Figure 18 Modafinil AUC Ratio [$AUC_{0-8, Day\ 7}$] / [$AUC_{0-infinity, Day\ 1}$] versus Dose of Modafinil During a 7-day Regimen of Once Daily Single Oral Doses (200, 400 or 600 mg) of Modafinil in Healthy Males

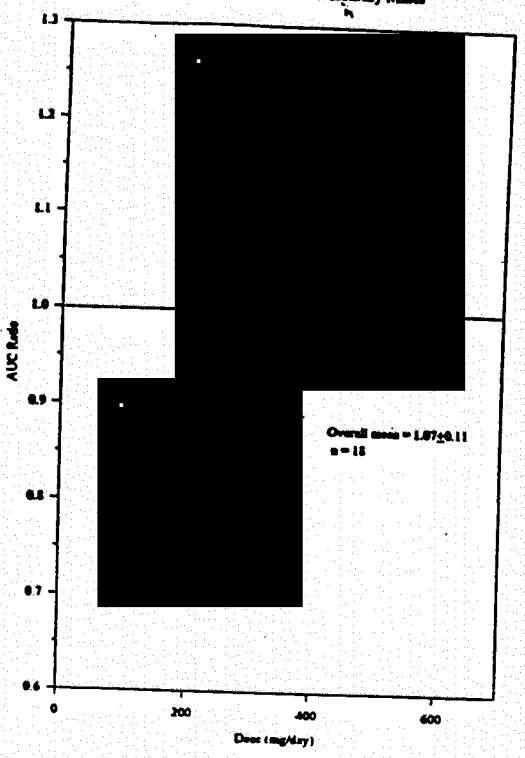
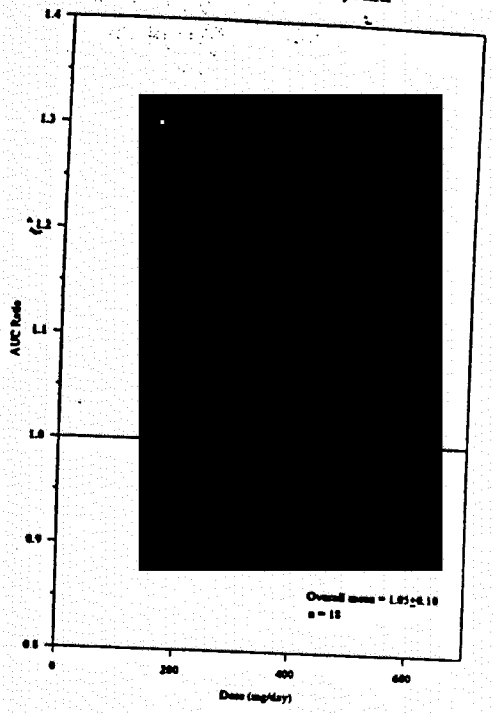
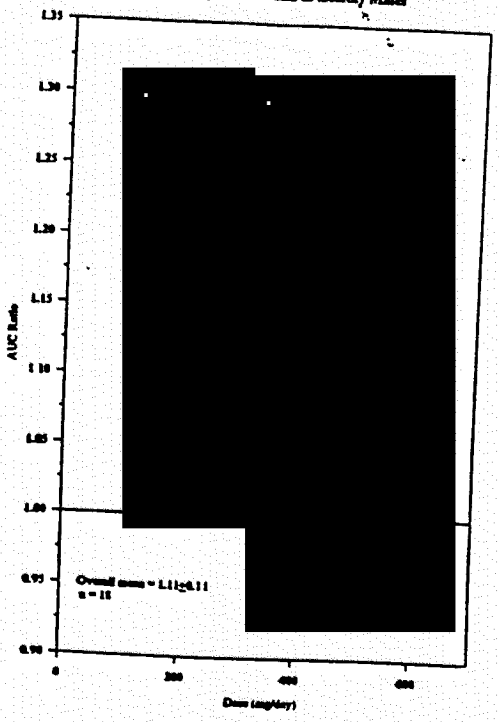


Figure 19. d-(+)-Modafinil AUC Ratio [$AUC_{0-8, Day\ 7}$] / [$AUC_{0-infinity, Day\ 1}$] versus Dose of Modafinil During a 7-day Regimen of Once Daily Single Oral Doses (200, 400 or 600 mg) of Modafinil in Healthy Males



ITEM 6 02054

Figure 20. l-(-)-Modafinil AUC Ratio [$AUC_{0-8, Day\ 7}$] / [$AUC_{0-infinity, Day\ 1}$] versus Dose of Modafinil During a 7-day Regimen of Once Daily Single Oral Doses (200, 400 or 600 mg) of Modafinil in Healthy Males



ITEM 6 02055

Table 6. Pharmacokinetic Parameters (Mean±SD) for Modafinil Acid in Healthy Males Following Day 1 and Day 7 Doses of Modafinil During a 7-Day Regimen of Once Daily Single Oral Doses of Modafinil

(Day 1)

Dose (mg/day)	n	C_{max} µg/mL	T_{max} hr	$t_{1/2}$ hr	$AUC_{0-\infty}$ µg•hr/mL
200	6	2.4±0.6	3.5±0.6	6.5±0.6	29±5
400	6	4.1±0.9	3.0±0.6	5.8±0.4[a]	47±9
600	6	6.8±1.2	3.8±0.4	6.2±0.6	81±13
800	6	7.8±0.9	3.7±0.5	6.7±0.8	95± 17
Overall mean±SD			**3.5±0.6**	**6.3±0.7**	

(Day 7)

Dose (mg/day)	n	C_{max} µg/mL	T_{max} hr	$t_{1/2}$ hr	$AUC_{0-\tau}$ µg•hr/mL
200	6	2.6±0.5	3.7±0.8	7.6±3.1[b]	29±7
400	6	4.1±0.8	3.0±0.9	11±2[c]	48±7
600	6	6.8±0.9	3.5±0.6	8.8±0.4[c]	80±11
800[d]	5	•	•	11±3[c]	•
Overall mean±SD			**3.4±0.8**	**9.3±2.5**	

[a] Significantly different than the 800 mg dose group.
[b] Significantly different than the 400 mg dose group.
[c] Significantly different from Day 1.
[d] Dosing was discontinued in the 800 mg/day dose group after 3 daily doses due to an adverse event (severe hypertension) observed in Subject 23. Only $t_{1/2}$ was determined after the third daily dose of modafinil in the 800 mg/day group.
• This parameter could not be calculated in the 800 mg/day dose group.

Table 7. Mean (±SD) Urinary Excretion (% Dose Excreted from 0-24 hr) Following the Day 1 Dose of Modafinil in Healthy Males (n=6)

	Modafinil		Modafinil Acid		Modafinil Sulfone	
Dose (mg)	Modafinil (mg)	% Dose Excreted	Modafinil Acid (mg)	% Dose Excreted	Modafinil Sulfone (mg)	% Dose Excreted
200	9.9±1.8	5.0±0.9	80±8	40±4	0.00	0.00
400	18±5	4.5±1.3	137±14	34±3	0.00	0.00
600	33±10	5.6±1.7	234±27	39±4	0.00	0.00
800	48±15	6.0±2.0	245±55	31±7	0.22±0.33	0.03±0.04

6. Pharmacokinetics of multiple doses of MODAFINIL in healthy humans (Lafon-MOD-019)

Clinical phase:	Phase II
Aims:	1. Study in healthy humans of the kinetics of MODAFINIL after multiple doses. 2. Study of variability in the kinetics of MODAFINIL in healthy humans. 3. Ex vivo study of the protein binding of MODAFINIL.
Method:	Double-blind trial: - one group of subjects given MODAFINIL daily for 15 days - one group of subjects given MODAFINIL only on days 1, 8 and 15
Number of subjects:	18 subjects in all, i.e. 12 in the treated group and 6 in the control group
Inclusion criteria:	Healthy male volunteers; 18 < age ≤ 35; cooperative, with no notable medical or psychological past history, with 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 (100 mg 2 AM, except D1 & Genuin D8 & D15 when 200 mg was given at once in the morning)
Treatment duration:	15 days
Reference treatment:	The control group was given MODAFINIL at the same daily dosage only on days 1, 8 and 15
Endpoints:	1. Plasma concentrations of MODAFINIL and its metabolite. 2. Pharmacokinetic parameters of MODAFINIL.

10 ml of blood was drawn before administration of Modafinil for evaluation of protein binding

The protein binding of MODAFINIL and that of potential interactions was undertaken in the [redacted] state dialysis [redacted]. The technique used was that of steady state dialysis [redacted]. In displacement studies, MODAFINIL was used at 5 $\mu g.ml^{-1}$, warfarin at 1 $\mu g.ml^{-1}$, diazepam at 400 $ng.ml^{-1}$ and propranolol at 40 $ng.ml^{-1}$. Steady state times were 3 hours for all substances. The temperature used was 37°C. Serum concentrations of albumin and of α1-acid glycoprotein (orosomucoid) were measured by radial immunodiffusion (Nor-Partigen plate).

Results (Attachment 6) and Conclusions:

Samples drawn just before administration of modafinil were used to evaluate the protein bindings of modafinil (in presence of its metabolites) and possible interactions with other substances strongly bound to serum proteins. Modafinil was approximately 60% bound to serum proteins. In another in vitro study (DP-96-014), the sponsor demonstrated that almost all the drug was bound to albumin, only 6-10% bound to α1-acid glycoprotein. Modafinil acid (0.5 or 100 μM) did not change modafinil protein binding. Drugs preferentially bound to albumin (warfarin and diazepam) or to α1-acid glycoprotein (propanolol) did not show any evidence that they may be displaced from the protein by modafinil. Only at supra-therapeutic concentrations of modafinil acid (5 mM), warfarin binding in plasma was reduced from 98% to 89%.

The PK from this study were essentially the same as those obtained from other studies. No difference in modafinil pharmacokinetic parameters was found between the treated group and the control group in Day 1. On Day 8 and Day 15, concentrations in the treated group were approximately 1.5 times higher than in the control group. This finding of accumulation of modafinil after multiple doses was to be expected with its biological elimination half life of ~ 10 hr, and for which dosage was based upon two daily administrations. The effective half life in the treated group is 13.61 ± 0.81 hr, longer than biological elimination half life. This observation was consistent with the results obtained from linearity study (MOD-018) and from multiple dose study (CEP-2101). This prolongation of half-life in multiple dosing could be caused by the nonlinear, saturation kinetics of biotransformation from modafinil to modafinil acid.

~~Study 5~~

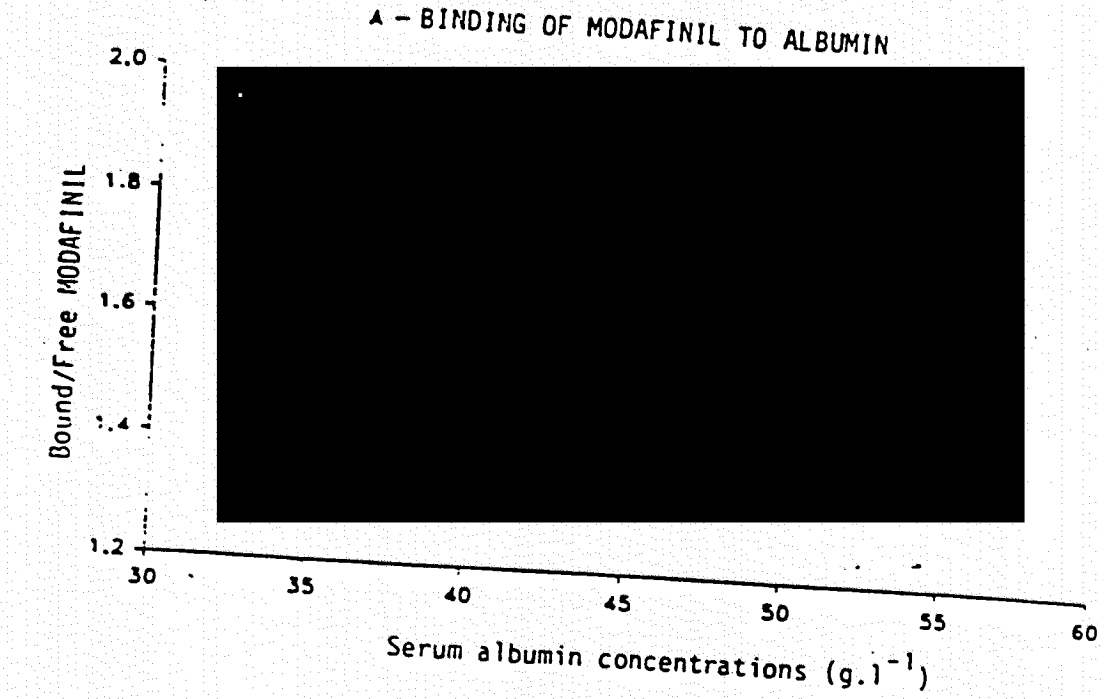
ATTACHMENT A-6

~~TABLE 1~~: Percentage binding of MODAFINIL, warfarin, diazepam and propranolol measured in the treated group and in the control group

	D1	D8	D15
MODAFINIL			
treated group (n=12)	62.11 ± 1.16	61.53 ± 2.41	61.31 ± 2.13
control group (n=6)	61.94 ± 1.84	60.45 ± 2.70	61.07 ± 2.32
warfarin			
treated group (n=12)	98.68 ± 0.16	98.66 ± 0.11	98.62 ± 0.14
control group (n=6)	98.60 ± 0.11	98.50 ± 0.20	98.62 ± 0.13
diazepam			
treated group (n=12)	97.42 ± 0.41	97.44 ± 0.48	97.50 ± 0.28
control group (n=6)	97.71 ± 0.08	97.62 ± 0.19	97.65 ± 0.32
propranolol			
treated group (n=12)	88.47 ± 2.83	87.41 ± 2.52	87.17 ± 2.33
control group (n=6)	89.03 ± 2.21	87.68 ± 3.13	88.26 ± 3.44

APPEARS THIS WAY ON ORIGINAL

study 5



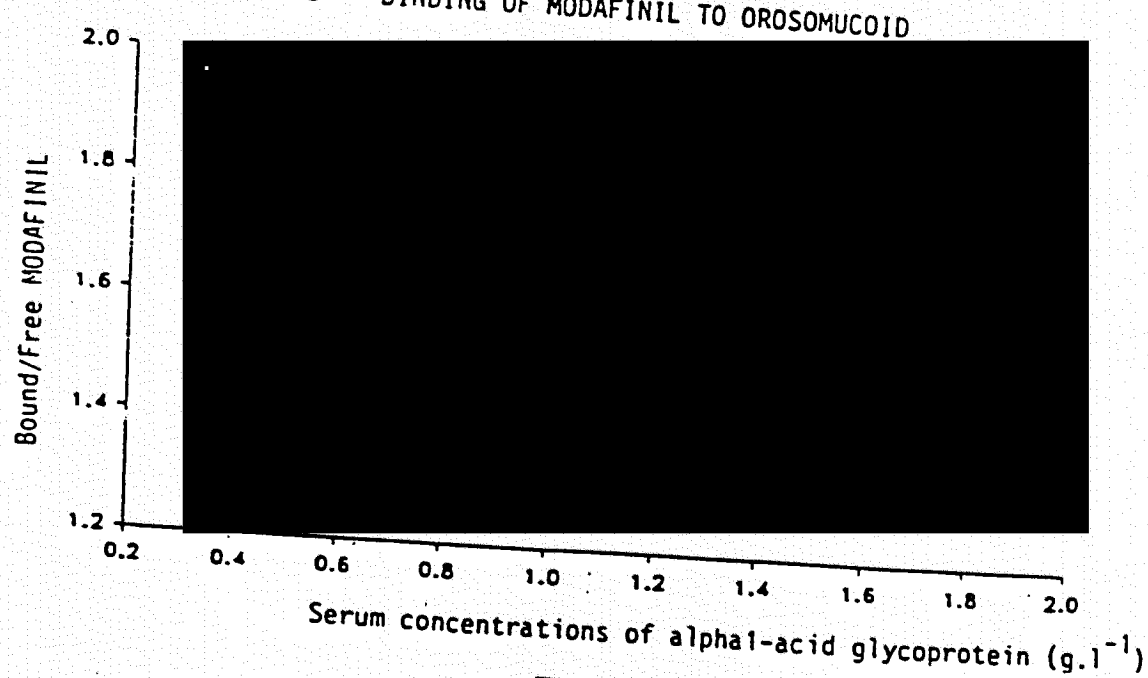


Figure 4

Relationship between binding of MODAFINIL to serum and concentration of albumin (A) or concentration of orosomucoid (B)

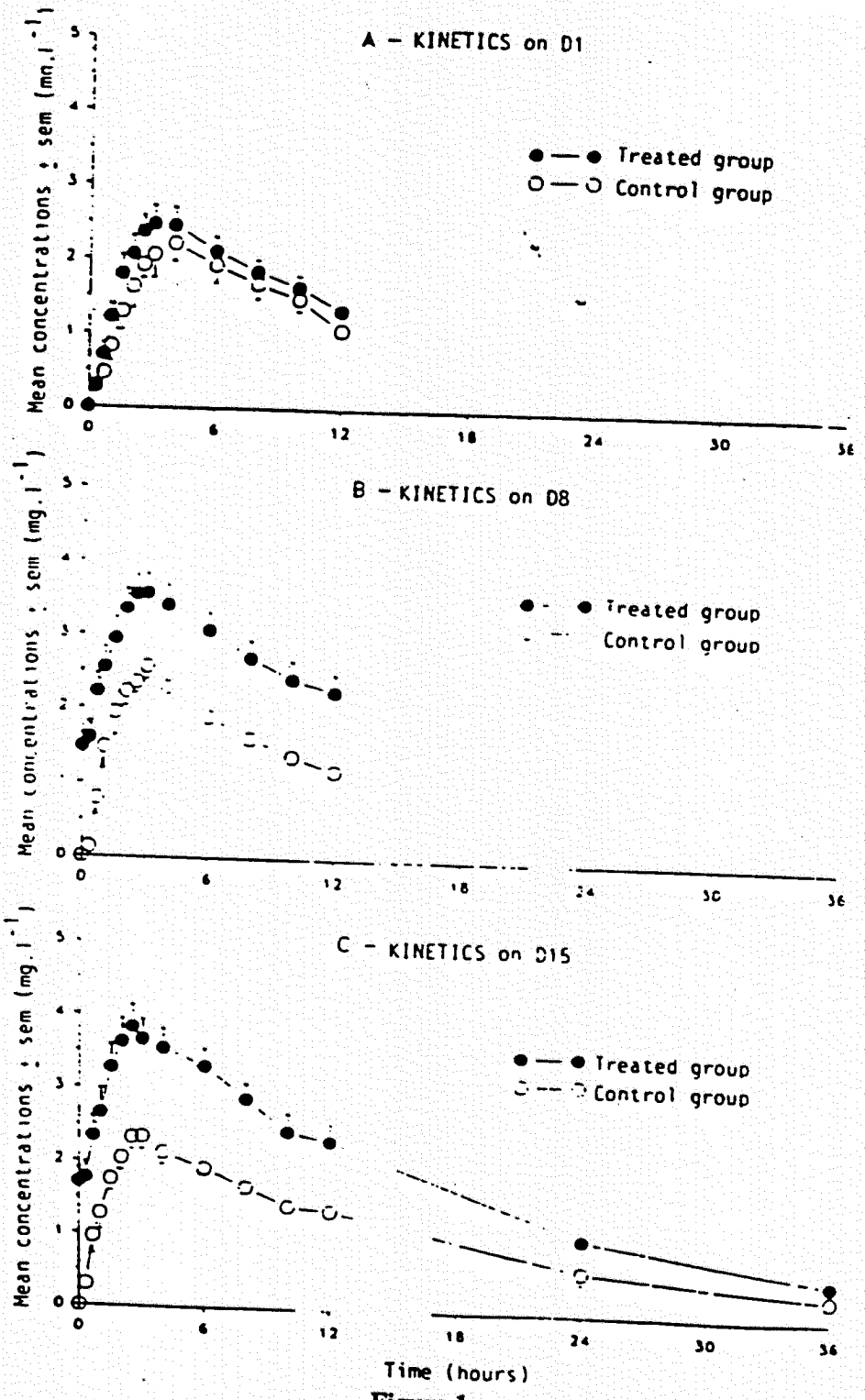


Figure 1

Plasma concentrations of MODAFINIL on days 1, 8 and 15 during multiple dose kinetics study

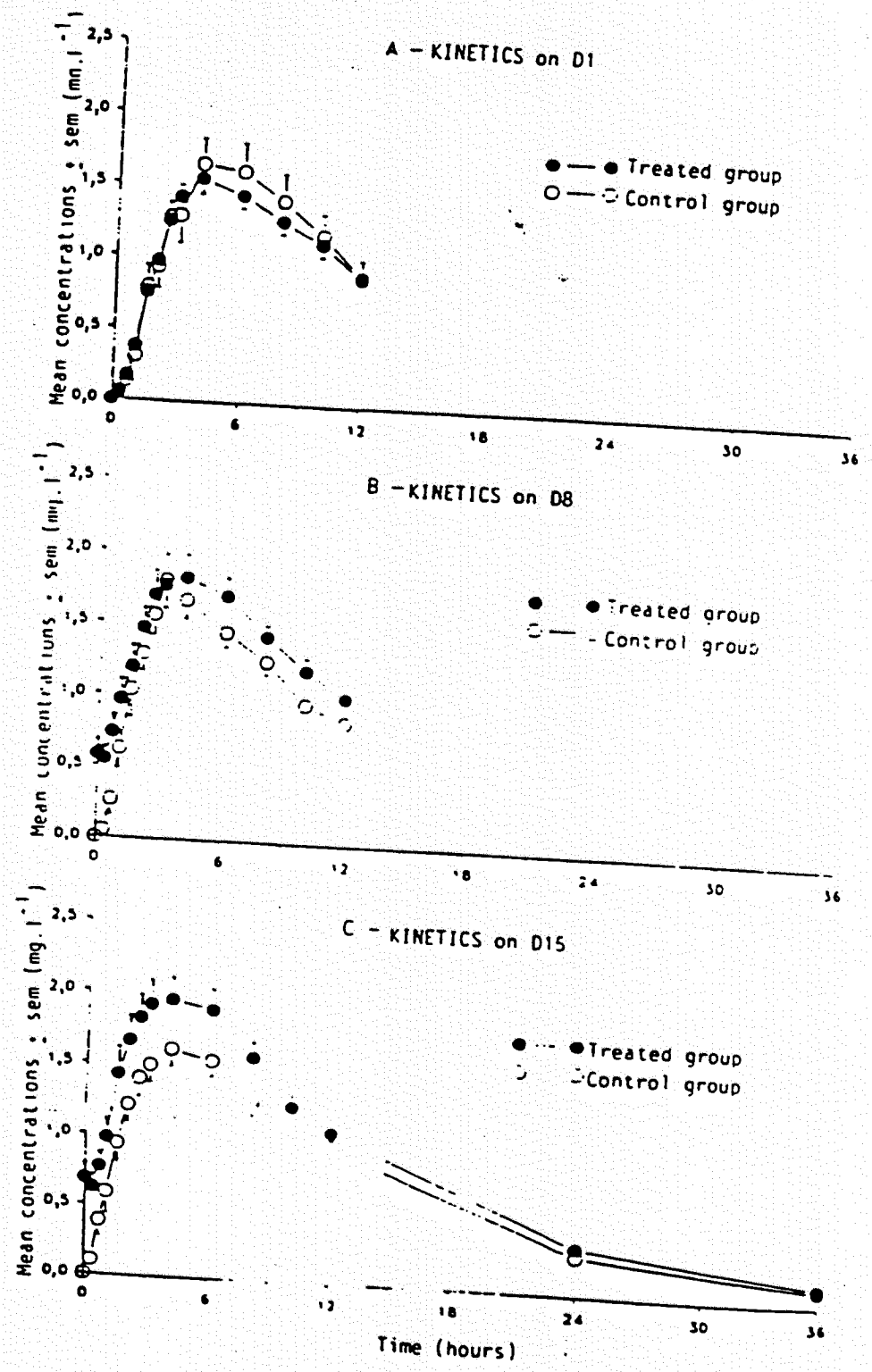


Figure 2

Plasma concentrations of acid MODAFINIL on days 1, 8 and 15 during multiple dose kinetics study of MODAFINIL

6.2.10 Summary of Human Pharmacokinetics and Bioavailability Study Results: *In Vitro/In Vivo* Metabolism Studies

6.2.10.1 DP-96-014 (B) — *In Vitro* Study of Plasma Protein Fixation

6.2.10.1.1 Objectives

The objective of this study was to determine binding of modafinil to plasma proteins *in vitro*.

6.2.10.1.2 Procedures and Methods

6.2.10.1.2.1 Study Design

Plasma protein binding of modafinil was evaluated by equilibrium dialysis for [redacted] hours at 37°C at a speed of [redacted] rpm. One-hundred-twenty µL of modafinil solution (1% methyl alcohol in pH 7.4, 0.067M Sorensen phosphate buffer) was added to 120 µL of pooled plasma or purified protein. The final plasma concentrations of modafinil were 0.1 and 50.5 µM. The protein binding of modafinil in serum albumin and α-acid glycoprotein was studied at the modafinil concentration range of 0.5-00.5 µM. The plasma protein binding of modafinil in the presence of modafinil acid (0.5-00 µM) as well as the binding of modafinil (0-1000 µM) to warfarin in the presence of modafinil acid (0-5000 µM) was also studied.

At the end of dialysis, an aliquot specimen was taken from each compartment and counted by liquid scintillation. Non-specific binding of modafinil to dialysis tanks or to the dialysis membrane was less than 10%.

For experiments involving competition with warfarin, binding of [^{14}C]-warfarin at a concentration close to the therapeutic range (1.5 µM) was studied in the presence of increasing concentrations of modafinil (0-1000 µM) or of its acid metabolite (0-5000 µM).

Table 6.2-81. Mean (±SD) Protein Binding of Modafinil in Plasma, Serum Albumin or α-acid Glycoprotein

Binding to	Concentration of Modafinil	Percent of Binding
Pooled Human Plasma	0.1-50.5 μM	61.1 ± 1.5%-64.5 ± 3.6%
Human Serum Albumin	0.5-300.5 μM	55.3 ± 0.3%-58.7 ± 0.5%
α-Acid Glycoprotein	0.5-300.5 μM	6.1 ± 0.7%-9.9 ± 0.6%
Plasma Protein in the Presence of Modafinil Acid	0.5-100 μM*	61.6 ± 0.2% (in the presence of 0.5 μM Modafinil Acid) 60.5 ± 0.5% (in the presence of 100 μM Modafinil Acid)

* = Concentration of Modafinil Acid

Table 6.2-82. Mean (±SD) Plasma Protein Binding of Warfarin (1.5 μM) in the Presence of Modafinil or Modafinil Acid

In the Presence of	Concentration of Modafinil or Modafinil Acid	Percent of Binding
Modafinil	0-1000 μM	98.5 ± 0.2% - 98.0 ± 0.3%
Modafinil Acid	0-500 μM - 5000 μM	98.4 ± 0.1% - 98.1 ± 0.1%-89.2 ± 0.3%

6.2.10.1.4 Conclusions

Modafinil is not a highly protein bound compound. At the concentration range of 0.1-50.5 μM, about 61-65% of the modafinil was bound to human plasma. The most likely binding site is albumin, and 58.7-55.3% of the modafinil binds to serum albumin. Only 6.1-9.9% of modafinil binds to α-acid glycoprotein. The binding characteristics of modafinil did not change whether the acid metabolite (modafinil acid) was present or not.

The binding characteristics of warfarin did not change in the presence of modafinil (1,000 μM). However, the protein binding of warfarin decreased to 89.2% in the presence of 5,000 μM of modafinil acid, suggesting that the binding of warfarin in plasma could be displaced by high concentrations of modafinil acid.

7. Evaluation of the Effect of Food on the Pharmacokinetic Profile of Modafinil and its Metabolite in a Single Dose Cross-over Study in Healthy Volunteers (MOD-022);

Objectives:

To study the effect of food on the PK profile of Modafinil.

Study Design and Sampling:

12 healthy male volunteers completed the trial in compliance with the protocol and the schedule.

The effect of food intake on the pharmacokinetic profile of modafinil (SR 96267) and its two metabolites (acid metabolite, CRL 40467 and sulfone metabolite, CRL 41056) was assessed after oral administration of a single dose of 200 mg (2 tablets containing 100 mg of SR 96267). The drug was administered after over-night fasting (fasting group), or right before standard breakfast (Fed group.) The fasting group did not take any food within 4 hr of modafinil admin. The study employed an open cross-over comparison design.

Each subject was to receive the 2 modes of administration (fasting and non fasting) separated by at least a week's interval, according to a randomised order.

Blood samples were all taken at the times provided for in the protocol, except for subject 7, period 1 (fasting group) for whom the sample H + 0.5h was performed at H + 0.63h. Real relative individual times are shown in ~~appendix 2~~. ATTACHMENT

Urine samples were all collected, except in 6 volunteers for whom the collected urine fractions were not complete. The time intervals are shown below :

Subject	Period	Group	Incomplete fraction
1	2	Fasting	72 - 96h
1	1	Non-fasting	72 - 96h
2	2	Non-fasting	24 - 36h
4	1	Non-fasting	72 - 96h
11	2	Fasting	72 - 96h
11	1	Non-fasting	72 - 96h

Results (Attachment 7) and Conclusions:

Food intake did not significantly affect the PK of modafinil. No change in bioavailability was observed, except that there was a slight decrease in C_{max} (3.61 vs. 4.01 mg/l) and a small increase in T_{max} (3.21 vs. 2.05 h) in non-fasting conditions, compared to the fasting conditions. But these changes did not affect the overall PK of the drug.

Table 4 : Pharmacokinetic parameters of SR 96267

Modafinil

Subject	Cmax (mg/l)		Tmax (h)		AUC 0-48hr (mg.h/l)	
	Fasting	Non-fasting	Fasting	Non-fasting	Fasting	Non-fasting
1	[redacted]					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	4.01	3.61	2.05	3.21	49.32	49.35
SD	0.90	1.01	0.46	1.32	12.09	14.57
Minimum	2.58	2.48	1.50	1.00	34.63	33.49
Maximum	5.75	5.27	2.53	5.00	73.87	81.46

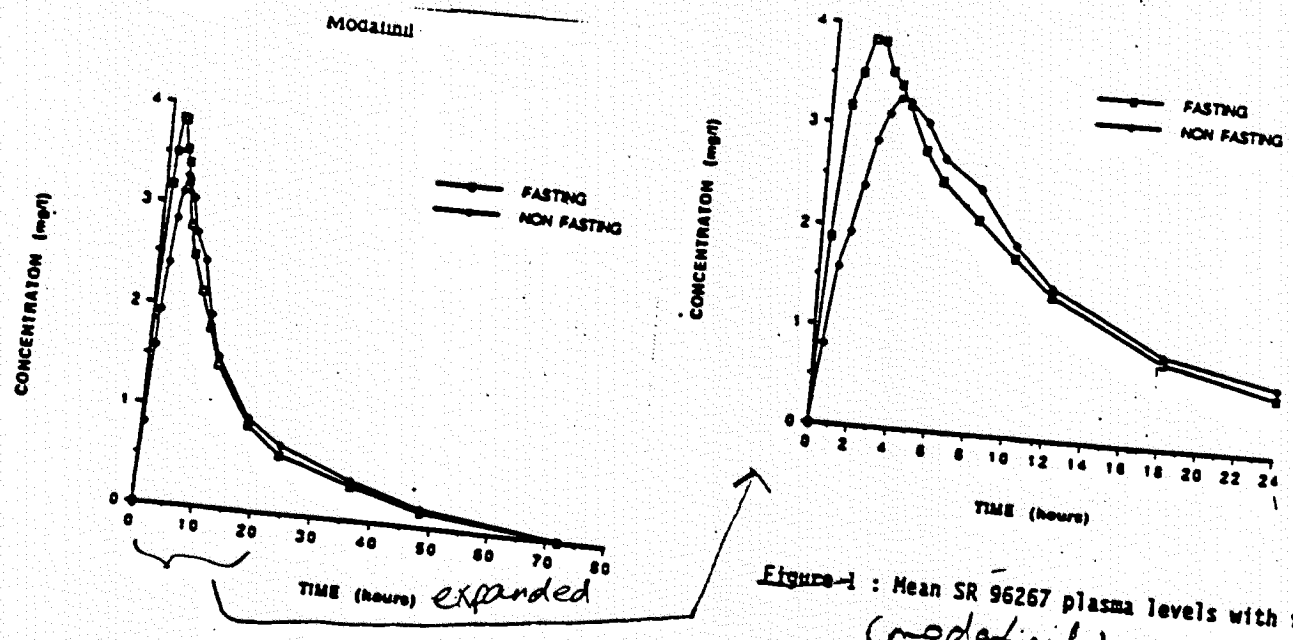
Subject	AUC 0-inf (mg.h/l)		T½ (h)	
	Fasting	Non-fasting	Fasting	Non-fasting
1	[redacted]			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	51.83	52.91	11.69	13.03
SD	12.58	15.14	2.18	2.75
Minimum	36.13	35.67	8.13	8.87
Maximum	78.28	88.05	15.22	18.08

ATTACHMENT A-7

~~Table 1~~ : Plasma concentrations (mg/l) of SR 96267 (mean ± SD)
(MODAFINIL)

Time (h)	Fasting	Non-fasting
0	*	*
0.5	1.86 ± 1.10	0.80 ± 0.90
1	3.18 ± 0.95	1.57 ± 1.27
1.5	3.51 ± 0.95	1.92 ± 1.31
2	3.84 ± 0.77	2.39 ± 1.17
2.5	3.82 ± 0.98	2.84 ± 0.96
3	3.53 ± 0.97	3.11 ± 0.85
3.5	3.41 ± 0.87	3.28 ± 0.93
4	3.21 ± 0.82	3.24 ± 1.03
5	2.78 ± 0.74	3.06 ± 0.96
6	2.49 ± 0.68	2.71 ± 0.93
8	2.14 ± 0.63	2.44 ± 0.81
10	1.78 ± 0.50	1.91 ± 0.65
12	1.43 ± 0.38	1.51 ± 0.54
18	0.85 ± 0.21	0.92 ± 0.32
24	0.58 ± 0.19	0.67 ± 0.25
36	0.34 ± 0.09	0.39 ± 0.13
48	0.14 ± 0.05	0.18 ± 0.08
72	*	*
96	*	*

* : Below quantification limit (0.05 mg/l)



~~Figure 1~~ : Mean SR 96267 plasma levels with time (modafinil)

Table 6.2-75. Mean (±SD) Pharmacokinetic Parameters of Modafinil After a Single Dose (200 mg) of Modafinil Administered Under Fed or Fasted Conditions in Healthy Males

	C_{max} (mg/L)		T_{max} (hr)		$t_{1/2}$ (hr)		$AUC_{0-\infty}$ (mg •hr/L)		$Ae_{(0-72)}$ (mg)	
	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted
Mean	3.61	4.01*	3.21	2.05*	13.03	11.69	52.91	51.83	11.07	9.02*
SD	1.01	0.90	1.32	0.46	2.75	2.18	15.14	12.58	2.34	1.12

* Significantly different ($p<0.05$) from corresponding values of the fed group.

Table 6.2-76. Mean (±SD) Pharmacokinetic Parameters of Modafinil Acid After a Single Dose (200 mg) of Modafinil Administered Under Fed or Fasted Conditions in Healthy Males

	C_{max} (mg/L)		T_{max} (hr)		$t_{1/2}$ (hr)		$AUC_{0-\infty}$ (mg •hr/L)		$Ae_{(0-72)}$ (mg)	
	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted
Mean	1.75	1.95*	4.49	2.75*	5.67	5.69	20.77	21.03	84.63	82.62*
SD	0.41	0.35	0.93	0.66	0.76	1.13	5.09	4.66	11.44	10.64

* Significantly different ($p<0.05$) from corresponding values of the fed group.

8. Kinetics of the Enantiomers of Modafinil after Oral Administration of the Racemate to Humans (MOD-022 Continuation Analysis).

Objectives:

To determine the kinetic profiles of the enantiomers of Modafinil after fasting or immediately after food intake.

Study Design and Sampling:

12 healthy male volunteers

They received a single dose of 200 mg of modafinil (2 tablets of 100 mg) at an interval of at least one week, after fasting or immediately after a standard breakfast. The sequences of administration with or without food intake were randomized over 2 periods.

The blood samples were taken 0, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 18 h, 24 h, 36 h, 48 h, 72 h and 96 h after the administration, and the urine was also collected to determine the pharmacokinetic parameters of modafinil. All the samples were analyzed in our department with a nonstereospecific method of determination (see *clinical report No. 578.6.042* of 3/27/92).

The samples of 6 subjects among the 12 were used for this kinetic study of the enantiomers: subjects 2, 4, 6, 7, 8 and 10. Each subject was selected by default, as a function of the number of samples for which there was sufficient plasma volume remaining to permit a second determination and not by making sure that the number of individuals for each sequence was distributed equitably.

PRODUCTS

- CRL 40476 hydrochloride, ref. 5/2435,
- CRL 40982, levorotary enantiomer, ref. 1/0054,
- CRL 40983, dextrorotary enantiomer, ref. 1/0055.

Results (Attachment 8) and Conclusions:

There was no evidence of any effect of food on the PK parameters of either enantiomers of modafinil. During the assay process, no stereo-conversion was found between the two enantiomers, because of the stability of the racemate and of the enantiomers demonstrated during the validation. The PK results from this study are comparable to those obtained in study CEP-2101.

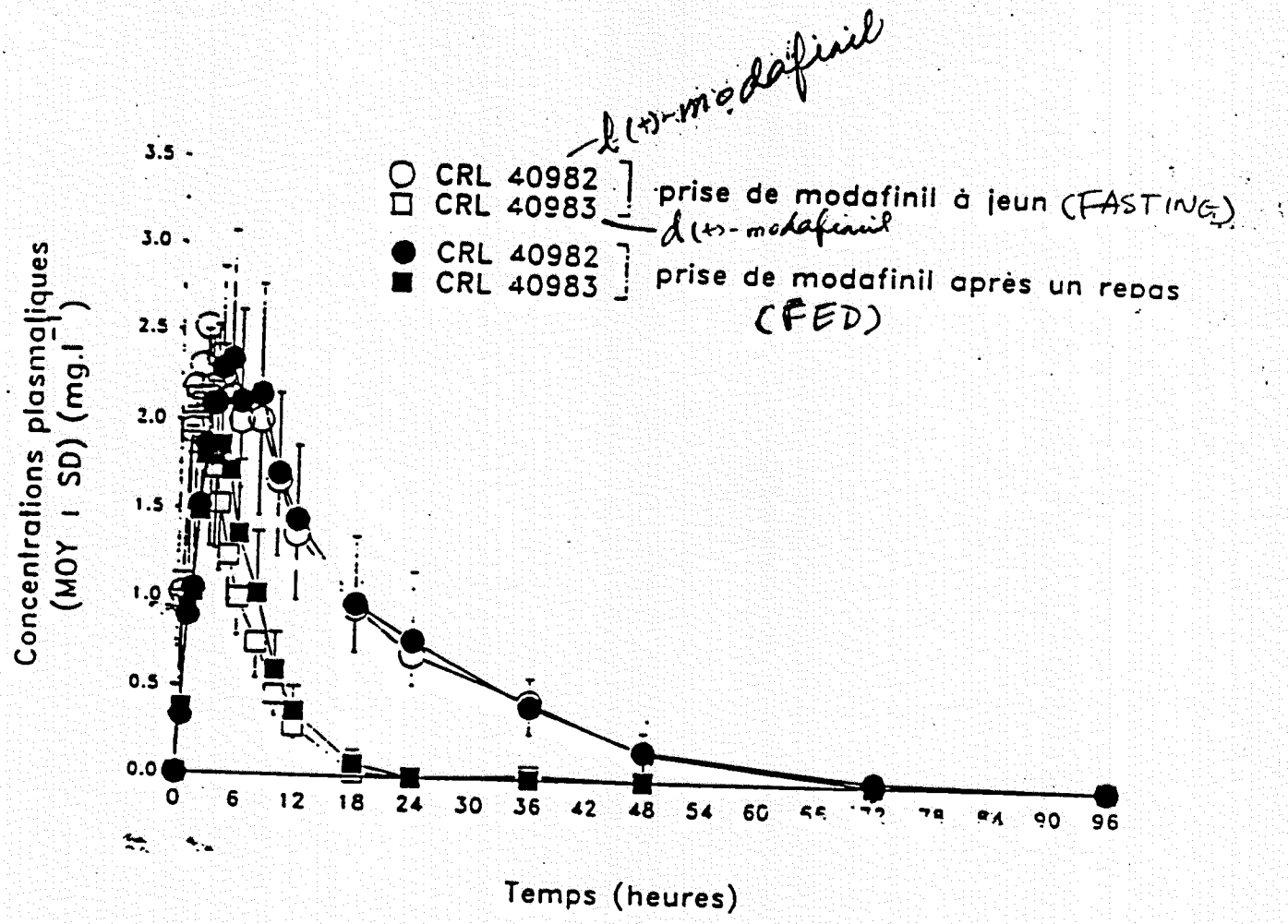


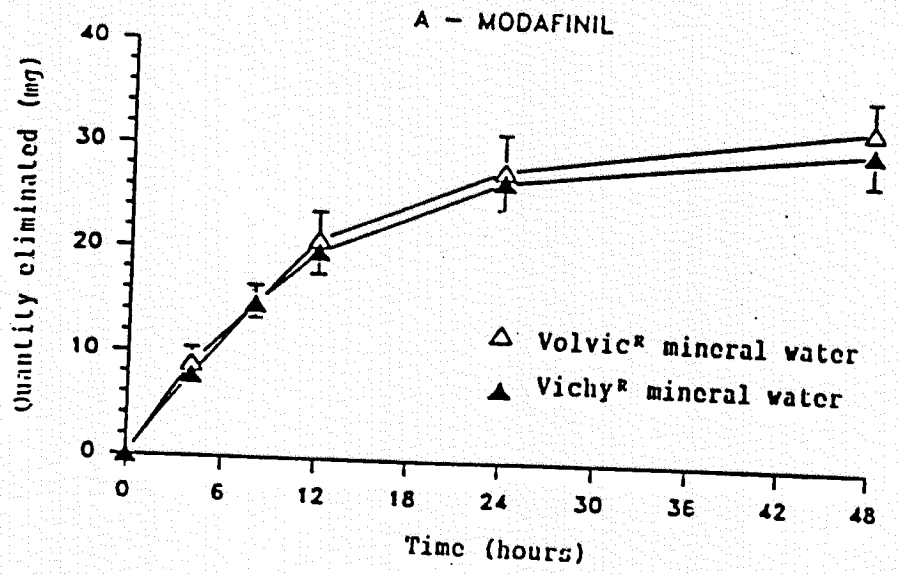
Figure 5 - Mean concentrations of the enantiomers of MODAFINIL after oral administration of 200 mg of MODAFINIL to six subjects after fasting or after a meal

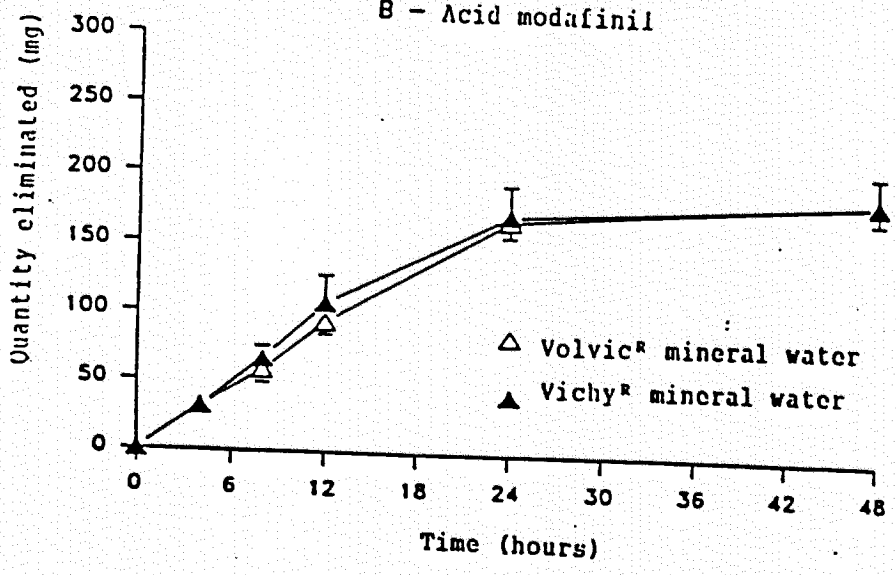
Table 6.2-77. Mean (± SD) Pharmacokinetic Parameters *d*-Modafinil and *l*-Modafinil in Healthy Male Subjects After a Single 200 mg Oral Dose of Modafinil

	Subjects after Fasting						Subjects after Food Intake					
	C_{max} (mg/L)	T_{max} (hr)	AUC_{∞} (mg·hr/L)	$t_{1/2}$ (hr)	CL/F (mL/min)	V/F (L)	C_{max} (mg/L)	T_{max} (hr)	AUC_{∞} (mg·hr/L)	$t_{1/2}$ (hr)	CL/F (mL/min)	V/F (L)
CRL 40982 (*l*-Modafinil)												
Mean	2.62	2.67	48.18	12.13	36.14	37.37	2.49	4.58	49.08	13.43	36.2	41.31
SD	0.40	1.08	11.53	1.23	7.87	5.56	0.62	1.96	14.37	3.46	9.46	11.75
CRL 40983 (*d*-Modafinil)												
Mean	2.37	1.83	14.42*	3.44*	119.34*	35.56	2.13	2.92	15.80*	3.50*	111.01*	34.01
SD	0.41	0.68	3.15	0.26	20.56	7.13	0.51	1.50	4.15	0.31	26.04	10.85

* Significantly different ($p<0.05$) from the corresponding *l*-modafinil value.

Urine alkalinization and kinetics of MODAFINIL





~~Figure 3~~ Cumulated urine elimination of MODAFINIL (A) and acid modafinil (B) expressed in mg (mean ± sem) under conditions of normal pH ([redacted]) or alkaline pH ([redacted]).

9. Evaluation of the Effect of Alkalized Urine on the Kinetics of Modafinil ([redacted]-MOD-023)

Objectives:

To evaluate the effect of urine alkalization on Modafinil PK.

Introduction:

At 400 mg of modafinil, urine excretion of unchanged drug is low (~10%), and the principal form of elimination is modafinil acid. A concomitant prescription of a urine alkalization treatment may accelerate the elimination of modafinil by increasing urine elimination of acid modafinil (ionization of the molecule with a reduction in its tubular reabsorption) and by shifting the balance between modafinil and its acid metabolite towards the production of the latter. This shift may reduce the concentration of the parent drug in plasma and therefore affect the therapeutic efficacy of modafinil.

Study Design and Sampling:

This open, controlled trial was performed as follows:

Six volunteer subjects who had fasted for 12 hours received an oral dose of 400 mg of MODAFINIL (4 tablets dosed at 100 mg). This dosage was chosen as it corresponded to the limit dose at which kinetics have been evaluated. The subjects received this dose either under normal conditions of pH (their drinking water was [redacted]) or under conditions of alkalinization (their drinking water was [redacted].

The protocol was designed to be carried out using a dosage of 600 mg MODAFINIL, but the Ethical Committee at the [redacted] requested that this dose be reduced to 400 mg.

The drinking water sequences were drawn by lot as follows:

Subject	1st period	2nd period
1	[redacted]	[redacted]
2		
3		
4		
5		
6		

Each dosing was given at an interval of one week. Treatment sequences were drawn by lot.

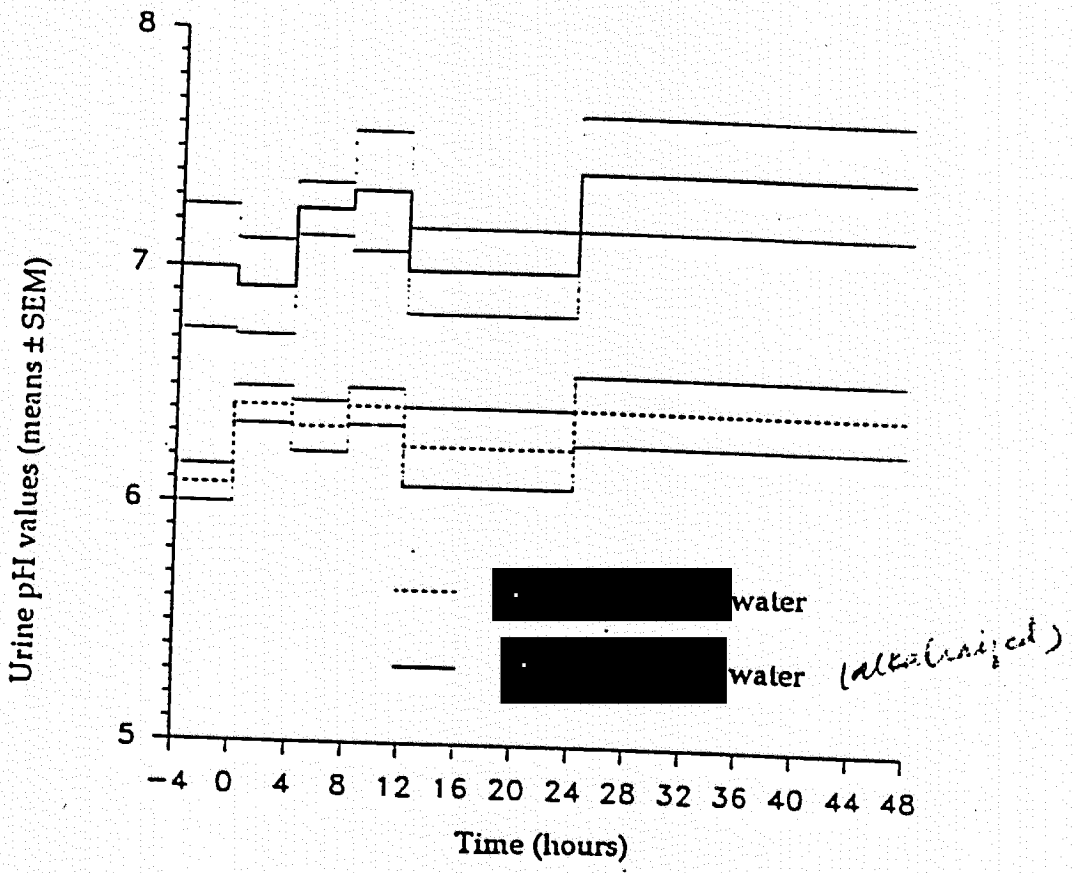
Blood and urine samples were taken at regular intervals:

- 10 ml of blood was taken on dry heparin before (control sample) and then 0.5, 1, 1.5, 2. 2.5, 3, 4, 6, 8, 10, 12, 15, 18, 24, 28, 32 and 48 hours after dosing. The blood was centrifuged, and after separation, the plasma stored at -20°C until assay.
- urines were collected before (control urine samples) and during the periods 0-4, 4-8, 8-12, 12-24 and 24-48 hours after administration, and stored at -20°C until assay.

Results (Attachment 9) and Conclusions:

There is no effect of urine alkalization on the plasma kinetics of modafinil. The profiles of plasma concentrations vs. time and urine elimination of modafinil vs. time were all identical between treatment group and nontreatment group. Urine alkalization had no effect on the plasma and urine kinetics of modafinil metabolites, either. The clinical and laboratory safety of modafinil showed no particular problem with a single dose of 400 mg administration.

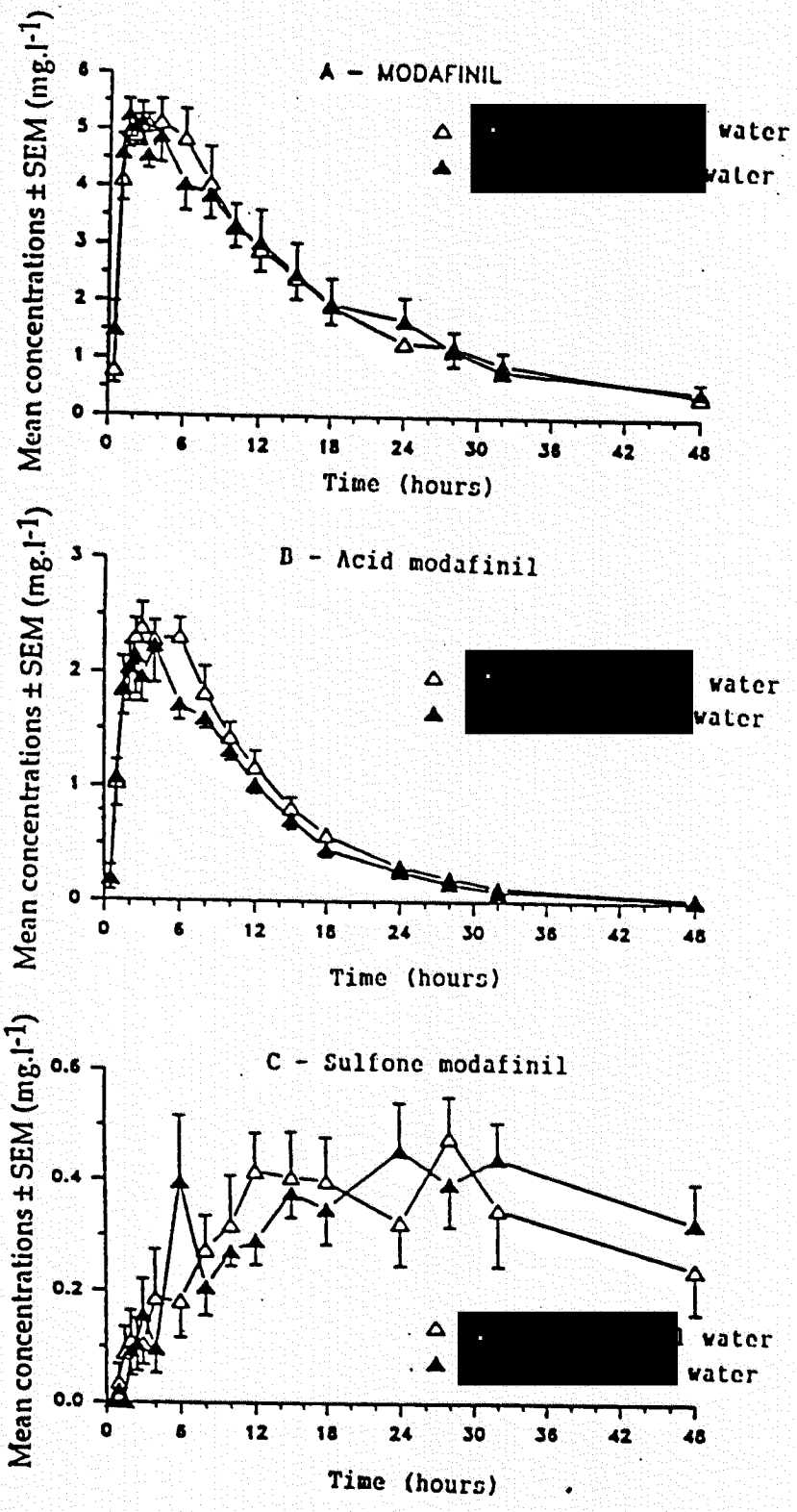
Urine alkalinization and kinetics of MODAFINIL



~~Figure 1.~~ Urine pH values (mean ± SEM) under [redacted] water or [redacted] water.

ATTACHMENT A9

Urine alkalinization and kinetics of MODAFINIL



~~Figure 2.~~ Mean plasma concentrations of MODAFINIL (A), acid modafinil (B) and sulfone modafinil (C) in man after dosing with 400 mg of MODAFINIL under conditions of normal pH ([redacted] water) or alkaline pH ([redacted] water).