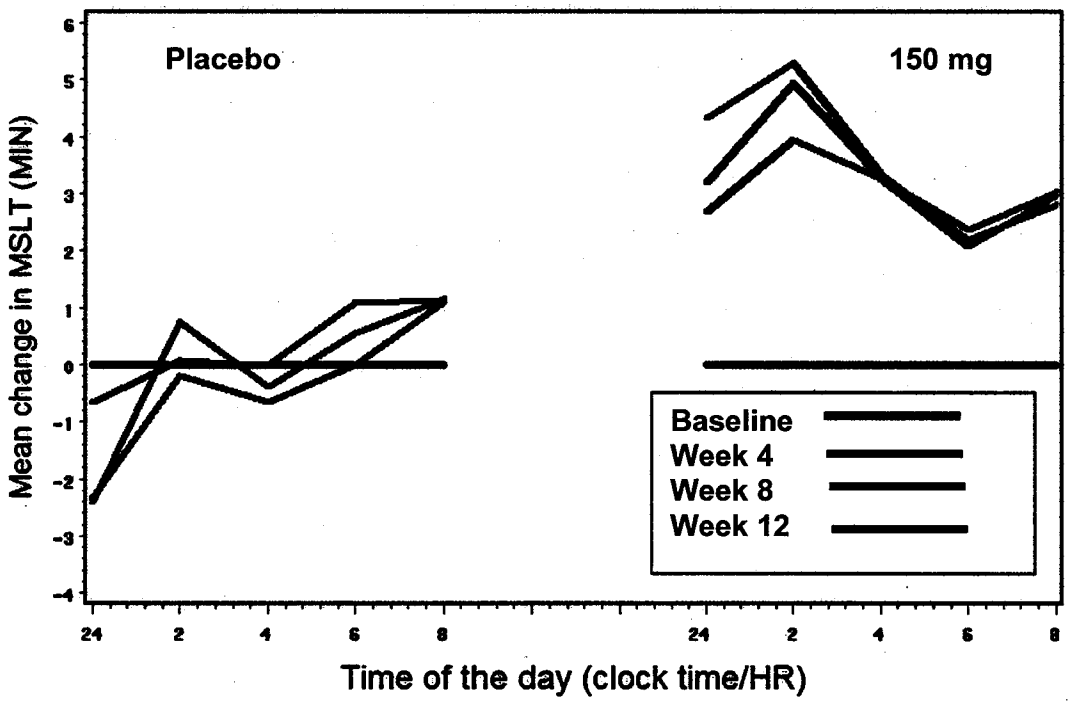
Figure 6: Time course of effect in patients with SWSD (Study 3022)



Is there a relationship between effect and headache?

Headache was the most common adverse event reported for 22%, 17% and 12% of the Nuvigil treated patients in narcolepsy, OSAHS and SWSD patient populations respectively. Among the placebo-treated patients the incidence of headache ranged from 8 -11% across the target populations. Further, patients treated with 150 mg/day Nuvigil had lesser percent of patients with headache compared with those receiving 250 mg/day (16% vs 28% for Narcolepsy, 15% vs 21% for OSAHS). Similarly the change in mean latency from baseline increases with increase in the dose from 150 mg/day to 250 mg/day (1.3 min vs 2.6 min for Narcolepsy, 1.7 min vs 2.2 min for OSAHS). Plots of change in MWT and the corresponding proportion of patients experiencing headache were generated to explore the relationship between effect and headache.

Narcolepsy:

Effect versus headache rate for various treatment arms are shown in the figure (Figure 7) below. No systematic relationship was seen across different treatment and placebo arms. However, in the treatment arms, an increase in MWT from baseline corresponding to the 4th quartile was associated with high proportion of patients with headache.

OSAHS:

Trends toward increase in the proportion of patients experiencing headache with the increase in MWT from baseline could be observed in the Nuvigil arms. Moreover, the change in MWT corresponding to 3rd and 4th quartiles were associated with the highest proportion of the patients reporting headaches for the arms in the trial.

SWSD:

No relationship was found between the change in MSLT and proportion of patients experiencing headache for the placebo and Nuvigil groups. However, in the treatment arm, increase in MWT was associated with increased proportion of patients with headache.

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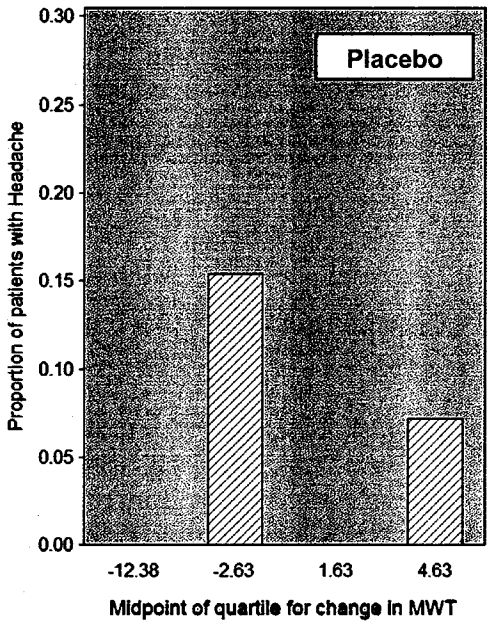
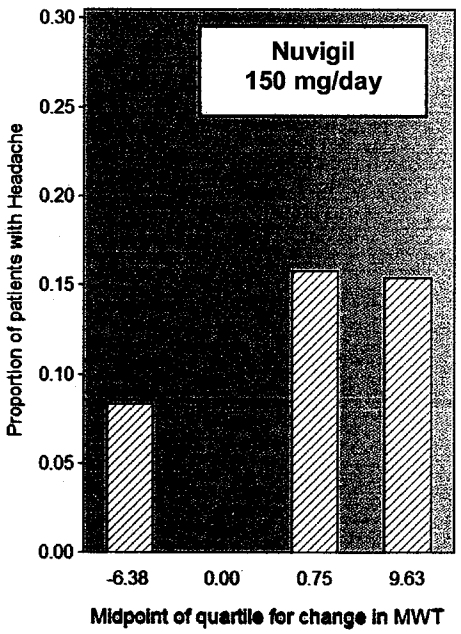
Figure 7: Relationship between proportion of patients with headache and MWT in Narcolepsy study.





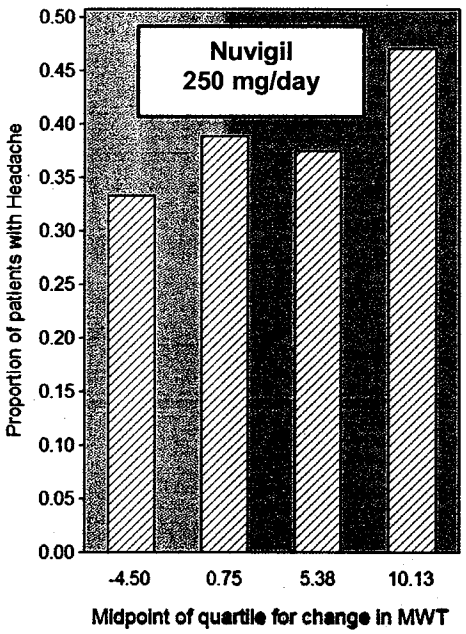
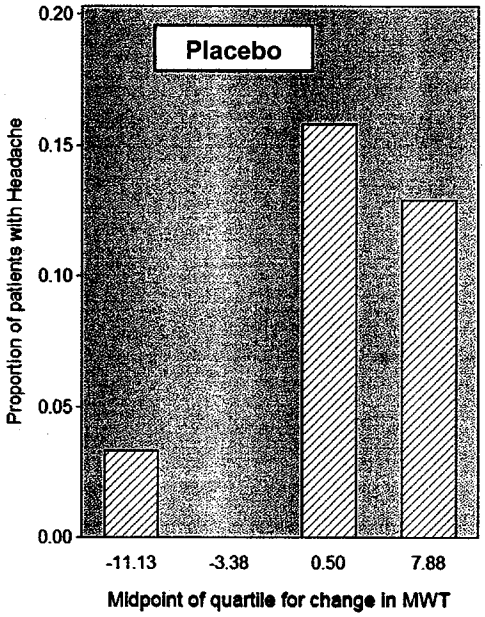


Figure 8: Relationship between proportion of patients with headache and MWT in OSAHS study.



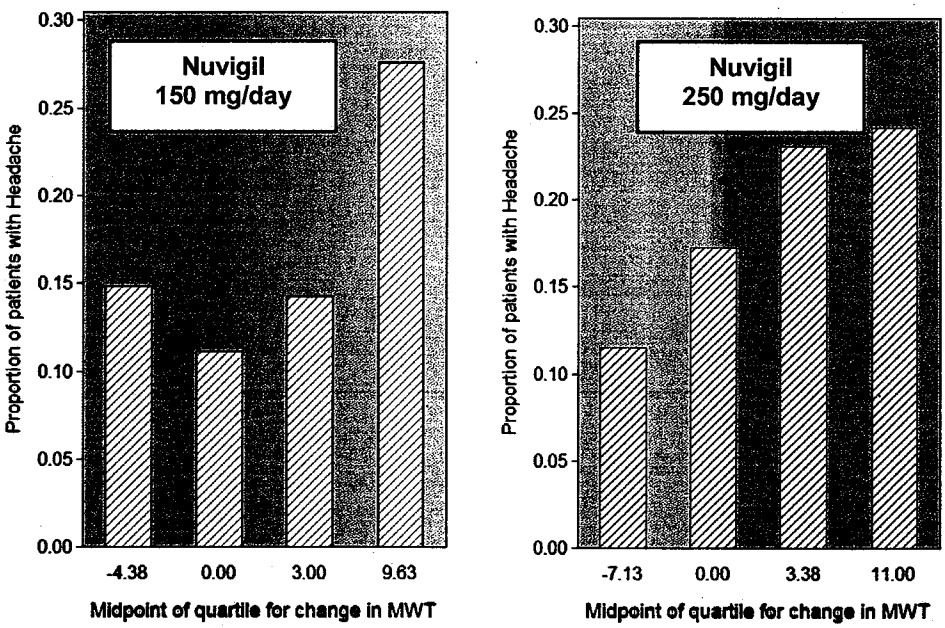
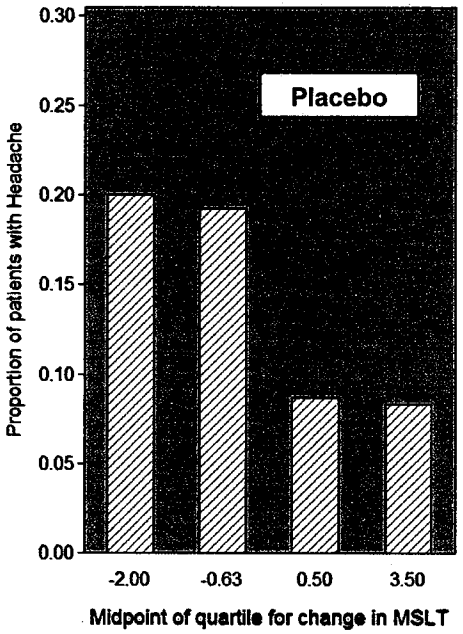
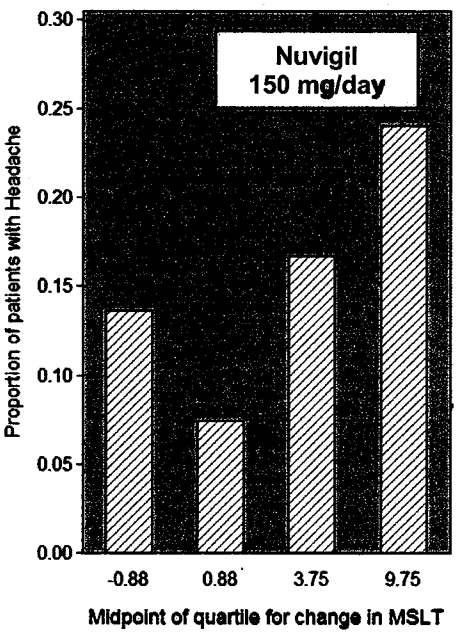


Figure 7: Relationship between proportion of patients with headache and MWT in SWSD study.





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Conclusion

Thus on the basis of the present analysis, it can be concluded that:

1. Treatment with Nuvigil increases the mean change in latency of sleep (MWT/MSLT) from baseline compared to placebo for all the three indications.
2. The effect of Nuvigil was maintained over a period of 8 hrs compared to placebo. Hence once a day dosing regimen for Nuvigil is justified.
3. No consistent increase in effect was observed between various doses tested in the trials.
4. In the treatment arms, the 4th quartiles corresponding to the increase in MWT from baseline were associated with a higher proportion of patients experiencing headaches.

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-875**	**Brand Name**	**Nuvigil**
OCPB Division (I, II, III)	**DPE-I**	**Generic Name**	**Armodafinil**
Medical Division	**HFD-120**	**Drug Class**	**Wakeful promoting agent**
OCPB Reviewer	**Ta-Chen Wu, PhD**	**Indication(s)**	**Treatment for Adults with Excessive Sleepiness**
OCPB Team Leader	**Ramana Uppoor, PhD**	**Dosage Form**	**Oral Tablets (Uncoated) 50, 100, 150, and 250 mg**
		Dosing Regimen	**Recommended dose is 150 or 250 mg QD morning dose for patients with OSAHS or narcolepsy, and 150 mg/day for SWSD patients 1 hour prior to start of work shift. Dose adjustment should be made based on potential DDI, severe hepatic function, and age (lower dose for elderly).**
Date of Submission	**March 31, 2005**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**11/07/05**	**Sponsor**	**Cephalon**
PDUFA Due Date	**1/31/06**	**Priority Classification**	**S**

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Division Due Date	12/09/05		

Clin. Pharm. and Biopharm. Information

Summary: **The sponsor is seeking approval of armodafinil (Nuvigil™), R-enantiomer of** modafinil (Provigil®), for the treatment of adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD). One BE study was conducted for 5 x 50 mg coated tablets (clinical formulation) vs. 1 x 250 mg uncoated tablets (TBM formulation). Composition of the TBM armodafinil tablets is shown in Appendix. Two Phase 1 studies were conducted to evaluate single- and multiple-dose PK, tolerability, and food effect. Potential drug-drug interactions were evaluated in additional three Phase 1 studies. Population PK analysis (based on armodafinil and Provigil Phase 1 studies) and PK/PD modeling and simulation (based on armodafinil Study 103 and Provigil Phase 3 studies) were performed to predict the efficacy of armodafinil and determine the dosing regimen for Phase 3 studies. Through these Phase 1 and 2 studies, the sponsor also provided comparison of armodafinil exposure compared to Provigil. Six Phase 3 studies (4 controlled, 2 uncontrolled and ongoing) provided the basis for efficacy and safety of the armodafinil treatment in patients with OSAHS, SWSD, and narcolepsy. In vitro dissolution profiles of TBM uncoated formulation of all four strengths were constructed in 5 media of different pH values, including deionized water. Comparative in vitro dissolution was also evaluated between 50 mg (clinical formulation) and 250 mg (TBM formulation) strengths.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X		[redacted]	Annotated Word file provided
Reference Bioanalytical and Analytical Methods	X			Validation report provided
I. Clinical Pharmacology	-	-	-	
Mass balance:	-	-	-	
Isozyme characterization:	-	-	-	
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	Study C10953a/**101**/PK/UK: Fasting: SAD 50-400 mg; fed: 100 mg (capsules).

multiple dose:	X	1	1	Study C10953a/**102**/PK/UK: Fasting: MAD 50-400 QD for 14 days (capsules)
Patients-				
single dose:	-	-	-	
multiple dose:	-	-	-	
Dose proportionality -				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:	X	3	3	1. Study C10953/**1021**/PK/US: effect of SD 400 mg on CYP2C19 (omeprazole as probe) 2. Study C10953/**1022**/PK/US: effect of MAD 100-250 mg QD effect on CYP3A4/5 (midazolam as probe) 3. Study C10953/**1025**/PK/US: effect of MAD 100-250 mg QD on CYP1A2 (caffeine as probe)
In-vitro:	-	-	-	
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	

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Phase 3:	X	**4 (controlled) + 2 (uncontrolled, safety data)**	**4**	Controlled trials (12 weeks, completed): 1. Study C10953/**3020**/NA/MN: 150 and/or 250 mg QD AM on Narcolepsy 2. Study C10953/**3021**/AP/MN: 150 and/or 250 mg QD AM on OSAHS 3. Study C10953/**3022**/CM/MN: 150 mg QD AM on chronic SWSD 4. Study C10953/**3025**/AP/MN: 150 mg QD AM on OSAHS Trough PK sampling; no dose- or exposure-response explored Uncontrolled trials (~12 months, ongoing, safety evaluation only): 1. Study C10953/**3023**/ES/MN: Safety data from 150~250 mg QD on Narcolepsy, OSAHS, or chronic SWSD 2. Study C10953/**3025**/AP/MN: Safety data from 150~250 mg QD on Narcolepsy, OSAHS, or chronic SWSD
PK/PD:				

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Phase 1 and/or 2, proof of concept:	X	1 + 10	11	PPK and PK/PD for determining dose regimen for Phase 3 trials. PK/PD (data on CD-R): 1. Study C10953a/**103**/PK/MN: SAD 100-300 mg (capsules), placebo-controlled, Provigil 200 mg as active control. 2. 4 Provigil Phase 3 studies PPK: Armodafinil Phase 1 studies (101, 102, and 103) and Provigil Phase 1 studies (103, 106, and 2101)
Phase 3 clinical trial:			-	
Population Analyses -				
Data rich:	-	-	-	
Data sparse:	-	-		
II. Biopharmaceutics			-	
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	Study C10953/1023/BE/US: 5x50 mg (clin formulation) vs. 1x250 mg (TBM); BE found
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	X	(1)	(1)	1. As part of the Study C10953a/**101**/PK/UK (2x50 mg capsules) 2. Standard fatty meal per FDA's specification

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Dissolution:	X		X	1. Dissolution profiles: 4 TBM strengths in 5 media; n=12 each strength 2. Comparative profiles: 5x50 mg BE/clinical batch vs. 1x250 mg TBM batch 3. F1 and F2 calculation 4. Comparative dissolution for 50 mg capsule vs. clinical formulation not conducted in multiple media 5. No individual data provided for each dissolution profile (only mean and range provided for comparative dissolution profiles)
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-	-	
BCS class	-	-	-	
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	36			
Total Number of Studies		13 + dissolution study	11 + dissolution study	
Filability and QBR comments				

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	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. Please forward to Sponsor: 1. Comparative dissolution for 50 mg capsule vs. 50 mg clinical formulation needs to be provided to bridge these two formulations. This is important since capsule formulation was used in Studies 101, 102 and 103, and data from these 3 studies were used for determining the dosing regimen for the pivotal Phase 3 trials. Individual data needs to be submitted. 2. Please provide individual data for dissolution profiles of each TBM strength in all the media tested. 3. Please specify the content of high-fat food for food-effect study 4. Please provide NONMEM control streams, output files, and datasets to support the population PK analysis. If SPlus was used, please submit SPlus scripts and datasets. 5. Please provide electronic datasets as SAS transport files (.XPT) for two Phase 1 PK studies (101, 102), and three Phase 1 DDI studies (1021, 1022, 1025).
QBR questions (key issues to be considered)	• **How does the exposure of armodafinil when administered as armodafinil compare to Provigil? [Can Provigil label for dose-adjustments and DDIs be directly used for armodafinil?]** • **Is clinical formulation bioequivalent to the TBM formulation?** • **Can a biowaiver be granted for the lower strengths of the TBM formulation?** • **Is it appropriate to conduct food effect study on lower dosage strength and is there a food effect on the bioavailability of armodafinil?** • **Is the dose regimen properly selected based on PPK and PK/PD?** • **What intrinsic and extrinsic factors impact the exposure?** • **Has the in vitro dissolution been adequately characterized?** • **Are there major drug-drug interactions and is dosage adjustment required?** • **Are the bioanalytical methods adequate and appropriately validated?**	
Other comments or information not included above	Project Manager: Please request DSI inspection of the clinical and the analytical sites for Study [redacted] Clinical sites: [redacted] Analytical site: [redacted]	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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CC: NDA 21-875, HFD-850(Electronic Entry or Lee), HFD-120(Calder), HFD-860 (R. Uppoor, M. Mehta)

Appendix. Composition of TBM Armodafinil Tablets

Component	Reference to standard	Function	Amount (mg)/ 50 mg tablet	Amount (mg)/ 100 mg tablet	Amount (mg)/ 150 mg tablet	Amount (mg)/ 250 mg tablet
Armodafinil drug substance	In-house standard	Drug substance	50.0	100.0	150.0	250.0
Lactose	NF					
Microcrystalline Cellulose	NF					
Pregelatinized Starch	NF					
Povidone	USP					
Croscarmellose Sodium	NF					
	USP					
Magnesium Stearate	NF					
Total tablet weight						

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/s/

Ta-Chen Wu
3/31/2006 03:00:01 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
3/31/2006 07:41:34 PM
BIOPHARMACEUTICS

Rajnikanth Madabushi
4/2/2006 03:52:16 PM
PHARMACOLOGIST

Atul Bhattaram
4/3/2006 11:54:53 AM
BIOPHARMACEUTICS

Mehul Mehta
4/3/2006 12:07:30 PM
BIOPHARMACEUTICS

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-875	Brand Name	Nuvigil
OCPB Division (I, II, III)	DPE-I	Generic Name	Armodafinil
Medical Division	HFD-120	Drug Class	Wakeful promoting agent
OCPB Reviewer	Ta-Chen Wu, PhD	Indication(s)	Treatment for Adults with Excessive Sleepiness
OCPB Team Leader	Ramana Uppoor, PhD	Dosage Form	Oral Tablets (Uncoated) 50, 100, 150, and 250 mg
		Dosing Regimen	Recommended dose is 150 or 250 mg QD morning dose for patients with OSAHS or narcolepsy, and 150 mg/day for SWSD patients 1 hour prior to start of work shift. Dose adjustment should be made based on potential D[redacted] severe hepatic function ([redacted] and age (lower dose for elderly).
Date of Submission	March 31, 2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	11/07/05	Sponsor	Cephalon
PDUFA Due Date	1/31/06	Priority Classification	S
Division Due Date	12/09/05		

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Healthy Volunteers-				
single dose:	X	1		Study C10953a/**101**/PK/UK: Fasting: SAD 50-400 mg; fed: 100 mg (capsules)
multiple dose:	X	1		Study C10953a/**102**/PK/UK: Fasting: MAD 50-400 QD for 14 days (capsules)
Patients-				
single dose:	-	-	-	
multiple dose:	-	-	-	
Dose proportionality -				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:	X	3		1. Study C10953/**1021**/PK/US: effect of SD 400 mg on CYP2C19 (omeprazole as probe) 2. Study C10953/**1022**/PK/US: effect of MAD 100-250 mg QD effect on CYP3A4/5 (midazolam as probe) 3. Study C10953/**1025**/PK/US: effect of MAD 100-250 mg QD on CYP1A2 (caffeine as probe)
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Subpopulation studies -				
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gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	

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PK/PD:				
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replicate design; single / multi dose:	-	-	-	
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(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-	-	
BCS class	-	-	-	
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	**36**			
Total Number of Studies		**13 + dissolution study**		

Filability and QBR comments

	"X" if yes	Comments
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Other comments or information not included above	Project Manager: Please request DSI inspection of the clinical and the analytical sites for Study [redacted] Clinical sites: [redacted] Analytical site: [redacted]
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

b(4)

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[redacted]						
Microcrystalline Cellulose	NF					
Pregelatinized Starch	NF					
Povidone K29/32	USP					
Croscarmellose Sodium	NF					
[redacted]	USP					
Magnesium Stearate	NF					
Total tablet weight		[redacted]				[redacted]
[redacted]						

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/s/

Ta-Chen Wu
5/24/05 01:47:02 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
5/24/05 02:08:47 PM
BIOPHARMACEUTICS

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