CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020717

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#: 20-717

OCT 31 1997

Applicant: Cephalon, Inc.

Name of Drug: Modafinil

Documents Reviewed: NDA Vols dated December 27, 1996 by sponsor's cover letter

Medical Officer: Robert Rappaport, M.D., HFD-120

Background

The sponsor has submitted two US multicenter, placebo-controlled, double-blind, parallel trials of modalfinil for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy. Although 4 other European trials have been submitted, this review covers only the US studies 301 and 302.

Design and Clinical Endpoints

Both trials had double-blind treatment periods of 9 weeks. Treatment arms were placebo, 200 mg/d, and 400 mg/d. Primary endpints were the MWT (Maintenance of Wakefulness Test) and the CGI-C (Clinical Global Impression of Change). The MWT was given 4 times during each visit (visits at baseline and at weeks 3, 6, and 9). The average of the 4 observations was used as the unit of analysis for the visit. **The maximum time to fall asleep was set at 20 minutes.** Secondary endpoints were the MSLT (Multiple Sleep Latency Test), the Epworth Sleepiness Scale (ESS), and the Steer Clear Performance Test (SCPT).

This review focuses on the "efficacy-evaluable" patients: those who took medication at least once and who had at least one post-baseline observation for *both* the MWT *and* the CGI-C.

The primary analysis was ANCOVA for MWT (baseline average MWT as the covariate along with study site as a factor) and CMH for the CGI-C using study site and baseline CGI-S as strata.

The trials were designed so that 95 patients/group would be sufficient to achieve 80% power to detect a difference of 4.0 change from baseline units compared to placebo.

Results

Patient characteristics were well-balanced at baseline. **Since the design and results of both studies are nearly identical, they will be discussed together.**

MWT (All tables come from the sponsor's NDA submission)

Table 1 displays the number of patients at each visit week of the study for the efficacy-evaluable subset. There does not appear to be a significant problem with dropouts. **Table 2** displays the entire set of results for both trials for this patient subset. See **Figure 1** for graphical displays of each trial's treatment means over time. In both studies, both doses were statistically significantly different from placebo for both primary endpoints ($p<.01$ or less). Part of this treatment difference was due to the percentages of patients who remained awake for the full 20 minutes.**Table 3** displays the percentage of patients in each treatment group who stayed awake for a given number (0, 1, 2, 3, or 4) of 20 minute periods. At endpoint in both studies, approximately 80% of the placebo patients fell asleep within 20 minutes, whereas only 55% of the modafinil patients did.

CGI-C

Table 4 displays the distribution of CGI-C scores in both studies. Both studies seem to show that a large part of the treatment effect comes from the category "much improved" in the 400 mg/d group. **Table 5** displays the percentage of patients who "improved", while **Figure 2** displays a bar chart of the percentage of patients who improved over time. **P-values for comparisons to placebo are clearly significant in both studies.**

Conclusion

The sponsor has submitted two clinical trials showing statistical evidence that modafinil is more effective than placebo in prolonging wakefulness. There is no evidence that 400 mg/d is more effective than 200 mg/d.

/S/ [redacted]

David Hoberman, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot /S/ [redacted] 10/23/97

Dr. Chi /S/ [redacted] 10/31/97

cc:
NDA#20-~~667~~ 717
HFD-120/Dr. Leber
HFD-120/Dr. Katz
HFD-120/Dr. Rappaport
HFD-120/Mr. Purvis
HFD-120/~~Mr. Hardeman~~ Ms. Nalanbrace [redacted]
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710Dr. Sahlroot
HFD-710/Dr. Hoberman

TABLE 1

Patient Disposition by Visit

Study C1538a/301/NA/US and Study C1538a/302/NA/US (Efficacy-Evaluable)

Study	Treatment Group	No. Patients Randomized	Baseline	Week 3	Week 6	Week 9	Endpoint
301	Placebo	94	92	92	89	87	92
	200 mg/d	96	95	95	94	94	95
	400 mg/d	95	86	85	82	82	86
302	Placebo	93	88	87	87	84	88
	200 mg/d	90	83	83	78	80	83
	400 mg/d	90	86	86	83	84	86
301/302 Combined	Placebo	187	180	179	176	171	180
	200 mg/d	186	178	178	172	174	178
	400 mg/d	185	172	171	165	166	172

Source: Table Following Text 1.1.
Abbreviations:
mg/d = milligram per day modafinil

APPEARS THIS WAY ON ORIGINAL

Summary of Results from Efficacy Parameters

Study C1538a/301/NA/US and Study C1538a/302/NA/US (Efficacy-Evaluable)

Study	Dose mg/d	N[4]	MWT sleep latency (min) mean ± S.D.		CGI-C N (%)		MSLT sleep latency (min) mean ± S.D.		ESS 0=not sleepy to 24=extreme mean ± S.D.		SCPT % of objects hit mean ± S.D.	
			Baseline	Change from Baseline to Endpoint	Improved	Greatly Improved	Baseline	Change from Baseline to Endpoint	Baseline	Change from Baseline to Endpoint	Baseline	Change from Baseline to Endpoint
301	0	92	5.8 ± 4.7	-0.7 ± 4.6	34 (37)	12 (13)	2.8 ± 2.2	0.5 ± 3.0	18.3 ± 3.3	-1.4 ± 3.7	7.1 ± 9.8	0.8 ± 7.2
	200	95	5.8 ± 5.0	2.3 ± 4.7 [a]	61 (64) [a]	32 (34) [a]	2.9 ± 2.5	1.9 ± 3.2 [a]	17.9 ± 3.8	-3.6 ± 4.7 [a]	9.5 ±12.4	-1.9 ±11.6 [ns]
	400	86	6.6 ± 5.2	2.3 ± 4.9 [a]	62 (72) [a]	43 (50) [a]	3.3 ± 2.9	1.9 ± 4.1 [a]	17.1 ± 4.2	-4.3 ± 4.8 [a]	7.5 ± 8.2	-1.5 ±11.6 [ns]
302	0	88	6.0 ± 5.0	-0.7 ± 4.2	33 (38)	12 (14)	2.2 ± 1.8	1.3 ± 2.6	17.6 ± 4.0	-1.7 ± 3.6	8.5 ± 9.8	0.6 ±11.1
	200	83	6.1 ± 4.9	2.2 ± 4.5 [a]	48 (58) [b]	28 (34) [b]	3.0 ± 2.2	2.0 ± 3.7 [ns]	17.4 ± 3.8	-4.3 ± 4.9 [a]	6.8 ± 8.1	-2.3 ± 8.2 [c]
	400	86	5.9 ± 4.4	2.0 ± 4.7 [a]	52 (60) [b]	29 (34) [b]	2.7 ± 2.0	2.3 ± 3.4 [c]	18.0 ± 3.4	-5.7 ± 5.0 [a]	6.5 ± 8.3	-1.7 ± 6.6 [c]
301/302 Combined	0	180	5.9 ± 4.8	-0.7 ± 4.4	67 (37)	24 (13)	2.5 ± 2.0	0.9 ± 2.8	18.0 ± 3.6	-1.5 ± 3.6	7.8 ± 9.8	0.7 ± 9.3
	200	178	5.9 ± 4.9	2.3 ± 4.6 [a]	109 (61) [a]	60 (34) [a]	2.9 ± 2.3	1.9 ± 3.4 [b]	17.7 ± 3.8	-3.9 ± 4.8 [a]	8.2 ±10.7	-2.1 ±10.2 [b]
	400	172	6.2 ± 4.8	2.1 ± 4.8 [a]	114 (66) [a]	72 (42) [a]	3.0 ± 2.5	2.1 ± 3.7 [a]	17.6 ± 3.8	-5.0 ± 5.0 [a]	7.0 ± 8.2	-1.6 ± 9.3 [b]

Source: Tables Following Text 5.0, 11.0, 16.0, 20.0, and 24.0.

[a] Significantly different compared to placebo, p<0.001.

[b] Significantly different compared to placebo, p<0.01.

[c] Significantly different compared to placebo, p<0.05.

[d] Sample sizes vary with efficacy parameter (MWT, CGI-C, etc.) and time; listed sample sizes indicate patients included in Efficacy-Evaluable population.

Note: Efficacy-Evaluable patients are those who received at least 1 dose of study medication and had at least 1 post-baseline assessment for both MWT and CGI-C.

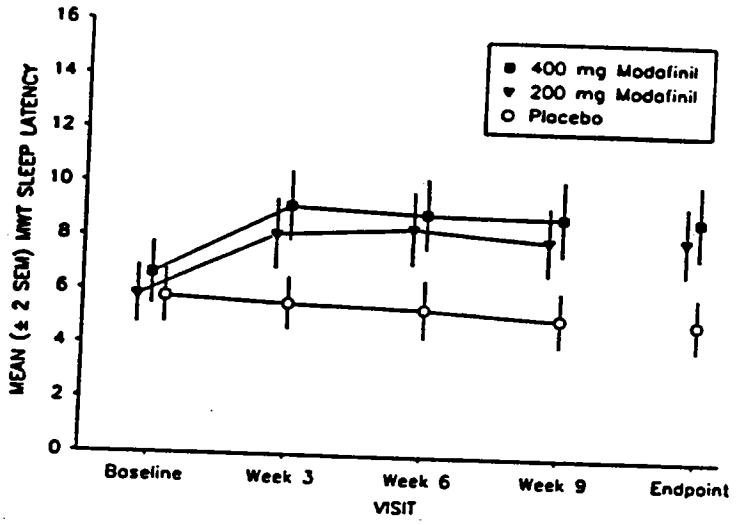
Abbreviations:

CGI-C = Clinical Global Impression of Change; mg/d = milligram per day modafinil; MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test; N = number of patients, ns = not significant; SCPT = Steer Clear Performance Test; S.D. = standard deviation.

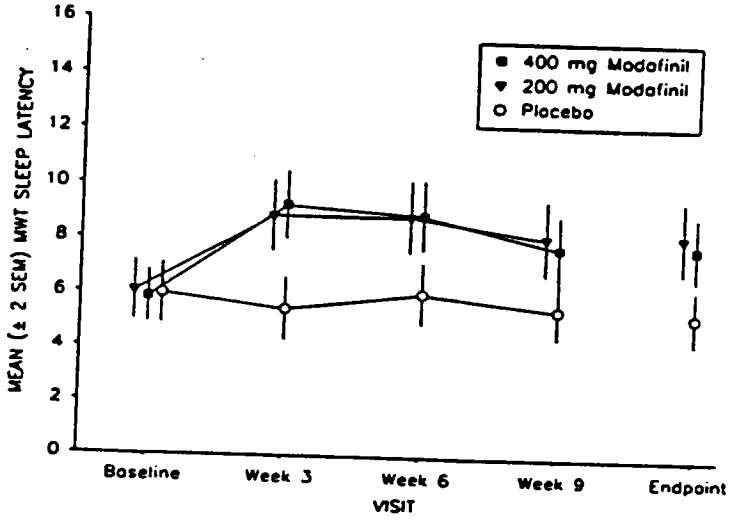
TABLE 2

FIGURE 1

Study C1538a/301/NA/US



Study C1538a/302/NA/US



Mean (± 2 SEM) MWT Sleep Latency versus visit in narcolepsy patients receiving once daily oral doses of 400 mg/d modafinil, 200 mg/d modafinil, or placebo for 9 weeks.

TABLE 3

Summary of MWT Results — Percentage of Patients Who Stayed Awake

Study C1538a/301/NA/US and Study C1538a/302/NA/US (Efficacy-Evaluable)

0 to 4 Tests	Baseline					Week 3					Week 6					Week 9					Endpoint*				
Dose	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Study 301																									
Placebo	79	11	7	2	1	78	13	4	4	0	75	15	6	5	0	85	10	1	1	2	85	11	1	1	2
200	79	11	6	2	2	63	17	4	8	7	56	18	11	8	8	57	20	9	11	3	56	20	9	11	4
400	71	16	9	3	0	46	27	15	5	7	57	14	17	6	6	57	17	6	11	9	57	17	6	10	9
Study 302																									
Placebo	78	14	5	3	0	77	13	8	1	1	76	9	10	3	1	76	18	2	1	2	77	17	2	1	2
200	77	16	2	0	5	58	14	13	10	5	56	16	17	5	6	59	23	6	4	8	58	23	7	4	8
400	79	15	3	1	1	52	16	16	11	5	52	23	9	12	4	56	24	8	10	2	56	24	8	9	2
Study 301/302 Combined																									
Placebo	79	12	6	3	1	78	13	6	3	1	75	12	8	4	1	81	14	2	1	2	81	14	2	1	2
200	78	13	4	1	3	61	16	8	9	6	56	17	14	6	7	58	22	8	8	5	57	21	8	7	6
400	75	16	6	2	1	49	22	16	8	6	55	18	13	9	5	57	20	7	10	5	56	21	7	10	6

Source: Table Following Text 10.0.

* Primary analysis at Endpoint: Significantly different from placebo - 400 mg/d modafinil $p<0.05$ (301, 302); - 200 mg/d modafinil $p<0.05$ (301, 302). Note: 301/302 combined analysis not done.

Note: Efficacy-Evaluable patients are those who received at least 1 dose of study medication and had at least 1 post-baseline assessment for both MWT and CGI-C. Only patients with a positive response at all four tests are included. Endpoint is defined based on average of four tests.

A value of 0 indicates that a patient stayed awake for none of the 4 MWT assessments while a value of 4 indicates a patient stayed awake for 20 minutes or longer for all of the 4 MWT assessments on a given day.

Abbreviations:

CGI-C = Clinical Global Impression of Change; mg/d = milligram per day modafinil; MWT = Maintenance of Wakefulness Test; N = number of patients.

TABLE 4

Summary of CGI-C — Endpoint* Values (Number [%] in Each Category)

Study C1538a/301/NA/US and Study C1538a/302/NA/US [Efficacy-Evaluable]

Study	Response Category	Treatment Group		
		Placebo - N(%)	200 mg/d - N(%)	400 mg/d - N(%)
301	Total Number of Subjects	92	95	86
	Very much improved	4 (4)	7 (7)	8 (9)
	Much improved	8 (9)	25 (26)	35 (41)
	Minimally improved	22 (24)	29 (31)	19 (22)
	No change	43 (47)	27 (28)	20 (23)
	Minimally worse	11 (12)	5 (5)	3 (3)
	Much worse	3 (3)	2 (2)	1 (1)
	Very much worse	1 (1)	0	0
302	Total Number of Subjects	88	83	86
	Very much improved	0	7 (8)	5 (6)
	Much improved	12 (14)	21 (25)	24 (28)
	Minimally improved	21 (24)	20 (24)	23 (27)
	No change	42 (48)	27 (33)	26 (30)
	Minimally worse	9 (10)	7 (8)	5 (6)
	Much worse	4 (5)	1 (1)	3 (3)
	Very much worse	0	0	0
301/302 Combined	Total Number of Subjects	180	178	172
	Very much improved	4 (2)	14 (8)	13 (8)
	Much improved	20 (11)	46 (26)	59 (34)
	Minimally improved	43 (24)	49 (28)	42 (24)
	No change	85 (47)	54 (30)	46 (27)
	Minimally worse	20 (11)	12 (7)	8 (5)
	Much worse	7 (4)	3 (2)	4 (2)
	Very much worse	1 (1)	0	0

Source: Table Following Text 11.0.

* Primary analysis at Endpoint: Significantly different from placebo - 400 mg/d modafinil $p<0.001$ (301, 301/302), $p=0.02$ (302); - 200 mg/d modafinil $p<0.001$ (301, 301/302), $p=0.01$ (302).

Note: Efficacy-Evaluable patients are those who receive at least 1 dose of study medication and had at least 1 post-baseline assessment for both MWT and CGI-C.

Abbreviations:
CGI-C = Clinical Global Impression of Change; mg/d = milligram per day modafinil; MWT = Maintenance of Wakefulness Test; N = number of patients.

TABLE 5

Summary of CGI-C Results — Number (%) of Patients Who Improved

Study C1538a/301/NA/US and Study C1538a/302/NA/US (Efficacy-Evaluable)

Study	Treatment Group	Number (%) of Patients Who Improved			
		Week 3	Week 6	Week 9	Endpoint*
301	Placebo	36 (40)	35 (40)	32 (37)	34 (37)
	200 mg/d	62 (67)	61 (66)	60 (65)	61 (64)
	400 mg/d	66 (80)	63 (78)	60 (74)	62 (72)
302	Placebo	33 (38)	38 (44)	32 (38)	33 (38)
	200 mg/d	45 (55)	55 (71)	46 (58)	48 (58)
	400 mg/d	60 (70)	51 (62)	51 (61)	52 (60)
301/302 Combined	Placebo	69 (39)	73 (42)	64 (38)	67 (37)
	200 mg/d	107 (61)	116 (68)	106 (62)	109 (61)
	400 mg/d	126 (75)	114 (70)	111 (68)	114 (66)

Source: Table Following Text 11.0.

* Primary analysis at Endpoint: Significantly different from placebo - 400 mg/d modafinil $p<0.001$ (301, 301/302), $p<0.01$ (302); - 200 mg/d modafinil $p<0.001$ (301, 301/302), $p<0.01$ (302).

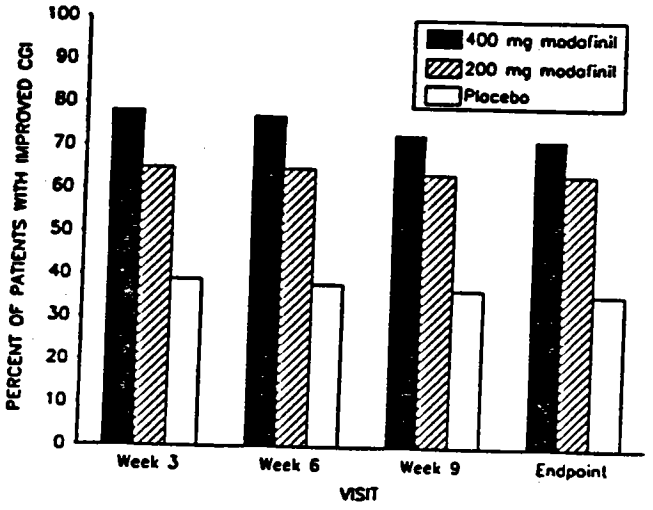
Note: Efficacy-Evaluable patients are those who received at least 1 dose of study medication and had at least 1 post-baseline assessment for both MWT and CGI-C.

Abbreviations:
CGI-C = Clinical Global Impression of Change; mg/d = milligram per day modafinil; MWT = Maintenance of Wakefulness Test.

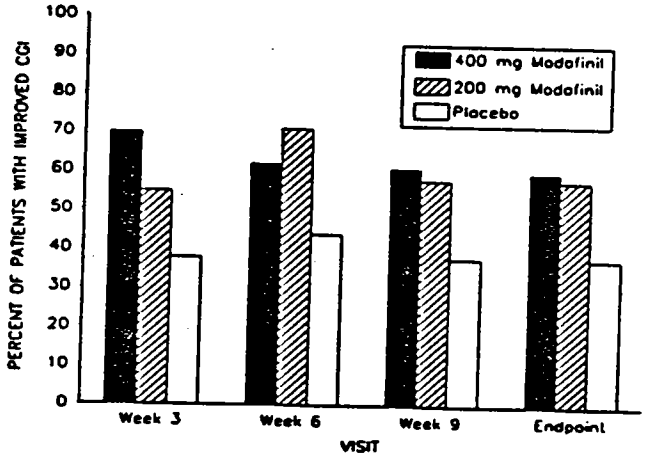
APPEARS THIS WAY ON ORIGINAL

FIGURE 2

Study C1538a/301/NA/US



Study C1538a/302/NA/US



Percentage of patients in each dose group at each visit whose CGI-C Scores Improved.

APPEARS THIS WAY ON ORIGINAL