

and 51% in the placebo group) of the patients consumed more than 10 standard drinks per day at study entry. Most subjects (65-69% ) had not had previous treatment for alcoholism. Approximately 10% had undergone more than three prior treatments. All patients in both treatment groups received detoxification prior to randomization and were abstinent at Baseline.

**Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study Tempesta**

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=164)	Placebo (N=166)
Gender	N	164	166
Male	n (%)	139 (85%)	134 (81%)
Female	n (%)	25 (15%)	32 (19%)
Age (years)	N	164	166
	Mean (SE)	45.9 (0.9)	46.0 (0.9)
Weight (kg)	N	164	166
	Mean (SE)	71.2 (0.7)	70.6 (0.7)
	Min, Max	57, 95	51, 102
Marital Status	N	164	166
Married	n (%)	111 (68%)	114 (69%)
Not Married	n (%)	53 (32%)	52 (31%)
Detoxification Prior to Randomization	N	164	166
Yes	n (%)	164 (100%)	166 (100%)
No	n (%)	0	0
Abstinence at Baseline	N	164	166
Yes	n (%)	164 (100%)	166 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)	N	95	105
	Mean (SE)	11.5 (0.9)	11.5 (0.9)
Average Standard Drinks per Day at Study Entry	N	164	166
<5	n (%)	6 ( 4%)	9 ( 5%)
5 – 10	n (%)	68 (41%)	72 (43%)
>10	n (%)	90 (55%)	85 (51%)
Prior Treatment or Detoxes for Alcoholism	N	164	166
0	n (%)	113 (69%)	108 (65%)
1	n (%)	17 (10%)	23 (14%)
2	n (%)	13 ( 8%)	12 ( 7%)
3	n (%)	6 ( 4%)	5 ( 3%)
>3	n (%)	15 ( 9%)	18 (11%)

Data Source: Table 8.7.2.2.2 and 8.7.2.3.2

Sponsor's In-Text Table 8.4.3.2:2 Note: Percentages are based on the number of patients in the ITT population who had data for the assessment.

Mean compliance was similar between treatment groups (95.1% for the acamprosate group and 92.6% for the placebo group).

The primary variables for evaluating efficacy were the cumulative abstinence duration (CAD), abstinence by visit, and time to first relapse.

The CAD was defined as the total number of days of abstinence and was calculated as the sum of only those periods of complete abstinence. To assess CAD as a fraction of the potential duration of treatment, the corrected cumulative abstinence duration (CCAD) was calculated.

The table below shows the mean CAD and CCAD for each treatment group. The 2 calculations for the cumulative abstinence duration show a statistically significantly longer duration of abstinence in the acamprosate treated patients.

**Cumulative Abstinence Duration (CAD) and Corrected CAD (CCAD) – European Short-Term Supportive Efficacy Study Tempesta**

Treatment period 0-180 days	CAD		CCAD	
	Days	SD	%	SD
Placebo n=166	89	±77	54	±44
Acamprosate n=164	110	±77	66	±42
T-test	p=0.016		p=0.008	
Data Source: Tempesta Study Report: Table 3.1.1.c				

Sponsor's In-Text Table 8.4.3.2:4

In the abstinence-by-visit analysis, more subjects randomized to acamprosate were abstinent at each visit than subjects on placebo. The difference was statistically significant at some visits but not at others, as shown in the table below.

**Abstinence or Non-Abstinence/Non-Attendance at Each Visit – European Short-Term Supportive Efficacy Study Tempesta**

Day	Acamprosate		Placebo		Mantel-Hänszel p=
	Abstinent (%)	Relapse or non-attendant (%)	Abstinent (%)	Relapse or non-attendant (%)	
0	163 (99.4)	1 ( 0.6)	166 (100.0)	0 -	0.314
30	112 (68.3)	52 (31.7)	93 ( 56.0)	73 (44.0)	0.022*
60	106 (64.6)	58 (35.4)	89 ( 53.6)	77 (46.4)	0.042*
90	96 (58.5)	68 (41.5)	79 ( 47.6)	87 (52.4)	0.047*
120	95 (57.9)	69 (42.1)	81 ( 48.8)	85 (51.2)	0.097
150	96 (58.5)	68 (41.5)	77 ( 46.4)	89 (53.6)	0.027*
180	95 (57.9)	69 (42.1)	75 ( 45.2)	91 (54.8)	0.021*
Data Source: Tempesta Study Report: Table 3.1.1.a					

Sponsor's In-Text Table 8.4.3.2:3

In the analysis of the time to first relapse, the median period of abstinence before the first relapse was significantly longer with acamprosate (135 days) than with placebo (58 days). In this analysis, 47% of acamprosate subjects and 31% of placebo subjects maintained abstinence through 180 days. (p=0.0091, Lee-Desu statistics).

From the safety data, there was no evidence of any adverse event for which the complaints were more likely to be associated with acamprosate than with placebo, providing reassurance that unblinding due to adverse events was unlikely to have occurred.

**Follow-up Period:** The 246 patients who completed the double-blind treatment entered the 90 day off-treatment observation period, with 234 (95%) completing this period. During this period the proportion of patients remaining abstinent in the acamprosate group compared with the placebo group gradually diminished. There was no statistically significant difference between treatment groups in the proportion of patients abstinent. The CAD and CCAD over the entire study period (treatment phase plus follow-up phase), however, remained significantly higher in the acamprosate group compared to the placebo group.

**10.2.3 AOTA/NL/91.1, AOTA/B/90.2 (BENELUX): Double-Blind Controlled Study Versus Placebo to Assess the Effectiveness and Tolerance of Acamprosate (Calcium Acetyl Homotaurinate) in Helping to Maintain Abstinence in the Weaned Alcoholic**  
AOTA/NL/91.1, AOTA/B/90.2 (BENELUX) was a prospective, multicenter (22 centers), randomized, double-blind, placebo-controlled, parallel group (2) comparison study of the efficacy and safety of acamprosate versus placebo in maintaining abstinence in alcohol-dependent outpatients after withdrawal from alcohol. The clinical portion of the study was conducted from May 1990 to October 1992 at 22 psychiatric clinics in the Benelux countries (Belgium, the Netherlands, and Luxembourg), under the overall supervision of Dr. C. Ansoms, M.D. (Head, Department of Psychiatry, Kliniek Broeders Alexianen, Tienen, Belgium) and Dr. P. Geerlings, M.D. (Head, Department of Psychiatry, Jellinek Centrum, Amsterdam, the Netherlands). All of the participating investigators were either psychiatrists or specialized physicians and the participating clinics and hospitals were all psychiatric facilities.

The BENELUX study was initially conducted under the study number AOTA/B/90.1 without ethical approval by the Belgian investigator Dr. Ansoms. The study was subsequently carried out with ethical approval by all other Belgian investigators using a common protocol with the study number AOTA/B/90.2. When Dutch investigative centers were included in the trial, the co-principal investigator, Dr. Geerlings, preferred to work with the AOTA/B/90.1 protocol. Since this protocol was still without ethical approval, the protocol was amended, given the number AOTA/NL/91.1, and was given ethical approval. Data from the 2 protocols AOTA/B/90.1 or AOTA/B/90.2 and AOTA/NL/91.1 were recorded on slightly different CRFs, but were analyzed as 1 study.

Eligible subjects were 18 to 65 years (Protocol AOTA/B/90.2) or 25 to 65 years (Protocol AOTA/NL/91.1) with DSM-III diagnosis or chronic or episodic alcohol dependence for at least 12 months. AOTA/NL/91.1 also required a minimum score on the Munich Alcoholism Test.

Subjects were required to undergo "weaning" and to be abstinent at study entry (at least 5 days (Protocol AOTA/B/90.2) or 8 days (Protocol AOTA/NL/91.1)).

Protocol AOTA/B/90.2 excluded subjects for pregnancy, inadequate contraception, psychiatric or medical disorders, or lack of cooperation with weaning treatment. In Protocol AOTA/NL/91.1

patients who remained for 2 or more weeks in a residential setting during the study period were excluded.

Eligible patients were randomly assigned to receive acamprosate or placebo in a ratio of 1:1. The total daily dose was adjusted according to the patient's weight, with patients >60 kg receiving 1998 mg/day and lighter patients receiving 1332 mg/day. Study medication was to be taken at meal times. The scheduled duration of treatment was 180 days. The study consisted of 7 visits: Visit -1 (Screening), Visit 0 (Baseline), and Visits 1-5 (at Day 30, 60, 90, 135, and 180, respectively).

Throughout the study, patients were provided with psychotherapy at each investigator's discretion according to each site's usual practices, although such therapy was to be held constant course of the study. Patients relapsing during treatment could continue or be readmitted to hospital to be weaned off alcohol while continuing their blinded medication. Subsequently, provided they had remained on their blinded medication, patients were returned to the trial on an outpatient basis if their detoxification period was less than 14 days.

The primary efficacy criteria were CAD and relapse rate at each visit. Safety criteria included laboratory screening of hematology and serum biochemistry and recording of spontaneously reported adverse events as well as completion of a questionnaire listing 44 complaints, organized according to W.H.O. body systems.

As shown in In-Text Table 8.4.3.4:1, a total of 262 patients were randomized into the 2 "studies" comprising the BENELUX trial. Ninety-two patients were randomized under protocol AOTA/LN/91.1 and 170 patients under protocol AOTA/B/90.2. A total of 128 patients (49%) were assigned to the acamprosate group and 134 patients (51%) were assigned to the placebo group. Twelve patients were not randomized because they failed to satisfy study entry criteria. A total of 70 patients completed the 180-day treatment phase, 38 (30%) in the acamprosate group and 32 (24%) in the placebo group.

A majority of patients in both the acamprosate group (90 patients, 70%) and the placebo group (102 patients, 76%) discontinued the double-blind treatment phase. The reasons for discontinuation were similar between treatment groups. Treatment failure was the leading reason for discontinuation (acamprosate 29% and placebo 34%), followed by "Other" (acamprosate 17% and placebo 20%) and Lost-to-Follow-up (acamprosate 16% and placebo 15%).

**APPEARS THIS WAY  
ON ORIGINAL**

**Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study BENELUX**

Parameter	Statistic	ACAMP (N=128)	Placebo (N=134)
Number of Patients Randomized	n	128	134
Number of Patients in the ITT Population	n (%)	128 (100%)	134 (100%)
Number of Patients Who Completed the Double Blind Treatment Phase	n (%)	38 ( 30%)	32 ( 24%)
Number of Patients Who Discontinued the Double Blind Treatment Phase	n (%)	90 ( 70%)	102 ( 76%)
<b>Reasons for Discontinuation:</b>			
Adverse Event	n (%)	9 ( 7%)	5 ( 4%)
Lost to Follow-up	n (%)	21 ( 16%)	20 ( 15%)
Treatment Failure	n (%)	37 ( 29%)	45 ( 34%)
Death	n (%)	0	0
Protocol Violation	n (%)	1 ( <1%)	5 ( 4%)
Other	n (%)	22 ( 17%)	27 ( 20%)
Data Source: Table 8.7.2.1.3			

Sponsor's In-Text Table 8.4.3.4:1

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

Note: Other includes concurrent illness, refusal to continue, non-compliance, and concomitant medication.

Demographic characteristics and history of alcohol use at Baseline were similar across treatment groups. Most patients were male (76% in both treatment groups) and the mean age was 41 years (40.3 years for the acamprosate group and 41.7 years for the placebo group). Patients had a mean duration of alcohol dependence or abuse of 11 years (11.2 years for the acamprosate group and 10.9 years for the placebo group) and 74% (78% in the acamprosate group and 70% in the placebo group) of the patients consumed more than 10 standard drinks per day at study entry. About 40% (44% in the acamprosate group and 36% in the placebo group) had not received prior treatment for alcoholism, and about 20% had one prior treatment. None had undergone treatment more than three times. All patients received detoxification prior to randomization and were abstinent at Baseline.

APPEARS THIS WAY ON ORIGINAL

**Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study BENELUX**

Parameter	Statistic	ACAMP (N=128)	Placebo (N=134)
Gender	n	128	134
Male	n (%)	97 (76%)	102 (76%)
Female	n (%)	31 (24%)	32 (24%)
Age (years)	n	126	132
	Mean (SE)	40.3 (0.8)	41.7 (0.7)
Weight (kg)	n	125	133
	Mean (SE)	71.6 (1.1)	73.3 (1.2)
	Min, Max	44, 105	43, 152
Marital Status	n	80	86
Married	n (%)	42 (53%)	42 (49%)
Not Married	n (%)	38 (48%)	44 (51%)
Detoxification Prior to Randomization	n	128	134
Yes	n (%)	128 (100%)	134 (100%)
No	n (%)	0	0
Abstinence at Baseline	n	128	134
Yes	n (%)	128 (100%)	134 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)	n	95	100
	Mean (SE)	11.2 (0.8)	10.9 (0.7)
Average Standard Drinks per Day at Study Entry	n	125	132
<5	n (%)	2 (2%)	6 ( 5%)
5 – 10	n (%)	26 (21%)	33 (25%)
> 10	n (%)	97 (78%)	93 (70%)
Prior Treatment or Detoxes for Alcoholism	n	124	132
0	n (%)	55 (44%)	47 (36%)
1	n (%)	21 (17%)	27 (20%)
2	n (%)	12 (10%)	22 (17%)
3	n (%)	11 ( 9%)	12 ( 9%)
>3	n (%)	25 (20%)	24 (18%)

Data Source: Table 8.7.2.2.3 and 8.7.2.3.3

Sponsor's In-Text Table 8.4.3.4:2

Note: Percentages are based on the number of patients in the ITT population who had data for the assessment.

Mean compliance was similar for both treatment groups (93.5% for the acamprosate group and 93.3% for the placebo group).

The primary variables for assessing efficacy were cumulative abstinence duration (CAD) and relapse rate at each visit. CAD was defined as the total number of days of abstinence and was calculated as the sum of only those periods of complete abstinence. If any relapse was recorded at a specific visit, the total period from the previous visit was considered as relapse. In determining the period between visits, the scheduled day of assessment was taken into consideration rather than the actual day of the visit. To assess CAD as a fraction of the potential

duration of treatment, the corrected cumulative abstinence duration (CCAD) was calculated. The potential treatment duration was 180 days for all patients excluding those with concurrent illness who were censored during the course of the study.

The table below provides the mean estimated CAD and CCAD for each treatment group and the results of statistical analyses. Both calculations show a statistically significantly longer duration of abstinent periods in the acamprosate treated patients.

**Cumulative Abstinence Duration (CAD) and Corrected CAD (CCAD) – European Short-Term Supportive Efficacy Study BENELUX**

Treatment period 0-180 days	CAD		CCAD	
	Days	SD	%	SD
Placebo	43.1	±58.0	24.4	±32.8
Acamprosate	61.1	±70.1	34.5	±39.0
T-test	p=0.025		p=0.026	
Data Source: BENELUX Study Report, Appendix 7.1, Table 5.8				

Sponsor's In-Text Table 8.4.3.4:3

During the double blind treatment period patients were assessed on treatment Days 30, 60, 90, 135 and 180 and were assigned by the investigator to 1 of 3 categories: abstinent (i.e., not even a single drink), relapsed (any drinking) or non-attendant. In a reported analysis that combined the categories "relapsed" and "non-attendant" into "treatment failures," the proportion of abstinent patients in the acamprosate group was statistically significantly higher some, but not all, assessment days.

**Abstinence or Non-Abstinence/Non-Attendance at Each Visit – European Short-Term Supportive Efficacy Study BENELUX**

Assessment Day	Treatment	Abstinent	Treatment Failure	Chi <sup>2</sup> Test p =
Day 30	Placebo	61 (46)	73 (54)	0.270
	Acamprosate	67 (52)	61 (48)	
Day 60	Placebo	40 (30)	94 (70)	0.117
	Acamprosate	50 (39)	78 (61)	
Day 90	Placebo	30 (22)	104 (78)	0.043
	Acamprosate	43 (34)	85 (66)	
Day 135	Placebo	23 (17)	111 (83)	0.047
	Acamprosate	35 (27)	93 (73)	
Day 180	Placebo	18 (13)	116 (87)	0.017
	Acamprosate	32 (25)	96 (75)	
Data Source: BENELUX Study Report				

Sponsor's In-Text Table 8.4.3.4:4

Over the 180 day period 15% of the acamprosate group and 10% of the placebo group (N.S.) were continuously abstinent.

Diarrhea, sleep disturbances, and dizziness were more frequently reported in the acamprosate than the placebo group, raising the possibility of unblinding due to adverse events.

**Follow-up Period:** At Day 180, study medication was withdrawn and the 70 patients who completed the double-blind treatment entered the 180-day observation period. Fifty three (76%) of these patients completed the observation period. Among the 38 patients receiving acamprosate, six patients were lost to follow-up and two patients refused to continue treatment. Of the 32 patients receiving placebo, three patients relapsed and six patients were lost to follow-up. During the observation period the larger proportion of patients maintaining abstinence in the acamprosate group in relation to the placebo group progressively diminished. There were no statistically significant differences between the treatment groups at any follow-up assessment. Fourteen (37%) acamprosate treated patients remained abstinent throughout the entire 360 days (treatment and follow-up phase) compared with seven (22%) patients in the placebo group (Chi<sup>2</sup> test p=0.173). Over the entire study period the cumulative abstinence duration for the acamprosate group was 221.8 days ± 140.1 days and 190.8 days ± 127.0 days in the placebo group. The difference between treatment groups was not statistically significant.

**10.2.4 AD 04 089 (Ladewig): A Clinical Study to Assess the Effectiveness and Tolerance of AOTA-Ca as Treatment Which Helps to Maintain Abstinence after Detoxification in the Alcoholic Patient. A Double-Blind Controlled Study Versus Placebo**

AD 04 089 (Ladewig) was a prospective, randomized, multicenter (3 centers), double-blind, placebo-controlled, parallel group (2) comparison of the efficacy and safety of acamprosate versus placebo in maintaining abstinence in weaned alcohol-dependent outpatients, over a 6 month treatment period. The clinical portion of the study was conducted from August 1989 to January 1991 at 3 centers in Switzerland, with Prof. D. Ladewig, M.D. (Head, Department of Psychiatry, Psychiatric University Clinic, Basel, Switzerland) as overall Principal Investigator. The investigators at the 2 other centers were both consulting psychiatrists and the centers were regional psychiatric clinics.

To be eligible, subjects were age 18-65 and had a DSM-III diagnosis of alcohol dependence x at least 12 months. All subjects were to undergo weaning therapy and be abstinent for at least 5 days before entering the study. Subjects were excluded for pregnancy, inadequate contraception, medical or psychiatric illness, renal insufficiency, hypercalcemia, and unsuitable living conditions.

Eligible patients were randomly assigned to receive acamprosate (1998 mg/day for 60 kg and over; 1332 mg/day for lighter subjects) or placebo in a ratio of 1:1. Study medication was to be taken at meal times. The scheduled duration of treatment was 180 days. The study consisted of 7 visits: Visit -1 (Screening), Visit 0 (Baseline), Visits 1-3 (at Day 30, 90, and 180) during the Treatment Phase and Visit 4 and Visit 5 (at Day 270 and Day 360, respectively). Throughout the study, patients could have psychotherapy or other psychosocial support as deemed necessary. Concomitant therapy with disulfiram was permitted during the study.

Primary efficacy criteria were CAD and relapse rate. Safety evaluations were performed at

Baseline and Visits 1-3, and consisted of recording of spontaneously reported treatment-emergent adverse events, clinical laboratory determinations (hematology and clinical chemistry), and a questionnaire that listed 44 symptomatic complaints, which included possible withdrawal symptoms as well as adverse events.

As shown in the table below, a total of 62 patients were screened but only 61 patients were randomized (29 to acamprosate and 32 to placebo) and included in the ITT population. The 1 patient who was not randomized required re-hospitalization on Day 0 for a further period of detoxification. Overall, 15 of the 61 randomized patients (24.6%) were <60 kg and received 4 tablets of either placebo or acamprosate (1332 mg/day) while others received the 1998 mg regimen. Although concomitant disulfiram was permitted, only 3 patients randomized to placebo and 2 randomized to acamprosate received it.

The percentage of patients that completed the study (66%) was the same for the 2 treatment groups. More placebo (22%) patients discontinued due to treatment failure than acamprosate patients (7%), while more acamprosate patients (17%) had "Other" (included concurrent illness, refusal to continue, and non-compliance) discontinuation reasons than placebo patients (6%).

**Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study Ladewig**

Parameter	Statistic	ACAMP (N=29)	Placebo (N=32)
Number of Patients Randomized	n	29	32
Number of Patients in the ITT Population	n (%)	29 (100%)	32 (100%)
Number of Patients Who Completed the Double Blind Treatment Phase	n (%)	19 ( 66%)	21 ( 66%)
Number of Patients Who Discontinued the Double Blind Treatment Phase	n (%)	10 ( 34%)	11 ( 34%)
Reasons for Discontinuation:			
Adverse Event	n (%)	1 ( 3%)	0
Lost to Follow-up	n (%)	2 ( 7%)	1 ( 3%)
Treatment Failure	n (%)	2 ( 7%)	7 ( 22%)
Death	n (%)	0	1 ( 3%)
Protocol Violation	n (%)	0	0
Other	n (%)	5 ( 17%)	2 ( 6%)
Data Source: Table 8.7.2.1.4			

Sponsor's In-Text Table 8.4.3.6:1 Note: ACAMP = Acamprosate 1332 mg/day for patients ≤60 kg or Acamprosate 1998 mg/day for patients >60 kg.

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

Note: Other includes concurrent illness, refusal to continue, and non-compliance.

Demographic characteristics and history of alcohol use at Baseline are summarized in the table below. A greater proportion of the acamprosate group was male (86% in the acamprosate group vs 69% in the placebo group). The mean ages of the groups were similar (47.7 years in the acamprosate group and 49.9 years in the placebo group). Duration of alcohol dependence or abuse averaged 12 years (11.9 years for the acamprosate and 12.6 years for the placebo group). More subjects in the acamprosate group had at least 1 prior treatment for alcoholism (90% vs

**NDA No. 21-431**  
**LIPHA PHARMACEUTICALS, INC.**  
**ACAMPROSATE TABLETS**

81% in the placebo group). The placebo group had more subjects with no previous treatment (19% vs. 10% in the acamprosate group) and more subjects with >3 previous treatments (19% vs. 7% in the acamprosate group). Baseline level of daily drinking was not reported. All of the patients received detoxification prior to randomization and were abstinent at Baseline.

**Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study Ladewig**

Parameter	Statistic	ACAMP (N=29)	Placebo (N=32)
Gender	n	29	32
Male	n (%)	25 (86%)	22 (69%)
Female	n (%)	4 (14%)	10 (31%)
Age (years)	n	29	32
	Mean (SE)	47.7 (2.0)	46.9 (1.7)
Weight (kg)	n	20	32
	Mean (SE)	68.0 (2.2)	68.9 (2.3)
	Min, Max	42, 97	48, 92
Marital Status	n	NA	NA
Married	n (%)		
Not Married	n (%)		
Detoxification Prior to Randomization	n	29	32
Yes	n (%)	29 (100%)	32 (100%)
No	n (%)	0	0
Abstinence at Baseline	n	29	32
Yes	n (%)	29 (100%)	32 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)	n	29	31
	Mean (SE)	11.9 (1.9)	12.6 (1.7)
Average Standard Drinks per Day at Study Entry	n		
<5	n (%)	NA	NA
5 – 10	n (%)		
>10	n (%)		
Prior Treatment or Detoxes for Alcoholism	n	29	32
0	n (%)	3 (10%)	6 (19%)
1	n (%)	13 (45%)	9 (28%)
2	n (%)	8 (28%)	4 (13%)
3	n (%)	3 (10%)	7 (22%)
>3	n (%)	2 ( 7%)	6 (19%)

Data Source: Table 8.7.2.2.4 and 8.7.2.3.4

Sponsor's In-Text Table 8.4.3.6:2 Note: ACAMP = Acamprosate 1332 mg/day for patients ≤60 kg or Acamprosate 1998 mg/day for patients >60 kg.

Note: Percentages are based on the number of patients in the ITT population who had data for the assessment. NA = Not Available.

Mean compliance in the acamprosate group was lower (84.8%) than in the placebo group (92.2%).

The primary variables for evaluating efficacy were the cumulative abstinence duration (CAD) and the relapse rate.

The cumulative abstinence duration (CAD) was defined as the total number of days of abstinence and is calculated as the sum of only those periods of complete abstinence. To assess CAD as a fraction of the potential duration of treatment the corrected cumulative abstinence (CCAD) was also calculated. The table below shows the mean CAD and CCAD for each treatment group. The acamprosate group had a statistically significantly longer CAD and higher CCAD.

**Cumulative Abstinence Duration (CAD) and Corrected CAD (CCAD) – European Short-Term Supportive Efficacy Study Ladewig**

Treatment period	CAD		CCAD	
	Days	SD	%	SD
0-180 days				
Placebo	46.88	±58.99	26	±33
Acamprosate	83.79	±78.30	47	±43
T-test	p=0.039		p=0.033	
Data Source: Ladewig Study Report, Table 7				

Sponsor's In-Text Table 8.4.3.6:4

At Days 30, 90, and 180 patients were placed into 1 of 3 categories by the investigator: abstinent, relapsed (any drinking) or non-attendant. The proportion of patients categorized as non-attendant is similar for each treatment. The observed proportion of abstinent patients is consistently higher in the acamprosate group. Significantly more patients were abstinent in the acamprosate group (p=0.031) at Day 30 but not at other observation points.

In a second analysis that combined patients in the relapsed and non-attendant groups and considered them to be treatment failures, the proportion of abstinent patients compared with treatment failures shows a statistically significantly higher proportion of patients abstinent at Day 30 in the acamprosate group compared with the placebo group (p=0.012), but not at other observation points.

**Number (%) of Patients Who Were Abstinent or Treatment Failures At Days 30, 90, and 180 – European Short-Term Supportive Efficacy Study Ladewig**

Assessment Day	Treatment	Abstinent	Treatment Failure	Chi <sup>2</sup> Test
Day 30	Placebo	13 (41)	19 (59)	0.01
	Acamprosate	21 (72)	8 (28)	
Day 90	Placebo	8 (25)	24 (75)	0.17
	Acamprosate	12 (41)	17 (59)	
Day 180	Placebo	7 (22)	25 (78)	0.10
	Acamprosate	12 (41)	17 (59)	
Data Source: Ladewig Study Report, Table 6				

Sponsor's In-Text Table 8.4.3.6:3

On assessment Days 30, 90 and 180, the investigator questioned the patient to determine the presence or absence of a total of 43 possible events and recorded the patients response on a questionnaire. Diarrhea was reported by 24% of acamprosate-treated patients compared with 13% in the placebo treatment group, while gastralgia was reported by 31% of acamprosate-treated patients compared with 15% of patients receiving placebo. This raises the possibility of unblinding due to adverse events.

**Follow-up Period:** After completing the 180 day treatment period, all patients in the Ladewig study were observed for a further 180 days, off-treatment, but maintaining the double-blind status. Forty subjects entered the follow-up observation period. The number of acamprosate-treated patients remaining abstinent on Day 360 was 6 (21%), compared to 3 placebo-treated patients (9%). Considering the entire 360-day study period (treatment phase plus follow-up phase), the difference in cumulative abstinence duration between placebo (69.4 days  $\pm$  85.0) and acamprosate (108.6 days  $\pm$  112.94) was not statistically significant ( $p=0.124$ ).

**10.2.5 AOTA/E/91.1 (ADISA): Controlled, Double-Blind Clinical Trial to Evaluate the Effect of Acamprosate Versus Placebo in Maintaining Abstinence in Alcohol-Dependent Patients, from the Initial suppression of Alcohol Consumption**

AOTA/E/91.1 (ADISA) was a prospective, multicenter (11 centers), randomized, double-blind, placebo-controlled, parallel group (2) comparison of the efficacy and safety of acamprosate versus placebo in alcohol-dependent patients in influencing alcohol consumption, when administered for 180 days, from the start of alcohol withdrawal. The clinical portion of the study was conducted from May 1993 to October 1994 at 11 hospitals or specialized alcohol centers in Spain, under the overall direction of principal investigator Dr. A. Gual, M.D., Unitat d'Alcoholologia (Alcoholology Unit), Provincial Hospital and Clinic, Barcelona, Spain. All of the investigators were psychiatrists and/or specialized physicians and the Spanish centers were either hospital-based or specialized alcohol centers.

The objective of this study was to evaluate the efficacy and safety of acamprosate versus placebo when prescribed from the beginning of alcohol suppression, in order to achieve steady-state levels of acamprosate as early as possible, and with the aim of stopping alcohol consumption over a 180-day double blind Treatment Phase. There was no follow-up phase in this study.

To be eligible, subjects were 18-65 with at least 1 year history of DSM-III alcohol dependence, committed to long-term abstinence, and actively drinking within 7 days of screening. A family member willing to take responsibility for keeping the investigator informed of the patient's compliance with the treatment and alcohol abstinence was also required.

Subjects were excluded for pregnancy, nursing, inadequate contraception, medical or psychiatric illness, renal impairment, hypercalcemia, or past six months' use of other drug abuse.

Eligible patients were randomized in a ratio of 1:1 to either 1998 mg of acamprosate or placebo per day, taken as 2 tablets of 333 mg acamprosate (or matching placebo) t.i.d. with meals.

**NDA No. 21-431**  
**LIPHA PHARMACEUTICALS, INC.**  
**ACAMPROSATE TABLETS**

Study medication began on day 1 of an 8 day alcohol detox, which could be inpatient or outpatient, according to the routine of the participating study center. The study consisted of 8 visits: Screening Visit, Randomization Visit, and Visits 1-6 (at Day 8, 30, 60, 90, 135, 180) during the Treatment Phase.

Primary efficacy criteria were CAD, time to relapse/continuous abstinence, and number of abstinent days after the last relapse. Safety evaluations consisted of clinical laboratory determinations (Days 0, 90, and 180), physical examination, vital signs, and review of adverse events, concomitant medications, and psychotherapeutic treatment.

As shown in the table below, 296 patients were screened and randomized (148 to each treatment group). One patient did not receive any medication for reasons unknown and 7 patients were excluded, as no key data were available after the Day 0 visit. These 8 were excluded from the ITT population, leaving 288 patients in the ITT population with 141 patients assigned to acamprosate and 147 patients assigned to placebo. A total of 186 patients completed the study, 96 patients in the acamprosate group (65%) and 90 patients in the placebo group (61%). The percentage of patients who discontinued for each individual reason was similar between treatment groups. Loss to follow-up was the predominant reason for patients discontinuing the study.

**Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study ADISA**

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=148)	Placebo (N=148)
Number of Patients Randomized	n	148	148
Number of Patients in the ITT Population	n (%)	141 ( 95%)	147 (>99%)
Number of Patients Who Completed the Double Blind Treatment Phase	n (%)	96 ( 65%)	90 ( 61%)
Number of Patients Who Discontinued the Double Blind Treatment Phase	n (%)	52 ( 35%)	58 ( 39%)
Reasons for Discontinuation:			
Adverse Event	n (%)	3 ( 2%)	4 ( 3%)
Lost to Follow-up	n (%)	24 ( 16%)	28 ( 19%)
Treatment Failure	n (%)	4 ( 3%)	7 ( 5%)
Death	n (%)	0	0
Protocol Violation	n (%)	9 ( 6%)	7 ( 5%)
Other	n (%)	12 ( 8%)	12 ( 8%)

Data Source: Table 8.7.2.1.6

Sponsor's In-Text Table 8.4.3.5:1 Note: Percentages are based on the number of patients randomized.  
Note: Other includes concurrent illness, refusal to continue, and non-compliance.

Demographic characteristics and history of alcohol use at Baseline were similar. Eighty percent (80% in the acamprosate group and 79% in the placebo group) of patients were male and the mean age was 41 years (41.4 years for the acamprosate group and 40.7 years for the placebo group). The mean duration of alcohol dependence or abuse was 12.6 years for acamprosate and 12.9 years for placebo. Approximately two-thirds (66%) of the patients consumed more than 10 standard drinks per day at study entry and 58% of the patients in each treatment group had at

**NDA No. 21-431**  
**LIPHA PHARMACEUTICALS, INC.**  
**ACAMPROSATE TABLETS**

least 1 prior treatment for alcoholism. Although, theoretically, alcohol withdrawal and medicated detoxification could have been administered on either an inpatient or an outpatient basis in this study, in fact, all patients were withdrawn from alcohol on an outpatient basis 34% in each group underwent non-medicated detox. During the 8-day withdrawal period, 6 patients in the acamprosate group and 1 patient in the placebo group dropped out of the study. At the end of the 8-day period, of the remaining patients, 13% in the acamprosate group and 16% in the placebo group were not abstinent.

**APPEARS THIS WAY  
ON ORIGINAL**

**Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study ADISA**

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=141)	Placebo (N=147)
Gender	n	141	147
Male	n (%)	113 (80%)	116 (79%)
Female	n (%)	28 (20%)	31 (21%)
Age (years)	n	141	147
	Mean (SE)	41.4 (0.8)	40.7 (0.8)
Weight (kg)	n	141	147
	Mean (SE)	67.8 (1.1)	69.2 (1.1)
	Min, Max	43, 103	43, 128
Marital Status	n	141	147
Married	n (%)	104 (74%)	91 (62%)
Not Married	n (%)	37 (26%)	56 (38%)
Detoxification at Study Onset	n	147	148
Yes	n (%)	97 (66%)	98 (66%)
No	n (%)	50 (34%)	50 (34%)
Detoxification Therapy			
Tetrabamate	n (%)	54 (36.7%)	61 (41.2%)
Chlormethiazole	n (%)	32 (21.8%)	25 (16.9%)
Vitamins	n (%)	5 (3.4%)	6 (4.1%)
Chlorazepate	n (%)	4 (2.7%)	3 (2.0%)
Miscellaneous	n (%)	2 (1.4%)	3 (2.0%)
Abstinence at Day 8 (end of "detox" period)	N	141	147
Yes	n (%)	123 (87%)	123 (84%)
No	n (%)	18 (13%)	24 (16%)
Duration of Alcohol Dependence/Abuse (years)	N	141	147
	Mean (SE)	12.6 (0.7)	12.9 (0.6)
Average Standard Drinks per Day at Study Entry	N	141	147
<5	n (%)	6 ( 4%)	5 ( 3%)
5 – 10	n (%)	45 (32%)	41 (28%)
>10	n (%)	90 (64%)	101 (69%)
Prior Treatment or Detoxes for Alcoholism	N	141	147
0	n (%)	59 (42%)	62 (42%)
1	n (%)	39 (28%)	51 (35%)
2	n (%)	22 (16%)	16 (11%)
3	n (%)	9 ( 6%)	6 ( 4%)
>3	n (%)	12 ( 9%)	12 ( 8%)

Data Source: Table 8.7.2.2.6 and 8.7.2.3.6

Sponsor's In-Text Table 8.4.3.5:2      Note: Percentages are based on the number of patients in the ITT population who had data for the assessment.

Compliance was similar across treatment groups (91.5% in the acamprosate group and 91.4% in the placebo group).

Primary efficacy parameters were cumulative abstinence duration (total number of abstinent days during the study), time to first relapse (to any drinking), and the number of abstinent days after the last relapse (stable recovery duration).

Cumulative abstinence duration represents the total number of days of abstinence during the study. For the ITT population, the mean ( $\pm$ SD) value was  $93\pm 75$  days for the acamprosate group and  $74\pm 75$  days for the placebo group ( $p = 0.006$ ). Because the duration of planned treatment was 180 days, it is possible to calculate a CCAD (or % days abstinent) using 180 days as the denominator. This calculation was not included in the Lipha summary report, and differs from the calculation of CCAD in some other studies because subjects who drop out for reasons such as adverse event or intercurrent illness have generally been assigned a shorter potential duration of treatment, rather than the full 180 days, as this uncensored denominator has the effect of imputing drinking to all remaining days. Nevertheless, for the purposes of comparison, the CCAD as calculated using the CAD/180 is shown in the table below.

	CAD	CCAD
Placebo	$74\pm 75$	41%
Acamprosate	$93\pm 75$	52%

For analysis of abstinence survival, abstinence was defined as self-declaration of abstinence with a gamma-GT less than the baseline value and less than 1.3 times the limit of normal values on Days 60, 90, 135 and 180. All patients lost to follow-up were considered treatment failures. By this definition, at Day 180 of 35% in the acamprosate group and 26% in the placebo group (Log Rank  $p = 0.068$ ). The highest frequency of first relapses occurred between Days 0 and 30, during which 95 patients relapsed. At each visit interval, there were more patients in the acamprosate group than in the placebo group who remained abstinent.

**Cumulative Continuous Abstinence Rate – European Short-Term Supportive Efficacy Study ADISA**

Visit Interval	Treatment	
	Acamprosate = 141 Patients continuously abstinent (%)	Placebo = 147 Patients continuously abstinent (%)
Day [0-30]	72	63
Day [30-60]	60	50
Day [60-90]	45	38
Day [90-120]	39	31
Day [120-150]	37	27
Day [150-180]	37	27
Day [180]	35	26

Data Source: ADISA Study report, Table 6.10

Sponsor's In-Text Table 8.4.3.5:3 Log rank:  $p = 0.068$

The stable recovery duration was defined as the number of days of abstinence between the last relapse and the end of the study. For the overall ITT population, the mean ( $\pm$ SD) value was  $56\pm 79$  days: for the acamprosate group the value was  $64\pm 81$  days compared to  $48\pm 75$  days for the placebo group ( $p = 0.021$ ).

From the safety data, gastrointestinal symptoms were reported more commonly in the acamprosate group (41%) than the placebo group (31%), raising some possibility of unblinding due to adverse events.

**10.2.6 AOTA/LP 90/N001 (UKMAS): A Phase III, Multi-Centre, Double-Blind Parallel Group Prospective Hospital Based Out-Patient Study to Compare the Efficacy and Safety of Calcium Acamprosate 666 mg tds with Placebo in the Management of Alcoholics Following Acute Alcohol Withdrawal**

AOTA/LP 90/N001 (UKMAS) was a prospective, multicenter (20 centers), randomized, double-blind, placebo-controlled, parallel group (2) study, the objective of which was to compare the efficacy and safety of acamprosate and placebo on maintaining abstinence in weaned alcohol-dependent outpatients, over a 6 month treatment period. This study had no follow-up phase. The clinical portion of the study was conducted from June 1990 to July 1993 at 20 psychiatric clinics in the United Kingdom, with Dr. Jonathan Chick, M.D. and Dr. E. B. Ritson, M.D. (University Department of Psychiatry, Royal Edinburgh Hospital, Edinburgh, UK) as coordinating Principal Investigators. All of the investigators were consulting psychiatrists at the participating hospitals.

This study recruited subjects who had undergone alcohol detoxification within 5 weeks prior to study participation, either as part of an in-patient treatment or at home. To be eligible, subjects were 18-65, with a body weight of at least 60 kg, and at least a 12-month history of DSM-III diagnosis of alcohol dependence of chronic or episodic type. Subjects were to be abstinent for at least 5 days before entering the study and to have a goal of alcohol abstinence at the time of the study.

Subjects were excluded for pregnancy, inadequate contraception, psychiatric or medical illness, renal insufficiency, hypercalcemia, or use of disulfiram, barbiturates, benzodiazepines, meprobamate, major tranquilizers, or hepatic enzyme inducers.

Following a baseline stabilization period of not less than 7 days following alcohol withdrawal when the patient received no medication (between Visit 1 [Screening] and Visit 2 [Baseline]), patients were randomized a ratio of 1:1 to either 1998 mg of acamprosate or placebo per day at meals. Dose reduction to 1332 mg/day was permitted for GI disturbance. The duration of blinded treatment was 24 weeks (168 days). The study consisted of 11 visits: Visit 1 (Screening), Visit 2 (Baseline), Visits 3-10 (Week 2, 3, 5, 9, 13, 17, 21, and 25) during the 24-week Treatment Phase, and Visit 11 (Week 29) during the 4-week Follow-up Phase. Primary efficacy criteria were relapse rate at each visit, time to first relapse/continuous abstinence, and study visit attendance. CAD was identified as a secondary criterion. Diary cards were used for subjects to record drinking. Safety was assessed on the basis of spontaneously reported adverse events and clinical laboratory tests (hematology and clinical chemistry). Adverse events were recorded at each visit and laboratory assessments were at Visits 1, 5, 7, 10, and 11.

A total of 664 patients were screened and 581 (289 acamprosate, 292 placebo) were randomized. The majority of the 83 screen failures dropped out, did not meet the selection criteria, or refused medication. A total of 203 patients completed the study, 100 patients (35%) in the acamprosate

**NDA No. 21-431**  
**LIPHA PHARMACEUTICALS, INC.**  
**ACAMPROSATE TABLETS**

group and 103 patients (35%) in the placebo group. The reasons for premature discontinuation are shown in the table below, which was prepared by Lipha after examination of case report forms. Discontinuation for adverse event was more common in the acamprosate group (13%) than the placebo group (8%). Otherwise, reasons for discontinuation were similar. Most commonly, discontinuations were due to loss to follow up (22% acamprosate and 25% placebo) and "other" (including concurrent illness, condition worsened, refused medication, and non-compliance), in 19% of each group.

**Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study UKMAS**

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=289)	Placebo (N=292)
Number of Patients Randomized	N	289	292
Number of Patients in the ITT Population	n (%)	289 (100%)	292 (100%)
Number of Patients Who Completed the Double Blind Treatment Phase	n (%)	100 ( 35%)	103 ( 35%)
Number of Patients Who Discontinued the Double Blind Treatment Phase	n (%)	189 ( 65%)	189 ( 65%)
Reasons for Discontinuation:			
Adverse Event	n (%)	38 ( 13%)	23 ( 8%)
Lost to Follow-up	n (%)	65 ( 22%)	73 ( 25%)
Treatment Failure	n (%)	20 ( 7%)	25 ( 9%)
Death	n (%)	1 (<1%)	1 (<1%)
Protocol Violation	n (%)	11 ( 4%)	12 ( 4%)
Other	n (%)	54 ( 19%)	55 ( 19%)
Data Source: Table 8.7.2.1.5			

Sponsor's In-Text Table 8.4.3.3:1 Note: Percentages are based on the number of patients randomized.  
 Note: Other includes concurrent illness, condition worsened, refused medication, and non-compliance.

Demographic characteristics and history of alcohol use at Baseline are presented below. There were more males in the acamprosate group (87%) than in the placebo group (80%). The mean age was 43 years (42.3 years in the acamprosate group and 43.3 years in the placebo group). Duration of alcohol dependence and history of prior treatments for alcoholism was not reported. More subjects in the acamprosate group (77% vs 67% in the placebo group) had been consuming more than 10 standard drinks per day at study entry. All subjects completed withdrawal prior to randomization, after which a "stabilization period" of variable duration occurred between screening and baseline. The length of this no-medication stabilization period averaged 24.6 days (43 to 56 days in about 6% of subjects). During this period, almost one-third of the patients had resumed drinking and were not abstinent at baseline.

**Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study UKMAS**

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=289)	Placebo (N=292)
Gender	N	289	292
Male	n (%)	252 (87%)	233 (80%)
Female	n (%)	37 (13%)	59 (20%)
Age (years)	N	289	292
	Mean (SE)	42.3 (0.6)	43.3 (0.6)
Weight (kg)	N	289	292
	Mean (SE)	73.5 (0.7)	73.5 (0.8)
	Min, Max	50, 119	50, 119
Marital Status	N		
Married	n (%)	NA	NA
Not Married	n (%)		
Detoxification Prior to Randomization	n	289	292
Yes	n (%)	289 (100%)	292 (100%)
No	n (%)	0	0
Abstinence at Baseline	n	280	284
Yes	n (%)	201 (70%)	195 (67%)
No	n (%)	79 (27%)	89 (30%)
Duration of Alcohol Dependence/Abuse (years)	n		
	Mean (SE)	NA	NA
Average Standard Drinks per Day at Study Entry	n	289	291
<5	n (%)	22 ( 8%)	29 (10%)
5 – 10	n (%)	44 (15%)	67 (23%)
>10	n (%)	223 (77%)	195 (67%)
Prior Treatment or Detoxes for Alcoholism	n		
0	n (%)		
1	n (%)		
2	n (%)	NA	NA
3	n (%)		
>3	n (%)		

Data Source: Table 8.7.2.2.5 and 8.7.2.3.5

Sponsor's In-Text Table 8.4.3.3:2 NA = Not Available.

Note: Percentages are based on the number of patients in the ITT population who had data for the assessment.

Compliance was similar across treatment groups (93.0% in the acamprosate group and 93.4% in the placebo group), indicating that most patients took study medication as prescribed.

The primary variables for evaluating efficacy were the attendance at every clinic, relapse rate/continuous abstinence (or controlled drinking) at every visit, and time to relapse/continuous abstinence duration. Diary cards were used for subjects to record drinking.

There were no statistically significant differences in attendance rates between the treatment groups at any time-point during the study. The attendance rates, up to and including Visit 7 (84

days), were 50.9% for acamprosate and 54.5% for placebo. The attendance rates up to and including Visit 10 (168 days) were 35.3% for acamprosate and 37.0% for placebo.

The table below lists the proportion of patients continuously abstinent at each visit and the mean number of days of continuous abstinence.

**Number (%) of Patients Abstinent at Each Visit and Mean Days of Continuous Abstinence – European Short-Term Supportive Efficacy Study UKMAS**

Visit number	Acamprosate		Placebo		Chi <sup>2</sup> test p=
	N	%	N	%	
2 (Prior to Rx)	289	100.0	292	100.0	
3 (7 days)	187	64.7	184	63.0	0.671
4 (14 days)	144	49.8	146	50.0	0.967
5 (28 days)	98	33.9	115	39.4	0.171
6 (56 days)	69	23.9	84	28.8	0.181
7 (84 days)	54	18.7	62	21.2	0.442
8 (112 days)	47	16.3	42	14.4	0.529
9 (140 days)	41	14.2	36	12.3	0.509
10 (168 days)	34	11.8	32	11.0	0.760
<b>Mean number of days of continuous abstinence:</b>	<b>Acamprosate</b>		<b>Placebo</b>		
N	289		292		
Mean	37.4		39.7		
S.D.	57.3		57.0		
<b>Mann-Whitney U test for comparison between treatments</b>	Acamprosate:		Mean Rank = 289.50 (n=289)		
	Placebo:		Mean Rank = 292.49 (n=292)		
			U=41760.0 Z=0.2200		
			2 tailed p-value (corrected for ties) = 0.826		
Data Source: UKMAS Study Report, Table 7					

Sponsor's In-Text Table 8.4.3.3:3

There were no differences between the 2 treatment groups at any visit for either of these parameters.

The secondary efficacy parameters included CAD which was calculated for each patient by totaling the number of abstinent days recorded on all diary cards between Visit 3 and Visit 10. The mean value for each treatment group was compared using a one-way analysis of variance. The mean CAD for the acamprosate group was 77.2 days and for placebo 80.9 days. The difference was not statistically significant (p=0.492). For comparison to other studies, it is possible to calculate a CCAD (% days abstinent) by dividing CAD by the planned duration of treatment (168 days). As noted above, this imputes drinking to all days after dropout, even for subjects whose dropout may have been unrelated to drinking. However, given the high proportion who dropped out due to "loss to follow-up," this is a reasonable estimate. The CAD and CCAD so calculated are shown below.

	CAD (days)	CCAD (%)	
Placebo	80.9	48%	
Acamprosate	77.2	46%	

From the safety data, there was no indication of unblinding due to adverse events.

This study provides no support for the efficacy of acamprosate in promoting abstinence time in alcoholics. Lipha interprets the failure of this study as evidence that acamprosate is most effective when initiated immediately after detoxification; however a subset analysis in the study report does not show a convincing effect of acamprosate in any subset. The relatively better performance in the acamprosate treated group in the subset initiating treatment shortly after completing detox is attributable to only 3 additional successful subjects.

Subset	Acamprosate	Placebo
	n successful/N in subset (%)	n successful/N in subset (%)
Days between detox and treatment		
0-14 days	4/61 (7%)	1/67 (2%)
15-28 days	17/135 (13%)	16/124 (13%)
29-42 days	10/74 (14%)	15/84 (18%)
43-56 days	3/18 (17%)	0/16 (0%)
Drinking pattern during stabilization (from diary card)		
Abstinent	31/201 (15%)	32/195 (16%)
Controlled	1/36 (3%)	0/48 (0%)
Uncontrolled	1/43 (0%)	0/41 (0%)
Missing data	1/9 (1%)	0/8 (0%)

UKMAS Study Report Table 23, Vol 88 p40.

**10.2.7 AD 10 089 (Lesch): Double-Blind Controlled Study versus Placebo to Assess the Effectiveness and Tolerance of AOTA-Ca in Treatment Which Helps to Maintain Abstinence after Detoxification in the Alcoholic Patient**

AD 10-089 (Lesch) was a prospective, randomized, multicenter (5 centers), double-blind, placebo-controlled, parallel group (2) comparison of the efficacy and safety of acamprosate versus placebo in maintaining abstinence in weaned alcohol-dependent outpatients, over a 1 year treatment period and a 1-year off-treatment follow-up period. The clinical portion of the study was conducted from December 1989 to March 1993 at 5 centers in Austria, with Prof. Otto M. Lesch, M.D., Psychiatrische Universitätsklinik (Psychiatric University Clinic), Vienna, Austria as overall Principal Investigator. The investigators at the other centers were all either consulting or resident psychiatrists and the centers were either psychiatric clinics in university hospitals or specialized alcoholism clinics.

To be eligible, subjects were 18-65, with at least a 1-year history of DSM-III alcohol dependence diagnosis and either a GGT value at least twice the upper limit of normal and/or a MVC  $\geq$ 93 fl. All subjects were to undergo detoxification and to be abstinent for at least 5 days at entry.

Subjects were excluded for pregnancy, inadequate contraception, psychiatric or medical disorders, renal insufficiency, or hypercalcemia.

Selected subjects were randomized to acamprosate (1998 mg/day at meal times for >60kg and 1332 mg/day for lighter subjects) or placebo in a ratio of 1:1. The scheduled duration of treatment was 360 days. The study consisted of 11 visits: Visit -1 (Screening), Visit 0 (Baseline) Visits 1-5 (at Day 30, 90, 180, 270, and 360) during the Treatment Phase and Visits 6-9 (at Day 450, 540, 630, and 720) during the Follow-up Phase. Throughout the study, patients could have psychotherapy or other psychosocial support as deemed necessary. Concomitant therapy with disulfiram was permitted during the study.

Primary efficacy criteria were CAD and relapse rate. Safety evaluations were performed at each visit and consisted of a review of adverse events (AEs) according to a questionnaire that listed 44 symptomatic complaints, including complaints which could be related to alcohol withdrawal. In addition, clinical laboratory determinations (hematology and clinical chemistry) and body weight measurements were made at each visit.

A total of 448 patients (224 per arm) were randomized. All randomized patients were included in the ITT population. Slightly more patients in the acamprosate group (94 patients, 42%) completed the double-blind treatment phase than in the placebo group (85 patients, 38%). The reasons for discontinuation were similar between the 2 treatment groups. The most frequent reasons for discontinuation in each group were treatment failure, loss to follow-up, and "other."

**Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Study Lesch**

	Statistic	ACAMP (N=224)	Placebo (N=224)
Number of Patients in the ITT Population	n (%)	224 (100%)	224 (100%)
Number of Patients Who Completed Treatment Phase	n (%)	94 ( 42%)	85 ( 38%)
Number of Patients Who Discontinued Treatment Phase	n (%)	130 ( 58%)	139 ( 62%)
Reasons for Discontinuation	n	130	139
Adverse Event	n (%)	11 ( 5%)	15 ( 7%)
Lost to Follow-up	n (%)	33 ( 15%)	36 ( 16%)
Treatment Failure	n (%)	52 ( 23%)	52 ( 23%)
Death	n (%)	2 ( <1%)	1 ( <1%)
Protocol Violation	n (%)	1 ( <1%)	0
Other	n (%)	31 ( 14%)	35 ( 16%)
<b>Data Source: Table 8.7.4.1.1</b>			

Sponsor's In-Text Table 8.4.5.1:1

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

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

Demographic characteristics and history of alcohol use at Baseline are were largely similar across groups. Most patients were male and between 40 and 59 years of age. There was a higher percentage of female patients in the acamprosate group (25%) compared to the placebo group

**NDA No. 21-431**  
**LIPHA PHARMACEUTICALS, INC.**  
**ACAMPROSATE TABLETS**

(17%). The percentage of married patients was higher in the placebo group (56%) than in the acamprosate group (48%). Neither years of alcohol dependence nor history of prior treatments for alcoholism were reported. The groups were similar with respect to drinking level at Baseline. Most patients (63% in each treatment group) consumed >10 standard drinks per day at study entry. All patients had detoxification prior to randomization and were abstinent prior to the initiation of study medication.

**Demographic and Baseline Characteristics – European Long-Term Supportive Efficacy Study Lesch**

Characteristic	Statistic	ACAMP (N=224)	Placebo (N=224)
Gender	n	224	224
Male	n (%)	168 ( 75%)	185 ( 83%)
Female	n (%)	56 ( 25%)	39 ( 17%)
Age (years)	Mean (SE) Min., Max.	42.3 (0.6) 22, 64	42.5 (0.6) 16, 70
Age Distribution (years)	n	224	224
16-39	n (%)	77 ( 34%)	83 ( 37%)
40-59	n (%)	141 ( 63%)	134 ( 60%)
≥60	n (%)	6 ( 3%)	7 ( 3%)
Weight (kg)	n Mean (SE) Min, Max	224 74.9 (0.9) 48, 122	224 76.0 (0.9) 43, 106
Marital Status	n	224	224
Married	n (%)	107 ( 48%)	125 ( 56%)
Not Married	n (%)	117 ( 52%)	99 ( 44%)
Detoxification Prior to Randomization	n	224	224
Yes	n (%)	224 (100%)	224 (100%)
No	n (%)	0	0
Abstinent at Baseline	n	224	224
Yes	n (%)	224 (100%)	224 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)		NA	NA
Average Standard Drinks Per Day at Study Entry	n	224	224
<5	n (%)	14 ( 6%)	13 ( 6%)
5 – 10	n (%)	69 ( 31%)	71 ( 32%)
>10	n (%)	141 ( 63%)	140 ( 63%)
Family History of Alcohol Problems		NA	NA
Prior Treatments or Detoxes for Alcoholism		NA	NA
Data Source: Tables 8.7.4.2.1 and 8.7.4.3.1			

Sponsor's In-Text Table 8.4.5.1:2 NA = Not Available

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

Note: Percentages for all rows are based on the number of patients in the ITT population.

The mean compliance was 92% for both treatment groups. During the study, overall disulfiram use was more frequent in the placebo group (2.68%) than the acamprosate group (1.79%).

The primary variables for evaluating efficacy were the cumulative abstinence duration (CAD) and the relapse rate. At each study visit, the investigator assessed each patient and assigned them to 1 of 3 categories: abstinent, relapsed or non-attendant. The CAD was defined as the total

number of days of abstinence on study and was calculated as the sum of only those periods of complete abstinence. The fraction of abstinent time over the potential study duration was also calculated (corrected cumulative abstinence duration or CCAD). The table below gives the mean CAD and CCAD for each treatment group.

**Cumulative Abstinence Duration (CAD) and Corrected CAD –  
European Long-Term Supportive Efficacy Study Lesch**

Treatment period 0-360 days	CAD		CCAD	
	Days	SD	%	SD
Placebo	103.79	±118.95	30	±34
Acamprosate	138.75	±137.53	39	±38
T-test (SQRT)	p=0.012		p=0.021	
Data Source: Lesch Study Report, Table 8				

Sponsor's In-Text Table 8.4.5.1:3

The 2 calculations for the cumulative abstinence duration and CCAD show a statistically significantly longer duration of abstinence and greater percentage of abstinent time on study in the acamprosate treated patients.

A relapse rate based on the score for alcohol consumption was determined at each visit. To be rated as abstinent, patients must have consumed no alcohol. As shown in the table below, statistically significant differences were reached in the 3 category variables on each assessment day except Day 30. At Day 360, 30% of acamprosate treated patients were abstinent compared with 21% in the placebo group.

**Number (%) of Patients Who Were Abstinent, Relapsed, or Non-Attendant at Study Visits  
– European Long-Term Supportive Efficacy Study Lesch**

Assessment Day/Treatment		Abstinent	Relapsed	Non-attendant	Chi <sup>2</sup> -test p=value
Day 30	Placebo	141 (63)	45 (20)	38 (17)	0.319
	Acamprosate	156 (70)	38 (17)	30 (13)	
Day 90	Placebo	86 (38)	54 (24)	84 (38)	0.035
	Acamprosate	113 (50)	42 (19)	69 (31)	
Day 180	Placebo	59 (26)	50 (22)	115 (51)	0.041
	Acamprosate	81 (36)	35 (16)	108 (48)	
Day 270	Placebo	49 (22)	45 (20)	130 (58)	0.045
	Acamprosate	70 (31)	32 (14)	122 (54)	
Day 360	Placebo	46 (21)	36 (16)	142 (63)	0.043
	Acamprosate	67 (30)	25 (11)	132 (59)	
Data Source: Lesch Study Report, Table 6					

Sponsor's In-Text Table 8.4.5.1:4

Similar results are found if the categories relapsed and non-attendant are combined into "treatment failures."

In an analysis of complete abstinence over the entire 360 days of the treatment phase, 18% of patients in the acamprosate group were totally abstinent compared to 7% of patients in the

placebo group. The difference between treatment groups was statistically significant (Mantel-Cox Test,  $p=0.0007$ ).

From the safety data, diarrhea was reported in 20% of acamprosate-treated subjects vs. 12% of placebo-treated subjects, raising some possibility of unblinding due to adverse events.

**Follow-up Period:** The 179 patients who completed the double-blind treatment entered the 360 day off-treatment observation period. One hundred and forty eight of these patients completed the observation period. During this period the proportion of patients remaining abstinent in the acamprosate group compared with the placebo group gradually diminished. There was no statistically significant difference between treatment groups in the abstinence, relapse, non-attendant analysis, nor in abstinence/treatment failure proportion. The CAD and CCAD over the entire study period (treatment phase plus observation phase) remained significantly higher in the acamprosate group compared to the placebo group (230.8 days  $\pm$  259.1 days in the acamprosate group compared to 183.0  $\pm$  235.2 days in the placebo group:  $p=0.039$ ). In all other parameters to determine efficacy the results were very similar in each treatment group.

**10.2.8 AOTA/P/89.1 (Barrias): A Study of the Efficacy and Safety of AOTA-Ca to Maintain Abstinence in the Weaned Alcoholic Patient. A Double-Blind Comparison Versus Placebo**

**AOTA/P/89.1 (Barrias)** was a prospective, randomized, multicenter (9 centers), double-blind, placebo-controlled, parallel group (2) comparison of the efficacy and safety of acamprosate versus placebo in maintaining abstinence in weaned alcohol-dependent outpatients, over a 1 year treatment period and a 180-day off-treatment follow-up period. The clinical portion of the study was conducted from November 1989 to October 1992 at 9 centers in Portugal, with Dr. José Barrias, M.D., (Psychiatrist and Chief, Porto Hospital Center, Porto, Portugal) as overall supervisory Principal Investigator. The investigators at the 9 centers were all consulting psychiatrists, either based at psychiatric clinics in hospitals or specialized mental health centers.

All patients were to undergo weaning therapy and be abstinent for at least 5 days before entering the study.

To be eligible, subjects were 18-65 with at least a 1 year history of DSM-II alcohol dependence and a GGT  $\geq 2x$  the upper limit of normal.

Subjects were excluded for pregnancy, inadequate contraception, psychiatric or medical disorders, renal insufficiency, hypercalcemia, lack of cooperation during detox, or unsuitable living situation.

Subjects underwent detox prior to participation and were required to be abstinent at least 5 days at entry. Eligible patients were randomly assigned to receive acamprosate (1998 mg/day at meal times for  $>60$  kg and 1332 mg/day for lighter subjects) or placebo in a ratio of 1:1. The scheduled duration of treatment was 360 days. The study consisted of 9 visits: Visit -1 (Screening), Visit 0 (Baseline), Visits 1-5 (at Day 30, 90, 180, 270, and 360) during the Treatment Phase and Visit 6-7 (at Day 450 and Day 540, respectively) during the Follow-up

Phase. Throughout the study, patients could have psychotherapy or other psychosocial support as deemed necessary.

The primary efficacy variables were CAD and relapse rate. Safety evaluations consisted of a review of adverse events (AEs) according to a questionnaire that listed 44 symptomatic complaints, including symptoms related to withdrawal from alcohol. Adverse event information and vital signs were collected/ measured at every visit during the Treatment Phase. Clinical laboratory determinations (hematology and clinical chemistry) were also performed at Visit -1 or Visit 0, Visit 3, and Visit 5.

As shown the table below, a total of 302 patients were randomized into the study and included in the ITT Population: 150 to acamprosate and 152 to placebo. Completion rate was similar between treatment groups (acamprosate, 57% vs placebo, 55%). The most common reason for discontinuation was the ill-defined category "other" (31% in placebo group and 25% in acamprosate group). A higher percentage of patients withdrew due to adverse events in the acamprosate group (6%) than in the placebo group (3%). No subjects were classified as dropping out due to treatment failure and only 9% in each group were lost to follow-up. Most of the discontinuations (>67%) from the study occurred during the first 180 days of treatment.

**Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Study Barrias**

	Statistic	ACAMP (N=150)	Placebo (N=152)
Number of Patients in the ITT Population	n (%)	150 (100%)	152 (100%)
Number of Patients Who Completed Treatment Phase	n (%)	86 ( 57%)	83 ( 55%)
Number of Patients Who Discontinued Treatment Phase	n (%)	64 ( 43%)	69 ( 45%)
Reasons for Discontinuation	n	64	69
Adverse Event	n (%)	9 ( 6%)	4 ( 3%)
Lost to Follow-up	n (%)	13 ( 9%)	14 ( 9%)
Treatment Failure	n (%)	0	0
Death	n (%)	1 (<1%)	1 (<1%)
Protocol Violation	n (%)	4 ( 3%)	3 ( 2%)
Other	n (%)	37 ( 25%)	47 ( 31%)
Data Source: Table 8.7.4.1.2			

Sponsor's In-Text Table 8.4.5.2:1

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

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

Demographic characteristics and history of alcohol use at Baseline were similar across groups. 92% of the patients were male. The mean age of patients in this study was 39.6 years for the acamprosate group and 41.0 years for the placebo group. Neither duration of alcohol dependence nor history of prior treatments for alcoholism were reported, but the treatment groups were also similar with respect to Baseline drinking level. At study entry, 65% of patients consumed an average of >10 standard drinks per day. All randomized patients had detoxification prior to randomization and were abstinent at Baseline.

**Demographic and Baseline Characteristics – European Long-Term Supportive Efficacy Study Barrias**

Characteristic	Statistic	ACAMP (N=150)	Placebo (N=152)
Gender	N	150	152
Male	n (%)	139 ( 93%)	139 ( 91%)
Female	n (%)	11 ( 7%)	13 ( 9%)
Age (years)	Mean (SE)	39.6 (0.6)	41.0 (0.8)
	Min., Max.	21, 64	23, 63
Age Distribution (years)	N	150	152
16-39	n (%)	78 ( 52%)	70 ( 46%)
40-59	n (%)	71 ( 47%)	79 ( 52%)
≥60	n (%)	1 ( <1%)	3 ( 2%)
Weight (kg)	N	150	152
	Mean (SE)	67.2 (0.9)	66.6 (0.9)
	Min, Max	43, 97	41, 108
Marital Status	N	150	152
Married	n (%)	112 ( 75%)	109 ( 72%)
Not Married	n (%)	38 ( 25%)	43 ( 28%)
Detoxification Prior to Randomization	N	150	152
Yes	n (%)	150 (100%)	152 (100%)
No	n (%)	0	0
Detoxification Prior to Randomization	N	150	152
Yes	n (%)	150 (100%)	152 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)		NA	NA
Average Standard Drinks Per Day at Study Entry	N	150	152
<5	n (%)	6 ( 4%)	6 ( 4%)
5 – 10	n (%)	49 ( 33%)	45 ( 30%)
>10	n (%)	95 ( 63%)	101 ( 66%)
Prior Treatments or Detoxes for Alcoholism		NA	NA
Data Source: Tables 8.7.4.2.2 and 8.7.4.3.2			

Sponsor's In-Text Table 8.4.5.2:2

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

Note: Percentages for all rows are based on the number of patients in the ITT population.

The mean compliance was 94.4% for the acamprosate group and 92.8% for the placebo group.

The primary variables for evaluating efficacy were the cumulative abstinence duration (CAD) and the relapse rate. At each study visit, the investigator assessed each patient and assigned them to 1 of 3 categories: abstinent, relapsed or non-attendant. The CAD was defined as the total number of days of abstinence on study and was calculated as the sum of only those periods of complete abstinence. The fraction of abstinent time over the potential study duration was also calculated (corrected cumulative abstinence duration or CCAD). The table below gives the mean CAD and CCAD for each treatment group.

**Cumulative Abstinence Duration (CAD) and Corrected CAD – European Long-Term Supportive Efficacy Study Barrias**

Treatment period 0-360 days	CAD		CCAD	
	Days	SD	%	SD
Placebo (n= 152)	128.50	±136.19	36	±38
Acamprosate (n = 150)	175.30	±150.81	49	±42
T-test	p=0.005		p=0.005	

Data Source: Barrias Study Report, Table 6

Sponsor's In-Text Table 8.4.5.2:3

The 2 calculations for the cumulative abstinence duration and CCAD show a statistically significantly longer duration of abstinence and greater percentage of abstinent time on study in the acamprosate treated patients.

The relapse rate based on the score for alcohol consumption was determined at each visit. To be rated as abstinent, patients must have consumed no alcohol. As shown below, statistically significant differences were reached in the 3 category variables some, but not all, assessment days. On Day 360, 39% of acamprosate treated patients were abstinent compared with 26% in the placebo group.

**Number (%) of Patients Who Were Abstinent, Relapsed, or Non-Attendant at Study Visits – European Long-Term Supportive Efficacy Study Barrias**

Assessment Day/Treatment		Abstinent	Relapsed	Non-attendant	Chi <sup>2</sup> -test p-value
Day 30	Placebo	104 (68)	45 (30)	3 ( 2)	0.028
	Acamprosate	122 (81)	25 (17)	3 ( 2)	
Day 90	Placebo	72 (47)	64 (42)	16 (11)	0.004
	Acamprosate	97 (65)	37 (25)	16 (11)	
Day 180	Placebo	56 (37)	59 (39)	37 (24)	0.125
	Acamprosate	68 (45)	42 (28)	40 (27)	
Day 270	Placebo	41 (27)	50 (33)	61 (40)	0.018
	Acamprosate	61 (41)	32 (21)	57 (38)	
Day 360	Placebo	39 (26)	47 (31)	66 (43)	0.029
	Acamprosate	59 (39)	33 (22)	58 (39)	

Data Source: Barrias Study Report, Table 7

Sponsor's In-Text Table 8.4.5.2:4

Similar results are seen if categories of relapsed and non-attendant are combined and considered to be treatment failures.

The median time to first relapse, according to survival analysis, was 54.55 days for placebo and 111.00 days for acamprosate. At Day 360, 34.7% of the acamprosate treated patients had remained abstinent compared to 20.2% of the placebo group (Mantel-Cox Test p=0.0009).

Gastralgia was reported more frequently by patients in the acamprosate group (9%) compared with the placebo group (3%) raising the possibility of unblinding due to adverse events.

**Follow-up Period:** The 169 patients who completed the double-blind treatment entered the 180 day off-treatment observation period. One hundred and forty two (84%) of these patients completed the observation period. During this period the proportion of patients remaining abstinent in the acamprosate group compared with the placebo group gradually diminished. There was no statistically significant difference between treatment groups in the abstinence, relapse, non-attendant analysis, nor in abstinence/treatment failure proportion. The CAD and CCAD over the entire study period (treatment phase plus observation phase) remained significantly higher in the acamprosate group compared to the placebo group (225.1 days  $\pm$  210.6 days in the acamprosate group compared to 172.7  $\pm$  198.7 days in the placebo group:  $p=0.025$ ). In all other parameters to determine efficacy the results were very similar in each treatment group.

**10.2.9 AA.11.088 (Besson): A Clinical Study to Assess the Efficacy and Tolerance of Acamprosate in Maintaining Abstinence in the Weaned Alcoholic Patient during the Detoxification Period. A Double-blind Study Versus Placebo**

AA.11.088 (Besson) was a prospective, randomized, multicenter (3 centers), double-blind, placebo-controlled, parallel group (2) comparison of the efficacy and safety of acamprosate versus placebo in maintaining abstinence in weaned alcohol-dependent outpatients, over a 1 year treatment period and a 1-year off-treatment observation period. The clinical portion of the study was conducted from January 1989 to January 1993 at 3 centers in Switzerland, with Prof. Jacques Besson, M.D., Consulting Psychiatrist at Clinique du Vallon, Lausanne, Switzerland as overall Principal Investigator. The investigators at the 2 remaining centers, included a consulting psychiatrist and a hospital-based physician. The centers were regional psychiatric clinics and a hospital.

To be included, subjects were outpatients 18-65 with at least 1 year history of DSM-III chronic or episodic alcohol dependence and either a GGT value at least twice the upper limit of normal and/or a MVC  $\geq$  95 fl.

Subjects were excluded for pregnancy, inadequate contraception, psychiatric or medical conditions, renal insufficiency, or hypercalcemia, or unsuitable living conditions.

Subjects were to undergo alcohol detox and were required to be abstinent at least 5 days at entry. Eligible patients were randomly assigned to receive acamprosate (1998 mg/day at meal times for  $>60$  kg and 1332 mg/day for lighter subjects) or placebo in a ratio of 1:1. The scheduled duration of treatment was 360 days. The study consisted of 11 visits: Visit -1 (Screening), Visit 0 (Baseline), Visits 1-5 (at Day 30, 90, 180, 270, and 360) during the Treatment Phase and Visits 6-9 (at Day 450, 540, 630, and 720) during the Follow-up Phase. Throughout the study, patients could have psychotherapy or other psychosocial support as deemed necessary. Concomitant therapy with disulfiram was permitted during the study and patients were stratified prior to randomization for use or non-use of disulfiram.

**NDA No. 21-431**  
**LIPHA PHARMACEUTICALS, INC.**  
**ACAMPROSATE TABLETS**

Primary efficacy criteria were CAD and relapse rate. Safety evaluations were performed at each visit and consisted of recording of spontaneously reported adverse events and a review of adverse events (AEs) according to a questionnaire that listed 44 symptomatic complaints, including complaints which could be related to alcohol withdrawal. In addition, clinical laboratory determinations (hematology and clinical chemistry) and body weight measurements were made at each visit.

As shown in the table below, a total of 118 patients were selected to participate. However, 8 patients were excluded from the analysis population: 4 patients were non-compliant and did not take the study medication and 4 patients did not meet the abstinence entry criteria. Treatment assignment of these subjects is not known. Thus, the population analyzed was comprised of 110 patients, 55 patients randomized to each of the acamprosate and placebo groups. Nineteen patients in each group completed the double-blind treatment phase (31% for acamprosate, 33% for placebo group). The most common reasons for discontinuation were treatment failure, loss to follow-up, and an ill-defined category of "other." Fewer in the acamprosate group (28%) reported the reason for discontinuation as treatment failure than acamprosate patients (35%). Conversely, more patients in the acamprosate group (15%) reported reason for discontinuation due to "Other" than patients in the placebo group (9%). Most of the patients (>50%) who discontinued from the study withdrew in the first 90 days of treatment.

**Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Study Besson**

	Statistic	ACAMP (N=61)	Placebo (N=57)
Number of Patients in the Analysis Population	n (%)	55 (90%)	55 (96%)
Number of Patients Who Completed Treatment Phase	n (%)	19 (31%)	19 (33%)
Number of Patients Who Discontinued Treatment Phase	n (%)	42 (69%)	38 (67%)
Reasons for Discontinuation	n	42	38
Adverse Event	n (%)	4 ( 7%)	2 ( 4%)
Lost to Follow-up	n (%)	9 (15%)	8 (14%)
Treatment Failure	n (%)	17 (28%)	20 (35%)
Death	n (%)	1 ( 2%)	1 ( 2%)
Protocol Violation	n (%)	2 ( 3%)	2 ( 4%)
Other	n (%)	9 (15%)	5 ( 9%)
Data Source: Table 8.7.4.1.3			

Sponsor's In-Text Table 8.4.5.3:1

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

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

Demographic characteristics were similar across groups. The majority of patients in the study were male (80%). The mean age of patients was 42 years. At study entry, the mean duration of alcohol dependence/abuse for patients in the acamprosate group was 13.5 years compared to 12.0 years for patients in the placebo group. History of prior treatment and baseline drinking level were not reported. All patients underwent detoxification treatment and all were abstinent at Baseline.

**NDA No. 21-431**  
**LIPHA PHARMACEUTICALS, INC.**  
**ACAMPROSATE TABLETS**

As indicated above, patients could elect to also receive concomitant disulfiram (Antabuse®) treatment. Over the course of the study, 24 patients in the acamprosate group (44%) and 22 patients in the placebo group (40%) received concomitant Antabuse. These subjects had a higher level of illness severity on multiple measures compared to those who did not choose concomitant Antabuse.

**Demographic and Baseline Characteristics – European Long-Term Supportive Efficacy Study Besson**

Characteristic	Statistic	ACAMP (N=55)	Placebo (N=55)
Gender	N	55	55
Male	n (%)	46 ( 84%)	42 ( 76%)
Female	n (%)	9 ( 16%)	13 ( 24%)
Age (years)	Mean (SE)	42.7 (1.2)	42.1 (1.1)
	Min., Max.	25, 61	25, 61
Age Distribution (years)	N	54	55
16-39	n (%)	22 ( 41%)	22 ( 40%)
40-59	n (%)	30 ( 56%)	32 ( 58%)
≥60	n (%)	2 ( 4%)	1 ( 2%)
Weight (kg)	N	55	55
	Mean (SE)	73.2 (1.7)	71.5 (1.7)
	Min, Max	46, 102	47, 113
Marital Status		NA	NA
Detoxification Prior to Randomization	N	55	55
Yes	n (%)	55 (100%)	55 (100%)
No	n (%)	0	0
Abstinent at Baseline	N	55	55
Yes	n (%)	55 (100%)	55 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)	N	55	54
	Mean (SE)	13.5 (0.9)	12.0 (1.1)
	Min., Max	2, 29	1, 40
Average Standard Drinks Per Day at Study Entry		NA	NA
Prior Treatment or Detoxes for Alcoholism		NA	NA
Data Source: Tables 8.7.4.2.3 and 8.7.4.3.3.			

Sponsor's In-Text Table 8.4.5.3:2 NA = Not Available

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

Note: Percentages for all rows are based on the number of patients in the ITT population.

Mean compliance was 86.8% and 90.2% for the acamprosate and placebo groups, respectively.

The primary variables for evaluating efficacy were CAD and relapse rate. At each study visit, the investigator assessed each patient and assigned 1 of 3 categories: abstinent, relapsed or non-attendant. The cumulative abstinence duration (CAD) was defined as the total number of days of abstinence and is calculated as the sum of only those periods of complete abstinence. To assess CAD as a fraction of the potential duration of treatment the corrected cumulative abstinence

(CCAD) was calculated. The table below shows the mean CAD and CCAD for each treatment group.

**Cumulative Abstinence Duration (CAD) and Corrected CAD: Global Results and Subdivided into Antabuse or Non-Antabuse Patient Groups – European Long-Term Supportive Efficacy Study Besson**

Treatment Period 0-360 days	CAD		CCAD	
	Days	SD	%	SD
<b>All Patients</b>				
Placebo n=55	74.73	±107.99	21	30
Acamprosate n=55	136.91	±147.51	40	41
T-test	p=0.013		p=0.008	
<b>Antabuse Patients</b>				
Placebo n=22	111.82	107.24	31	30
Acamprosate n=24	185.00	151.34	55	42
<b>Non-Antabuse Patients</b>				
Placebo n=33	50.00	102.74	14	29
Acamprosate n=31	99.68	135.36	28	38
Data Source: Besson Study Report, Table 7				

Sponsor's In-Text Table 8.4.5.3:4

The difference between treatments was statistically significant (p=0.013, p=0.008) in favor of acamprosate for CAD and CCAD values, respectively. Subset analysis based on Antabuse use revealed CCAD of 14% for placebo subjects who did not choose Antabuse, 31% for placebo subjects who were treated with Antabuse, 28% for acamprosate-treated subjects who did not choose Antabuse, and 55% for the subjects who received both acamprosate and Antabuse. The better response rate in Antabuse-treated subjects may be considered a reflection of the higher level of motivation in this group, given their greater baseline level of illness severity.

The relapse rate based on the score for alcohol consumption was determined at each visit. To be rated as abstinent, patients must have consumed no alcohol since the preceding evaluation. As shown below, the proportion of patients categorized as non-attendant is similar for each treatment. The observed proportion of abstinent patients is consistently higher in the acamprosate treated group, but statistical significance was not reached at all time points.

**APPEARS THIS WAY  
ON ORIGINAL**

**Number (%) of Patients Who Were Abstinent, Relapsed, or Non-Attendant at Study  
Visits – European Long-Term Supportive Efficacy Study  
Besson**

Assessment Day	Treatment	Abstinent	Relapsed	Non-Attendant	Chi <sup>2</sup> Test P=
Day 30	Placebo	26 (47)	24 (44)	5 ( 9)	0.019
	Acamprosate	40 (73)	11 (20)	4 ( 7)	
Day 90	Placebo	18 (33)	19 (35)	18 (33)	0.081
	Acamprosate	29 (53)	11 (20)	15 (27)	
Day 180	Placebo	9 (16)	22 (40)	24 (44)	0.010
	Acamprosate	19 (35)	9 (16)	27 (49)	
Day 270	Placebo	8 (15)	14 (25)	33 (60)	0.028
	Acamprosate	18 (33)	6 (11)	31 (56)	
Day 360	Placebo	8 (15)	11 (20)	36 (65)	0.141
	Acamprosate	14 (25)	5 ( 9)	36 (65)	

Data Source: Besson Study report, Table 5

Sponsor's In-Text Table 8.4.5.3:3

Similar results are obtained if the relapsed and non-attendant categories are combined and considered to be treatment failures.

At the end of 360 days double-blind treatment, 25% of acamprosate treated patients had remained totally abstinent compared with 5% of the placebo treated patients (p=0.048).

From the safety data, over 30% of the acamprosate subjects reported diarrhea, vs. only 7% in the placebo group, while conversely, over 20% of the placebo subjects reported constipation, vs. only 3% in the acamprosate group, raising the possibility of unblinding due to adverse events.

**Follow-up Period:** At Day 360, the double-blind medication was withdrawn and the 38 patients who completed the double-blind treatment period entered the 360 day observation period. Eighteen patients (47%) completed the observation period. Over the entire study period (treatment phase plus follow-up phase), 8 of 55 placebo-treated patients (15%) and 10 of 55 acamprosate-treated patients (18%) completed the entire study. The small number of patients entering the 360 day observation period was too small to provide information to determine whether the efficacy of acamprosate was maintained once treatment had ceased.

APPEARS THIS WAY  
ON ORIGINAL

**NDA 21-431**

**ACAMPROSATE ENTERIC COATED TABLETS 333 MG**

**Submission Received Date: December 27, 2001**

**Action Due Date: June 27, 2002**

**Sponsor: Lipha Pharmaceuticals, Inc.**

**Review of Safety For Data Sources, Exposure, Deaths, Serious Adverse Events,  
Discontinuation Due to Adverse Events, and Common Adverse Events - 6/7/02**

**APPEARS THIS WAY  
ON ORIGINAL**

## **NDA 21-431 ACAMPROSATE ENTERIC COATED TABLETS 333 MG**

Submission Received Date: December 27, 2001

Action Due Date: June 27, 2002

Sponsor: Liplha Pharmaceuticals, Inc.

### **Integrated Review of Safety For Data Sources, Exposure, Deaths, Serious Adverse Events and Common Adverse Events - 6/7/02**

Primary Review conducted by:

---

Michael J. Sevka, M.D.  
Medical Officer  
Division of ACCAD Products (HFD-170)

Secondary Review conducted by:

---

Bob A. Rappaport, M.D.  
Deputy Director,  
Division of ACCAD Products (HFD-170)

## **INTRODUCTION**

This portion of the NDA safety review for NDA 21-431 discusses the findings from review of data sources, patient exposure to study treatments, deaths, non-death serious adverse events, discontinuations due to adverse events, and common non-serious adverse events. Other portions of the safety review were conducted by C. Cooper, M.D. and the efficacy review was conducted by Celia Winchell, M.D. The purpose for dividing the review of this NDA was to ensure timely completion of this NDA that was designated a priority review.

## **DATA SOURCES**

The sponsor has grouped all clinical studies in the development program into 4 groups (see **Attachment 1**):

Group 1 (Short-term and Long-term Placebo-Controlled Clinical Studies of safety and efficacy);

Group 2 (Clinical Pharmacology Studies predominantly in healthy volunteers);

Group 3 (Early Clinical Experience Studies);

Group 4 (Phase 4 Open-Label Studies).

### **Primary Data Source**

The ISS focuses on the Group 1 studies as the primary data source for safety data (see **Attachment 1**). This group consists of 13 placebo-controlled, parallel group studies, 3 of which were considered pivotal in support of efficacy (Paille, Pelc II, and PRAMA). The Group 1 studies are considered the primary data source for safety because they were placebo-controlled, conducted in alcohol-dependent patients, and have the largest exposure to the 1998/2000 mg/day acamprosate (ACAMP) dose that is proposed for marketing. Additionally, the safety review focuses primarily on Group 1 studies that collected adverse events spontaneously because these studies were more likely to capture a broader range of adverse events than studies which collected adverse events from a restricted list of pre-identified adverse events (see further discussion below). All Group 1 studies were initiated prior to July 1, 1991 except for ADISA and US 96.1; and all were conducted in Europe except US 96.1 that was conducted in the U.S. There were no open-label studies among Group 1 studies. Some studies had variable lengths of patient follow-up periods from none to 52 weeks (see **Attachment 1**) during which patients did not take medication; but study, Paille, had a single-blind placebo 6-month follow-up period.

**Doses studied across Group 1 studies: patients randomized to acamprosate**

3000 mg/day – 83 patients, only in the US study - US 96.1;

1998/2000 mg day – 1749 patients across all placebo-controlled studies; 1128 in short-term studies and 621 in long-term studies;

1332 mg/day – 440 patients across all placebo-controlled studies; 135 in short-term placebo-controlled studies and 305 in long-term studies.

All Group 1 studies used the enteric coated 333 mg tablet formulation proposed for marketing with a proposed dosing regimen of 2 tablets (666 mg) 3 times a day except the U.S. study. The US study, US 96.1, used a 500 mg enteric coated tablet to administer the 2000 and 3000 mg/day doses divided into a twice a day dosing regimen. The 500 mg tablet was compositionally identical to the 333 mg enteric coated tablet. Some non-Group 1 studies used other formulations: capsules, non-enteric coated tablets, oral solution, and intravenous solution.

Group 1 studies differed in duration and were sub-grouped for analysis into long-term studies (48–51 weeks in duration) and short-term studies (24-26 weeks in duration with one study 13 weeks in duration). Additionally, US 96.1 was analyzed separately because of some unique differences in study design compared to the European studies: 1) abstinence from alcohol was not required for admission, 2) patients had to describe their treatment goal at baseline which could vary from no goal to complete abstinence, 3) non-dependent cannabis use and other illicit drug use was permitted, 4) exclusion criteria had no upper age limit for entrance, 5) use of standardized psychosocial support, special blister “reminder” packaging for study medication, daily drinking diaries, weekly phone contacts with participants to supplement monthly clinic visits, and mandatory follow-up algorithms for missed clinic visits or phone contacts. Consequently 50% of patients in the U.S. study had not discontinued drinking at randomization and only 10% had undergone medicated detoxification.

Group 1 studies collected safety data in 2 ways (see **Attachment 1**): recording all adverse events that were spontaneously reported (PRAMA, Paille ADISA, UKMAS, US 96.1) or by recording adverse events after being asked by the investigator if an event occurred based on a list of 43 specific adverse events (BENELUX and Lesch - see **Attachment 2** for list of AE items). The six other Group 1 studies collected events both ways but recorded an event only if specifically listed on the adverse event list and simply checking “other” for spontaneously reported events without textual description. According to the sponsor the 43-item check list was developed to capture AEs associated with either alcohol withdrawal or prevalent in early clinical experience with acamprosate.

The sponsor indicates that only treatment-emergent adverse events (TEAEs) were summarized. TEAEs were defined as “those events with a start date on or after the date of the first dose of double-blind medication and less than or equal to 10 days after treatment stop date, or any ongoing AE with a start date prior to first dose of double-blind medication that worsened in severity after the first dose and before 10 days after treatment stop date.” The sponsor does not explain why they selected a 10 day time period to analyze TEAEs. The sponsor should be asked to explain their reason for selection of 10 days as opposed to the more conventional 30 days.

Although all Group 1 studies were parallel, placebo-controlled studies in alcohol-dependent patients, the sponsor analyzed the safety data in several ways because of the differences in study designs across the group. Short-term and long-term studies were examined separately and combined. Further, the single U.S. study was also examined separately, combined with short-term European studies, and also combined with all European studies. Additionally, all Group 1 studies were examined separately according to method of adverse event collection (spontaneous reporting vs adverse event list). Not all studies collected other safety data in the same way for vital signs, laboratory assessments, and ECGs (see **Attachment 1**). Further, patients from Poldrugo, BENELUX, Ladewig, PRAMA, Lesch, Barrias, and Besson studies were categorized based on body weight ( $\leq 60$  kg or  $>60$  kg). Patients with a body weight  $\leq 60$  kg received 1332 mg acamprosate daily; and patients with a body weight  $>60$  mg received 1998 mg acamprosate daily. AEs by body weight were also analyzed.

### **Secondary Data Sources**

Studies in Groups 2, 3, and 4 are not included in the ISS and are considered a secondary data source for safety (see **Attachment 3** for list on non-Group 1 studies). Group 2 clinical pharmacology studies were conducted predominantly in healthy volunteers. Although some Group 3 studies were placebo-controlled, the sponsor indicates that they were conducted 10-20 years ago and were not included in the European dossier because CRFs were not available and an

electronic database could not be generated. Group 4 studies were open-label from 2 weeks to 12 months in duration. Nonetheless, deaths from these groups were identified by the sponsor and other safety data is provided if it was available. The approximate number of patients exposed to acamprosate was:

Group 2 (33 studies) – approximately 499 subjects enrolled with 477 completing (Source: Appendix 8.8.21.1 Vol 71 p 10);

Group 3 (6 studies) – approximately 482 patients enrolled with 285 completing (Source: Appendix 8.8.21.2 Vol. 71 p 12);

Group 4 (10 studies) – approximately 3665 patients enrolled with 2294 completing assuming all enrolled received treatment when the number of subjects who received treatment is not specified in the study report (Source: Appendix 8.8.21.3 Vol. 71 p 13).

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

## OVERALL SUMMARY STATEMENTS OF FINDINGS AND RECOMMENDATIONS

Overall, the safety profile for acamprosate has not been adequately characterized. It appears that potentially all SAEs have not been captured and/or identified as SAEs and captured AEs appear to be inconsistently subsumed to hierarchical preferred terms and/or preferred term body systems. Further, discrepancies exist between various files within the safety databases. The following comments describe these issues and provide examples characterizing deficiencies.

- 1) **Adequacy Of Exposure to Meet ICH Guidelines:** In the review, a table (page 9) displaying exposure and duration during treatment periods shows only 71 patients to have been exposed to acamprosate 1998/2000 mg for 52 weeks or more, yet other patients are known to have been exposed up to and more than 48 weeks. The sponsor should be asked to examine the database for the number of patients exposed to acamprosate for 48 weeks or more at the 1998/2000 mg/day dose and to evaluate their compliance with study treatment to be certain that there has been adequate exposure for 1 year in accordance ICH guidelines. Additionally, the proposed labeling includes .L

└ in the NDA database; the wording of this sentence should be modified for clarity.

- 2) **Explanation Of 10 Day Post-Exposure Time Period for Capturing AEs:** The sponsor indicates that events occurring only up to 10 days after the last dose of double-blind medication were captured as opposed to the more conventional 30 days. This implies that AEs beyond 10 days of last exposure were not captured and that the safety database is incomplete. The sponsor should be asked to examine their databases for AEs and SAEs occurring up to 30 days after last exposure to study treatment.
- 3) **Categorization of Reasons for Patient Discontinuation:** Approximately half of the randomized population completed their study. The largest reason for non-completion was *other* ranging from 11 to 30%. The sponsor should be asked to subgroup *other* into categories reflecting reasons for patient non-compliance and/or refusal to continue due to adverse events and/or lack of efficacy (i.e. treatment failure).
- 4) **Adequacy of SAE Capture Methodology and Consistency of Assignment to SAE Categories:** The sponsor indicates that serious adverse events were identified prospectively in the database for only the US 96.1 study. In order to identify an SAE from non-U.S. studies according to the current regulatory definition, the sponsor indicates that study reports for the double-blind placebo-controlled studies were examined for SAEs using patient narratives, concurrent illnesses as a reason for withdrawal, and AE listings. In addition, for studies with spontaneously reported AEs, SAEs that meet the current regulatory definition were identified in the database by searching for the following terms or part of terms: *hospitalization, hospital, surg, admit, inpatient, cancer, melanoma, carcinoma, suicide, and overdose*. The use of these few descriptors of SAEs implies that the database may be incomplete regarding capture of SAEs because the terms used in the search are not broad and are few in numbers. It is not clear why other potential descriptors or part of descriptor terms were not included in the search in an effort to broaden the capture rate from non-U.S. studies. Examples of additional search terms include but not limited to: *fatality, fatal, death, died, arrest, coma, life-threatening, suicidal, depression, psychosis, arrhythmia, gast/gastro, bleed, abdominal pain, diarrhea, vomiting, syncope, fall, paralysis, stroke, convulsion, seizure, renal/kidney failure/dysfunction, hepatic/liver failure/dysfunction, hepatitis, anaphylaxis, agranulocytosis, aplastic anemia, neutropenia, rash, pruritis, exfoliation, Stevens-Johnson, toxic epidermal necrolysis, rhabdomyolysis, tumor, birth defect, congenital anomaly*. The sponsor should be asked to re-examine their databases from non-US studies, using these descriptors or part of descriptor terms as search terms, determine if the AEs fit the definition of a SAE, and analyze them according to short-term and long-term groups.

Of additional concern is the consistency of the capture of the outcome of death. Two patients (Barrias-63; UKMAS-484) were not counted in the paper version of the ISS with an outcome of death even though both died within 10 days of last exposure to study treatment. The sponsor should be asked to explain how this came about, re-examine their databases and identify any other such cases.

Further, audit of the electronic database for spontaneously reported AEs suggests a lack of consistency in assignment to SAE categories. Audit for hospitalizations shows that some patients who were hospitalized for various reasons were not flagged as SAEs but were flagged as TEAEs and suggests that database integrity may be compromised by

this type of inconsistency. Examination of the electronic dataset SS\_AEs.xpt for hospitalization yielded approximately 40 unique patients hospitalized for various reasons who were not flagged as SAEs. Examination of those who were flagged as TEAEs but not flagged as serious yielded at least 7 unique subjects hospitalized for depression (4), epileptic crisis (1), foot fracture (1), and new hospitalization for GI hemorrhage; these patients are not listed in this examination of the data as being admitted for *relapse*. The sponsor should be asked to re-examine their AEs and flagging of SAEs and reconcile discrepancies. The following are specific patient examples from various searches of the electronic databases, two of which were noted also in the search described above.

**Patient – Study Number – Term**

37	11	Colitis (described in SAE narrative)
184	15	MI (described in SAE narrative)
294	15	Accidental Injury (foot fracture – no narrative)
360	15	GI hemorrhage (no narrative)
383	15	Neurosis (no narrative)
532	15	Colitis (no narrative).

- 5) **Verbatim AE terms were coded using the COSTART dictionary.** Review of the coding of verbatim terms under preferred COSTART terms shows that the coding may not be appropriate or consistent and raises concern over the reliability of the database. The sponsor should be asked to re-examine their coding of AEs and reconcile discrepancies. The following are examples:
  - A) Hypertensive terms have been subsumed in *hypertension* and then in the nervous system instead of cardiovascular system. Although the COSTART system provides for inclusion in the nervous system as a body system, it seems more appropriate to link systemic hypertension to the cardiovascular system.
  - B) Verbatim terms denoting relapse have been coded to *alcohol intolerance*. Consideration should be given to re-coding them to *drug dependence* and further to the nervous system as provided by the COSTART system rather to the nutritional and metabolic body system. Alternatively, because of the context in which relapse is observed in these studies coding to *treatment failure* might also be considered.
  - C) Specific joint pain terms are subsumed in *pain* and then in body as a whole and should be subsumed in arthralgia;
  - D) *Suicide* verbatim terms are not consistently coded – for example, in the SS\_AEs database subject 32 (study 4) has a verbatim term of *suicide (strangulation)* and is coded to the terms *death* and *suicide attempt*; but subjects 203 and 236 (study10) have a verbatim term of *suicide* but are coded only to *suicide attempt* and not to *death* yet both have *death* listed as an outcome. A similar comparison can be made for subject 106 (study 3) and subject 29 (study 3). Completed suicides should be consistently coded to both *death* and *suicide attempt*.
  
- 6) **Discrepancies between various files within the safety databases.** Examination of the various electronic databases for this NDA discrepancies were noted between some of the AE databases regarding patient inclusion. For example database SS\_AECPT is the database that contains data found in either dataset SS\_SPT (Dataset for spontaneously reported AEs) and SS\_QPT (Dataset for checklist reported AEs). Examination of the combined dataset for the partial term, *suicide*, yields 12 unique patients (9 – acamprosate treated; 3 – placebo treated) with all 12 coming from studies reporting AEs spontaneously and none from studies reporting AEs by checklist, yet narratives are available for suicide deaths from checklist-reporting studies. Similarly, examination of the checklist derived database does not yield any cases with the partial term, *suicide*.
  
- 7) **Overall conclusion and recommendation:** Limited initial conclusions can be drawn from the ISS as currently constructed because supporting databases are of questionable accuracy and integrity. An overall recommendation regarding the safety profile of acamprosate can not be made with confidence based the character of information available. The current submission needs to have the deficiencies listed above corrected before a more reliable examination of the safety profile can be undertaken.
  
- 8) **CURRENT ISS - AE safety profile based on the database as presented in the current ISS**  
**Deaths and SAEs** – Across the NDA there were a total of 50 deaths with 22 occurring in the Group 1 placebo-controlled studies (13-acamprosate ; 9-placebo). There were 124 narratives for patients who experienced non-death SAEs in Group 1 placebo-controlled studies (12-1332 acamprosate mg/day; 62-1998 acamprosate mg/days; 50-placebo). Review of the death and SAE reports reveals no clear causal relationship between exposure to acamprosate

and death or treatment emergent serious adverse events (TESAEs). However one patient from the Phase IV NEAT study who experienced sudden death and had no cause of death identified on autopsy study was classified as “possibly associated to acamprosate exposure. In the US study only depression occurred as an SAE in more than one patient (i.e. 2 patients) compared to none in the placebo treated group; and overall only 9 terms were identified as TESAEs for acamprosate treated patients. From the combination of all short-term placebo-controlled studies (US and European studies reporting AEs spontaneously) – *depression, anxiety, accidental injury, overdose, suicide attempt and GI hemorrhage* occurred in more than one acamprosate treated patient from the pooled acamprosate dose group and all were reported with an incidence of <1%. From the long-term European placebo-controlled trials reporting AEs spontaneously the following AEs occurred in more than one acamprosate treated patient and were reported with an incidence of <1%: *accidental injury, suicide attempt and MI*. When TESAEs are combined from short-term and long-term Group I studies reporting AEs spontaneously, notable small numerical differences between placebo and pooled acamprosate groups are noted for *suicide attempt* (5 acamprosate; 1-placebo), *GI hemorrhage* (4-acamprosate; 1 placebo), and *MI* (4-acamprosate; 0-placebo). The sponsor did not conduct incidence analyses for SAEs reported from studies collecting AEs using a checklist.

#### **Common TEAEs –**

**Spontaneously Reported** - The following common AEs were observed in the US study, that may be associated with acamprosate exposure at the proposed dose level for marketing, 2000 mg/day, and reported at a greater rate than or equal to 2% and occurring at a 2 fold or greater incidence than placebo: *diarrhea* (33%), *flatulence* (9%), *dyspepsia* (4%), *increased appetite* (2%), *vomiting* (5%), *GI disorder* (2%), *hypertension* (5%), *hypertonia* (3%), *sweating* (2%), *dry skin* (2%), *menstrual disorder* (2%), *urinary frequency* (2%), *eosinophilia* (2%); the US study had the most carefully collected spontaneously reported AEs. Using the same criteria, other AEs emerged: *malaise* (2%), and *arthralgia* (3%) from short-term European studies, and *convulsion* (2%), *weight gain* (6%), and *weight loss* (2%) from European long-term studies. *Diarrhea* and *flatulence* were confirmed across all three groups of studies collecting AEs spontaneously (US and European short-term and long-term). From the US trial at the 3000 mg/day dose level, *fever* (4%), *dyspepsia* (8%), *anxiety* (6%), *contact dermatitis* (2%), *hyperglycemia* (10%), *hyperuricemia* (4%), and *impotence* (2%) occurred at approximately 2 fold greater rate in the 3000 mg/day acamprosate group compared to the 2000 mg/day group, suggesting a possible dose response. From the short-term European controlled trials alone (UKMAS, ADISA) only *diarrhea* (21%) and *flatulence* (6%) occurred at 5% or greater and at approximately 2 fold greater rate than placebo. From the long-term European controlled trials only *diarrhea* (12%) and *weight gain* (6%) occurred at greater than 5% and 2 fold greater rate than placebo. AEs occurring at a rate greater than 2 fold in the 1998 mg/day dose group compared to the 1332 mg/day dose group, suggestive of a dose effect, are *flu syndrome* (4%), *flatulence* (2%) and *weight gain* (6%).

**Reported Using the 43-Item Checklist** – For short-term European studies, no AE was reported at a rate below 2% in the placebo or acamprosate groups except *metrorrhagia* at 1% in the 1998 mg/day group. In general, reporting rates for the limited number of patients in the lower dose group, 1332 mg/day, appears to have a higher rate of reporting than the higher dose group, 1998 mg/day. The sponsor explains this observation by the inclusion of data from Pelc II, which had the highest AE reporting rates across trials and that excluding Pelc II data eliminates this observation. With the Pelc II data included there are no AEs occurring at greater than or equal to 2% in either acamprosate dose group and that are also 2 fold greater in the 1998 mg dose group compared to placebo, except *metrorrhagia* - (5% in 1332 mg; 1% in 1998 mg; 2% in placebo). In the 1998 mg dose group *nervousness* (14%), *libido decrease* (10%), *asthenia* (14%), *diarrhea* (14%), *anorexia* (10%) occurred at greater or equal to 10%. For the long-term European studies *taste perversion* (7%-acamprosate; 1%-placebo) and *syncope* (3%-acamprosate; 1%-placebo) emerge as AEs that are greater than 2% incidence and 2 fold greater in the acamprosate group compared to the placebo group.

**AEs and LFTs** – The table (page 36) in this review comparing TEAEs in patients with and without clinically significant elevated LFTs at baseline, does not appear to suggest an increased risk of hepatic or renal toxicity from acamprosate exposure compared to placebo. However, certain AEs from this table The sponsor should be asked to describe in greater detail the cases of patients with normal LFTs at baseline but who had hepatic events or laboratory test abnormalities after that. They are enumerated in the table below:

Numbers of Patients With Normal LFTs at Baseline Experiencing Changes		
Event	Acamprosate Pooled N=968	Placebo N=774
Acities	1	0
Liver Cirrhosis	1	0
Hepatitis	2	0
LFTs Abnormal	12	4
Lab Test Abnormal	5	2

Source : Post-Text Tables 8.8.16.0.1 and 8.8.16.0.0

**Metabisulfite Traces** –Of special note, because of concern over metabisulfite traces from acamprosate synthesis, two patients were reported to have had serious asthmatic AEs. One patient with a history of asthma and COPD (37 yo M – Integral 81004) died but no clear casual relationship could be attributed to acamprosate . The other patient with a history of asthma (49 yo F – US 96.1 13R007) was admitted to hospital for acute asthmatic bronchitis which resolved with treatment.

**AEs of Special Concern:** During the review certain AEs emerged as concerning because they represent a potential SAE or a group of SAEs if combined but not readily recognizable if coded to multiple hierarchical terms. This is especially concerning if the safety profile is inadequately characterized, or AEs are inadequately captured, or inconsistently categorized. The following table lists AEs that deserve special careful re-examination by the sponsor following verification of the accuracy of the safety database. They were extracted from the combined (spontaneously reported and checklist reported AEs) Group 1 AE database, SS\_AECPT.xpt.

Adverse Events	ACAMPROSATE Pooled	Placebo	Comment- analyze also with terms
MI	5	0	Angina and chest pain
Suicide	10	3	Depression and ideation
Hemorrhage	15	7	Melena and hematemesis
Rash	22	16	other dermatological terms denoting rash
Eosinophilia	6	0	
Convulsion	11	6	Seizures

From database SS\_AECPT.xpt

## PATIENT EXPOSURE

### Patient Exposure in Group 1 Studies

The sponsor indicates that prior to integration of the 13 Group 1 study databases, an evaluation was conducted by their contract research organization (CRO) to see if any patients were randomized more than once by looking at available demographic data (patient initials, birth date, gender, race). Comparisons were made within each study; and comparisons were also made across studies for countries in which more than one study was conducted. No patient was deemed to be randomized in more than one Group 1 study.

The following four tables display patient exposure. There appears to be adequate long-term exposure at the proposed dose to fulfill ICH exposure requirements for a drug intended for chronic administration (i.e. a total of 1000-1500 patients and 100 for 1 year and 300 patients for 6 months).

A total of 1749 patients were exposed to the 1998/2000 mg acamprosate dose and 1962 to placebo across all placebo-controlled studies.

Number of Patients Exposed in Group 1 (Placebo-Controlled) Studies				
	Acamprosate 1332 mg/ day	Acamprosate 1998/2000 mg/ day	Acamprosate 3000 mg/ day	Placebo
US 96.1 (U.S.)	0	258	83	260
Total Short-Term Controlled Studies (US and European)	135	1128	0	1218
Total Long-Term Controlled Studies	305	621	0	744
Total All Controlled Studies	440	1749	83	1962
Source – In-Text Table 8.8.1.3:1				

The following table displays the numbers of patients exposed within duration intervals. Adding the numbers of patients within each interval sums to the total number exposed. The number of patients exposed for approximately 1 year at the acamprosate 1998/2000 mg/ dose group looks small, 71 for  $\geq 52$  weeks; but this table does not show the number of patients close to 1 year, between 48-51 weeks of exposure for all the long-term studies which had durations of 48 weeks (PRAMA) and 51 weeks (Paille, Lesch, Barrias, Besson). The sponsor should be asked to examine the database for the number of patients exposed to acamprosate for 48 weeks or more at the 1998/2000 mg/day dose to show that there has been adequate exposure for 1 year according to ICH guidelines.

Exposure and Duration During Treatment Periods in All Group 1 (Placebo-Controlled) Studies				
	ACAMP 1332 mg	ACAMP 1998/2000 mg	ACAMP 3000 mg	POOLED ACAMP
0 – < 4 weeks	41 (9%)	221 (13%)	10 (12%)	272
4 – < 8 weeks	45 (10%)	198 (11%)	10 (12%)	253
8 – < 13 weeks	64 (15%)	215 (12%)	12 (14%)	291
13 – < 26 weeks	100 (23%)	614 (35%)	41 (49%)	755
26 – < 39 weeks	24 (5%)	180 (10%)	10 (12%)	214
39 – < 52 weeks	114 (26%)	250 (14%)	0	364
$\geq 52$ weeks	52 (12%)	71 (4%)	0	123
Total Number of Patients	440	1749	83	2272
Patients $\geq 75\%$ Compliant - n (%)	303 (69%)	1301 (74%)	67 (81%)	
Sources: Post-Text Tables –8.8.4.0.0; 8.8.4.0.3; 8.8.5.0.0; 8.8.5.0.3 (Vol 67)				

The table below shows the numbers of patients who completed placebo-controlled studies. In the acamprosate 1998/2000 mg group 48-50% of patients completed the treatment phase across all placebo-controlled trials; but in study US 96.1 alone only 41% completed in the acamprosate group compared to 55% in the placebo group. In long-term trials alone it was 48% in the acamprosate 1998/2000 mg/day group compared to 40% for placebo. With 302 patients completing the acamprosate arm in the long-term trials this would be the number of patients that would be expected to have been exposed to acamprosate 1998/2000 mg/ day for approximately 1 year.

Number of Patients Completing Treatment Phase in Group 1 (Placebo-Controlled) Studies				
	Acamprosate 1332 mg	Acamprosate 1998/2000 mg	Acamprosate 3000 mg	Placebo
US 96.1 (U.S.)		106 (41%)	43 (52%)	143 (55%)
Total Short-Term Controlled Studies (US and European)	74 (55%)	561 (50%)	43 (52%)	590 (48%)
Total Long-Term Controlled Studies	145 (47%)	302 (48%)	NA	302 (40%)
Source – Post-Text Tables 8.8.1.0.0; 8.8.1.0.1; 8.8.1.0.3 (Vol 67)				

APPEARS THIS WAY  
ON ORIGINAL

The table below shows the exposure-time in patient-years computed from exposure time provided by the sponsor (see Attachment 4). A similar amount of exposure-time in patient-years was experienced between acamprosate 1998/2000 mg group (754 patient-years), and the placebo group (807 patient-years).

Exposure Time in Group 1 (Placebo-Controlled) Studies		
	Acamprosate 1998/2000 mg	Placebo
US96.1 (Patient-Weeks)	4042.0	4623.1
Total Short-Term Controlled Studies (Patient-Weeks)	18644.4	19752.9
Total Long-Term Controlled Studies (Patient-Weeks)	20577.9	22234.7
Total All Controlled Studies (Patient-Weeks)	39222.3	41987.6
Total All Controlled Studies (Patient-Years)	754.3	807.5

Source: Submission Dated 3/21/02 (see Attachment 4)

The table below shows patient compliance with study treatments. For the acamprosate 1998/2000 mg group 89% in short-term and 82% in long-term studies were equal to or greater than 75% compliant with study treatment. Compliance was calculated by dividing the number of tablets taken by the number of tablets prescribed and multiplying the result by 100. The tables below display the 75% compliance levels across the NDA (range 79% to 94%) suggests that patients actually took their prescribed treatment and were in fact exposed to study drug.

Number and Percent of Patients Greater Than or Equal to 75% Compliant With Study Drug				
	ACAMP 1332 mg	ACAMP 1998/2000 mg	ACAMP 3000 mg	Placebo
US 96.1	NA	221 (86%)	67 (81%)	230 (88%)
Short-Term European Studies	96 (94%)	653 (91%)	NA	688 (91%)
Long-Term European Studies	207 (79%)	427 (82%)	NA	471 (79%)

Source: Post-Text Tables 8.8.5.0.1; 8.8.5.0.2; 8.8.5.0.3

### Patient Exposure in Non-Group 1 Studies

Exposure to acamprosate in open-label Group 4 studies (see Attachment 5) amounted to the following:  
 1332 mg/ day – 17530 patient-weeks or 337 patient-years;  
 1998 mg/day – 30757 patient-weeks or 591 patient-years;  
 2000 mg/day – 407 patient-weeks or 7 patient-years.

## PATIENT DISPOSITION

### Patient Disposition in Group 1 Studies

Approximately half of the randomized population completed their study. The largest reason for non-completion was *other* ranging from 11 to 30%. The sponsor should be asked to subgroup *other* into categories reflecting reasons for patient non-compliance and/or refusal to continue due to adverse events and/or lack of efficacy (i.e. treatment failure).

Additionally, the U.S. study used an additional subgroup, "patient decision," that included the following 7 additional sub-subgroups:

- 1) "geographic conflict,"
- 2) "social/psychosocial concerns,"
- 3) "seeking alternative treatment" that suggests treatment failure ,
- 4) "experimental medication concerns" that does not specify what these concerns represent (i.e. AEs or treatment failure),
- 5) "unwilling to change drinking,"
- 6) "not otherwise specified,"
- 7) "other health reasons."

These additional subgroups will need to be re-categorized by the sponsor to reasons for discontinuation more reflective of their significance.

Patient Disposition in Group 1 Studies									
	US 96.1			Short-Term European			Long-Term European		
	Acamp 1998/ 2000mg	Acamp 3000mg	Placebo	Acamp 1332mg	Acamp 1998/ 2000mg	Placebo	Acamp 1332mg	Acamp 1998/ 2000mg	Placebo
Number Randomized	258	83	260	135	871	958	306	627	748
Number in Safety Population	258	83	260	135	870	958	305	621	744
Number Completing	106 (41%)	43 (52%)	143 (55%)	74 (55%)	455 (52%)	447 (47%)	145 (47%)	302 (48%)	302 (40%)
<b>Primary Reasons For Withdrawal:</b>									
Adverse Event	4%	4%	3%	7%	7%	5%	6%	6%	5%
Lost to Follow Up	18%	12%	13%	10%	15%	16%	10%	16%	15%
Protocol Violation	2%	0	1%	<1%	3%	3%	<1%	<1%	1%
Treatment Failure	5%	5%	5%	16%	10%	14%	19%	14%	15%
Death (n)	0	0	0	0	<1% (2)	<1% (2)	<1% (3)	1% (7)	<1% (6)
Other	30%	28%	23%	11%	13%	14%	17%	14%	22%
<b>Secondary Reasons for Withdrawal</b>									
Adverse Event	7%	2%	3%	NL	NL	NL	NL	NL	NL
Lost to Follow Up	2%	2%	2%	NL	NL	NL	NL	NL	NL
Protocol Violation	3%	0	<1%	NL	NL	NL	NL	NL	NL
Treatment Failure	3%	1%	2%	NL	NL	NL	NL	NL	NL
Death (n)	0	0	0	NL	NL	NL	NL	NL	NL
Other	9%	8%	7%	NL	NL	NL	NL	NL	NL

Source: Post-Text Tables – 8.8.1.0.1 Vol 100 p 16; 8.8.1.0.2; 8.8.1.0.3 Vol 67 p 21-24

NL = None Listed

## DEATHS

### Deaths Across the NDA

A total of 50 deaths occurred across all studies in the NDA:

22 in Group 1 studies (3-acamprosate 1332 mg/d; 9-acamprosate 1998/2000 mg/d; 8-placebo);

12 in Group 1 follow-up studies (1-acamprosate 1332 mg/d; 6-acamprosate 1998/2000 mg/d; 5-placebo);

0 in Group 2 studies – No deaths in Group 2 clinical pharmacology studies;

16 in Group 3 and 4 studies (2-placebo; 14-acamprosate unspecified dose- see foot-note 3 in the table below). The table below displays the number of deaths across the NDA by treatment.

Number of Deaths Across the NDA by Treatment							
Study Group	ACAMP 1332 mg/day	ACAMP 1998/2000 mg/day	ACAMP 3000 mg/day	ACAMP 1332 mg/day or 1998/2000 mg/day	PLACEBO	No Treatment Follow-Up Observation Period <sup>1</sup>	Totals
Group 1 <sup>2</sup> (Placebo- Controlled)	3	10	0	NA	9	NA	22
Group 1 Follow-Up	NA	NA	NA	NA	NA	12	12
Group 2 (Clinical Pharmacology)	0	0	0	0	0	0	0
Group 3 (Early Clinical)	1 <sup>3</sup>	0	0	0	2	0	3
Group 4 (Open-Label)	4 <sup>3</sup>	1 <sup>3</sup>	0	8	NA	NA	13
Total	9	11	0	7	11	12	50
<sup>1</sup> Paille used single-blinded placebo for this period.							
<sup>2</sup> These counts include 2 patients: UKMAS-484 and Barrias-63 who were not listed in the source tables as deaths but should have been.							
<sup>3</sup> Dose not specified in source ISS document but could be determined from study design as the only acamprosate dose administered in the identified study.							
Source: In-Text Tables 8.8.8.0.1; 8.8.8.0.2; Errata Sheet Vol 72, p 335); Narratives for W/D due to AEs Vol 71 p 385							

### Deaths in Group 1 Studies

Although the sponsor reports 20 deaths in the ISS from Group 1 studies (In-Text Table 8.8.8.0.1, Vol 66, p 184), 2 additional patients were identified during the review that had died within approximately 10 days of the last dose of double-blind treatment, the cut-off time point for deaths used by the sponsor. One of these patients was randomized to placebo (UKMAS – 484) and reported on the errata sheet (Vol. 72, p 335) died of *liver failure* approximately 10-11 days after hospital admission for a second episode of abdominal pain. The other patient was randomized to acamprosate 1998 mg/day (Barrias – 63) is listed among the narratives for dropouts due to AEs (page 285) but died within one day of hospital admission from *pneumonia and uncontrolled diabetes mellitus* and should have been listed among the deaths. These 2 patients are added to the list of Group 1 deaths in **Attachment 6** bring the total number of deaths in Group 1 studies to 22 from 20.

Another patient randomized to placebo (Ladewig-32) also described on the errata sheet withdrew from study due to treatment failure (relapse) and committed suicide 2 days later. Although this patient (In-Text Table 8.8.8.0.1, Vol 66, p 184) is listed by the sponsor among the deaths for Group 1 patients in the in-text ISS table (In-Text Table 8.8.8.0.1, Vol 66, p 184), the sponsor indicates that certain disposition and withdrawal post-text tables have him listed as a withdrawal due to an AE instead of death. It is unclear why he was not included consistently across tables as a death since his death occurred within 10 days of his last dose.

Observing that the 3 patients discussed above were not accurately entered into the database, raises concern about the accuracy of the database.

For Group 1 placebo-controlled studies, there were a total of 22 deaths (see Attachment 6) – 13 on acamprosate and 9 on placebo.

The listed causes of death for the 10 deaths on acamprosate 1998/2000 mg/day are:

suicide (3),  
atrial fibrillation in setting of ARF/ acites/ hepatic failure (1),  
death by natural cause (1 – patient did not take any study medication),  
mesenteric infarction (1),  
acute subdural hemorrhage (1),  
accidental fall with subdural hemorrhage (1),  
cardiac failure due to alcohol related cardiomyopathy (1),  
pneumonia and uncontrolled diabetes mellitus (1).

The causes of death for the 3 patients on acamprosate 1332 mg/day were:

craniocerebral trauma due to seizure – unspecified if new onset (1),  
car crash of unreported association to ETOH (1),  
hematemesis (1).

There were no deaths in patients on acamprosate 3000 mg/day.

The listed causes of death for the 9 patients on placebo are:

suicide (2),  
motorbike accident associated with ETOH (1),  
accidental fall and cranial trauma without concomitant alcohol intake (1),  
accidental fall with intracranial hemorrhage with unknown alcohol intake (1),  
liver failure (1),  
heart failure (1),  
left ventricular hypertrophy due to alcohol-related cardiomyopathy (1),  
cardiac arrest after MI (1).

Of the 13 patients randomized to acamprosate who died, 6 might be considered to be considered consequences of alcoholism if trauma (3), alcoholic cardiomyopathy (1), hematemesis (1) and automobile accident (1) are considered complications of alcoholism; an additional 3 might be included if suicide (3) is also included. For the 9 patients in the placebo group, 4 might be considered consequences of alcoholism if trauma (2), motor bike accident (1), and alcoholic cardiomyopathy (1) are included; an additional 2 might be included if suicide (2) is also included.

The table below displays the causes of death in Group 1 studies that occurred in **more than one patient**. The numbers of patients is similar between acamprosate and placebo. There were no deaths attributed to overdose of acamprosate alone.

Causes of Death that Occurred in More Than One Patient in Group-1 Studies			
Cause of Death	ACAMP 1332 mg/day	ACAMP 1998/2000 mg/day	Placebo
Suicide	0	3	2
Trauma/ Fall	1	2	2
Seizures Accompanied by Trauma <sup>1</sup>	1	1	0
MVA Accident	1	0	1
Cardiac Failure <sup>2</sup>	0	1	2
Cardiac Arrest	0	1 (Barrias-63 pneumonia and DM followed by cardiac arrest)	1 (MI)

<sup>1</sup> These patients were also counted in the row above for trauma.  
<sup>2</sup> One each in acamprosate and placebo were reported as due to alcohol-related cardiomyopathy.

## Death Narratives For Group 1 Studies

Narratives in the ISS are provided for the 22 Group 1 patients who died. Review of the narratives for the patients who were randomized to **acamprosate** in Group 1 studies and died shows no clear causality of acamprosate to events leading to death. The majority of narratives for both acamprosate and placebo do not provide information regarding time of last treatment dose, an estimate of patient compliance with administration of study medication, concomitant medications, laboratory assessments, radiological assessments or alcohol status surrounding the time of the event leading to death. Without this information, persuasive attribution of death event to study drug is diminished. The nature of the events described in a number of these cases can possibly be described as one or more consequences of alcoholism. The following are summaries of available information for patient deaths in Group 1 studies during treatment phase with acamprosate.

- 1) PRAMA-168: 35 yo F randomized to acamprosate 1332 mg/d; approximately 22.7 weeks after starting treatment she experienced a symptomatic **epileptic seizure and fell from a ladder, sustained a basal skull fracture** and died of head trauma/skull fracture the next day in a surgical clinic; the date of last acamprosate dose is not stated; prior medical history including prior seizures, concomitant medications, and alcohol status at the time of the event were not included in the narrative. **Assessment:** seizure and/or trauma are known associated consequences in alcohol dependent populations and the length of exposure to drug seems adequate so that the event could have occurred before 22.7 weeks; **No clear causal association of acamprosate to the events can be asserted.**
- 2) PRAMA-236: 33 yo M randomized to acamprosate 1998 mg/d; approximately 0.5 weeks after starting treatment committed **suicide by strangulation/hanging**; the date of last acamprosate dose is not stated; prior medical history, concomitant medications, and alcohol status at the time of the event were not included in the narrative. **Assessment:** suicide can be an associated consequence of alcoholism but any potential contributing factor of acamprosate can not be fully assessed with information provided; **No clear causal association of acamprosate to the event can be asserted.**
- 3) Paille-282: 55 yo M randomized to acamprosate 1998 mg/d; approximately 33.9 weeks after starting treatment experienced **mesenteric occlusion/infarction** and died on the day of the event; the date of last acamprosate dose is not stated; medical history was significant for active cancer of the tongue and death was thought to be due to metastases; other prior medical history, concomitant medications, and alcohol status at the time of the event were not included in the narrative. **Assessment:** this event is more likely to be due to a consequence of malignancy or other pathologic states associated with malignancy but any potential contribution of acamprosate in precipitating the event can not be fully assessed with the information provided; **No clear causal association of acamprosate to the event can be asserted.**
- 4) Paille-307: 41 yo Ms randomized to acamprosate 1332 mg/d; approximately 0.6 weeks after starting treatment experienced an **unspecified accidental injury during a car crash** and died on the day of the event; the date of last acamprosate dose is not stated; prior medical history, concomitant medications and alcohol status at the time of the event were not included in the narrative. **Assessment:** traffic accidents are not uncommon in this patient population but any potential contribution of acamprosate in precipitating the event can not be fully assessed with the information provided; **No clear causal association of acamprosate to the event can be asserted.**
- 5) Paille-319: 57 yo M randomized to acamprosate 1998 mg/d; approximately 1.4 weeks after starting treatment experienced an unspecified accidental injury and after 1.6 weeks experienced an **accidental fall and cranial trauma** requiring hospitalization and died due to a **subdural hematoma approximately 28 weeks** after his presumed last dose of acamprosate, the day of hospitalization; past medical history is significant for multiple fractures due to alcohol intake and concomitant meprobamate; other medical history, concomitant medications and alcohol status at the time of the events were not included in the narrative. **Assessment:** falls and trauma are known associated consequences of alcoholism and fractures due to alcohol intake is significant in this patient's past medical history; additionally the sedating or synergistically sedating effects of meprobamate with alcohol can not be ruled out at the time of the event; **No clear causal association of acamprosate to the event can be asserted.**
- 6) Paille-485: 46 yo M randomized to acamprosate 1332 mg/d; approximately 17.6 weeks after starting treatment experienced hematemesis, was hospitalized, and transfused; acamprosate treatment was interrupted for 3 days and the

- patient died 3 days after resuming treatment due to **uncontrollable bleeding**; past medical history is significant for hepatic cirrhosis; other medical history including coagulation status, concomitant medications and alcohol status at the time of the events were not included in the narrative. **Assessment:** the past medical history is significant for hepatic cirrhosis and raises the possibility of coagulopathy and/or bleeding from esophageal varices or other sites in the upper GI tract as the precipitating cause of death in this patient although the narrative does not specifically mention esophageal varices as the site of bleeding for this patient; **No clear causal association of acamprosate to the event can be asserted.**
- 7) Poldrugo-1: 64 yo M randomized to acamprosate 1998 mg/day; 12.9 weeks after starting treatment experienced **acute kidney failure, ascites and hepatic failure** and was hospitalized on the day of the events; he died 4 days after the events; the date of last acamprosate dose is not stated; prior medical history and alcohol status at the time of the events were not included in the narrative; Zantac is the only concomitant medication reported. **Assessment:** the presence of ascites makes the event more likely due to alcohol-induced hepatic failure as an associated consequence of alcoholism but any potential precipitating contribution of acamprosate to the event can not be fully assessed with the information provided; **No clear causal association of acamprosate to the event can be asserted.**
  - 8) 8UKMAS-297: 61 yo M randomized to acamprosate 1998 mg/d; approximately 3.9 weeks after starting treatment experienced an **accidental injury/ acute subdural hematoma, multiple grand mal seizures, focal neurological signs, and unconsciousness after falling while intoxicated after drinking for the previous 10 days**; he was hospitalized and died from brain death secondary to acute subdural hematoma on the day after the events; the date of last acamprosate dose is not stated but return of study medication revealed he had not take his study medication; prior medical history is significant for blackouts due to alcohol dependence; concomitant medications at the time of the event were not included in the narrative. **Assessment:** falls, trauma and seizures are known associated consequences of alcoholism and these events occurred while intoxicated after drinking for the previous 10 days; additionally his past medical history is significant for blackouts due to alcohol; further it is reported that he had not taken his study medication but how this factor was verified is not provided; **Unlikely due to acamprosate.**
  - 9) Lesch-106: 56 yo M randomized to acamprosate 1998 mg/d; approximately 8-9 months after starting treatment experienced death by **suicide by massive doses of meclobamides** 12 days after discontinuing study because he refused to continue and his depressive symptoms increased; an empty box of meclobamide was found beside him; the date of last acamprosate dose is not stated; prior medical history is significant for severe depression for which he was taking antidepressants; concomitant medications included Noverilk, Tryptizol, Microbamat, and Aurorix (meclobemide); alcohol status at the time of the event was not included in the narrative; autopsy reported coronary sclerosis, heart muscle degeneration, and heart failure; no toxicology screen was reported in the narrative. **Assessment:**– suicide is an associated consequence of alcoholism and an empty box of meclobamide was found beside him; additionally the patient had discontinued participation in the study 12 days prior to the event; **Unlikely due to acamprosate.**
  - 10) Lesch-183: 47 yo M randomized to acamprosate 1998 mg/d; approximately 4 weeks after starting treatment experienced **death by natural cause due to alcohol intoxication and change blood glucose** of unstated direction, hyperglycemia vs hypglycemia; study medication box was found almost full at his home; prior medical history is significant for DM II, concomitant medications at the time of the event were not included in the narrative. **Assessment:** medical history for DM and the identification of alcoholic intoxication at the time of the event are more likely contributing factors to these events but the fact that some study medication was gone precludes completely excluding acamprosate as a potential contributory factor; **Unlikely due to acamprosate.**
  - 11) Barrias-2023: 34 yo M randomized to acamprosate 1998 mg/d; approximately 26 weeks after starting treatment experienced **cardiac failure due to alcohol induced myocardiopathy**; the date of last acamprosate dose is not stated; other prior medical history, concomitant medications, and alcohol status at the time of the event were not included in the narrative. **Assessment:** medical history of alcohol-induced cardiomyopathy makes this the more likely cause of this event; **Unlikely due to acamprosate.**
  - 12) Besson-1054: 53 yo M randomized to acamprosate 1998 mg/d; approximately 11.5 months after starting treatment experienced death by **suicide by car accident** having left a suicide letter; the date of last acamprosate dose is not stated; prior medical history is significant for depression; concomitant medications included dibenzepin, thioridazine,

and thiamine; alcohol status at the time of the event was not included in the narrative. **Assessment:** suicide can be a consequence of this patient population but any contribution of acamprosate can not be fully assessed with the information provided; **No clear causal relationship to acamprosate can be asserted.**

- 13) Barrias-63: 44 yo M randomized to acamprosate 1998 mg/day but was deemed non-compliant; approximately 40 weeks after starting treatment was admitted to hospital for **pneumonia and uncontrolled diabetes mellitus and suffered a cardiac arrest** the next day and did not recover from his coma following resuscitation; medical history is significant for diabetes mellitus and chronic bronchitis; concomitant medication included insulin, vitamins, and flunitrate. **Assessment:** pneumonia and uncontrolled diabetes mellitus are more likely contributing factors, especially when questioning compliance status at the time of hospital admission: **Unlikely due to acamprosate.**

#### Death Rates from Group 1 Studies

The table below displays death rates in patient-years of exposure during treatment phase. By my calculation, using the sponsor's calculation of patient-weeks as the denominator in placebo-controlled studies, there does not appear to be an large excess of all-cause deaths in patients treated with acamprosate 1998/2000 mg/day compared to placebo expressed as deaths per 1000 patient-years of exposure. The relative risk is 1.12 (13.2/11.2).

Deaths During Treatment Phase or Within 10 Days <sup>2</sup> of Treatment Discontinuation in Placebo-Controlled Studies			
	Acamprosate 1332 mg	Acamprosate 1998/2000 mg	Placebo
US96.1	0	0	0
Total Short-Term Controlled Studies	0	2	3
Total Long-Term Controlled Studies	3	8	6
Total Deaths in Controlled Studies	3 (2 M; 1 F)	10 (10 M; 0 F)	9 (8 M; 1 F)
Patient Deaths as Percent of Exposed	3/440 (0.7%)	10/1749 (0.6%)	9/1962 (0.5%)
<b>Deaths per 1000 Patient-Years</b>	<b>12.7 (3/236)<sup>1</sup></b>	<b>13.2 (10/754)<sup>1</sup></b>	<b>11.2 (9/807)<sup>1</sup></b>
Source – In-Text Tables 8.8.1.0.0; 8.8.1.0.3;			
<sup>1</sup> Patient-Years calculated from sponsor's data submitted on 3/21/02			
<sup>2</sup> The sponsor indicates that one patient is included who died within 12 days of last study visit because exact death date is not known			

#### Deaths During the Follow-Up Phase for Group 1 studies

During the follow-up phase no patients were on acamprosate or placebo except in the Paille study where patients were on single blind placebo. The sponsor did not provide narratives for these deaths but provides them in tabular format without the period of time that had elapsed before death following the last dose of double-blind medication. The follow-up time period varied in length across studies (see Attachment 1).

There were 12 deaths (10 M; 2 F) (age range 38-63):

for the 7 patients who had been on acamprostale during the double-blind period, the listed causes of death were:

*pancreatic carcinoma (1),*

*GI hemorrhage (1),*

*inhalation of gastric contents and alcohol (1),*

*cardiac arrest (1),*

*car crash with unreported association to ETOH (1),*

*suicide (1),*

*unknown cause (1)*

for the 5 patients who had been in placebo treatment group during the double-blind treatment period, the listed causes of death were:

suicide (2),  
accidental fall (1),  
heart attack (1),  
hepatic coma (1).

(Source: Post-Text Table 8.8.9.0.1 – Vol 68 p238)

### Deaths During Non-Group 1 Studies

No deaths were reported for Group 2 studies. Sixteen deaths (14 acamprosate; 2 placebo) occurred during:

Group 3 studies (3 deaths in placebo-controlled study Lhuintre; 3 males with 2 on placebo; age range 46-71 and;

Group 4 open-label (13 in open label NEAT, Meram and Integral) studies: (9 M; 3 F; 4 unknown gender) (age range 36-71; 4 unknown age).

Causes of death for more than one patient in Non-Group 1 Studies were: suicide (3); trauma/accident (2); ---

*decompensation of cirrhosis/cirrhosis* (2). (Source: Post-Text Appendix 8.8.2.1:13 – Vol 71 p 81) (see Attachment 7 ).

Of the 14 patients who received acamprosate, the listed cause of death was:

---suicide (3),  
---variceal bleeding (1),  
---alcohol intoxication (1),  
---acute necrotic pancreatitis (1),  
---sudden death (1),  
---trauma (1),  
---homicide (1),  
---decompensation of cirrhosis (1),  
---asthma attack (1),  
---accident of unreported association to ETOH (1),  
---cirrhosis (1),  
--- unspecified surgical complications (1).

### Available Death Narratives For Non-Group 1 Studies

Deaths for patients in non-Group 1 studies are reported in tabular (see Attachment 7) and as narratives if available in the individual clinical study reports. If available, narratives for these patients are summarized below from the individual clinical study reports. No narratives were submitted for the 3 patients in the placebo-controlled study, Lhuintre, nor the 4 patients in the Meram open-label study. Below are summaries of the available non-Group 1 narratives; none provide information regarding compliance with study medication. One case of *sudden death* (#5) could be considered to have possible association to acamprosate because autopsy found no cause of death. Another case *homicide* (#7) could be considered not associated to acamprosate because the reported cause of death is murder.

1) NEAT-Extension – 1: 38 yo F received acamprosate (unspecified dose) for approximately 1 month after entering the extension phase **commit suicide by massive overdose** of her father's medications (digoxin, enalapril, flurazepam, naproxen, and dytenside), developed arrhythmia, cardiogenic shock, and failed resuscitation efforts; medical history is significant for alcoholic cirrhosis. **Assessment:** suicide could be a consequence of alcoholism but any potential contributing factor of acamprosate can not be assessed; **No clear causal relationship to acamprosate can be asserted.**

2) NEAT-UK – 2: 36 yo M received acamprosate (unspecified dose) for approximately 18 days after entering study developed **catastrophic GI bleeding** during endoscopy for banding esophageal varices and underwent 2 intrahepatic portosystemic shut placements (the first was unsuccessful) but continued to bleed; medical history is significant hepatic cirrhosis with esophageal varices; an autopsy deemed the cause of death to be bleeding esophageal varices in a patient with alcoholic liver disease. **Assessment:** bleeding esophageal varices as cause of death was confirmed by post-mortem exam but any potential contributing factor of acamprosate can not be fully assessed; **No clear causal relationship to acamprosate can be asserted.**

3) NEAT-Portugal – 3: 38 yo M received acamprosate (unspecified dose) for an unspecified period after entering study but was not compliant with treatment, **died at home in profound state of alcohol intoxication**; presumed cause of death was MI; medical history is NOT significant for cardiovascular disease but WAS significant for smoking; **Assessment:** profound intoxication is the more likely cause of death because it predisposes to metabolic alterations which can place this

population risk for serious events including death; further this patient was viewed as non-compliant with acamprosate treatment. **No clear causal relationship to acamprosate can be asserted.**

4) NEAT-Belgium – 5: 43 yo M received acamprosate (unspecified dose) for approximately 5 months after entering study and 3 days after discontinuing treatment during relapse, experienced **acute necrotic pancreatitis** and died; medical history is significant for several episodes of acute pancreatitis and chronic hepatic disorders. **Assessment:** **Unlikely due to acamprosate** - past medical history is significant for episodes of acute pancreatitis and the event occurred during a massive relapse making this the more likely precipitating factor as cause of death but any potential contributing factor of acamprosate can not be fully assessed; **No clear causal relationship to acamprosate can be asserted.**

5) NEAT-Belgium – 7: 45 yo M received acamprosate (unspecified dose) for approximately 1 month after entering study experienced **sudden death** without signs of alcohol intake; medical history is NOT significant for cardiovascular disease; concomitant medications included benzodiazepines and propranolol for tremor and palpitations; autopsy found no cause for sudden death; **Assessment:** No other factor as cause of death is reported following post mortem exam, although the extent of the post mortem exam is not provided; **Possible relationship to acamprosate.**

6) NEAT-Belgium – 9: 39 yo F received acamprosate (unspecified dose) for unspecified duration after entering study, experienced **trauma during a fall probably related to intoxication**; medical history is significant for depression; concomitant medications were fluoxetine, diazepam and tetracyclic antidepressant. **Assessment:** trauma from a fall is a known consequence of alcoholism particularly during intoxication; **No clear causal relationship to acamprosate can be asserted.**

7) NEAT-Belgium – 12: 48 yo F received acamprosate (unspecified dose) for unclear duration after entering study was the victim of **homicide** committed by an acquaintance; no medical history, concomitant medications or alcohol status provide; **Assessment:** cause of death appears to be clear: **Not related to acamprosate.**

8) NEAT-Belgium – 13: 37 yo M received acamprosate (unspecified dose) for approximately 1 month after entering study, commit **suicide** by massive dose of alcohol and medication; medical history is significant for prior suicide attempts; concomitant medications clorazepate and trazodone. **Assessment:** suicide is possible consequence of alcoholism and this patient attempted suicide in the past and compliance with acamprosate administration is not provided; **No clear causal relationship to acamprosate can be asserted.**

9) Integral – 81004: 37 yo M received acamprosate (unspecified dose) for an unspecified duration after entering study, experienced **status asthmaticus** 1 day after being treated in the ER for an asthmatic attack and 1 month after being hospitalized for worsening asthma; medical history is significant for asthma and COPD; concomitant medications included theophylline, budesonide, salbutamol, and multiple vitamin. **Assessment:** this patient has medical history of asthma and COPD but a sensitivity to metabisulfite can not be excluded; **No clear causal relationship to acamprosate can be asserted.**

**APPEARS THIS WAY  
ON ORIGINAL**

## SERIOUS ADVERSE EVENTS (SAEs)

### Treatment Emergent Serious Adverse Events (TESAEs) for Group 1 Studies

The sponsor indicates that serious adverse events were identified prospectively in the database for only the US 96.1 study. In order to identify an SAE from non-U.S. studies according to the current regulatory definition, the sponsor indicates that study reports for the double-blind placebo-controlled studies were examined for SAEs using patient narratives, concurrent illnesses as a reason for withdrawal, and AE listings. In addition for studies with spontaneously reported AEs, SAEs that met the current regulatory definition were identified in the database by searching for the following terms or part of terms: *hospitalization, hospital, surg, admit, inpatient, cancer, melanoma, carcinoma, suicide, and overdose*. The use of these few descriptors of SAEs raises the concern that SAEs would have been missed because use of so few terms would not be expected to capture many SAEs. It is not clear why other potentially important descriptors or part of descriptor terms were not included in an effort to broaden the capture rate from non-U.S. studies: examples include *fatality, fatal, death, died, arrest, coma, life-threatening, suicidal, depression, psychosis, arrhythmia, gast/gastro, GI bleed, abdominal pain, diarrhea, vomiting, syncope, fall, paralysis, stroke, convulsion, seizure, renal/kidney failure/dysfunction, hepatic/liver failure/dysfunction, anaphylaxis, agranulocytosis, aplastic anemia, neutropenia, rash, pruritis, exfoliation, Stevens-Johnson, toxic epidermal necrolysis, tumor, birth defect, congenital anomaly*. The sponsor should be asked to re-examine their databases using these descriptors or part of descriptor terms as search terms, determine if the AEs fit the definition of a SAE, and analyzed them according to short-term and long-term groups. For these terms that are not COSTART terms, the verbatim database should be searched.

Serious adverse events related to hospitalization for alcohol relapse (i.e. COSTART terms – withdrawal syndrome, drug dependence, stupor, alcohol intolerance) were not considered SAEs for the European studies; and although the US trial prospectively captured AEs related to hospitalization for alcohol relapse the sponsor analyzed the data with and without relapse data using the same COSTART terms to identify relapse. It seems reasonable to exclude relapse data from the AE database because relapse represents treatment failure rather than an AE. Therefore, alcohol relapse would not be included in the SAE pool but would still be included in the overall AE pool and would come from the studies collecting AE spontaneously but not from the studies collecting AEs using 43-item questionnaire because the 4 COSTART preferred terms have no AEs subsumed to them. (Source: SS\_AEQ in attachment 2 of the 3/21/02 submission – showing how verbatim terms were subsumed to preferred terms).

### Spontaneously Reported TESAEs During US Study, US 96.1

Below is a table of TESAEs in the acamprosate group but not in the placebo group (i.e. 0 AEs reported) from the US 96.1 study. Only *depression* that included subsumed suicidal ideation in this study occurred in more than one patient. By my calculation, using the sponsor's calculation of patient-weeks as the denominator for study US 96.1, there does not appear to be an excess of SAEs in patients treated with acamprosate (pooled) compared to placebo expressed as events per 1000 patient-years of exposure – ACAMP 0.9/1000 patient years vs Placebo 1.1/1000 patient-years.

TESAEs in the ACAMP Group from Study US 96.1 but None in the Placebo Group (Shaded rows contain more than 1 acamprosate treated patient)	Acamprosate 2000 mg/day (N=258)	Acamprosate Pooled 2000 mg and 3000 mg/ day (N=341)	Placebo (N=260)
Number of patients with a serious adverse event in the overall database for study US 96.1	7 ( 3%)	9 ( 3%)	5 ( 2%)
Back pain	1 (<1%)	1 (<1%)	0
Cellulitis	1 (<1%)	1 (<1%)	0
Infection	1 (<1%)	1 (<1%)	0
Infection parasitic	1 (<1%)	1 (<1%)	0
Gastrointestinal hemorrhage	1 (<1%)	1 (<1%)	0
Breast carcinoma	1 (<1%)	1 (<1%)	0
Depression	2 (<1%)	2 (<1%)	0
Agitation	0	1 (<1%)	0
Asthma	0	1 (<1%)	0

Source: In-Text Table 8.8.7.1.2.1. from Post-Text Table 8.8.8.0.1 Vol 68 p 188