- One recording 50 minutes after administering 40% whiskey, dosed to achieve a blood alcohol level of 0.25 to 0.40 g/l (Period 2).
- One recording on Day 14 of acamprosate dosing, at a daily dose of 1332 mg (two 333 mg tablets in the morning, 1 at midday, and 1 in the evening) (Period 3).
- One recording on Day15 after administration of both acamprosate and a ethanol (Period 4).

Volunteers abstained from other alcohol consumption, as well as from consumption of coffee, tea, caffeinated carbonated drinks or other stimulants.

Blood alcohol levels, obtained 45 minutes after the start of the ingestion of alcohol, ranged from 0.09 – 0.29 g/L. All subjects but one (at 0.09) had BAC above the 0.10 level considered evidence of intoxication in the U.S. Notably, however, 4 of 14 subjects had much lower BACs during the acamprosate/EtOH interaction condition (Period 4) than during the EtOH-only condition (period 2), rendering an evaluation of acamprosate's effects on EtOH-induced changes questionable in these subjects.

Comparison of the different EPG findings showed the following :

As expected, alcohol disrupted sleep patterns, increasing the proportion of intrahypnic waking (IW) and the proportion of stage IA (drowsiness) of non-REM sleep (NREMS), while decreasing Stage III of NREMS (established sleep).

The mean values for period 3 (acamprosate alone) did not differ at a statistically different level from the reference recording in proportions of IW. However, about half the subjects did have increases in IW comparing period 2 to the reference recording. (Note also that the dose used is lower than the dose proposed for marketing.) For the various stages of sleep, there were no statistically significant differences in group mean values between period 3 and the reference recording. However, about a third of the subjects did show an increase in stage IA sleep and a decrease in Stage III sleep, comparable to that seen in the EtOH condition.

Both mean values and individual values for period 4 suggest that the presence of acamprosate tended to normalize stage IA and to increase stage II of NREMS (light sleep) as compared with alcohol on its own. For about half the subjects, the percentage of IW was lower in the acamprosate + EtOH condition than in the EtOH alone condition (although two of these were subjects whose BAC was lower in the combination condition).

The mean percentage of Stage IV sleep (deep sleep) did not differ significantly between the 4 periods. Large inter-subject variations in rapid-eye-movement sleep (REMS) precluded meaningful comparison across conditions.

The study report concluded that acamprosate 1332 mg/day did not disturb sleep and had a tendency to normalize the sleep abnormalities induced by alcohol. Because the dose is lower

than that proposed for marketing (and because the individual results in some cases suggested an effect not seen in group mean comparisons), the claim of lack of effect of acamprosate on sleep architecture is not fully supported. There does appear to be an indication that acamprosate normalizes the effect of alcohol on Stage IA sleep. The clinical significance of this finding is unclear.

3.2.1.2 AFB 06/0081-89 (Hermann): Pharmaco-EEG and Psychometric Study to Assess the Central Nervous Effect of AOTAL in Two Dosages (400 and 800 mg) in Comparison to Diazepam (10 mg) and Placebo in Healthy Male Volunteers

This was a double-blind, placebo- and active-controlled, 4-way crossover study in healthy volunteers which compared the effects of single doses of acamprosate (400 mg or 800 mg) and 10 mg diazepam vs placebo (given in random sequence with 1 week washout between periods) on electroencephalograms and various psychometric tests. The study was conducted in 1989 under the direction of W. M. Hermann, M.D., in Berlin, Germany.

Twenty healthy male volunteers subjects entered the study, with 16 completing all study periods. Electroenchephalographic (EEG) recordings were made under 2 conditions which differed in the degree of activation of the subject: a high activation condition, during which time subjects had to perform a reaction time (RT) task (considered suitable for detecting sedative drug effects) and a low activation condition, during which time no stimulus was presented, but subjects were instructed to stay awake (considered suitable for detecting CNS stimulation). During each period, EEG records were taken prior to drug intake and subsequently 1.5, 3, and 4.5 hours after single oral drug administration at each session. Before and after each EEG recording subjects completed a 100 mm visual analog scale to document tiredness. Psychometric tests included an automated test of calculation and the EWL 60-S adjective check list (pre-, 2, 3.5, and 5 hours after drug intake).

There were no systematic differences between acamprosate and placebo in any of the EEG frequency bands, while diazepam differed significantly from both placebo and acamprosate. Diazepam induced systematic changes in the EEG with a reduction of power in the theta and the 2 alpha frequency bands and an increase of power in the 3 beta bands. There were significant treatment effects on the tiredness rating by visual analogue scale. Diazepam also increased ratings of subjective tiredness, compared to placebo, while acamprosated did not.

Performance in a demanding calculation test was clearly impaired under diazepam, both in total number of attempted tasks as well as number of correctly solved tasks. Both doses of acamprosate also reduced performance at the later time periods (3.5 and 5 hours post-dosing).

The applicability of these findings to the steady-state condition is uncertain, as steady-state Tmax after the recommended dosing regimen is nearly four times the single-dose Tmax after

666 mg (which is higher than the 400 mg dose tested in this study but lower than the 800 mg dose).

3.2.2 Effect of Acamprosate on Performance Tasks Relevant to Driving Ability

3.2.2.1 Moser I: The Effects of Aota-Ca on Performances Relevant to Driving

Moser I (Oct. 19, 1987) was a randomized, double-blind, placebo- and active-controlled, 3-way crossover study in 18 healthy volunteers, comparing the effects of single doses of acamprosate 666 mg, diazepam 10 mg, and placebo (separated by 7-day washout) on psychometric tests relevant to driving. The study was conducted in 1987 under the direction of Dr. Liselotte Moser in Cologne, Germany.

Volunteers received each of the following study drugs on a single occasion, all of which were over-encapsulated so as to appear identical: 666 mg acamprosate (two 333 mg tablets); 10 mg diazepam + 1 placebo tablet; or 2 placebo tablets. At each of the 3 sessions, psychometric testing was performed pre-dosing and exactly 1 hour post-dosing. Because this is substantially prior to Tmax for acamprosate, the results of this study do not seem applicable to the clinical situation (further complicated by the observation that Cmax at steady state is nearly 4x that after a single 666 mg dose) and will not be further described in this review.

3.2.2.2 Moser II: The Effects of Aota-Ca Combined with Alcohol on Performances Relevant to Driving in Healthy Volunteers

This was a randomized, double-blind, placebo- and active-controlled, 3-way crossover study in 24 healthy male volunteers, comparing the effects of alcohol loading in association with single doses of acamprosate, diazepam, and placebo (separated by a 7-day washout period) on psychometric tests relevant to driving. The study was conducted in 1987 under the direction of Dr. Liselotte Moser in Cologne, Germany.

Volunteers received each of the following study drugs on a single occasion, all of which were over-encapsulated so as to appear identical: 666 mg acamprosate (two 333 mg tablets); 10 mg diazepam + 1 placebo tablet; or 2 placebo tablets. Immediately after study medication was administered, subjects began consuming 0.75 g/kg of alcohol, given as neat whiskey (40 vol% alcohol content), over 30 minutes, intended to yield a breath alcohol of 0.57 to 0.59 parts per thousand (at least 3 hours after the last meal and 45 minutes after the end of drinking). Testing began 45 minutes after the end of alcohol drinking, timed to approximate Cmax for alcohol, but only 1:15 after study medication and therefore well before Tmax of acamprosate (4.5 hr).

In this study, subjects in the acamprosate + EtOH performed no worse than subjects in the EtOH + placebo condition; however it must be noted that subjects were too intoxicated to complete subjective scales or to perform a task requiring standing without swaying for 30 seconds. The lack of an additive effect of acamprosate (prior to Tmax after a single dose) on the impairment seen in extremely intoxicated subjects is of uncertain clinical significance.

4 DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Overall Data

All of the data in the application are from the development programs of Laboratories Meram and Lipha Pharmaceuticals.

The sponsor has grouped the clinical data as follows:

- **Group I:** These are the double-blind, placebo-controlled clinical trials related to claims of effectiveness. Within this group are the controlled, pivotal efficacy studies and the European and U.S. controlled, supportive efficacy studies.
- **Group II:** Clinical Pharmacology studies.
- **Group III:** Early clinical experience studies.
- **Group IV:** Phase IV, uncontrolled studies related to claims of effectiveness

Group I:

All Group I studies are double-blind, placebo-controlled studies in alcohol-dependent patients. These include 3 pivotal studies (referred to as *Pelc II, PRAMA, and Paille*) and 10 supportive studies, 7 of which are considered "short-term", because the duration of the Treatment Phase was 6 months or less, and 3 of which are designated "long-term", because the Treatment Phase was 1 year. All studies were conducted in Europe except for the U.S. study, ACAMP/US/96.1. Only ACAMP/US/96.1 was conducted under IND #51,809. Among the supportive short-term studies, the American study, ACAMP/US/96.1 (US 96.1) is given greater emphasis because it involves a U.S. population and also because of the greater available detail in and relevance of safety information.

The summary of safety information for the NDA focuses on data from the Group I studies and presents additional safety data from all other study groupings, as available. Accordingly, the ISS database collectively consists of data from the 3 double-blind, placebo-controlled pivotal efficacy studies (1 short-term and 2 long-term), the European and US Controlled Short-Term Supportive efficacy studies, and the European Long-Term Supportive efficacy studies (Group I studies). In addition, the ISS presents and discusses data from the study reports of clinical pharmacology (Group II) studies, from the study reports of early clinical experience (Group III) studies, and from the study reports of Phase IV European Uncontrolled Short-Term Studies (Group IV) studies, as well as pharmacovigilance information.

4.2 Tables Listing the Clinical Trials

The table below, sponsor's In-text table 3.8.4.1, summarizes the studies included in the efficacy database.

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Table 4.2:1 Summary of Group I Studies: Controlled Clinical Studies Related to Claims of Effectiveness

Study #, (*Common Name*) Principal Investigator, Country	Status (Start – End Dates)[1]	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
			Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
AOTA/B/90.3 (*Pelc II*) I. Pelc, Belgium, France	C (June, 1990 to April, 1992)	Pro, MC (11), R, DB, PC, PG (3: Group A: P vs Group B: acamp, 1332 mg/day vs Group c: acamp, 1998 mg/day) S/E study in ADS, after withdrawal from alcohol. (90 days)	Placebo, tabs (#1623) Acamp, tabs, 333 mg (#1624)	*Grp. A:* 6 P tabs *Grp. B:* 1332 + 2 P tabs *Grp. C:* 1998	*Grp. A:* 2 tabs tid *Grp. B:* 2 acamp tabs in morning, 1 acamp tab + 1 P tab at midday, 1 acamp tab + 1 P tab in evening *Grp. C:* 2 tabs tid	*Grp. A:* 62 ADS (32) *Grp. B:* 63 ADS (44) *Grp. C:* 63 ADS (43)	*Grp. A:* 26-59 (40.9) *Grp. B:* 21-71 (43.3) *Grp. C:* 26-59 (40.5)	*Grp. A:* 55/7 (89/11) *Grp. B:* 51/12 (81/19) *Grp. C:* 54/9 (86/14)	ND ND ND
AOTA 411.198 (*PRAMA*) H. Sass, Germany	C (Oct. 16, 1990 to Dec. 3, 1992)	Pro, MC (12), R, DB, PC, PG (2: acamp vs P, with pre-randomization stratification according to body weight) S/E study in ADS, after withdrawal from	Acamp, tabs, 333 mg (#3251) Placebo, tabs (#3248)	1998*[2] (1332) 6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid 2 tabs tid 2-1-1 tabs tid	136 ADS (79) 136 ADS (55)	21-58 (41.9) 21-65 (40.5)	102/34 (75/25) 109/27 (80.1/ 19.9)	ND ND

[1] Dates will be given as M/D/Y, when available

[2] For studies where acamprosate dose is marked with an asterisk, daily dosage was on the basis of body weight. For patients with a bodyweight greater than 60 kg (or for PRAMA, ≥60 kg): 2 tabs of acamprosate (666 mg) or placebo in the morning, 2 tabs of acamprosate (666 mg) or placebo at midday, and 2 tabs of acamprosate (666 mg) or placebo in the evening (*total daily dose of 1998 mg*). For patients with a bodyweight less than or equal to 60 kg (or for PRAMA, <60 kg): 2 tabs of acamprosate (666 mg) or placebo in the morning, 1 tab of acamprosate (333 mg) or placebo at midday, and 1 tab of acamprosate (333 mg) or placebo in the evening (*total daily dose of 1332 mg*). In these same studies, number of patients entered per treatment group and number of patients completing per treatment group are provided for the entire group, irrespective of weight considerations.

Study #, (*Common Name*) Principal Investigator, Country	Status (Start – End Dates)[1]	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
			Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
		alcohol. (48 weeks)							
544 (*Paille*) F. Paille, France	C (April, 1989 to Nov., 1992)	Pro, MC (31), R, DB, PC, PG (3: Treatment 1 = P; vs Treatment 2 = acamp, 1332 mg; vs Treatment 3 = acamp, 1998 mg) S/E study in ADS, committed to abstinence, after withdrawal from alcohol. (360 days)	Placebo, tabs (#41320) Acamp, tabs, 333 mg (#41319, 41328, 41368)	*Trt. 1:* 6 tabs *Trt. 2:* 1332 + 2 P tabs *Trt. 3:* 1998	*Trt. 1:* 2 tabs tid *Trt. 2:* 2 acamp morning: 1 acamp + 1 P midday; 1 acamp + 1 P evening. *Trt. 3:* 2 acamp tabs tid	*Trt.1:* 177 ADS (62) *Trt.2:* 188 ADS (85) *Trt.3:* 173 ADS (90)	*Trt.1:* ND (42.5) *Trt.2:* ND (43.7) *Trt.3:* ND (43.3)	*Trt.1:* 147/30 (83/17) *Trt.2:* 146/42 (78/22) *Trt.3:* 137/36 (79/21)	*Trt.1:* ND *Trt.2:* ND *Trt.3:* ND
AOTA/I/89.4 (*Poldrugo*) F. Poldrugo, Italy	C (Oct., 1989 to July, 1992)	Pro, MC (7), R, DB, PC, PG (2: acamp vs placebo) with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#1580) Placebo, tabs (#1579)	1998* (1332) 6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid 2 tabs tid 2-1-1 tabs tid	122 ADS (65) 124 ADS (47)	ND (42.9) ND (44.9)	84/38 (69/ 31) 95/29 (77/23S)	ND ND
AOTA/I/90.1 (*Tempesta*) E. Tempesta, Italy	C (Oct., 1989 to April, 1993)	Pro, MC (18), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#3250) Placebo, tabs (#3247)	1998 6 tabs	2 tabs tid 2 tabs tid	164 ADS (124) 166 ADS (122)	ND (45.9) ND (46.0)	139/25 (84.8/ 15.2) 134/32 (80.7/ 19.3)	ND ND

Study #, (*Common Name*) Principal Investigator, Country	Status (Start – End Dates)[1]	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
			Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
AOTA/LP90/ N001 *(UKMAS)* J. Chick, United King.	C (June, 1990 to July, 1993)	Pro, MC (20), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS, after withdrawal from alcohol. A no-treatment period of ≥7 days was to occur between end of alcohol withdrawal and randomization. (24 weeks)	Acamp, tabs, 333 mg (#1624)	1998	2 tabs tid	289 ADS (100)	ND (42.8)	252/37 (87.2/ 12.8)	ND
			Placebo, tabs (#1623)	6 tabs	2 tabs tid	292 ADS (103)	ND (43.8)	233/59 (79.8/ 20.2)	ND
AOTA/NL/91.1 AOTA/B/90.2 *(BENELUX)* P. Geerlings and C. Ansoms, Belgium, The Netherlands	C (May, 1990 to Oct., 1992)	Pro, MC (22), R, DB, PC, PG (2: acamp vs placebo) with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#1519, 3306, 1580 and 3250)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	128 ADS (38)	19-65 (40.3)	97/31 (76/24)	ND
			Placebo, tabs (#1518, 3305, 1579 and 3247)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	134 ADS (32)	21-63 (41.7)	102/32 (76/24)	ND
AOTA/E/91.1 *(ADISA)* A. Gual, Spain	C (May, 1993 to Oct., 1994)	Pro, MC (11), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS from onset of alcohol withdrawal. (180 days)	Acamp, tabs, 333 mg (#3306)	1998	2 tabs tid	148 ADS (96)	21-61 (41.4)	119/29 (80/20)	ND
			Placebo, tabs (#3305)	6 tabs	2 tabs tid	148 ADS (90)	22-64 (40.6)	117/31 (79/21)	ND
AD 04 089 *(Ladewig)* D. Ladewig, Switzerland	C (Aug., 1989 to Jan., 1991)	Pro, MC (3), R, DB, PC, PG (2: acamp vs placebo) with pre-randomization stratification according to body weight, S/E study in ADS, after	Acamp, tabs, 333 mg (#1580)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	29 ADS (19)	28-68 (47.7)	25/4 (86/14)	ND
			Placebo, tabs (#1579)	6 tabs	2 tabs tid	32 ADS (21)	31-70 (46.9)	22/10 (69/31)	ND

Study #, (*Common Name*) Principal Investigator, Country	Status (Start – End Dates)[1]	Study Design (Drug Treatment Duration)	Treatment Groups: Drug, Dosage Form, Strength (Formulation & Batch #)	Treatment Groups: Total Daily Dose in mg	Treatment Groups: Regimen	Treatment Groups: #, Type of Patients Entered per Group (# completed)	Demographics: Age Range (mean)	Demographics: Sex: M/F (%)	Demographics: Race: W/B/H/O (%)
		withdrawal from alcohol. (180 days)		(4 tabs)	2-1-1 tabs tid				
ACAMP/US/ 96.1 (*US 96.1*) B. Mason, United States	C (May, 1997 to Jan., 1999)	Pro, MC (21), R[3], DB, PC, PG (3: P vs acamp, 2 g vs acamp, 3g), with pre-randomization stratification according to alcohol detoxification (yes/no), S/E study in ADS. (6 months)	Placebo, tabs (#3557 and 3569) Acamp, tabs, 500 mg (#3356 and 3570)	*Placebo:* 6 P tabs *Acamp 2g:* 2000 + 2 P tabs *Acamp 3g:* 3000	*Placebo:* 3 tabs bid *Acamp 2g:* 2 acamp tabs + 1 P tab bid *Acamp 3g:* 3 acamp tabs bid	*Placebo:* 260 ADS (143) *Acamp 2g:* 258 ADS (106) *Acamp 3g:* 83 ADS (43)	*Placebo:* 22-69 (44.4) *Acamp 2g:* 23-72 (44.9) *Acamp 3g:* 21-66 (43.6)	*Placebo:* 166/91 (65/35) *Acamp 2g:* 176/77 (70/30) *Acamp 3g:* 59/23 (72/28)	*Placebo:* 220/18/11/8 (86/7/4/3) *Acamp 2g:* 217/24/12/0 (86/9/5/0) *Acamp 3g:* 71/8/3/0 (87/10/4/0)
AD 10 089, (*Lesch*) O. Lesch, Austria	C (Dec., 1989 to March, 1993)	Pro, MC (5), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days)	Acamp, tabs, 333 mg (#1624) Placebo, tabs (#1623)	1998* (1332) 6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid 2 tabs tid 2-1-1 tabs tid	224 ADS (94) 224 ADS (85)	22-64 (41.9) 15-70 (42.0)	168/56 (75/25) 185/39 (82.6/ 17.4)	ND ND
AOTA/P/89.1 (*Barrias*) J.C. Barrias, Portugal	C (Nov., 1989 to Oct., 1992)	Pro, MC (9), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E study in ADS, after	Acamp, tabs, 333 mg (#1580) Placebo, tabs	1998* (1332) 6 tabs	2 tabs tid 2-1-1 tabs tid 2 tabs tid	150 ADS (86) 152 ADS (83)	21-64 (39.7) 23-63	139/11 (92.7/ 7.3) 139/13 (91.4/	ND ND

[3] Randomization was in a ratio of 3:3:1 for the treatment groups placebo, acamp 2 g/day and acamp 3g/day, respectively.

Study #, (*Common Name*) Principal Investigator, Country	Status (Start – End Dates)[1]	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
			Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
		withdrawal from alcohol. (360 days)	(#1579)	(4 tabs)	2-1-1 tabs tid		(41.0)	8.6)	
AA 11 088 (*Besson*) J. Besson, Switzerland	C (Jan., 1989 to Jan., 1993)	Pro, MC (3), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight and open-label use (yes/no) of Antabuse (disulfiram) as associated therapy, S/E study in ADS, after withdrawal from alcohol. (360 days)	Acamp, tabs, 333 mg (#1243 and 3249)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	61 ADS (19)[4]	25-62 (42.6)	50/11 (82.0/ 18)	ND
			Placebo, tabs (#1242 and 3247)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	57 ADS (19)	26-62 (42.6)	43/14 (75.4/ 24.6)	ND

Sponsor's In-Text Table 3.8.4:1

The following abbreviations are used throughout the table above:

AC	=	Active comparison	MC	=	Multicenter	Pro	=	Prospective
AAS	=	Alcohol abusing subjects	MD	=	Multiple dose	R	=	Randomized
ADS	=	Alcohol dependent subjects	ND	=	No data or Not done	RI	=	Renal-impaired subjects
AC	=	Acamprosate	NR	=	Non-randomized	Ret	=	Retrospective
C	=	Completed	O	=	Ongoing	SB	=	Single blind
CrCl	=	Creatinine clearance	OE	=	Over-encapsulated	SC	=	Single center
DB	=	Double blind	OL	=	Open label	S/E	=	Safety and efficacy
HI	=	Hepatic-impaired subjects	P	=	Placebo	SnD	=	Single dose
HV	=	Healthy volunteers	PC	=	Placebo-controlled	WO	=	Wash-out period
I	=	Incomplete	PG	=	Parallel group	XO	=	Cross-over (number of arms)
LBW	=	Lean body weight						

[4] In this study, 24 patients (20 male, 4 female) in the acamprosate treatment group and 24 patients (17 male, 7 female) in the placebo group also received Antabuse®.

The overall exposure to acamprosate at the to-be-marketed dose (or higher) in the Group I studies, for which the most detailed safety information and meaningful denominators are available, was 1749 patients. The duration of exposure was distributed as follows.

Table 4.2:2 Overall Exposure to Acamprosate 1998 mg/day or more in Group I Studies

Duration	N (total = 1749)	%
Total	1749	
<4 wks	221	13%
4-8 wks	198	11%
8-13 wks	215	12%
13-26 wks	614	35%
26-39 wks	180	10%
39-52	250	14%
52+	71	4%

4.3 Postmarketing Experience

Pharmacovigilance data from Europe was incorporated in Dr. Cooper's safety review.

4.4 Clinical Efficacy Review Methods

4.4.1 Description of Review Conduct

The three trials identified by the sponsor as pivotal efficacy studies (known as "Pelc-II," "Paille," and "PRAMA") were reviewed individually for evaluation of study design and conduct and assessment of the validity of the sponsor's efficacy conclusions. The single American study, US96.1, was reviewed individually to try to resolve the inconsistent efficacy results between the European studies and the American study. Ten additional "supportive" studies were reviewed only as study summaries.

(Note that the safety review was conducted by Drs. Michael Sevka and Charles Cooper, whose methods are described in their reviews.)

4.4.2 Overview of Materials Consulted in Review

None of the three pivotal efficacy trials were submitted to the IND. In fact, all were completed at the time the sponsor first met with the agency prior to opening the IND. Therefore, the only materials relevant to these studies were submitted in the NDA. The original protocols and case report forms were carefully examined to reconstruct study procedures. Two sets of documents were used to evaluate study outcome: the original study reports/statistical reports submitted to the European dossier (vol 76-83) and the sponsor's integrated summary of efficacy (Section 8.7). In addition, electronic datasets were examined for these studies.

4.4.3 Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations (DSI) was asked to audit one site from each of the long-term European pivotal trials (PRAMA and Paille). Particular attention to sources of bias and unblinding was requested.

Inspection of one site participating in the Paille trial and one site participating in the PRAMA trial revealed no concern about fraud. However, some "sloppiness" was observed, such as a subject being classified as abstinent despite elevated blood alcohol levels recorded in the CRF, and a subject being classified as non-abstinent due to "missing data" which was, in fact, present in the CRF.

The sponsor's efficacy conclusions were also cross-checked via analysis of primary datasets to reproduce the findings in the various NDA tables.

4.4.4 Adherence to Accepted Ethical Standards in Trial Conduct

According to the sponsor, the pivotal trials (and all "Group I" studies other than the U.S. study and study "ADISA") were initiated prior to July 1, 1991, the date when the EC Guidelines on Good Clinical Practice (GCP) came into effect. Lipha asserts that the earlier studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and fulfilled local GCP requirements. ADISA and the U.S. study were carried out according to Good Clinical Practice standards.

4.4.5 Evaluation of Financial Disclosure

Lipha notes that the clinical studies submitted in support of this NDA were conducted and completed prior to February 2, 1999, predating the effective date of 21CFR 54. However, Lipha certifies to the absence of financial interests and arrangements regarding compensation affected by outsome of the clinical studies, financial interests and arrangments regarding significant equity interest in the sponsor of a covered study, proprietary interest in the tested product, and significant payments of other sorts, for all investigators who enrolled patients into the submitted studies.

5 INTEGRATED REVIEW OF EFFICACY

5.1 Brief Statement of Conclusions

In three European pivotal efficacy studies, subjects randomized to acamprosate were more likely than subjects randomized to placebo to be assessed by the clinician as abstinent, using either continuous abstinence or intermittent periods of abstinence as the success measure. These measures of efficacy differ from the sponsor's labeling claim, which reports the '[redacted]'. The method of ascertainment of the number of drinking days in the European studies was insufficiently systematic to allow for precise counting of number of days drinking or not drinking. Therefore, although the data support the claim that acamprosate is effective in maintaining abstinence in recently-detoxified alcoholics, it is not possible to quantify the effect in terms of specific duration of abstinence. The single U.S. study failed to support the efficacy of acamprosate, and this discrepancy was addressed in a meeting of the Psychopharmacologic Drugs Advisory Committee on May 10, 2002. The recommendation of the Committee was to accept the validity of the European studies (pending inspection), and to regard the American study as a failure, providing neither evidence of *lack* of efficacy, nor

evidence of efficacy in any particular subgroup. The constrained setting in which evidence of efficacy has been demonstrated in European studies (i.e., only in patients who had completed an inpatient detox) was noted.

5.2 General Approach to Review of the Efficacy of the Drug

Four studies were provided for review with full study reports and primary datsets. Three were European studies (known by sponsor's names "Pelc-II," "PRAMA," and "Paille") for which the final study reports were prepared for the submission of the European dossier and did not conform to the FDA guidelines on format and content. The study plan as presented in the European protocols (provided as appendices) was less detailed than typically seen in protocols submitted to FDA. The study procedures, time-and-events tables, and methods for translating the information collected into data for analysis were reconstructed by the reviewer from a combination of protocol descriptions, study reports, sample case report forms, and analysis descriptions by the sponsor (NDA Section 10). Considerable attention was given to understanding how drinking behavior data was captured and analyzed.

A fourth study, the only US study in the database, was examined to attempt to identify reasons that the study was unable to demonstrate efficacy of acamprosate.

The application also contains study reports for 9 additional European placebo-controlled studies, including 3 with a duration of treatment of 1 year and 6 shorter-term studies. These were reviewed primarily through Lipha's summary reports and the original European final study reports and are summarized in Section 5.7. Detailed descriptions of the studies and their individual results are found in the appendix.

Table 5.2.1 Studies Included in Detail in Efficacy Review

Study Name/ Protocol #/ PI/Location/Dates	Design	Duration	Dosage Form, Regimen, Total Daily Dose	Type of Patients, # Entered per Group (# completed), Age range/mean, Gender
Pelc II (AOTA/B/90.3) I. Pelc, Belgium, France June, 1990 to April, 1992	Prospective, Multi-Center (11), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate 1332 mg/day vs Acamprosate 1998 mg/day)	90 days	*A (placebo):* 2 Placebo tabs tid *B (1332 mg/day):* 333 mg acamprosate tabs, 2 in morning, 1 acamprosate tab + 1 placebo tab at midday, 1 acamp rosate tab + 1 placebo tab in evening (total 1332 mg) *C (1998 mg/day)* 333 mg acamprosate tabs, 2 tabs tid (total 1998 mg)	Alcohol-dependent subjects after detoxification *A:* 62 entered (32 competed) Age 26-59 (40.9) 89% M /11%F *B:* 63 entered (44 completed) Age 21-71 (43.3) 81% M/19%F *C:* 63 entered (43 completed) Age 26-59 (40.5) 86%M/14%F
Paille (544) F. Paille, France April, 1989 to Nov., 1992	Prospective, Multi-Center (31), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate 1332 mg/day vs Acamprosate 1998 mg/day)	360 days	Placebo: 2 placebo tabs tid Trt 2 (Acamprosate 1332 mg/day): 333 mg acamprosate tabs, 2 in morning, 1 acamprosate tab + 1 placebo tab at midday, 1 acamp rosate tab + 1 placebo tab in evening (total 1332 mg) Trt 3 (Acamprosate 1998 mg/day) 333 mg acamprosate tabs, 2 tabs tid (total 1998 mg)	Alcohol-dependent subjects after detoxification Placebo: 177 entered (62 completed) Mean age 42.5 83% M/17%F Acamprosate 1332 mg/day: 188 entered (85 completed)Mean age: 43.7 78%M/22%F Acamprosate 1998 mg/day: 173 entered (90 completed) Mean age: 43.3 79%M/21%F
PRAMA (AOTA 411.198) H. Sass, Germany Oct. 16, 1990 to Dec. 3, 1992	Prospective, Multi-Center (12), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate with pre-randomization stratification according to body weight)	48 weeks	Acamprosate: ≥60 kg: 333 mg acamprosate tabs, 2 tabs tid (total 1998 mg) <60 kg: 333 mg acamprosate tabs, 2 in morning, 1 at midday, 1 in evening	Alcohol-dependent subjects after detoxification Acamprosate: 136 entered (79 completed) Age: 21-58 (41.9) 75%M/25%F

Study Name/ Protocol #/ PI/Location/Dates	Design	Duration	Dosage Form, Regimen, Total Daily Dose	Type of Patients, # Entered per Group (# completed), Age range/mean, Gender
			(total 1332 mg) Placebo: ≥60 kg: 2 placebo tabs tid <60 kg: placebo tabs, 2 in morning, 1 at midday, 1 in evening	Placebo: 136 entered (55 completed) Age: 21-65 (40.5) 80% M/20%F
US 96.1 (ACAMP/US/96.1) B. Mason USA	Prospective, Multi-Center (21), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate 2g vs Acamprosate 3 g, 3:3:1), with pre-randomization stratification according to alcohol detoxifica-tion (yes/no)	6 months	Acamprosate 2 g: 500 mg acamprosate tabs, 2 tabs + 1 placebo tab, b.i.d Acamprosate 3 g: 500 mg acamprosate tabs, 3 tabs b.i.d Placebo: Placebo tabs, 3 tabs b.i.d.	Alcohol-dependent subjects Acamprosate 2 g: 258 entered (106 completed) Age 23-72 (44.9) 70%M/30%F Acamprosate 3 g 83 entered (43 completed) Age 21-66 (43.6) 72%M/28%F Placebo: 260 entered (143 completed) Age 22-69 (44.4) 65%M/35%F

5.3 Protocol AOTA/B/90.3 ("Pelc-II"): A study of the Activity and Tolerance of Calcium Acetyl Homotaurinate (AOTA-Ca) in Helping to Maintain Abstinence in the Weaned Alcoholic Double-Blind Versus Placebo

Conducted 6/6/90-4/17/92

5.3.1 Protocol

5.3.1.1 Objective/Rationale

The purpose of the study was to compare the efficacy and safety of 2 dose levels of acamprosate and placebo in maintaining abstinence in weaned alcohol-dependent outpatients over 90 days of treatment.

5.3.1.2 Overall Design

This was a prospective, multicenter (11 centers), randomized, double-blind, placebo-controlled, parallel group study comparing the efficacy and safety of 2 dose levels of acamprosate and placebo in alcoholics who had completed inpatient detoxification.

5.3.1.3 Population and Procedures

5.3.1.3.1 Inclusion/Exclusion Criteria

A total of 189 subjects were to be recruited (126 in Belgium and 63 in France).

To be eligible, subjects were required to meet the following criteria:

- Age 18-65
- Weight > 60 kg
- DSM-III diagnosis of alcohol dependence
- "the duration of the disruption must be at least one year"
- Abstinent for at least 5 days
- "Monitored as outpatients"

Subjects were excluded for:

- Pregnancy, or "likely to become pregnant"
- "Associated psychiatric pathology involving the induction of a medicinal treatment during the weaning period or during the follow-up period"
- Significant medical illness (examples included "decompensated diabetes, poorly compensated areterial hypertension, septicemia, active TB, poorly compensated cardiac decompensation, progressive neoplasms")
- Epilepsy (not alcoholic withdrawal seizures)
- Renal insufficiency (Cr > 14 mg/L)
- Hypercalcemia
- "Patients whose condition is incompatible with the conditions of the study"
- "Obvious lack of collaboration with the general weaning treatment"
- Prior treatment with acamprosate

Disallowed concomitant medications included:

- Enzymatic inducers of GGT (other than oral contraceptives)
- Antidepressants (with the exception of amitriptyline "if the mental condition justifies it")
- Neuroleptics
- Barbiturates, meprobamate
- Benzodiazepines "will have to be stopped at least 14 days before the treatment begins, with the exception of benzodiazepines taken for over 3 months before the beginning of the trial which may be continued"
- Valproic acid, carbamazepine
- Disulfiram
- Clonidine
- Clomethiazole ("except during weaning")
- Hypnotics (the exception being Zolpidem (Ambien) allowed over a period of not more than 15 days)

5.3.1.3.2 Procedures

Eligible subjects were to be randomized in blocks of 9 to treatment with:
Group I: Acamprosate 1332 mg (333 mg tablets, 2 qam, 1 at middday, and 1 in the evening, with meals)
Group II: Acamprosate 1998 mg (333 mg tablets, 2 with breakfast, lunch, and dinner)
Group III: Placebo (2 tablets with breakfast, lunch, and dinner)

The protocol allowed for the dose to be reduced (midday dose eliminated) for no more than 7 days in response to adverse events.

Between selection and Day 0, the protocol called for a "drying out cure." The nature of this treatment was not specified in the protocol; it appears that subjects reporting recent abstinence were admissable.

Treatment with Acamprosate or Placebo began on Day 0 continued for 90 days.

Nine study visits were planned: day of selection, day 0, day 8, day 15, day 30, day 45, day 60, day 75 and day 90. This provided for seven on-treatment follow-up study visits.

The following time-and-events table illustrates the planned schedule of assessments:

Table 5.3.1.3.2: Time-and-Events Schedule, Pelc-II

	Selection	D0	D8	D15	D30	D45	D60	D75	D90
Review of inclusion/exclusion criteria	X	X							
Medical History		X							
Pex		X			X		X		X
VS		X	X	X	X	X	X	X	X
Psychiatric History		X							
Ham-D, Ham-A		X			X				X
"Psychosocial Adaptation"	X								
Alcoholism History	X								
MAST	X								
CAGE	X								
Alcohol consumption	X	X	X	X	X	X	X	X	X
Alcohol dependency (inquiry re: subjective need for alcohol)	X	X	X	X	X	X	X	X	X
Observable signs of withdrawal	X	X	X	X	X	X	X	X	X
Urine sample for alcohol	X	X	X	X	X	X	X	X	X
Blood sample for GGT and transaminases	X	X			X		X		X
CBC, Chemistry	X				X		X		X
Adverse Events (spontaneous + questionnaire read aloud)		X	X	X	X	X	X	X	X
CGI		X	X	X	X	X	X	X	X
Pill count		X	X	X	X	X	X	X	X
Concomitant meds		X	X	X	X	X	X	X	X
Distribution of "monitoring booklet"		X	X	X	X	X	X	X	X

Regarding the collection of alcohol consumption data, the case report form contains fields for "Quantity: Average daily consumption on those days on which the patient drinks. 0= abstinent, 1= drinks a maximum of 5 drinks per day, 2= drinks between 5 and 10 drinks per day, 3= drinks more than 10 drinks per day" It does not indicate how this data is to be collected. Similarly, a field exists for "Frequency: Assessment of average frequency of alcohol consumption (regardless of quantity). 0 = abstinent, 1 = drinks a maximum of twice weekly, 2= drinks more than twice a week but not every day, 3 = drinks every day" Again, the method for collecting this information is not specified. Subjects are given self-assessment booklets at each visit and are apparently to mail in the booklet at the one-week point between visits; however, the CRF contains no fields for this mailed-in information.

A "monitoring booklet" was to be distributed to patients, allowing for the "daily recording and quantification by the patient of nervousness, sleeping disorders, shaking of the hands, and desire for alcohol." The protocol called for the booklet to be returned at each study visit and indicated that it "will be used to monitor the patient." The CRF indicates that subjects were to be

instructed to mail back the first week's booklet at the mid-point between the biweekly visits. The CRF does not contain fields for the data collected in the booklets.

Adverse events were assessed "by the spontaneous collection of the somatic complaints and with the aid of a systematic questionnaire." No specific open-ended probe for adverse events is indicated in the protocol or CRF.

There is no description of any psychosocial therapy to be delivered at study visits or external to the study, nor is the receipt (or lack thereof) of such therapy captured in the case report form.

5.3.1.4 Evaluations/Endpoints

The pre-specified "main criterium of judgement" listed in the protocol was "the consumption of alcohol." No a priori strategy for transforming the data collected into an overall assessment of alcohol consumption was identified.

In addition, the protocol called for evaluation of "clinical signs linked to alcoholism," "biological signs" (GGT, AST/ALT, urine alcohol), and "tolerance to the treatment."

The selection of analytic approaches to the data appears to have been left entirely to the statistics department[illegible] The analysis was carried out in blinded fashion.

5.3.1.5 Statistical Plan

The statistical analysis was not prespecified in the protocol, which reads only, "Statistical analysis: This will be carried out by the computer and statistics department [illegible] and will relate to the quantitative parameters (variance analysis) and qualitative parameters (at a minimum the test of the Chi^2), the progress within the group and comparison between the groups of the quantitative parameters will be analyzed according to the example of repeated measures."

5.3.2 Results

5.3.2.1 Study Conduct/Outcome

5.3.2.1.1 Subject Characteristics

189 subjects were selected for enrollment. There is no indication of how many were screened in order to enroll 189.

5.3.2.1.1.1 Enrollment by Center

Of the total of 189 patients who were selected to participated, 188 patients were randomized: 125 in the 10 Belgian centers (range 3-37) and 63 in the French center (1 Belgian patient withdrew consent). Sixty-three patients were randomized to acamprosate 1998 mg/day, 63 to acamprosate 1332 mg/day, and 62 to placebo. All patients took at least 1 dose of study medication and are included in the ITT population.

Enrollment was distributed among centers as listed in the table below:

Table 5.3.2.1.1.1 Enrollment by Center, Pelc-II

Center	Investigator	Subjects
1	Prof. Isidore PELC Hôpital Brugmann Service de Psychiatrie Brussels BELGIUM	38
2	Dr Serge ZOMBECK Hôpital St Pierre Brussels BELGIUM	9
3	Dr Alain MOINET Clinique Sans Souci Brussels BELGIUM	15
4	Dr Xavier BONGAERTS Hôpital Psych. Chênes aux Haies Mons BELGIUM	3
5	Dr Jean-Paul PIRSON Clinique ND des Anges Glain BELGIUM	5
6	Dr Fernand RIHOUX Centre Hospitalier Reine Fabiola Auvelais BELGIUM	13
7	Dr Jacques BIENFAIT Clinique Notre Dame Charleroi BELGIUM	15
8	Dr Guy DEJAIFFE Inst. Neuro-Psych. La Clairière Bertrix BELGIUM	7
9	Dr Willy SAMAIN Centre Hospitalier de Tivoli La Louvière BELGIUM	12
10	Dr Louis BOTTE Clinique Saint Bernard Manage BELGIUM	9
France	Dr Jean-Pierre JOLY Centre Hospitalier Universitaire Bois Guillaume Bois GuillaumeFRANCE	63

5.3.2.1.1.2 Subject Disposition

The table below illustrates patient disposition and reasons for premature discontinuation. More patients in the placebo group discontinued because of being lost to follow-up (24%) compared to 10% for the acamprosate 1332 mg/day and 13% for the acamprosate 1998 mg/day groups. Otherwise, the reasons for premature discontinuation were similar among treatment groups. No deaths occurred during the treatment phase.

Table 5.3.2.1.1.2 Patient Disposition-Pelc-II

	Statistic	ACAMP 1332 mg/day (N=63)	ACAMP 1998 mg/day (N=63)	Placebo (N=62)
Number of Patients Randomized	N	63	63	62
Number of Patients in the ITT Population	n (%)	63 (100%)	63 (100%)	62 (100%)
Number of Patients Who Completed Treatment Phase	n (%)	44 (70%)	43 (68%)	32 (52%)
Number of Patients Who Discontinued Treatment Phase	n (%)	19 (30%)	20 (32%)	30 (48%)
Reasons for Discontinuation:				
Adverse Event	n (%)	4 (6%)	2 (3%)	4 (6%)
Lost to Follow-up	n (%)	6 (10%)	8 (13%)	15 (24%)
Treatment Failure	n (%)	6 (10%)	9 (14%)	10 (16%)
Death	n (%)	0	0	0
Protocol Violation	n (%)	1 (2%)	0	0
Other	n (%)	2 (3%)	1 (2%)	1 (2%)
Data Source: Sponsor's Table 8.7.1.1.1.				

5.3.2.1.2 Demographics

The table below illustrates demographic and baseline characteristics of the 3 treatment groups. Most patients in this study were male (81% to 89% across treatment groups) and the mean age ranged from 40.5 to 43.3 years.

With respect to alcohol use histories, the mean duration of alcohol dependence ranged from 7.5 years (placebo group) to 10.1 years (acamprosate 1332 mg group). Almost all subjects drank 5 or more standard drinks per drinking day prior to treatment. In the placebo group, relatively more (87%) were in the >10 drinks/day category compared to the other groups (71% in each of the acamprosate groups). More than half (62%) of the patients had previously undergone treatment or detoxification for alcoholism, and the groups were similar with respect to the number of patients with 0-1 previous detoxes (67% in acamprosate 1332 mg group, 62% in acamprosate 1998 mg group, and 63% in placebo group) and the number with 3 or more previous detoxes (23%, 20%, and 25%). Not noted in the table below, but reported by the sponsor, the majority did not attend alcoholism self-help groups. All of the patients in the study had undergone detoxification and were abstinent at baseline.

Table 5.3.2.1.5 Demographic and Baseline Characteristics - Pelc II

Characteristic	Statistic	ACAMP 1332 mg/day (N=63)	ACAMP 1998 mg/day (N=63)	Placebo (N=62)
Gender	N	63	63	62
Male	n (%)	51 (81%)	54 (86%)	55 (89%)
Female	n (%)	12 (19%)	9(14%)	7 (11%)
Age (years)	N	63	63	62
	Mean (SE)	43.3 (1.1)	40.5 (1.0)	40.9 (1.1)
	Min, Max	21, 71	26, 59	26, 59
Weight (kg)	N	63	63	62
	Mean (SE)	74.0 (1.5)	71.4 (1.2)	72.1 (1.7)
	Min, Max	58, 122	52, 94	56, 137
Marital Status	N	63	63	62
Married	n (%)	30 (48%)	34 (54%)	29 (47%)
Not married	n (%)	33 (52%)	29 (46%)	33 (53%)
Detoxification Prior to Randomization	N	63	63	62
Yes	n (%)	63 (100%)	63 (100%)	62 (100%)
No	n (%)	0	0	0
Normalized GGT at Selection Day[1]	N	63	63	62
	Mean (SD)	4.78 ((1.0)	4.96 ((1.0)	4.57 (1.0)
	Min, Max	0.17, 43.74	0.34, 35.18	0.24, 38.60
Abstinent at Baseline	N	63	63	62
Yes	n (%)	63 (100%)	63 (100%)	62 (100%)
No	n (%)	0	0	0
Duration of Alcohol Dependence/Abuse (years)	N	63	63	62
	Mean (SE)	10.1 (1.1)	8.3 (0.9)	7.5 (1.0)
	Min, Max	1, 40	1, 45	1, 35
Average Standard Drinks per Day at Study Entry	N	63	63	62
<5	n (%)	1 (2%)	2 (3%)	0
5-10	n (%)	17 (27%)	16 (25%)	8 (13%)
>10	n (%)	45 (71%)	45 (71%)	54 (87%)
Prior Treatment or Detoxes for Alcoholism	n	63	63	62
0	n (%)	25 (40%)	26 (41%)	21 (34%)
1	n (%)	17 (27%)	15 (21%)	18 (29%)
2	n (%)	6 (10%)	9 (14%)	8 (13%)
3	n (%)	4 (6%)	2 (3%)	9 (15%)
>3	n (%)	11 (17%)	11 (17%)	6 (10%)
Data Source: Sponsor's Table 8.7.1.2.1 and Table 8.7.1.3.1				

Sponsor's In-Text Table 8.4.3.1.2
[1]Ratio of GGT to ULN in specific laboratory used

5.3.2.1.3 Dosing Information

The table below illustrates exposure duration and compliance with medication across treatment groups. Mean compliance was quite high (97%-100%) and most subjects were >75% compliant. Groups were similar with respect to compliance.

Drug Exposure – Pivotal Efficacy Study Pelc II

Parameter	Statistic	ACAMP 1332 mg/day (N=63)	ACAMP 1998 mg/day (N=63)	Placebo (n=62)
Duration of Exposure (weeks)	n	63	63	62
	Mean (SE)	10.6 (0.5)	11.2 (0.5)	9.4 (0.6)
	Median	12	12	12
	Min, Max	0, 16	1, 17	1, 16
Exposure by Duration Category (weeks)	n	63	63	62
0 - <4	n (%)	8 (13%)	5 (8%)	13 (21%)
4 - <8	n (%)	6 (10%)	4 (6%)	7 (11%)
8 - <13	n (%)	31 (49%)	35 (56%)	23 (37%)
13 - <26	n (%)	18 (29%)	19 (30%)	19 (31%)
≥26	n (%)	0	0	0
Compliance (%)	n	55	53	49
	Mean (SE)	97.4 (1.5)	96.7 (1.8)	100.4 (1.6)
	Median	99	99	100
	Min, Max	50, 119	69, 129	76, 129
Number of Patients Who Were ≥75 % Compliant	n (%)	52 (95%)	50 (94%)	49 (100%)
Data Source: Table 8.7.1.4.1				

Sponsor's In-Text Table 8.7.2.6:1

Note: Compliance is calculated as the number of study drug tablets taken divided by the number of study drug tablets prescribed times 100.

Note: Percentages for ≥75% compliant are based on the number of patients for whom compliance was calculated.

5.3.3 Efficacy Results

5.3.3.1 Sponsor's Analysis

The analysis by the sponsor regarded the calculation of "cumulative abstinence time" as primary. As noted above, the case report form contained fields for "Quantity: Average daily consumption on those days on which the patient drinks. 0= abstinent, 1= drinks a maximum of 5 drinks per day, 2= drinks between 5 and 10 drinks per day, 3= drinks more than 10 drinks per day." Similarly, a field exists for "Frequency: Assessment of average frequency of alcohol consumption (regardless of quantity). 0 = abstinent, 1 = drinks a maximum of twice weekly, 2= drinks more than twice a week but not every day, 3 = drinks every day" The protocol did not indicate how this data was to be collected, and it appears to have been a global judgment of some sort by the clinician. It is not known whether the interviewing clinician was external to the treatment team or was the subject's treating therapist. Again, the method for collecting this information is not specified. Subjects were given self-assessment booklets at each visit and apparently were to mail in the booklet at the one-week point between visits; however, the CRF contains no fields for this mailed-in information.

For the sponsor's analysis, the following procedure was used to transform the CRF data into daily drinking data across the inter-visit interval was as follows:

"The total number of abstinent days was created using the concept that if a patient did not report abstinence since the last visit that they were not abstinent for any days since the last visit. For each interval between visits, a patient was considered abstinent for all days since the last visit if they reported abstinence, otherwise the patient was considered drinking for all days. The number of days of abstinence were then added up across all visits.

"The treatment duration was considered 90 days for all patients who completed or discontinued for reasons other than concomitant illness or protocol violation. For those patients who discontinued due to concomitant illness or protocol violation, the treatment duration was considered to be the number of scheduled days to the last visit for which a patient had indicators of abstinence at that visit and all preceding visits." [From Section 10.7, statistical methods.]

In other words, although the "cumulative abstinence duration" (CAD) calculation is made based on a summation of the "number of days abstinent," and the "corrected cumulative abstinence duration" (CCAD) is calculated as the number of abstinent days divided by the number of days of observation, it is actually a largely imputed value. A subject with one drinking day in the preceding month would not be distinguishable from one with continuous drinking, because both would have 30 days of drinking imputed for the calculation.

The sponsor's result, using this method, is shown in the table below (from Section 8.4.2.1.3 of NDA submission; means and SD's verified by the reviewer using primary datasets):

Table 5.3.3 Mean Cumulative Abstinence Duration (CAD) and Corrected CAD

Parameter	Acamprosate 1332 mg/day N=63	Acamprosate 1998 mg/day n=63	Placebo n=62
Mean±SD Cumulative Abstinence Duration (days)	51.9 (±37.2)	56.6 (±33.7)	34.3 (±33.8)
Mean±SD Corrected Cumulative Abstinence Duration (%)	59.1 (±41.2)	62.9 (±37.4)	38.1 (±37.6)

From Sponsor's In-Text Table 8.4.2.1:3, citing "Data Source: Pelc II Study Report, Table 6"; means and SE's verified by reviewer via analysis of dataset PE_EFFPT + PE_POP

Statistical analysis by the sponsor yielded p values ≤ 0.05 for the pairwise comparisons of acamprosate 1332 mg/day vs placebo and acamprosate 1998 mg/day vs placebo (Student-Newman-Keuls test), and an overall p-value (one-wayANOVA) of $p = 0.001$.

5.3.3.2 Reviewer's Analysis

In an attempt to identify an analysis that does not go beyond the actual information available, I conducted two different explorations of the data. I evaluated the numbers of patients in each treatment arm who were assessed as abstinent at each of the study visits, and I did a responder analysis comparing the numbers of subjects who were assessed as abstinent for the entire study. Note that the first analysis resembles CAD, in that it acknowledges that periods of abstinence are clinically significant even if they are interrupted by periods of drinking. The second analysis is the most conservative, and may represent a higher standard of success than is clinically appropriate.

It is possible that the methods of data collection (the apparent lack of separation between data collection personnel and treatment personnel) may have introduced demand characteristics which would discourage subjects from reporting drinking. One might conclude that the subjects listed in the dataset as having "remained abstinent" are more accurately characterized as being those subjects who managed to convey the impression of abstinence to the evaluating clinician. Given tendency of therapists to look for improvement, it is likely that this number over-estimates the actual abstinence rate. If the treatment was somehow unmasked (perhaps by the occurrence of adverse events), there would be obvious bias in the data. However, given the relatively benign safety profile one can hope that the bias towards underreporting drinking and the bias towards seeing improvement would be randomly distributed across treatment groups.

5.3.3.2.1 Non-Continuous Abstinence

This analysis compares the patterns of the number of visits at which each subject was assessed as abstinent by the evaluating clinician.

The table below illustrates the distribution of "abstinent visits" across treatment groups. For this analysis, the dataset PE_EFFVS was combined with PE_POP (to obtain treatment assignments). Visits coded as "1" (abstinent) under the column QUANCON2. This column contained a categorical description of the drinking level (abstinent, yes/no).

Table 5.3.3.2.1 Number of Visits at which Subject was Assessed as Abstinent—Pelc-II

# abstinent visits	Acamprosate 1332 mg N = 63		Acamprosate 1998 mg N = 63		Placebo N = 62	
	N	%	N	%	N	%
0	0	0%	0	0%	2	3%
1	8	13%	7	11%	16	26%
2	8	13%	2	3%	9	15%
3	8	13%	7	11%	5	8%
4	2	3%	4	6%	3	5%
5	5	8%	9	14%	8	13%
6	3	5%	5	8%	5	8%
7	3	5%	3	5%	5	8%
8	26	41%	26	41%	9	15%

There is a statistically significant difference (t-test) between either dose of acamprosate vs. placebo. The results are driven primarily by the difference in the number of subjects with complete abstinence (8 abstinent visits, here), but in addition, there was a tendency for more of the placebo subjects to have 0, 1, or 2 visits where they were assessed as abstinent (43%) as compared to acamprosate subjects (25% in the low dose group and 14% in the 1998 mg/day group), strengthening the finding.

5.3.3.2.2 Responder Analysis: Continuous Abstinence
The rates of complete abstinence across the various treatment groups are shown in the table below.

Table 5.3.3.2.2 Continuous Abstinence in Study Pelc-II

	Acamprosate 1332 mg/day N = 63		Acamprosate 1998 mg/day N = 63		Placebo N = 62	
Total	Abstinent	Non-Abstinent	Abstinent	Non-Abstinent	Abstinent	Non-Abstinent
188	26 (41%)	37 (59%)	26 (41%)	37 (59%)	9 (15%)	53 (85%)

Table prepared by reviewer from datasets PE_EFFPT + PE_POP; numbers represent subjects coded as 0 (no) in column = RELAPITT; identical numbers may be generated from selecting subjects with CAD≥90 days, or from the number of subjects with 8 abstinent visits.

5.3.3.2.2.1 Analysis by Gender

Too few women were included in the study to permit meaningful subset analysis by gender. In the acamprosate 1332 mg/day group, 2 of 12 (17%) women were abstinent throughout the study, compared to 2 of 9 (22%) in the acamprosate 1998 mg/day group and 1 of 7 (14%) in the placebo group.

5.3.3.2.2.2 Analysis by Center

By-center analysis reveals abstinence rates between 0 and 100% in the acamprosate 1332 mg/day group, between 0 and 67% in the acamprosate 1998 mg/day group, and 0-50% in the placebo group. By-center results are shown in the table below, generated by the reviewer from datasets PE_EFFPT + PE_POP.

Table 5.3.3.2.2.2 Continuous Abstinence by Center--PelcII

Center	N	Acamprosate 1332 mg/day		Acamprosate 1998 mg/day		Placebo	
		Abstinent	Non-Abstinent	Abstinent	Non-Abstinent	Abstinent	Non-Abstinent
1	63	10 (48%)	11 (52%)	10 (48%)	11 (52%)	2 (10%)	19 (90%)
2	37	7 (54%)	6 (46%)	4 (31%)	9 (69%)	2 (18%)	9 (82%)
3	9	1 (33%)	2 (67%)	2 (67%)	1 (33%)	0 (0%)	3 (100%)
4	15	2 (40%)	3 (60%)	3 (60%)	2 (40%)	1 (20%)	4 (80%)
5	3	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)
6	5	1 (100%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)
7	13	2 (40%)	3 (60%)	1 (25%)	3 (75%)	0 (0%)	4 (100%)
8	15	2 (40%)	3 (60%)	1 (25%)	3 (75%)	2 (33%)	4 (67%)
9	7	1 (50%)	1 (50%)	1 (50%)	1 (50%)	0 (0%)	3 (100%)
10	12	0 (0%)	4 (100%)	3 (60%)	2 (40%)	0 (0%)	3 (100%)
11	9	0 (0%)	3 (100%)	0 (0%)	3 (100%)	1 (33%)	2 (67%)
Total	188	26 (41%)	37 (59%)	26 (41%)	37 (59%)	9 (15%)	53 (85%)

5.3.3.3 Conclusions Regarding Efficacy Data in Study

This study, although short-term, provides evidence that recently-detoxified alcoholic subjects treated with acamprosate were more frequently assessed as abstinent by the treating physician than were subjects treated with placebo.

Although the sponsor's analysis of CAD and CCAD are questionable, in that what were essentially binary assessments have been transformed into continuous data, the overall conclusion is supported. Both an analysis of continuous abstinence and an analysis of the pattern of visits at which the investigator assessed the subject to be abstinent support the sponsor's conclusions. Concerns about the validity of the data include the likelihood that both subject and investigator (who apparently also served as therapist) would be biased in reporting and assessment. This would be expected to occur evenly across treatment assignment, however, unless unmasking occurred. The safety results (per submitted datasets) show that very few adverse events occurred at a higher rate in the treatment groups than in placebo groups, and that diarrhea (a recognized acamprosate-related event) occurred at a high enough rate in the placebo group (39% vs 43% in acamprosate 1332 mg and 48% in acamprosate 1998 mg) that its occurrence would not be expected to unblind the study.

5.4 Protocol 544 ("Paille"): A Multicentre Controlled and Double-Blind Comparative Study of the Efficacy of AOTA-Ca Studied at Two Dosages and Placebo Over a 1 Year Period of Treatment. Followed by a 6 Month Post-Treatment Period of Placebo on Alcoholic Patients who were Followed as Outpatients After Withdrawal

Conducted April 1989 to November 1992

5.4.1 Protocol

5.4.1.1 Objective/Rationale

The objectives of the study were to compare the safety and efficacy of 2 dose levels of acamprosate: 1332 mg/day and 1998 mg/day versus placebo in maintaining abstinence over the 12-month treatment period in alcohol-dependent outpatients withdrawn from alcohol; and to observe the outcome over an additional 6-month period while patients continued on (or were switched to) placebo (single-blind) at the end of the double-blind treatment period.

5.4.1.2 Overall Design

This was a prospective, multicenter (31 centers), randomized, double-blind, placebo-controlled, parallel group (3) study comparing the efficacy and safety of 2 dose levels of acamprosate and placebo given for 12 months for maintenance of abstinence in alcohol-dependent patients who had been withdrawn from alcohol.

5.4.1.3 Population and Procedures

A sample size of 480 (160 per arm) was planned. Each of 30 centers was to provide a minimum of 6 and a maximum of 36 subjects.

5.4.1.3.1 Inclusion/Exclusion Criteria

Subjects "about to start a withdrawal cure" (inpatient or outpatient detoxification) were to be recruited. To be eligible, subjects were required to meet the following criteria:

- Age 18-65
- DSM-III (R) diagnosis of alcohol dependence x at least 1 year
- Clinical signs of "alcohol impregnation" ("appearance of the face, conjunctivae, or tongue, tremor of the mouth, tongue, or extremities") and/or elevated GGT (>2 xULN) or MCV>98 μ^3.
- In outpatient treatment at a specialized center for alcoholics
- Abstinent 1 week – 1 month at Day 0
- "Clearly stated desire to maintain abstinence"
- "Lifestyle compatible with follow-up"

Subjects were excluded for:

- Assessment at "unlikely to comply with treatment over the 18 month period"
- More than 3 courses of detox in previous 2 years
- Previous treatment with acamprosate
- Recent (past 6 months) participation in clinical trial

- Pregnancy, nursing, or "likely to become pregnant"
- Severe psychiatric disorder
- Significant medical illness (examples included "poorly controlled diabetes, poorly controlled arterial hypertension, septicemia, active TB, cardiac failure, progressive neoplasia")
- Epilepsy (not alcoholic withdrawal seizures)
- Renal insufficiency (Cr > 14 mg/L)
- Hypercalcemia
- "Patients whose physical or mental state is incompatible with the trial conditions"
- Intellectual limitations or language barrier precluding completion of diaries
- Lack of fixed address; residence in "post-cure center"
- "Lack of obvious cooperation during the global withdrawal treatment"
- Incompatible medication
- Recent (past 3 months) institution of chronic medication

Concomitant medications permitted included:

- Psychotropic medication, as an exception, and "for a short period of time"
- Antidepressants, preferably Ludiomil (maprotiline)
- Lorazepam
- Somatic treatment begun > 3 months before trial
-

Disallowed concomitant medications included:

- SSRIs (to be "avoided")
- Barbiturates
- Anxiolytics/hypnotics other than lorazepam (or in some circumstances, flunitrazepam)
- Valproic acid, carbamazepine
- Lithium
- Disulfiram
- Clonidine
- Clomethiazole ("except during weaning")
- IV magnesium

5.4.1.3.2 Procedures

Eligible subjects were to be randomized in blocks of 9 to treatment with:

Group I: Acamprosate 1332 mg (333 mg tablets, 2 qam, 1 at middday (+ 1 placebo), and 1 in the evening (+ 1 placebo), with meals)
Group II: Acamprosate 1998 mg (333 mg tablets, 2 with breakfast, lunch, and dinner)
Group III: Placebo (2 tablets with breakfast, lunch, and dinner)

Treatment with Acamprosate or Placebo began on Day 0 continued for 12 months. The protocol called for (but did not explicitly describe) single-blind switching of all subjects to placebo for an additional 6 months, for a total of 18 months' participation.

The protocol called for monthly study visits for the first 6 months and bimonthly visits thereafter. An "auto-evaluation notebook" containing "global questions" is also described in the protocol, giving the opportunity for "patient's evaluation of efficacy and tolerance." The protocol indicated that, each month, the subject was to return "the corresponding pages directly to the co-ordinating center. These pages encourage the patient to remain in the study." No fields for data from these diaries are included in the CRF and the data does not appear to have been included in analysis. The evaluation of abstinence in the CRF is represented by a section reading, "Evaluation of abstinence (assessed by the clinician)," and including fields for "Estimated number of days of non-abstinence in the course of the last month" and "Estimated mean consumption of alcohol during these days of non-abstinence" (in g/day).

Safety was to be evaluated using open ended inquiry such as "Have you observed any disorders which you feel may be related to the treatment?"

The following time-and-events table illustrates the planned schedule of assessments. Note that the table was constructed by the reviewer from sample case report forms and was not a part of the protocol. Some assessments (e.g. MCV at intervals) are described in the protocol but not included in the CRF:

Table 5.4.1.3.2 Time-and-Events Schedule--Paille

	BL[1]	D0	D30	D60	D90	D120	D150	D180	D240	D300	D360	D420	D480	D540
DSM-III-R criteria for EtOH dependence	X													
Clinical and/or lab signs of "alcohol impregnation"	X													
Inclusion/exclusion criteria	X	X												
EtOH history	X													
Pex	X	X			X			X			X			X
VS	X	X			X			X			X			X
Covi Anxiety Scale, Raskin Depression Scale (both clinician-rated)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QOL index	X													
CGI	X				X			X			X			X
Cr, MCV,	X													
GGT, AST/ALT	X	X			X			X			X			X
Serum EtOH		X			X			X			X			X
Meds dispensed		X	X	X	X	X	X	X	X	X	X	X	X	
Pill count, compliance estimate			X	X	X	X	X	X	X	X	X	X	X	X
Clinician estimate of EtOH consumption			X	X	X	X	X	X	X	X	X	X	X	X
Clinician estimate of EtOH craving					X			X			X			X
Relatives' report of EtOh consumption, when possible					X			X			X			X
Concomitant meds			X	X	X	X	X	X	X	X	X	X	X	X
Inquiry re: non-pharmacologic alcoholism tx			X	X	X	X	X	X	X	X	X	X	X	X
AE's "possibly related to the treatment"			X	X	X	X	X	X	X	X	X	X	X	X

[1]Day -30 to Day –7, prior to detox

5.4.1.4 Evaluations/Endpoints

The protocol specified main efficacy parameters were the number of non-abstinent days , the average alcohol consumption on non-abstinent days, and a responder analysis classifying subjects as success/partial success/failure. These were based on "clinical evaluation" and "biological evaluation of the efficacy" (GGT, MCV, transaminases).

The clinical evaluation is described in the protocol as follows:
"After considering all the elements at his disposition, the physician will evaluate: (a) the number of non-abstinent days during the month preceding the visit; (b) the average quantity of pure alcohol absorbed during these periods of non-abstinence during the preceding month. For the analysis "success/partial success/failure," the patient is classified as a good resopnder if he is considered abstinent on D180 and D360. He is classified as a partial responder if he is considered to be abstinent at only one of these visits. For the interpretation of relapses, the analysis will be based on the number, the period of time between the withdrawal (D0) and the first relapse and the resolving nature of these relapses during the trial."

The evaluation of abstinence in the CRF is represented by a section reading, "Evaluation of abstinence (assessed by the clinician)," and including fields for "Estimated number of days of non-abstinence in the course of the last month" and "Estimated mean consumption of alcohol during these days of non-abstinence" (in g/day).

5.4.1.4.1 Statistical Plan

The protocol did not contain a statistical plan. However, the statistical analysis was conducted in a blinded fashion and may therefore be considered prospective. In the statistical report, all analysis was conducted on the basis of intention to treat, and missing data due to non-attendance or failure to complete data fields was handled as treatment failure.

The principal efficacy variable defined in the statistical analysis was continuous abstinence since the start of treatment. Patients were considered to be continously abstinent only if they attended all clinic visits and the number of non-abstinent days was recorded as zero. The three pairs of treatment groups were compared using the non-parametric Mann-Whitney U test.

Days of controlled drinking (40g or less) were also calculated and compared.

Categorical analysis of classification at each visit (abstinent/controlled/uncontrolled/treatment failure, where treatment failure was coded if the subject did not attend or if no data on alcohol consumption were available) was undertaken using Mantel-Hanszel test.

Cumulative abstinence duration was also calculated through either day 360 or the date of visit J360 and compared across treatment groups using a one-way ANOVA and Mann-Whitney U tests.

For the purposes of this application, however, Lipha chose to identify CAD as the primary variable of interest as a common analysis across studies.

5.4.2 Results

5.4.2.1 Study Conduct/Outcome

5.4.2.1.1 Subject Characteristics

A total of 538 subjects were selected for enrollment and randomized to treatment(188 to acamprosate 1332 mg/day, 173 to acamprosate 1998 mg/day, and 177 to placebo). There is no indication of how many were screened in order to enroll 538.

5.4.2.1.1.1 Enrollment by Center

Thirty-one centers (there was no center #19) enrolled between 5 and 36 subjects each. Enrollment across centers is delineated in the table below.

Table 5.4.2.1.1.1 Enrollment by Center--Paille

Center No.	Num. Patients	Investigator	Address
01	12	Prof. Hubert ALLEMAND	Hôpital Jean Minjoz 2 Place St Jacques 25030 Besançon FRANCE
02	36	Prof Jean-Louis BALMÈS	Service CCAA Nimes 1 rue Terraube 30000 Nîmes FRANCE
03	22	Dr Claude BROCHIER (MRS)	Service CHRA Centre Hospitalier 64 avenue du Dr. Saty 26 008 Valence FRANCE
04	05	Dr. Jean BUISSON	Centre de Santé 5 rue du Dr Pesqué 93300 Aubervilliers FRANCE
05	10	Dr Michel CHOUSTERMANN	Centre Hospitalier Intercommunal 40, avenue de Verdun 94010 CRETEIL Cedex FRANCE
06	18	Prof. Sylvain DALLY	Hôpital Fernand Widal 200 rue du Faubourg Saint Denis 75010 PARIS FRANCE
07	10	Dr François DE LAHARPE	Hôpital Civil-Pavillon Leriche 1 place de l'Hôpital 67000 Strasbourg FRANCE
08	09	Prof Damien DELAMAIRE	CHR Ponchaillou 2, rue Henri Le Guilloux 35000 Rennes FRANCE
09	09	Dr Jacques WEMEAU	Centre Clinique d'Alcoologie 73, rue Sainte Thérèse 59100 Roubaix FRANCE
10	9	Prof. Jacques DUBRUJEAUD	Hôpital André Mignot 177, rue de Versailles 78157 Le Chesnay Cedex FRANCE

11	36	Prof. Jean-Dominique FAVRE	Service de Psychiatrie Hopital Percy 92140 Clamart FRANCE
12	12	Prof. Michel AMOURETTI	Hôpital du Haut Lévêque Service U.S.N Avenue Magellan 33604 Pessac FRANCE
13	18	Dr Gilles-Loïc GUIDON	Ancien Hôpital des Armées Service de sevrage alcoolique et tabagique 56110 Lorient FRANCE
14	9	Dr Jean-Paul LATRIVE	Centre Hospitalier de Compiegne 8, rue Adenot 60208 Compiegne FRANCE
15	22	Dr Claude LE DEVÉHAT/ Dr Alain LEMOINE	Centre hospitalier Centre de Diabétologie Pavillon Jules Renard 1, avenue Colbert 58000 Nevers FRANCE
16	15	Prof. Gabriel LE MENN	Hôpital La Cavale Blanche 29200 Brest FRANCE
17	36	Dr Daniel VOIRIN	Hôpital d'instruction des Armées Clermont Tonnerre rue du Colonnel Fonferrier 29200 Brest FRANCE
18	18	Dr Meri LIENHART	Centre Hospitalier de Saint-Cloud 3, Place Silly 92211 Saint Cloud FRANCE
20	22	Prof. Dominique BARRUCAND	Centre Hospitalier Emile Roux 48, rue Henri Barbuse 94450 Limeil Brevannes FRANCE
21	16	Dr Pierre MECHINAUD	62, rue du Chêne Creux 44410 Rèze FRANCE
22	5	Dr Gérald BERTHON	Hôpital St André Service de Médecine Interne et Thérapeutique 1 rue Jean Burguet 33075 Bordeaux Cedex FRANCE
23	17	Prof. François PAILLE	Hôpital Fournier Service de Médecine Interne/ Alcoologie 34 Quai de la Bataille 54037 Nancy FRANCE
24	18	Dr Roger PLANCHE	C.H.R.U. Service de Psychiatrie 63000 Clermont Ferrand FRANCE
25	36	Prof. Yves POINSO	Hôpital Ste Marguerite Pavillon Ouest 270 Bd Ste Marguerite

			13214 Marseille FRANCE
26	25	Prof. Bernard RUEFF	Hôpital Beaujon 100, boulevard du Général Leclerc 92110 Clichy FRANCE
27	12	Dr Michel SALFATI/ Dr Anne VALLI/	Centre Hospitalier Jean Rostand 141 Grande Rue 92311 Sèvres FRANCE
28	13	Dr Chantal VENON	Service CCAA Centre Verlaine 14 Place Pierre Sémard 94190 Villeneneuve-Saint-Georges FRANCE
29	7	Prof. Michel MARIE-CARDINE	Service Prof. Terra Centre Hospitalier le Vinatier 95 Bvd Pinel 69500 Bron FRANCE
30	26	Prof. François BLANC	CHU Gui de Chauliac (Hôpital Ste Eloi) Médecine Interne E 4 Avenue Bertin-Sans 34000 Montpellier FRANCE
31	18	Dr Bernard JOZELSON	Centre Hospitalier Centre d'alcoologie 73200 Albertville FRANCE
32	15	Dr Yves RAOUL	H.I.A. Ste Anne 3 Bld Ste Anne 83000 Toulon FRANCE

5.4.2.1.1.2 Subject Disposition

The table below illustrates patient disposition and reasons for premature discontinuation. Completion rate (for the 360-day treatment period) was higher in the acamprosate groups (45% for acamprosate 1332 mg/day and 52% for acamprosate 1998 mg/day) compared to the placebo group (35%). Compared to patients in the acamprosate groups, a greater percentage of Subjects in the placebo group were more likely to discontinue the study for the reason of "Other" (which included patient refusal and noncompliance). Otherwise, the reasons for discontinuation of treatment were similarly distributed among the groups. Six patients died during the 1 year treatment phase of the study (2 in each treatment group).

Table 5.4.2.1.1.2 Patient Disposition During Treatment Phase –Paille

Parameter	Statistic	ACAMP 1332 mg/day (N=188)	ACAMP 1998 mg/day (N=173)	Placebo (N=177)
Number of Patients Randomized	n	188	173	177
Number of Patients in the ITT Population	n (%)	188 (100%)	173 (100%)	177 (100%)
Number of Patients Who Completed Treatment Phase	n (%)	85 (45%)	90 (52%)	62 (35%)
Number of Patients Who Discontinued Treatment Phase	n (%)	103 (55%)	83 (48%)	115 (65%)
Reasons for Discontinuation:				
Adverse Event	n (%)	13 (7%)	10 (6%)	12 (7%)
Lost to Follow-up	n (%)	22 (15%)	26 (15%)	27 (15%)
Treatment Failure	n (%)	42 (22%)	28 (16%)	35 (20%)
Death	n (%)	2 (1%)	2 (1%)	2 (1%)
Protocol Violation	n (%)	0	0	3 (3%)
Other	n (%)	24 (13%)	17 (10%)	36 (20%)
Data Source: Table 8.7.1.1.3.				

Sponsor's In-Text Table 8.4.2.3:1 Note: Percentages are based on the number of patients randomized.

5.4.2.1.2 Demographics

The table below illustrates demographic and baseline characteristics of the 3 treatment groups.

Most patients in this study were male (78% to 83% across treatment groups) and the mean age ranged from 42.5 to 43.7 years.

With respect to alcohol use histories, the mean duration of alcohol dependence ranged from 8.5 years (placebo group) to 10.1 years (acamprosate 1998 mg group). Almost all subjects drank 5 or more standard drinks per drinking day prior to treatment. In the placebo group, relatively more (76%) were in the >10 drinks/day category compared to the other groups (64% and 68% in the acamprosate groups). Half (50%) of the patients had previously undergone treatment or detoxification for alcoholism, but very few had been treated repeatedly. The groups were similar with respect to the number of patients with 0-1 previous detoxes (83% in acamprosate 1332 mg group, 79% in acamprosate 1998 mg group, and 81% in placebo group). Slightly fewer (4%) in the placebo group had undergone multiple (3 or more) previous detoxes (vs 7% in acamprosate 1332 mg group and 6% in acamprosate 1998 mg group). All of the patients in the study had undergone detoxification and were abstinent at baseline.

Table 5.4.2.1.2 Demographic and Baseline Characteristics – Pivotal Efficacy Study Paille

Characteristic	Statistic	ACAMP 1332 mg/day (N=188)	ACAMP 1998 mg/day (N=173)	Placebo (n=177)
Gender	N	188	173	177
Male	N (%)	146 (78%)	137 (79%)	147 (83%)
Female	N (%)	42 (22%)	36 (21%)	30 (17%)
Age (years)	N	188	173	177
	Mean (SE)	43.7 (0.6)	43.3 (0.6)	42.5 (0.7)
	Min, Max	27, 68	26, 65	25, 65
Weight (kg)	N	187	173	177
	Mean (SE)	69.3 (1.0)	67.8 (0.9)	70.8 (1.0)
	Min, Max	43, 130	40, 105	48, 124
Living situation	N	188	172	177
Lives alone	N	38	35	37
Lives with family	N (%)	145 (77%)	133 (77%)	131 (74%)
Lives in home/hostel	N	5	4	9
Detoxification Prior to Randomization	N	188	173	177
Yes	N (%)	188 (100%)	173 (100%)	177 (100%)
No	N (%)	0	0	0
Abstinent at Baseline	N	188	173	177
Yes	N (%)	188 (100%)	173 (100%)	177 (100%)
No	N (%)	0	0	0
Duration of Alcohol Dependence/Abuse (years)	N	188	173	176
	Mean (SD)	9.8 (7.7)	10.1 (7.1)	8.5 (6.5)
Average Standard Drinks per day at Study Entry	N	187	173	176
	Mean (SE)	15.7 (1.0)	15.0 (0.6)	16.0 (0.7)
	Min, Max	4, 167	1, 42	1, 67
<5	N (%)	3 (2%)	6 (3%)	8 (5%)
5-10	N (%)	56 (30%)	57 (33%)	35 (20%)
>10	N (%)	128 (68%)	110 (64%)	133 (76%)
Prior Treatment or Detoxes for Alcoholism	N	188	173	176
0	N (%)	99 (53%)	87 (50%)	84 (48%)
1	N (%)	57 (30%)	50 (29%)	59 (34%)
2	N (%)	19 (10%)	26 (15%)	26 (15%)
3	N (%)	10 (5%)	4 (2%)	4 (2%)
>3	N (%)	3 (2%)	6 (3%)	3 (2%)
Data Source: Table 8.7.1.2.3 and Table 8.7.1.3.3				

Sponsor's In-Text Table 8.4.2.3:2 NA = Not Available

5.4.2.1.3 Dosing Information

The table below illustrates exposure duration and compliance with medication across treatment groups. Mean compliance was slightly higher (88%) in the acamprosate 1998 mg/day group than in the other two groups (82-83%). 73%-81% of subjects were >75% compliant. Duration of exposure to study medication was shorter in the placebo group (mean 32 weeks) than in the acamprosate groups (mean 35-38 weeks). Less than half of patients in the placebo group (44%)

completed at least 26 weeks of treatment, whereas 59% of the patients in the acamprosate group completed at least 26 weeks of treatment.

Drug Exposure – Pivotal Efficacy Study Paille

Parameter	Statistic	ACAMP 1332 mg/day (N=188)	ACAMP 1998 mg/day (N=173)	Placebo (N=177)
Duration of Exposure (weeks)	n	188	173	177
	Mean (SE)	35.3 (1.4)	37.7 (1.4)	31.6 (1.5)
	Median	44	50	31
	Min, Max	1, 62	0, 58	0, 60
Exposure by Duration Category (weeks)	n	188	173	177
0 - <4	n (%)	11 (6%)	8 (5%)	9 (5%)
4 - <8	n (%)	12 (6%)	11 (6%)	18 (10%)
8 - <13	n (%)	12 (6%)	12 (7%)	14 (8%)
13 - <26	n (%)	34 (18%)	17 (10%)	36 (20%)
26 - <39	n (%)	17 (9%)	20 (12%)	24 (14%)
39 - <52	n (%)	54 (29%)	57 (33%)	36 (20%)
≥52	n (%)	48 (26%)	48 (28%)	40 (23%)
Compliance (%)	n	167	154	158
	Mean (SE)	82.5 (1.8)	88.4 (1.7)	83.2 (1.6)
	Median	90	96	88
	Min, Max	11, 153	27, 167	14, 116
Number of Patients Who Were ≥75 % Compliant	n (%)	125 (75%)	125 (81%)	116 (73%)
Data Source: Table 8.7.1.4.3				

Sponsor's In-Text Table 8.7.2.6:3

Note: Compliance is calculated as the number of study drug tablets taken divided by the number of study drug tablets prescribed times 100.

Note: Percentages for ≥75% compliant are based on the number of patients for whom compliance was calculated.

5.4.3 Efficacy Results

5.4.3.1 Sponsor's Analysis

For the purpose of this application, Lipha chose CAD as the outcome of interest to be evaluated across studies.

The evaluation of abstinence in the CRF is represented by a section reading, "Evaluation of abstinence (assessed by the clinician)," and including fields for "Estimated number of days of non-abstinence in the course of the last month" and "Estimated mean consumption of alcohol during these days of non-abstinence" (in g/day). This data was used as follows in the calculation of "Cumulative Abstinence Duration" by the sponsor:

> "The number of abstinent days was calculated from Day 0 to either Day 360, the date that Day 360 occurred, or the date treatment stopped, whichever gave the shorter time interval; the treatment duration was defined based on the same interval. The number of abstinent days between each pair of subsequent visits

was calculated by subtracting the number of non-abstinent days from the total days between visits. The total number of abstinent days was then calculated by summing the abstinent days over all relevant visits. If a patient did not attend a particular visit, then the patient was assumed to be non-abstinent since the preceding visit." [Section 10.7]

Again, this data relies extensively on investigator's judgment and imputation of data. Using this approach, the sponsor's analysis yielded the following results:

Table 5.4.3.1 Cumulative Abstinence Duration--Paille

Efficacy Parameter	Placebo	Acamprosate 1332 mg/day	Acamprosate 1998 mg/day	p value
Mean cumulative abstinence duration (CAD) (days)	173.4	198.4	223.4	0.0005
Mean % time abstinent (analagous to CCAD)	48%	55%	62%	
Data Source: Paille Study Report, Tables 6-9				

From Sponsor's In-Text Table 8.4.2.3.4, % time abstinent calculated by reviewer as CAD/360

5.4.3.2 Reviewer's Analysis

Again, to perform an analysis that does not go beyond the actual information available, I conducted two different explorations of the data. I evaluated the number of visits at which each subject was assessed as abstinent, and compared the pattern across treatment arms, and I did a responder analysis comparing the numbers of subjects who were assessed as abstinent for the entire study. Note that the first analysis resembles CAD, in that it acknowledges that periods of abstinence are clinically significant even if they are interrupted by periods of drinking. The second analysis is the most conservative, and may represent a higher standard of success than is clinically appropriate.

Again, it should be noted that the methods of data collection (the apparent lack of separation between data collection personnel and treatment personnel) may have introduced demand characteristics which would discourage subjects from reporting drinking. Subjects described as being "abstinent" may be more accurately characterized as being those subjects who managed to convey the impression of abstinence to the evaluating clinician. Given tendency of therapists to look for improvement, it is likely that this number over-estimates the actual abstinence rate. If the treatment was somehow unmasked (perhaps by the occurrence of adverse events), there would be obvious bias in the data. However, given the relatively benign safety profile one can hope that the bias towards underreporting drinking and the bias towards seeing improvement would be randomly distributed across treatment groups.

5.4.3.2.1 Non-Continuous Abstinence

This analysis compares the patterns of the number of visits at which each subject was assessed as abstinent by the evaluating clinician. This approach acknowledges that subjects whose abstinence is not continuous may also be regarded as successful. Rather than transforming this

binary assessment into an arbitrary number of days, I simply counted the "abstinent visits" and analyzed the distribution across treatment groups.

For this study, I included only the first 10 visits, representing the treatment period. The table below shows the number of subjects having various numbers of abstinent visits during the treatment period. . For this analysis, the dataset PI_EFFVS was combined with PI_POP (to obtain treatment assignments). Visits coded as "0" under the column STDCAT were counted as visits assessed as abstinent. This column contained a categorical description of level of consumption. (Inexplicably, no subjects had 10 abstinent visits, although several patients are described as "continuously abstinent" in the dataset. This may reflect the handling of missing visits.)

Table 5.4.3.2.1 Number of Visits at Which Subjects Were Assessed as Abstinent--Paille

Number of visits at which subject was assessed as abstinent	Acamprosate 1332 N = 188		Acamprosate 1998 N = 173		Placebo N = 177	
	N	%	N	%	N	%
0	50	27%	29	17%	56	32%
1	24	13%	23	13%	24	14%
2	15	8%	17	10%	16	9%
3	11	6%	15	9%	15	8%
4	14	7%	10	6%	10	6%
5	12	6%	11	6%	9	5%
6	10	5%	10	6%	7	4%
7	8	4%	14	8%	18	10%
8	11	6%	11	6%	3	2%
9	33	18%	33	19%	19	11%

Table prepared by reviewer using datasets PI_EFFVS + PI_POP

A t-test shows a statistically significant difference between acamprosate 1998 mg and placebo.

Inspection of the distribution of abstinent visits shows that the difference is driven primarily by the subjects who were abstinent for 9 visits. However, if those abstinent at 8 visits are added, the difference between active and placebo groups is strengthened. In each acamprosate group, 44 subjects (24-25%) had 8 or 9 abstinent visits, vs 22 (12%) in the placebo group.

This demonstrates that subjects randomized to acamprosate 1998 mg/day spent more time in a state the investigator perceived as "abstinent" than did subjects randomized to placebo.

5.4.3.2.2 Responder Analysis: Continuous Abstinence

The rates of complete abstinence for the entire treatment period across the treatment groups are shown in the table below. For this analysis, PI_EFFPT was combined with PI_POP (to obtain treatment assignments). Subjects with "TMCABST" ≥360 days were counted as continuously abstinent throughout the treatment period.

Table 5.4.3.2.2 Continuous Abstinence Throughout Treatment--Paille

Number (%) with continuous abstinence of ≥360 days from day 0	Acamprosate 1332 N = 188	Acamprosate 1998 N = 173	Placebo N = 177
	33(18%)	33 (19%)	20 (11%)*
			*p <.05 vs acamprosate 1998 mg Chi-Square

Table prepared by reviewer from sponsor's datasets PI_EFFPT + PR_POP, with explanatory material on dataset submitted by sponsor on 3/8/02

5.4.3.2.2.1 Analysis by Gender

The table below shows the number and percent of subjects continuously abstinent for 360 days or longer by gender. Because of the small number of female participants, firm conclusions cannot be drawn, but acamprosate appears to be equally effective in men and women in this study.

	Total			Acamprosate 1332 mg/day			Acamprosate 1998 mg/day			Placebo		
	N	N Abstinent	% Abstinent	N	N Abstinent	% Abstinent	N	N Abstinent	% Abstinent	N	N Abstinent	% Abstinent
Female	108	15	14%	42	6	14%	36	7	19%	30	2	7%
Male	430	71	17%	146	27	18%	137	26	19%	147	18	12%

5.4.3.2.2.2 Analysis by Center

By-center rates of continuous abstinence ranged from 0-50%. Rates of continuous abstinence across groups by center are shown in the table below. The table lists the number of subjects at each center with a continuous abstinence duration of 360 days or longer, and the % of enrollees represented by this number.

	Total		Acamprosate 1332 mg/day		Acamprosate 1998 mg/day		Placebo	
Center #	N Abstinent	% Abstinent	N Abstinent	% Abstinent	N Abstinent	% Abstinent	N Abstinent	% Abstinent
1	1	8%	0	0%	1	33%	0	0%
2	10	28%	3	25%	6	50%	1	8%
3	3	14%	1	11%	2	29%	0	0%
4	0	0%	0	0%	0	0%	0	0%
5	2	20%	2	50%	0	0%	0	0%
6	1	6%	0	0%	0	0%	1	17%
7	0	0%	0	0%	0	0%	0	0%
8	1	11%	0	0%	1	33%	0	0%
9	3	30%	1	33%	2	67%	0	0%
10	3	33%	1	33%	2	67%	0	0%
11	5	14%	1	8%	2	17%	2	17%
12	0	0%	0	0%	0	0%	0	0%
13	3	17%	2	33%	0	0%	1	17%
14	1	11%	1	33%	0	0%	0	0%
15	3	14%	2	25%	1	14%	0	0%

16	3	20%	1	20%	2	40%	0	0%
17	6	17%	1	8%	4	33%	1	8%
18	2	11%	0	0%	0	0%	2	33%
20	3	14%	2	25%	0	0%	1	13%
21	1	6%	1	20%	0	0%	0	0%
22	1	20%	0	0%	0	0%	1	50%
23	2	12%	0	0%	2	40%	0	0%
24	6	33%	3	50%	2	33%	1	17%
25	11	31%	4	33%	2	17%	5	42%
26	1	4%	1	11%	0	0%	0	0%
27	1	8%	0	0%	1	20%	0	0%
28	1	8%	1	20%	0	0%	0	0%
29	3	38%	1	33%	1	50%	1	33%
30	1	4%	0	0%	1	11%	0	0%
31	7	39%	3	50%	1	17%	3	50%
32	1	7%	1	20%	0	0%	0	0%

5.4.3.3 Conclusions Regarding Efficacy Data in Study

This study provides additional evidence that recently-detoxified alcoholic subjects treated with acamprosate were more frequently assessed as abstinent by the treating physician than were subjects treated with placebo.

Although the sponsor's analysis of CAD and CCAD are questionable, because the reconstruction of days drinking vs. abstinent relies on more detail than was collected, the overall conclusion is supported. Both an analysis of continuous abstinence and an analysis of the pattern of visits at which the investigator assessed the subject to be abstinent support the sponsor's conclusions. Concerns about the validity of the data include the likelihood that both subject and investigator (who apparently also served as therapist) would be biased in reporting and assessment. This would be expected to occur evenly across treatment assignment, however, unless unmasking occurred. The safety results (per submitted datasets) show that few adverse events occurred at a higher rate in the treatment groups than in placebo groups. However, diarrhea (a recognized acamprosate-related event) occurred in 14% of the acamprosate 1998 mg group, 9% of the acamprosate 1332 mg group, and only 4% of the placebo group. This difference may have been sufficient that the occurrence of diarrhea in a subject would lead the investigator to deduce (usually correctly) treatment assignment.

5.5 Protocol # AOT 411.198 ("PRAMA"): Prevention of Relapses in Alcoholics with Acamprosate

Conducted 10/90-12/92 (treatment period)
10/91-1/94 (follow-up period)

5.5.1 Protocol

5.5.1.1 Objective/Rationale
The objective of the study was to compare the efficacy and safety of acamprosate and placebo on maintaining abstinence in weaned alcohol-dependent outpatients, over a 48 week treatment period.

5.5.1.2 Overall Design
The study was designed as a 48 week, randomized, double-blind, placebo-controlled, outpatient multicenter study. At least 6 centers were planned, with each contributing 24-48 subjects. Subjects were required to be recently detoxified, abstinent from alcohol for at least 14 days (but no longer than 4 weeks), and to have no symptoms of alcohol withdrawal. Acamprosate therapy was to be offered in addition to "any psychotherapy usually carried out by the individual center."

5.5.1.3 Population and Procedures
The planned sample size was 200-300 subjects.

5.5.1.3.1 Inclusion/Exclusion Criteria
To be eligible, subjects were required to meet the following inclusion criteria:

- Age 18 to 65 years
- DSM-III-R diagnosis of alcohol (5 of 9 criteria)
- History of at least 3 years of alcohol dependence in males and at least 2 years of alcohol dependence in females
- Munich Alcoholism Test (MALT) test score of at least 11 points
- A minimum of 14 consecutive days abstinence following detoxification
- Intelligence level of at least 13 points on the MWT-B questionnaire

Subjects were excluded for:

- "Controlled abstinence" of more than 4 weeks;
- Existing withdrawal symptoms;
- Existing mental disease necessitating the start of psychotropic drug therapy during the study;

- Epilepsy not due to alcoholism, severe general changes in the EEG and/or epileptic foci;
- Severe hepatic damage, particularly alcoholic hepatitis and alcoholic cirrhosis, plasma cholinesterase less than the normal;
- Hypercalcemia of all etiologies;
- A planned stay of more than 3 weeks at a specialist residential clinic for addicts or at a psychiatric clinic;
- Lack of fixed address;
- Severe drug addiction or drug dependence in the past 3 years;
- Known excretory pancreatic failure;
- Pregnancy/nursing/inadequate contraception
- Severe systemic disease (e.g., poorly controlled diabetes mellitus, noncompensated hypertension, decompensated heart failure);
- ECG-confirmed cardiac arrhythmias requiring treatment, ventricular extrasystoles;
- Creatinine >120 µmol/L or >1.4 mg/dL);
- Malignancies;
- "Pronounced organic psychological syndrome which prevented an understanding of the nature of the trial and of the questionnaires"; and
- History of gastrointestinal surgery resulting in GI narrowing

Eligible subjects were randomly assigned in blocks of 8 to receive acamprosate or placebo in a ratio of 1:1. The total daily dose was adjusted according to the subject's weight:

> Subjects with a body weight ≥60 kg were to receive 1998 mg of acamprosate or placebo per day, taken as 2 tablets of 333 mg acamprosate (or matching placebo) in the morning, at mid-day, and in the evening.
>
> Subjects with a body weight <60 kg were to receive 1332 mg of acamprosate or placebo per day, taken as 2 tablets of 333 mg acamprosate (or placebo) in the morning, and 1 tablet of 333 mg acamprosate (or placebo) at mid-day and in the evening.

Study medication was to be taken at meal times. The scheduled duration of treatment was 48 weeks. Throughout the study, subjects were provided with psychotherapy at each investigator's discretion according to each site's usual practices.

On selection day, subjects were assessed for eligibility prior to entering alcohol withdrawal treatment. Once detoxification had been completed and the patient had remained abstinent for 14 days, Day 0 reassessment for baseline parameters was performed. Subsequent assessments were made at Weeks 4, 8, 12, 24, 36 and 48 at the study center. However, the protocol was amended 3/1/91 to stipulate that "In the time when the individual examinations have a frequency of 12 weeks a contact between the investigational physician and the patient should take place at least each 4 weeks. This patient contact is documented on a special sheet that is added to the CRF between the respective main individual examination numbers. If patient contacts are even more frequent this has to be mentioned on this sheet."

Patients relapsing during treatment could continue with their study medication or, if the severity of the relapse necessitated, undergo detoxification and subsequently restart study medication. Psychotherapy was permitted throughout treatment.

An off-treatment follow-up period of an additional 48 weeks was planned, with visits at weeks 60, 72, 84, and 96.

Assessments occurred on the following schedule (constructed from sample Case Report Form):

	Screen	Baseline (Day 0)	Wk 4	Wk 8	Wk 12	Wk 24	Wk 36	Wk 48	Wk 60	Wk 72	Wk 84	Wk 96
Inclusion/Exclusion criteria	X											
DSM III-R diagnosis	X											
Height/weight	X											
MALT	X											
IQ screening	X											
Drinking history		X										
Addiction history		X										
ECG		X										
EEG		X										
VS, weight		X	X	X	X	X	X	X	X	X	X	X
Alcohol-related clinical findings		X	X	X	X	X	X	X	X	X	X	X
Breathalyzer			X	X	X	X	X	X	X	X	X	X
Alcohol craving		X	X	X	X	X	X	X	X	X	X	X
Self-report of drinking behavior			X	X	X	X	X	X	X	X	X	X
Family report of drinking behavior			X	X	X	X	X	X	X	X	X	X
"Doctor's evaluation of therapy success"			X	X	X	X	X	X	X	X	X	X
GGT/MCV			X	X	X	X	X	X	X	X	X	X
Serum Variant Transferrin		X	X	X	X	X	X	X	X	X	X	X
Urine drug screen		X	X	X	X	X	X	X		X		X
CBC		X	X		X	X		X				
U/A		X	X		X	X		X				
Serum chemistry		X	X		X	X		X				
Acamprosate level (urine)			X	X	X	X	X	X				
Medication dispensed		X	X	X	X	X	X					
Pill count/ Compliance assessment			X	X	X	X	X	X				
Symptom checklist (completed by subject)		X	X	X	X	X	X	X	X	X	X	X
AEs (open-ended probe)			X	X	X	X	X	X	X	X	X	X
Concomitant meds		X	X	X	X	X	X	X	X	X	X	X
Addiction-related consequences			X	X	X	X	X	X	X	X	X	X
Documentation of concomitant therapy received			X	X	X	X	X	X	X	X	X	X
Substance abuse assessment			X	X	X	X	X	X	X	X	X	X

The protocol called for the following approach to determining abstinence vs. non-abstinence:

- Breathalyzer was to be administered
- Subject was to be questioned about abstinence or drinking habits
- Where possible, subjects partner/relatives were to be questioned
- GGT and MCV were to be determined (local lab); if there were no other known medical reasons, then
  - GGT > 2xULN or "marked increase" was to be considered indicative of alcohol consumption
  - MCV > normal laboratory value was to be considered indicative of alcohol consumption

Using the above information, together with his "clinical impression," the investigator was to form a global assessment and complete a field indicating "relapse in the preceding therapy phase: yes/no." The time of the relapse was to "be determined as exactly as possible."

5.5.1.4 Evaluations/Endpoints (how measured/appropriateness)

The protocol-specified outcome measure was "abstinence in the patient, evaluated by the trial physician under consideration of clinical and laboratory variables (reports by the patient and his family, clinical impression, gamma-GT and MCV)."

The planned primary variable was time to first relapse. Any consumption of alcohol defined a relapse. A relapse was "short-term" if alcohol was consumed up to 24 hours and "long-term" if it continued for a period longer than 24 hours. "Constant" alcohol consumption was termed a "continuous relapse." The protocol specified that "the point in time when a relapse occurs will be defined as the day on which alcohol consumption starts again."

5.5.1.5 Statistical Plan

The statistical evaluation methods included in the protocol specified that:

- The evaluation of the study would be according to the intent-to-treat principle; wherever possible, all patients were to be fully documented during the entire planned therapy and follow-up observation phase.
- The primary variable for the evaluation was to be the point in time when a relapse occurred; to be evaluated in the form of an event analysis using a log-rank test, whereby a patient enters the statistics as an event at the time of his first relapse.
- Patients who were lost to observation and for whom to further information could be obtained were to be evaluated up to the point of the last available information.
- The total incidence of relapses in both groups was to be evaluated as a secondary variable using a comparison of incidence.
- Interim evaluation was called for when the last patient recruited to the study had completed the 24 week evaluation.

- A global evaluation of the study was to be carried out after the completion of the 48 week follow-up phase.

5.5.2 Results

5.5.2.1 Study Conduct/Outcome

5.5.2.1.1 Subject Characteristics

A total of 272 subjects were selected for enrollment. There is no indication of how many were screened in order to enroll 272. Of these, 163 were randomized to placebo and 163 were randomized to acamprosate. Acamprosate dose was based on weight, with subjects >60 kg receiving 1998 mg/day and smaller subjects receiving 1332 mg/day. Only 44 subjects (28 of 61 women and 16 of 211 men) weighed 60 kg or less. Of these, 13 women and 11 men were randomized to acamprosate. Thus, only 24 subjects in the study received the 1332 mg/day dose

5.5.2.1.1.1 Enrollment by Center

Twelve centers, all in Germany, enrolled between 7 and 64 subjects. Enrollment was distributed among centers as listed in the table below.

Table 5.5.2.1.1.1 Enrollment by Center--PRAMA

Site No.	Number of Patients Randomized	Investigator(s)	Study Center Location
--	--	**Overall Principal Investigator:** Prof. Dr. med. Henning SASS, MD	**Psychiatrische Fachabteilung der RWTH Aachen** Pauwelsstrasse 30 52074 Aachen GERMANY
1	19	Prof. Dr. med. HIPPIUS, MD *(principal investigator)* [ ]	**Klinikum der Universität München** **Klinik und Poliklinik für** **Psychiatrischie und Psychotherapie** Nußbaumstrasse 7 80336 München (Munich) GERMANY
2	18	Prof. Dr. med. H. DILLING, MD *(principal investigator)* [ ]	**Medizinische Universität Lübeck** **Klinik für Psychiatrie** Ratzeburger Allee 160 23562 Lübeck GERMANY
3	9	Prof. Dr. med. Karl F. MANN, MD (Zentralinst. f. Seelische Gesundheit) *(principal investigator)* [ ]	**Psychiatrische Universitäts-Klinik der Eberhard-Karls-Universität Tübingen** Osianderstrasse 22 72076 Tübingen GERMANY
4	39	Dr. med. K. D. SEGERATH, MD *(principal investigator)* [ ]	**Katholisches Krankenhaus Philippusstift** **Fachabteilung für Suchkrankheiten** Hülsmannstrasse 17 45355 Essen-Borbeck

Site No.	Subjects Randomized	Investigator	Study Center Location
		[redacted]	GERMANY
5	10	Prof. Dr. J. GROSS, MD *(principal investigator)* [redacted]	**Universitätsklinik Eppendorf Psychiatrische Klinik** Martinistraße 52 20246 Hamburg GERMANY
6	64	[redacted]	**Bezirksnervenklinik Schwerin** **Abteilung 1b** Wismarsche Strasse 393 - 395 19055 Schwerin GERMANY
7	7	Dr. med. Heinz Georg BIALONSKI, MD *(principal investigator)* [redacted]	**Zentrum für soziale Psychiatrie Rheinblick** Kloster-Eberbach-Strasse 4 65346 Eltville GERMANY
8	13	PD Dr. Hubert KUHS *(principal investigator)* [redacted]	**Klinik für Psychiatrie des Klinikums der Westfälischen Wilhelms-Universität** Albert-Schweitzer-Strasse 11 48149 Münster GERMANY
9	--		
10	14	Frau Prof. Dr. med. D. ZIEGLER, MD *(principal investigator)* [redacted]	**Universitäts-Kliniken des Saarlandes** **Nervenklinik und Poliklinik** Psychiatrie, Gebäude 90 66421 Homburg/Saar GERMANY
11	30	Dr. med. Roland WEISE, MD *(principal investigator)* [redacted]	**Klinik für forensische Psychiatrie** Chemnitzer Strasse 50 04289 Leipzig GERMANY
12	25	Dr. med. Volker KIELSTEIN (principal investigator) [redacted]	**Tagesklinik an der Sternbrücke** Dr. Kielstein GmbH Planckstraße 4 – 5 39104 Magdeburg GERMANY
13	24	Prof. Dr. med. Jobst BÖNING *(principal investigator)* [redacted]	**Psychiatrische Universitäts-Klinik und-Poliklinik** Füchsleinstrasse 15 97080 Würzburg GERMANY

5.5.2.1.1.2 Subject Disposition

The table below illustrates patient disposition and reasons for premature discontinuation. Many more patients in the placebo group discontinued for reasons coded as "other" compared to the acamprosate group. Overall, completion was higher in the acamprosate group.

Table 5.5.2.1.1.2 Patient Disposition During Treatment Phase – PRAMA

	Statistic	ACAMP (N=136)	Placebo (N=136)
Number of Patients Randomized	n	137	138
Number of Patients in the ITT Population	n (%)	136 (99%)	136 (99%)
Number of Patients Who Completed Treatment Phase	n (%)	73 (53%)	53 (38%)
Number of Patients Who Discontinued Treatment Phase	n (%)	63 (46%)	83 (60%)
Reasons for Discontinuation:			
Adverse Event	n (%)	8 (6%)	6 (4%)
Lost to Follow-up	n (%)	25 (18%)	27 (20%)
Treatment Failure	n (%)	8 (6%)	5 (4%)
Death	n (%)	2 (1%)	1 (<1%)
Protocol Violation	n (%)	0	0
Other	n (%)	20 (15%)	44 (32%)
Data Source: Table 8.7.1.1.2			

Sponsor's In-Text Table 8.4.2.2:1

Note: Percentages are based on the number of patients randomized.

Note: ACAMP = Acamprosate 1332 mg/day for patients ≤60 kg or Acamprosate 1998 mg/day for patients >60 kg.

5.5.2.1.2 Demographics

The table below illustrates demographic and baseline characteristics of the two treatment groups. Most patients in this study were male (75% in acamprosate group and 80% in placebo group) and the mean age was 42 years in the acamprosate group and 41 in the placebo group.

With respect to alcohol use histories, the mean duration of alcohol dependence was 10.4 years in both groups. Almost all subjects drank 5 or more standard drinks per drinking day prior to treatment. The rate of very heavy drinking (>10 drinks/drinking day) did not differ across treatment groups (77-80%). Most (73%) of the patients had previously undergone treatment or detoxification for alcoholism, and the groups were similar with respect to the number of patients with 0-1 previous detoxes (49% in acamprosate group and 53% in placebo group) and the number with 3 or more previous detoxes (35% in each group). All of the patients in the study had undergone detoxification and were abstinent at baseline.

Table 5.5.2.1.2 Demographic and Baseline Characteristics –Study PRAMA

Characteristic	Statistic	ACAMP (N=136)	Placebo (n=136)
Gender	n	136	136
Male	n (%)	102 (75%)	109 (80%)
Female	n (%)	34 (25%)	27 (20%)
Age (years)	n	136	136
	Mean (SE)	41.9 (0.7)	40.5 (0.7)
	Min, Max	21, 58	21, 65
Weight (kg)	n	136	136
	Mean (SE)	72.4 (1.0)	73.9 (1.1)
	Min, Max	46, 130	41, 107
Marital Status	n	136	136
Married	n (%)	58 (43%)	67 (49%)
Not married	n (%)	78 (57%)	69 (51%)
Detoxification Prior to Randomization	n	136	136
Yes	n (%)	136 (100%)	136 (100%)
No	n (%)	0	0
Abstinent at Baseline	n	136	136
Yes	n (%)	136 (100%)	136 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)	n	136	136
	Mean (SE)	10.4 (0.5)	10.4 (0.6)
	Min, Max	2, 30	2, 30
Average Standard Drinks per Day at Study Entry	n	134	136
	Mean (SE)	17.9 (0.8)	18.7 (0.8)
	Min, Max	3, 46	1, 45
<5	n (%)	3 (2%)	6 (4%)
5-10	n (%)	28 (21%)	21 (15%)
>10	n (%)	103 (77%)	109 (80%)
Prior Treatment or Detoxes for Alcoholism	n	136	136
0	n (%)	33 (24%)	40 (29%)
1	n (%)	34 (25%)	32 (24%)
2	n (%)	22 (16%)	17 (13%)
3	n (%)	13 (10%)	13 (10%)
>3	n (%)	34 (25%)	34 (25%)
Data Source: Table 8.7.1.2.2 and Table 8.7.1.3.2			

Sponsor's In-Text Table 8.4.2.2:2

Note: ACAMP = Acamprosate 1332 mg/day for patients ≤60 kg or Acamprosate 1998 mg/day for patients >60 kg.

As dosing was based on weight, it should be noted that only 44 subjects (28 of 61 women and 16 of 211 men) weighed 60 kg or less. Of these, 13 women and 11 men were randomized to acamprosate. Thus, only 24 subjects in the study received the 1332 mg/day dose.

5.5.2.1.3 Dosing Information

The table below illustrates exposure duration and compliance with medication across treatment groups. Mean compliance was over 80% in each group, and 68-70% of subjects were >75% compliant. Groups were similar with respect to compliance. Duration of exposure to study medication was shorter in the placebo group (mean 26 weeks) than in the acamprosate group

(mean 32 weeks). Less than half of patients in the placebo group (44%) completed at least 26 weeks of treatment, whereas 59% of the patients in the acamprosate group completed at least 26 weeks of treatment.

Drug Exposure – Pivotal Efficacy Study PRAMA

Parameter	Statistic	ACAMP (N=136)	Placebo (N=136)
Duration of Exposure (weeks)	n	136	136
	Mean (SE)	32.2 (1.7)	26.1 (1.8)
	Median	40	18
	Min, Max	0, 61	0, 65
Exposure by Duration Category (weeks)	n	136	136
0 - <4	n (%)	19 (14%)	24 (18%)
4 - <8	n (%)	7 (5%)	10 (7%)
8 - <13	n (%)	8 (6%)	21 (15%)
13 - <26	n (%)	22 (16%)	21 (15%)
26 - <39	n (%)	11 (8%)	7 (5%)
39 - <52	n (%)	54 (40%)	40 (29%)
≥52	n (%)	15 (11%)	13 (10%)
Compliance (%)	n	118	109
	Mean (SE)	80.8 (1.7)	80.7 (2.3)
	Median	87	88
	Min, Max	17, 106	5, 173
Number of Patients Who Were ≥75% Compliant	n (%)	83 (70%)	74 (68%)
Data Source: Table 8.7.1.4.2			

Sponsor's In-Text Table 8.7.2.6:2

Note: ACAMP = Acamprosate 1332 mg/day for patients ≤60 kg or Acamprosate 1998 mg/day for patients >60 kg.
Note: Compliance is calculated as the number of study drug tablets taken divided by the number of study drug tablets prescribed times 100.
Note: Percentages for ≥75% compliant are based on the number of patients for whom compliance was calculated.

5.5.3 Efficacy Results

5.5.3.1 Sponsor's Analysis

The protocol-specified primary analysis was time to relapse. However, for the purpose of this application, the sponsor analyzed all the pivotal trials according to a common outcome measure, cumulative abstinence duration (CAD).

In the sponsor's analysis of CAD, the binary assessment of the investigator was transformed into a number of days abstinent for the purposes of analysis. The method of calculating the duration of abstinence is described as follows:

> "The total number of abstinent days was created assuming that visits occurred according to the visit schedule. [Reviewer's note: a difference of ±3 days was permitted by protocol; no table of protocol violations indicating the extent to which this was adhered to is presented.] The physician's global assessment helped determine how much of that time would be abstinent. If using these two

items and summing across all visits resulted in fewer abstinent days than indicated by the time to first relapse, then the number of abstinent days was set to the number of days to relapse, otherwise it was set to the number of abstinent days as summed across all visits.

"If the physician's global assessment indicated success, then all days since the previous visit were considered abstinent. When failure was indicated, then the number of abstinent days was determined using the patient's and relative's report on drinking, where the higher category was used if there was a difference between the two and the patient's report if the categories reported were the same. When there was no reported category of relapse, then half of the days between visits were considered abstinent. When the relapse was considered to have started as a continuous relapse between visits, all days between visits were considered non-abstinent. The number of brief relapses plus three times the number of longer relapses were subtracted from the number of days since the previous visit if either type of relapse was indicated; if either type of relapse was indicated and no numbers were provided, it was assumed that the patient was abstinent for half of the days.

"Several methods of determining the number of abstinent days were used when there was no physician global assessment provided. In cases where there were two consecutive post-baseline visits with the assessment missing but there was a nonmissing assessment later, then both time visit intervals were considered abstinent if either the prior or next visit was indicated as a success by the physician's global assessment; both visit intervals were considered non-abstinent if both visits were indicated as failures by the physician's global assessment. When no assessment was made for Visit 1, the patient was assumed to have been abstinent half of the days. For all other cases, a missing global assessment following a successful one was considered to indicate abstinence for half the period, while a missing global assessment following a missing or failure was considered to indicate non-abstinence for the period."

Using this complex method to transform a binary (yes/no) assessment into a continuous variable (number of days abstinent), and dividing the number of abstinent days by 360 (duration of the treatment portion of the study) to generate the "corrected cumulative abstinence duration), the sponsor reported the following results (statistically significant by their analysis):