Gender Study

10. A Nine-Week Placebo-Controlled, Double-Blind, Randomized, Parallel-Group Study of the Safety and Efficacy of Two Fixed Doses (200 mg, 400 mg) of Oral Modafinil in Patients with Narcolepsy Followed By a 40 Week, Open-Label, Flexible-Dose continuation Study (C1538a/301/NA/US).

Objectives:

To evaluate the steady-state plasma trough levels of Modafinil in male and female patients with narcolepsy. The study was one of the pivotal clinical trials.

Study Design

The double-blind segment of this multicenter study was a randomized, placebo-controlled study of modafinil (200 and 400 mg) and placebo in patients with narcolepsy. Patients received modafinil or placebo once daily for nine consecutive weeks. The treatment groups were: placebo (Group I), 200 mg modafinil (Group II), and 400 mg modafinil (Group III). All patients received placebo between washout period (Weeks 9 to 11). Blood samples were collected from each patient at baseline visit and predose at the clinic visit during Weeks 3, 6, and 9. Blood samples were also drawn at the end of the two-week post double-blind segment (washout period). These latter samples served as the washout baseline after the double-blind segment and predose baseline before the open-label segment. Plasma was separated from blood cells by centrifugation and kept frozen at -20°C.

Results (Attachment 10) and Conclusions:

In patients with narcolepsy, there was no gender difference on steady state plasma trough concentrations of modafinil. In each gender, modafinil plasma concentration have reached steady state by week 3. At 200 mg daily dose, the $C_{trough, steady\ state}$ of Modafinil remained unchanged throughout study period, but at 400 mg daily dose, $C_{trough, steady\ state}$ of modafinil in week 9 was significantly lower than those of week 3 in both gender. This suggested an induction of self-metabolism of chronic administration of modafinil at 400 mg dose.

Comments:

The similar values of $C_{trough, steady\ state}$ in patients with narcolepsy to that in healthy volunteers (CEP-2101) indicate the similar elimination rate between these two populations.

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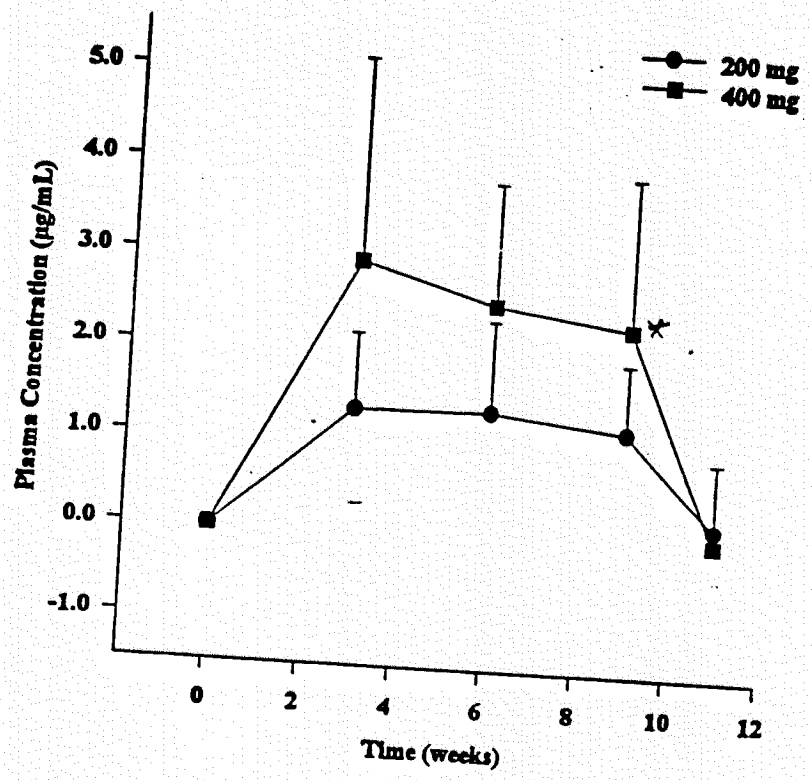
~~Figure 1~~: Profiles of Mean Plasma Trough Levels of Modafinil Versus Time After Daily Administration of Modafinil in Narcolepsy Patients



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ATTACHMENT A-10

~~Table 1.~~ Mean (± SD) Plasma Trough Levels (μg/mL) of Modafinil after Daily Administration of Modafinil or Placebo in Narcolepsy Patients

VISIT	PLACEBO			200 mg			400 mg		
	SEX (N)	MEAN (±SD)	MEAN (± SD) Both Sexes	SEX (N)	MEAN (±SD)	MEAN (±SD) Both Sexes	SEX (N)	MEAN (±SD)	MEAN (±SD) Both Sexes
Baseline	F (49)	BLQ	BLQ	F (49)	BLQ	BLQ	F (45)	BLQ	BLQ
	M (40)	BLQ		M (42)	BLQ		M (40)	0.129 * (0.519)	
Week 3	F (49)	BLQ	BLQ	F (51)	1.28 (0.9)	1.33 [a] (0.828)	F (45)	2.94 (2.09)	2.95 [a, b] (2.21)
	M (42)	BLQ		M (42)	1.39 (0.732)		M (39)	2.97 (2.37)	
Week 6	F (48)	BLQ	BLQ	F (52)	1.23 (0.943)	1.35 [a] (0.992)	F (42)	2.50 (0.995)	2.52 [a, b] (1.33)
	M (40)	BLQ		M (41)	1.50 (1.04)		M (35)	2.55 (1.65)	
Week 9	F (47)	0.144 * (0.648)	0.117 * (0.590)	F (49)	1.07 (0.483)	1.21 [a] (0.730)	F (41)	2.45 (1.90)	2.36 [a, b, c] (1.63)
	M (38)	BLQ		M (42)	1.37 (0.920)		M (37)	2.27 (1.28)	
Washout Baseline (Week 11)	F (37)	BLQ	BLQ	F (44)	0.193 * (0.891)	0.167 * (0.734)	F (30)	BLQ	BLQ
	M (35)	BLQ		M (34)	0.133 * (0.468)		M (31)	BLQ	

BLQ: Below Limit of Quantitation (< 0.1 μg/mL)

[a] Significantly different ($p < 0.0001$) from the corresponding pretreatment and Week 11 baseline values

[b] Significantly different ($p < 0.0001$) from the corresponding 200 mg group value

[c] Significantly different ($p < 0.01$) from the corresponding Week 3 value

* There is no current definitive explanation for the detection of low concentrations of modafinil in the placebo group or at the end of the washout in the 200 mg group. It may be the result of background noise of the instrumentation or the presence of some other chemical compounds co-eluting at the same [redacted] retention time.

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11. Blood Kinetics Trial of Modafinil (CRL40476) in the Elderly Subject Before and After Repeated Administration [redacted] MOD-020)

Objectives:

To investigate PK behavior of modafinil in elderly subjects.

Study Design and Sampling:

This was an open trial for 7 days on 12 elderly patients, among whom six were male and six were female. The criteria for inclusion of subjects in the trial were (1) > 65 years old, permanently hospitalized (2) presenting a deficit pathological condition on ideomotor slowing down of the reactions, inhibition and sadness and other symptoms of depression; (3) with no underlying organic condition: hepatic (normal state of the liver for the patient's age), Renal (blood creatinine normal for the patient's age), pulmonary, digestive (no surgical or gastroduodenal history), endocrine and metabolic, major excess or insufficiency of body weight in relation to height and age; (4) If possible, no associated treatment during the 7 days preceding and during the trial; (5) Wherever possible: No benzodiazepines or barbiturates on Day 7, No aspirin or glafenine from Day 1 to Day 7 during treatment.

SAMPLING AND DOSES

Day 1: Sampling T0
ON AN EMPTY STOMACH, single dose of 2 x 150 mg tablets (300 mg) in a glass of water.
Sampling T 2 h
Breakfast
T 4 h
T 7 h
T 10 h
(Adhesive labels supplied for attachment to the sample tubes)

Day 2 to Day 6:
Morning and midday, administration of 1 x 150 mg tablet in a glass of water.

Day 7: As for Day 1.

SAMPLING AND STORAGE CONDITIONS

- Take a 10 ml blood sample on dry heparin (ionogram tube).
- Centrifuge (800 g) for 10 min.
- Separate, collect and freeze the plasma at -20°C.

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Results (Attachment 11) and Conclusions:

With 300 mg administration, modafinil produced higher plasma concentrations in elderly men than elderly women on both D1 and D7. The higher concentration of modafinil acid in men than women was only found on D1. The drug appeared to be safe in both genders of the elderly.

Comment:

1. Due to the limited number of subjects and relatively large variations among the subjects, statistically significant difference of modafinil concentrations between elderly male and elderly female was only found at 7 and 10 hr on D1.
2. The sponsor requested dose adjustment on elderly patients, based on the results from this study and those from study MOD-018 (linearity study). They noted that with 300 mg dosing, Cmax obtained in this study was higher than that from 400 mg dosing in study MOD-018. However, the reviewer compared MOD-018 (the French study) with CEP-2101 (US study), and found that with the same dosing, Cmax, AUC values in MOD-018 and CEP-2101 are ~50% of those in CEP-2101 study (see the attachment). As a result, the clearance calculated in MOD-018 (5 L/hr) was higher than that from CEP-2101 and other US studies. This difference may be due to the formulation of modafinil used in MOD-018 (cachet) and the bioassay in the study which has higher detection limit (0.13 ug/ml) than other studies (0.1 ug/ml). By point-to-point comparison, the reviewer demonstrated that the modafinil concentration between the elderly and the young are comparable (see the attachment).
3. The sponsor has conducted another PK study following single dose of modafinil on healthy and elderly male healthy volunteers (C1538a/103/PK/US). The results showed at all the PK parameters in the male elderly were similar to those in the young subjects, with the exception of clearance which is statistically significantly lower in the elderly than in the young (by 10-20%). Correspondingly, the formation of modafinil acid is higher in the elderly than that in the young subjects by the same percentage. The elderly handles the enantiomers the same with as the young subjects, again, with the exception of clearance which is lower (for both enantiomers) in the elderly subjects (by ~20%).

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ATTACHMENT A-11

3.2 PHARMACOKINETICS

~~3.2.1~~ STUDY OF THE PLASMA CONCENTRATIONS

Individual values for the MODAFINIL plasma concentrations are shown in Table V below.

~~Table V~~ **Plasma concentrations of MODAFINIL after repeated administrations in the elderly subject**

Plasma concentration of MODAFINIL in women

Time	Case 101	Case 102	Case 103	Case 104	Case 105	MEAN	SME
2	[redacted]						
4						5.90	0.60
7						6.14	0.88
10						3.94	0.52
144						3.78	0.49
146						4.16	0.72
148						8.30	1.29
151						8.06	1.54
154						6.60	1.45
						5.91	1.00

p6

Plasma concentrations of MODAFINIL in men

Time	Case 106	Case 201	Case 202	Case 203	Case 204	Case 205	Case 206	MEAN	SME
2	[redacted]				[redacted]				
4								5.30	1.47
7								7.31	1.38
10								7.32	1.38 ← p=0.04
144								6.27	1.06 ← p=0.0
146								4.88	0.44
148								9.21	0.94
151								9.26	0.78
154								9.68	1.13
								7.78	0.76

Figures 1 A and B below [p. 12] show the mean plasma concentrations of MODAFINIL and its metabolite, acid MODAFINIL respectively:

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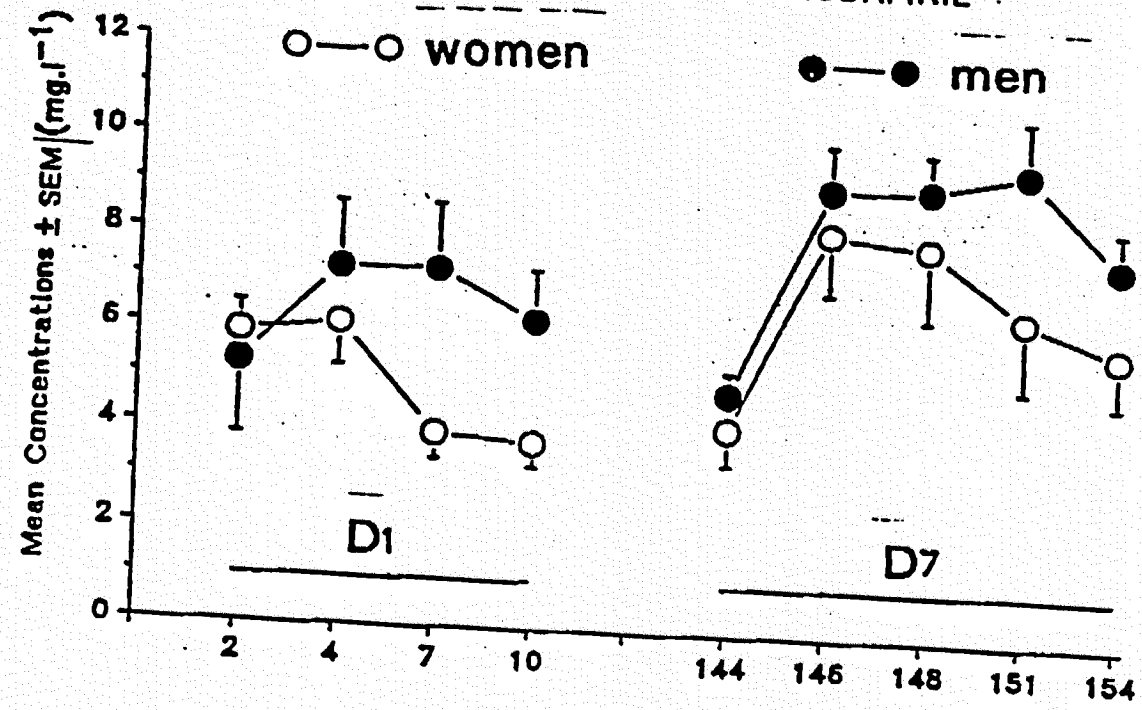
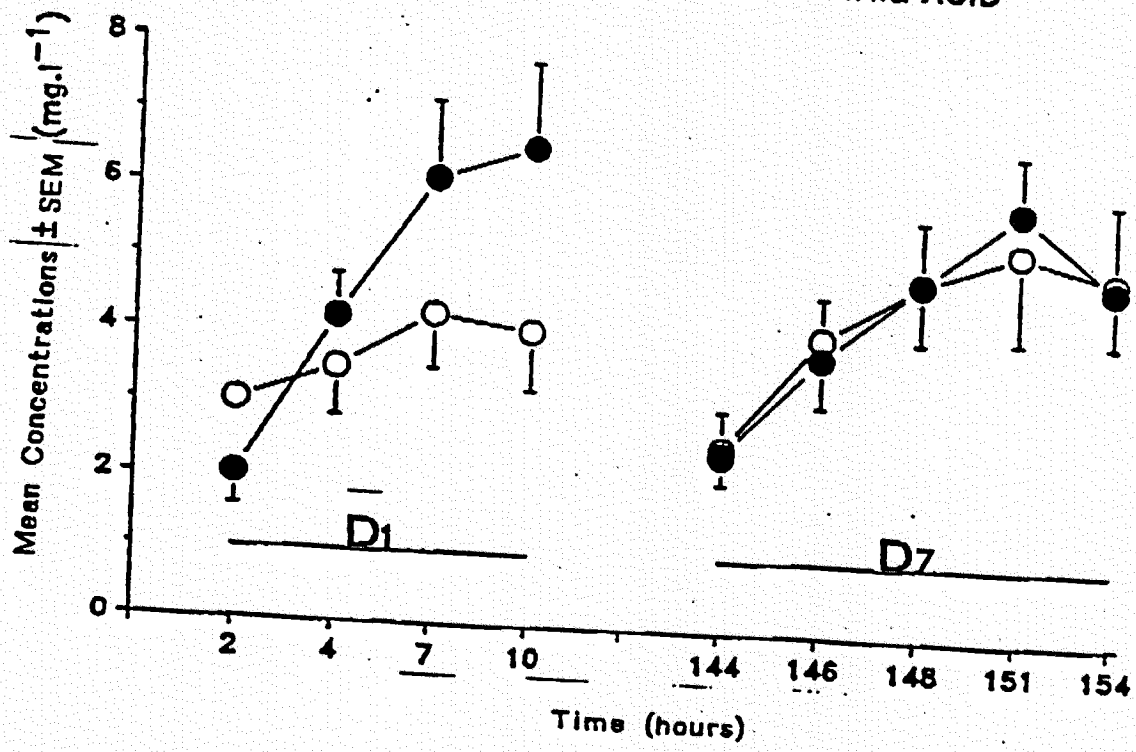
[redacted]

A – CONCENTRATIONS OF MODAFINIL



B – CONCENTRATIONS OF MODAFINIL ACID



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3.3 COMPARISON OF CLINICAL AND PHARMACOKINETIC DATA

Plasma concentrations on D1 and/or D7 Physical and/or psychological/behavioural effects correlated with the pharmacological activity	High values	Normal values
Clearly apparent	F : 101 = 103 M : 201 - 202 203 - 206	M : 106 - 205
Doubtful	-	F : 102 - 105 M : 204
None	-	F : 104

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The underlined cases were receiving associated sedative psychotropics.

Examination of the above table reveals that the 6 subjects with high MODAFINIL concentrations exhibited in all cases effects correlated with the pharmacological activity. The high MODAFINIL concentrations detected in 2 of these subjects (see Table V: Cases 103 and 202) may explain the occurrence of these effects in spite of the simultaneous prescription of sedatives (benzodiazepine or Haldol(R)).

Cases 106 and 205 with normal MODAFINIL concentrations, comparable with those of the young subjects, nevertheless exhibited the corresponding effects on D1. It is to be noted that they were not receiving associated sedatives.

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6.2.1 Summary of Human Pharmacokinetics and Bioavailability Study Results: Single Dose

6.2.1.1 C1538a/103/PK/US — Open-Label, Single-Dose Pharmacokinetic Study of Modafinil Tablets: Influence of Age and Gender in Normal Subjects

6.2.1.1.1 Objectives

The objective of this study was to examine the effect of age and gender on the pharmacokinetic parameters of modafinil following administration of a single 200 mg oral dose of modafinil.

6.2.1.1.2 Procedures and Methods

6.2.1.1.2.1 Study Design

Single-center, Single-dose, Open-label, Parallel-group:

Subjects received 200 mg oral dose of modafinil. Blood and urine samples were collected for pharmacokinetic analysis.

6.2.1.1.2.2 Subject Demographics

Thirty-six healthy subjects (12 per group) were enrolled and completed the study. The range of the ages for the three groups differ between the clinical and pharmacokinetic reports. This is due to the clinical report determining the age of each individual at the end of the study and by calculating each age by the year and month and rounding to the nearest whole year. In the pharmacokinetic report, the age was calculated from the beginning of the study and was not rounded to the whole year. In the pharmacokinetic report the demographics were as follows:

- Young males mean age of 29.4 years (range 22-37 years)
- Young males mean weight of 82.9 kg (range 64.1-98.2 kg)
- Young females mean age of 26.1 years (range 19-40 years)
- Young females mean weight of 64.3 kg (range 51.8-86.8 kg)
- Elderly males mean age of 62.7 years (range 53-72 years)
- Elderly males mean weight of 81.5 kg (range 69.1-97.7 kg)

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RESULTS:

Table 6.2-9. Mean (±SD) Pharmacokinetic Parameters of Modafinil After a Single 200 mg Oral Dose of Modafinil in Healthy Subjects

Subject	n	C_{max}	T_{max}	$t_{1/2}$	$AUC_{0-\infty}$	CL/F	V/F	CL_{renal}
		µg/mL	hr	hr	µg hr/mL	mL/min	L	mL/min
Young Males	12	4.21 (0.44)	2.0 (1.0)	12.7 (3.2)	57.0 (7.6)	59.5 (9.3)	64.1 (11.9)	3.43 (1.01)
Young Females	11[a]	5.20 (0.83)	1.7 (0.9)	10.5 (1.5)	61.3 (12.6)	56.2 (9.5)	50.3 (8.2)	2.36 (1.01)
Elderly Males	12	4.81 (0.89)	1.7 (0.7)	14.4 (3.2)	67.7 (12.7)	50.9[b] (9.7)	61.7 (10.3)	2.81 (1.51)

[a] Subject #209 was excluded from pharmacokinetic analysis because assay interfering peaks prevented the determination of modafinil levels in plasma.
[b] Significantly different ($p<0.05$) from the corresponding values for young males.

Table 6.2-10. Mean (±SD) Pharmacokinetic Parameters of Modafinil Acid After a Single 200 mg Oral Dose of Modafinil in Healthy Subjects

Subject	n	C_{max}	T_{max}	$t_{1/2}$	$AUC_{0-\infty}$	f_m	CL_m	$CL_{r(m)}$
		µg/mL	hr	hr	µg hr/mL	mL/min	mL/min	
Young Males	12	2.06 (0.32)	2.8 (1.0)	5.7 (0.5)	22.8 (3.0)	0.51 (0.05)	30.3 (6.8)	75.6 (16.8)
Young Females	11[a]	2.65 (0.46)	2.9 (0.9)	4.7 (0.5)	25.5 (4.9)	0.36 (0.09)	20.2 (7.1)	48.8 (17.7)
Elderly Males	12	2.65 (0.66)	3.5 (1.1)	8.0 (5.4)	35.1[b] (10.7)	0.60[b] (0.12)	30.6 (8.8)	62.6 (27.9)

[a] Subject #209 was excluded from pharmacokinetic analysis because assay interfering peaks prevented the determination of modafinil acid levels in plasma.
[b] Significantly different ($p<0.05$) from the corresponding values for young males.

Table 6.2-11. Mean (±SD) Pharmacokinetic Parameters of *d*-Modafinil After a Single 200 mg Oral Dose of Modafinil in Healthy Subjects

Subject	n	C_{max}	T_{max}	$t_{1/2}$	$AUC_{0-\infty}$	CL/F	V/F	$t_{1/2,a}$	MAT	MRT_{iv}[a]
		µg/mL	hr	hr	µg·hr/mL	mL/min	L	hr	hr	hr
Young Males	12	1.93 (0.44)	2.1 (1.0)	3.3 (0.6)	12.3 (3.2)	145 (41)	39.9 (7.7)	0.62 (0.29)[b]	0.89 (0.42)[b]	4.75 (0.98)[b]
Young Females	12	2.52 (0.39)	1.5 (1.0)	2.9 (0.4)	13.4 (2.0)	126 (17)	31.4 (4.3)	0.63 (0.37)	0.91 (0.53)	3.91 (0.84)[b]
Elderly Males	12	2.39 (0.47)	1.5 (0.7)	3.7 (1.0)	15.5 (2.9)	112 (23)[b]	34.4 (6.1)[b]	0.44 (0.09)[b]	0.63 (0.14)[b]	5.35 (1.59)[b]

[a] n=11.
[b] Significantly different ($p<0.05$) from the [illegible]
n=10

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Table 6.2-12. Mean (±SD) Pharmacokinetic Parameters of *l*-Modafinil After a Single 200 mg Oral Dose of Modafinil in Healthy Subjects

Subject	n	C_{max}	T_{max}	$t_{1/2}$	$AUC_{0-\infty}$	CL/F	V/F	$t_{1/2,a}$	MAT	MRT_{iv}
		µg/mL	hr	hr	µg•hr/mL	mL/min	L	hr	hr	hr
Young Males	12	2.29 (0.44)	2.3 (1.0)	11.5 (2.4)	38.6 (10.4)	46.1 (12.5)	44.7 (9.9)	0.71 (0.50)[a]	1.03 (0.72)[a]	15.1 (2.6)[a]
Young Females	12	2.89 (0.32)	2.0 (0.8)	9.7 (1.7)	41.9 (7.7)	40.9 (6.5)	33.8 (4.3)	0.46 (0.37)[ab]	0.67 (0.53)[a]	13.4 (2.2)[a]
Elderly Males	12	2.52 (0.41)	2.0 (0.9)	14.3 (2.6)	49.0 (9.2)	35.0 (5.9)[b]	42.5 (5.9)	0.90 (0.83)[a]	1.30 (1.20)[a]	19.4 (5.0)[c]

[a] n=11.
[b] Significantly different (p<0.05) from the corresponding values for young males.
[c] n=8.

Table 6.2-13. Mean (±SD) of Percentage of Dose Excreted in Urine (0-72 hr) After a Single 200 mg Oral Dose of Modafinil in Healthy Subjects

Subject	n			
		Modafinil	Modafinil Acid	Modafinil Sulfone
Young Males	12	5.3 (1.0)	51 (5)	0.0
Young Females	12	3.7 (1.5)[a]	35 (9)[a]	0.0
Elderly Males	12	5.1 (1.9)	60 (12)[a]	0.0

[a] Significantly different (p<0.05) from the corresponding values of young males.

6.2.1.1.4 Conclusions

The absorption of modafinil was rapid as indicated by ~ one hour for both absorption half-life and mean absorption time. An apparent volume of distribution of ~ 60 L suggests extensive tissue binding. The plasma clearance of modafinil was ~ 50-60 mL/min and renal clearance accounted for ~ 5% of the plasma clearance. Stereospecific pharmacokinetics of modafinil enantiomers were demonstrated, *i.e.*, *d*-modafinil was eliminated faster than *l*-modafinil. The *l*-modafinil and modafinil were cleared at a similar rate and the oral clearance of modafinil for males decreased as the age increased. Modafinil acid was the major metabolite in urine and females appeared to excrete less modafinil acid in urine than males.

200 mg Time	Sub. 1	Sub. 2	Sub. 3	Sub. 4	Sub. 5	Sub. 6	CEP-2101 US Study on Young Mean	Sd.	[redacted] MOD-018 Study on Young Mean	Sd.	Time (Fr)
0.5	[redacted]			[redacted]			0.40	0.52	0.85	0.71	0.5
1							2.43	1.16	1.64	0.69	1
1.5							4.17	0.71	2.01	0.55	1.5
2							4.68	0.47	2.22	0.39	2
3							4.56	0.60	2.42	0.24	2.5
4							4.16	0.62	2.33	0.1	3
6							3.32	0.32	2.32	0.17	4
8							2.70	0.31	2.21	0.63	6
12							1.83	0.19	1.71	0.41	8
24							0.91	0.14	0.57	0.22	24
144							1.73	0.25			
144.5							2.51	0.81			
145							4.41	1.03			
145.5							5.62	0.62			
146							6.17	0.59			
147							5.99	0.81			
148							5.71	0.96			
150							4.52	0.57			
152							4.04	0.85			
156							2.92	0.79			
168							1.48	0.58			
192							0.58	0.16			

300 mg Time	Old/fem Mean (S.D) Conc	Old/male Conc	[redacted] (MOD-018) Young Conc	US (CEP-2101) Young Conc
2	5.9 (1.20)	5.3 (3.6)	3.33	7.02
4	6.14 (1.76)	7.31 (3.38)	3.50	6.24
7 *	3.94 (1.04)	7.32 (3.38)	2.94	4.57
10 *	3.78 (0.96)	6.27 (2.60)	2.25	3.45
144	4.16 (1.44)	4.88 (1.08)	1.30 Pred.	2.59
146	8.3 (2.58)	9.21 (2.31)	4.63	9.25
148	8.06 (3.08)	9.26 (1.91)	4.28	8.57
151	6.6 (2.90)	9.68 (2.77)	3.30	6.60
154	5.91 (2.00)	7.78 (1.86)	2.85	5.70

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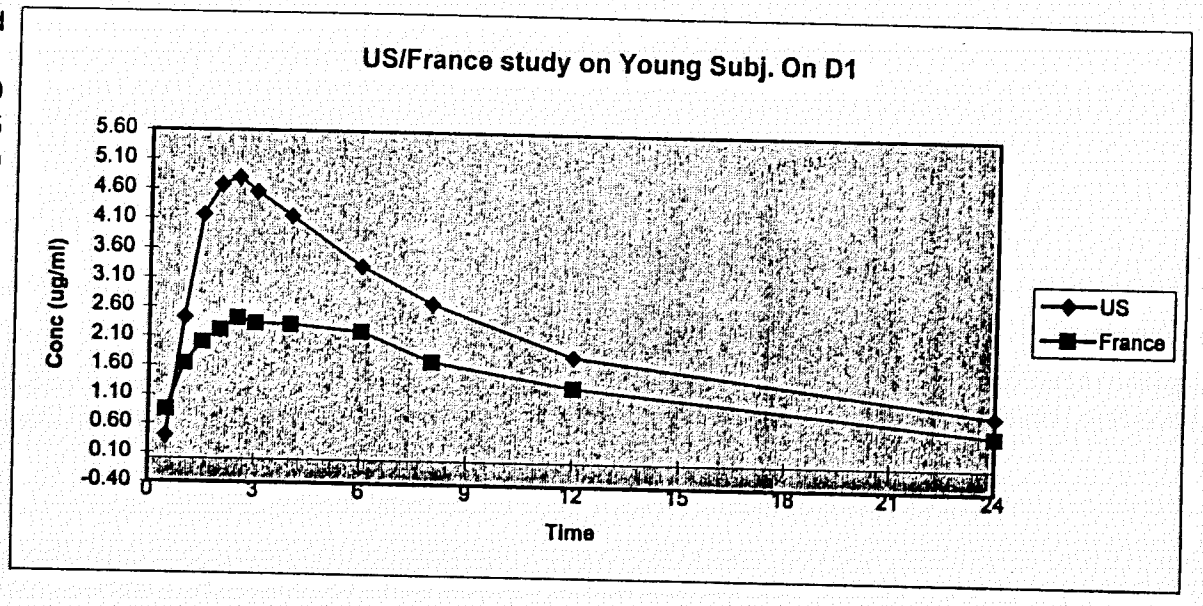
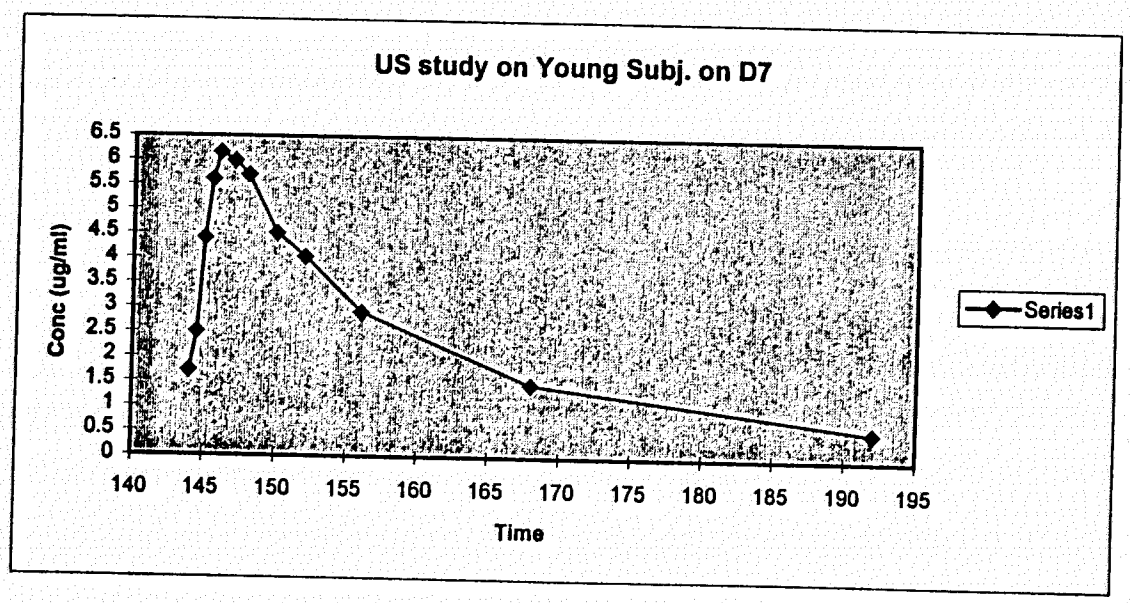
Time	US	France	US-std	France-std
0.5	**0.40**	**0.85**	0.52	0.71
1	**2.43**	**1.64**	1.16	0.69
1.5	**4.17**	**2.01**	0.71	0.55
2	**4.68**	**2.22**	0.47	0.39
2.5	4.80	**2.42**		0.24
3	**4.56**	**2.33**	0.60	0.096
4	**4.16**	**2.32**	0.62	0.17
6	**3.32**	**2.21**	0.32	0.63
8	**2.70**	**1.71**	0.31	0.41
12	**1.83**	1.3	0.19	
24	**0.91**	**0.57**	0.14	0.22



Time	US study Mean	std
144	1.73	0.251
144.5	2.51	0.807
145	4.41	1.034
145.5	5.62	0.618
146	6.17	0.589
147	5.99	0.806
148	5.71	0.964
150	4.52	0.567
152	4.04	0.85
156	2.92	0.789
168	1.48	0.579
192	0.58	0.161



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12. Pharmacokinetics of Multiple Doses of Modafinil in Humans with Severe Chronic Hepatic Insufficiency [redacted]-MOD-021)

Clinical phase:	Phase III
Aims:	Comparison in humans with hepatic insufficiency and healthy humans of the kinetics of MODAFINIL after multiple doses
Method:	Open trial
Number of subjects:	9 subjects, i.e.: 6 men and 3 women
Inclusion criteria:	Patients with severe hepatic insufficiency; cooperative, no combined or previous (7 days) treatment
Trial compound:	Two tablets of MODAFINIL (ref. 12156, active ingredient 5/1939), i.e. 200 mg per day
Treatment duration:	8 days (D1 & D8: single Dose 200 mg; D2–D7: Single morning & midday doses of 100 mg)
Reference treatment:	Not applicable
Endpoints:	1. Plasma concentrations of MODAFINIL and its metabolite. 2. Pharmacokinetic parameters of MODAFINIL.
Statistical methods:	1. Modelling of kinetics. 2. Parametric test (Student's "t" test for grouped data).

Nine subjects received an oral dose of 200 mg of MODAFINIL in the form of two non-coated 100 mg tablets (ref. 12156) for 8 days. This dose was given as one tablet in the morning and one at noon. This dosage was selected since it corresponded to the usual therapeutic schedule. On days D1 and D8, the total dose of 200 mg was given as a single amount in the morning and a series of blood samples obtained.

Blood samples were drawn on days D1 and D8, when the drug was given as a single dose of 200 mg:

- 10 ml of blood was drawn into a dry heparin tube before (control specimen) then at times 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hours after administration on D1, with additional points at 24 and 36 h on D8. Blood was centrifuged and, after separation, plasma frozen at -20°C until assay.

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Results (Attachment 12) and Conclusions:

The elimination of MODAFINIL is essentially hepatic (only 10% of the dose administered being found intact in urine).

1. **In patients with hepatic insufficiency (severe cirrhosis), the kinetics of MODAFINIL after multiple doses were different as compared to those found in healthy individuals:**
   - **elimination half-life was more than doubled, increasing from 13.6 h in treated healthy subjects to almost 27.7 h in hepatic insufficiency patients**
   - **the volume of distribution at steady state was decreased, falling from 82.1 l in healthy subjects to almost 60.5 l in hepatic insufficiency patients**
   - **these changes were reflected by steady state plasma concentrations of MODAFINIL approximately twice as high as in the healthy individual (C_{max}: 7.90 $mg.l^{-1}$ in hepatic insufficiency patients as compared with 3.73 $mg.l^{-1}$ in health subjects).**
2. **This increase in concentrations clearly reflected the hepatic metabolism of MODAFINIL and the decreased capacity of patients with liver disease to produce the pharmacologically inactive acid metabolite, which was found at lower concentrations in hepatic insufficiency patients.**
3. **Despite the very marked increase in plasma concentrations, safety (based upon clinical and laboratory parameters) of MODAFINIL in hepatic insufficiency patients was very good. A reduction by half in the dosage of MODAFINIL is therefore suggested in patients with severe liver disease, rather than an actual contraindication of the use of this drug in such a high risk population.**

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Comments:

1. The PK parameters for healthy subjects were from another study (MOD-19) where the dose regimen is the same as this study. On D1, the increased Tmax from hepatic dysfunction subjects (7.1 ± 1.1 hr), compared to that from the normal subjects (4.0 ± 0.6 hr), suggested slow absorption of modafinil in liver impaired patients.
2. On D8, Cmax, AUC0-∞, Cmin and t1/2 of modafinil from liver patients were all significantly higher than the corresponding values from normal subjects, suggesting that the major elimination route of modafinil was liver.
3. The patients with mild and moderate liver impairment function should be included in the study.

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ATTACHMENT A-12

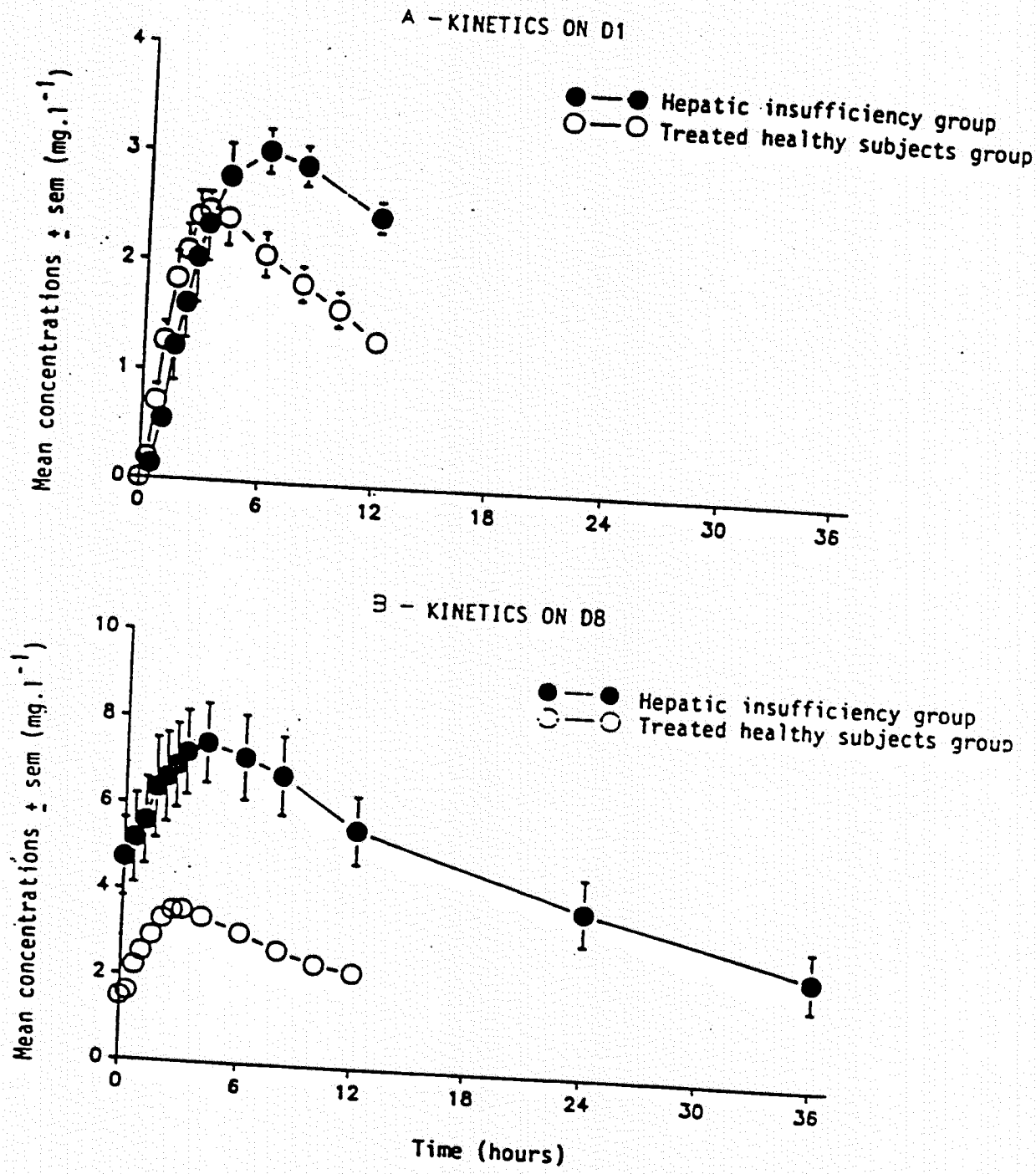

Figure 1

Plasma concentrations of MODAFINIL on days 1 and 8 during multiple dose kinetic study

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Table 6.2-78. Mean (±MSE) Pharmacokinetic Parameters of Modafinil and Modafinil Acid After Oral Doses (200 mg/day) of Modafinil in Hepatic Dysfunctional Patients

		Hepatic Insufficiency Patients	Healthy Subjects[a]	Hepatic Insufficiency Patients	Healthy Subjects[a]
Parameter	Day 1	Modafinil		Modafinil Acid	
C_{max} (mg/L)	Mean	3.26	2.60	0.82[b]	1.60
	MSE	0.22	0.24	0.13	0.11
T_{max} (hr)	Mean	7.11[b]	4.04	8.89[b]	4.96
	MSE	1.11	0.61	0.82	0.71
AUC_{0-12} (mg•hr/L/hr)	Mean	28.36[b]	21.92	6.20[b]	13.60
	MSE	1.72	1.99	1.13	0.78
Parameter	Day 8	Modafinil		Modafinil Acid	
C_{max} (mg/L)	Mean	7.90[b]	3.73	1.44	1.90
	MSE	0.98	0.25	0.30	0.15
T_{max} (hr)	Mean	3.88	2.92	5.88	4.00
	MSE	0.51	0.30	1.17	0.46
AUC_{0-12} (mg•hr/L)	Mean	78.68[b]	33.85	14.17	16.80
	MSE	10.71	2.88	2.99	1.31
Vd_{ss} (L)	Mean	60.54[b]	82.09	NA	NA
	MSE	4.42	5.61	NA	NA
$t_{1/2}$ (hr)	Mean	27.72[b]	13.61	NA	NA
	MSE	5.37	0.81	NA	NA
$AUC_{0-\infty}$ (mg•hr/L)	Mean	142.6[b]	54.0	NA	NA
	MSE	23.4	4.8	NA	NA
C_{min} (mg/L)	Mean	4.73[b]	1.49	0.82	0.58
	MSE	0.9	0.17	0.20	0.10

[a] Data obtained from a multiple dose kinetics study [redacted] MOD-019).
[b] Significantly different ($p<0.05$) from corresponding values of the healthy subjects.

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