6.4 PROTOCOL 544 ("PAILLE"): A MULTICENTRE CONTROLLED AND DOUBLE-BLIND COMPARATIVE STUDY OF THE EFFICACY OF AOTA-CA STUDIED AT TWO DOSAGES AND PLACEBO OVER A 1 YEAR PERIOD OF TREATMENT. FOLLOWED BY A 6 MONTH POST-TREATMENT PERIOD OF PLACEBO ON ALCOHOLIC PATIENTS WHO WERE FOLLOWED AS OUTPATIENTS AFTER WITHDRAWAL

Conducted April 1989 to November 1992

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mg/day versus placebo in maintaining abstinence over the 12-month treatment period in alcohol-dependent outpatients withdrawn from alcohol; and to observe the outcome over an additional 6-month period while patients continued on (or were switched to) placebo (single-blind) at the end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

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of acamprosate and placebo given for 12 months for maintenance of abstinence in alcohol-dependent patients who had been withdrawn from alcohol.

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

6.4.1.3.1 Inclusion/Exclusion Criteria

Subjects "about to start a withdrawal cure" (inpatient or outpatient detoxification) were to be recruited. To be eligible, subjects were required to meet the following criteria:
- Age 18-65
- DSM-III (R) diagnosis of alcohol dependence x at least 1 year
- Clinical signs of "alcohol impregnation" ("appearance of the face, conjunctivae, or tongue, tremor of the mouth, tongue, or extremities") and/or elevated GGT (>2 xULN) or MCV>98 Φ^3.
- In outpatient treatment at a specialized center for alcoholics
- Abstinent 1 week – 1 month at Day 0
- "Clearly stated desire to maintain abstinence"
- "Lifestyle compatible with follow-up"

Subjects were excluded for:
- Assessment at "unlikely to comply with treatment over the 18 month period"
- More than 3 courses of detox in previous 2 years
- Previous treatment with acamprosate

- Recent (past 6 months) participation in clinical trial
- Pregnancy, nursing, or "likely to become pregnant"
- Severe psychiatric disorder
- Significant medical illness (examples included "poorly controlled diabetes, poorly controlled arterial hypertension, septicemia, active TB, cardiac failure, progressive neoplasia")
- Epilepsy (not alcoholic withdrawal seizures)
- Renal insufficiency (Cr > 14 mg/L)
- Hypercalcemia
- "Patients whose physical or mental state is incompatible with the trial conditions"
- Intellectual limitations or language barrier precluding completion of diaries
- Lack of fixed address; residence in "post-cure center"
- "Lack of obvious cooperation during the global withdrawal treatment"
- Incompatible medication
- Recent (past 3 months) institution of chronic medication

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

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

6.4.1.3.2 Procedures

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

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

The protocol called for monthly study visits for the first 6 months and bimonthly visits thereafter.

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

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

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

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Table 5.4.1.3.2 Time-and-Events Schedule--Paille

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

[1] Day -30 to Day -7, prior to detox

6.4.1.4   Evaluations/Endpoints

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

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

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

The following data were used in this amendment to determine the patient's drinking status at each visit:

- Blood alcohol;

- Number of non-abstinent days since the previous visit;

- Quantity of alcohol consumed; and

- Relative's evaluation of abstinence.

A patient was considered as "not abstinent" at a given visit if:

(1) Blood alcohol > 0.05 g/L; OR

(2) Number of non-abstinent days since the previous visit > 0; OR

(3) Quantity of alcohol consumed > 0; OR

(4) Relative's evaluation of abstinence = one of the following:
1 = has been drinking little and rarely
2 = is drinking less than before the treatment
3 = is drinking as much as or more than before the treatment.

A patient was considered as "abstinent" at a given visit if:

(1)   Blood alcohol is either missing or ≤0.05 g/L; AND

(2)   Number of non-abstinent days since the previous visit = 0; AND

(3)   Quantity of alcohol consumed = 0; OR one of the values (of number and quantity) = 0 and the other value is missing; AND

(4)   Relative's evaluation of abstinence is either missing or = 0 = has not been drinking at all.

A patient's status at a given visit was considered as "unknown" if the patient was not considered "not abstinent" using the algorithm above and:

(1)   The number of non-abstinent days since the previous visit is missing; AND

(2)   Quantity of alcohol is missing.

This differs from the original analysis in that the main evaluations for abstinence in the final study report were based solely upon the reported number of non-abstinent days and the reported quantity of alcohol consumed. A patient was considered abstinent if the quantity of alcohol consumed was zero or if the number of non-abstinent days was zero and the quantity was not provided.

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

6.4.2.1.1.1 Enrollment by Center
Thirty-one centers (there was no center #19) enrolled between 5 and 36 subjects each. Enrollment by center is tabulated in the original NDA review in Table 5.4.2.1.1.1.

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

Patient Disposition During Treatment Phase and Follow-up Phase - Paille

Parameter	Statistic	ACAMP 1332 mg/day (N=188)	ACAMP 1998 mg/day (N=173)	Placebo (N=177)
Number of Patients Randomized	n	188	173	177
Number of Patients in the ITT Population	n (%)	188 (100%)	173 (100%)	177 (100%)
Number of Patients Who Completed Treatment Phase	n (%)	85 (45%)	90 (52%)	62 (35%)
Number of Patients Who Discontinued Treatment Phase	n (%)	103 (55%)	83 (48%)	115 (65%)
Reasons for Discontinuation from Treatment Phase				
Adverse Event	n (%)	17 (9%)	13 (8%)	19 (11%)
Lost to Follow-up	n (%)	24 (13%)	27 (16%)	31 (18%)
Treatment Failure	n (%)	41 (22%)	29 (17%)	36 (20%)
Death	n (%)	2 (1%)	2 (1%)	2 (1%)
Patient Decision	n (%)	13 (7%)	10 (6%)	19 (11%)
Protocol Violation	n (%)	1 (<1%)	0	3 (2%)
Other	n (%)	5 (3%)	2 (1%)	5 (3%)
Data Source: Table 8.7.1.1.3.				

Lipha's In-Text Table 8.7.2.2:4

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

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

Most patients in this study were male (78% to 84% across treatment groups) and the mean age ranged from 42.5 to 43.7 years.

With respect to alcohol use histories, the mean duration of alcohol dependence ranged from 8.6 years (placebo group) to 10.1 years (acamprosate 1998 mg group). Almost all subjects drank 5 or more standard drinks per drinking day prior to treatment. In the placebo group, relatively more (76%) were in the >10 drinks/day category compared to the other groups (64% and 68% in the acamprosate groups). Half (50%) of the patients had previously undergone treatment or detoxification for alcoholism, but very few had been treated repeatedly. The groups were similar with respect to the number of patients with 0-1 previous detoxes (83% in acamprosate 1332 mg group, 79% in acamprosate 1998 mg group, and 81% in placebo group). Slightly fewer (4%) in the placebo group had undergone multiple (3 or more) previous detoxes (vs 7% in acamprosate 1332 mg group and 6% in acamprosate 1998 mg group). All of the patients in the study had undergone detoxification. Patients who had a positive lab evaluation for alcohol at baseline were considered non-abstinent at baseline. The groups differed somewhat in the number of patients who were not abstinent at baseline, with 8 (5%) in the placebo group, 16 (9%) in the acamprosate 1332 mg/day group, and 19 (11%) in the acamprosate 1998 mg/day group.

Demographic and Baseline Characteristics –Paille

Characteristic	Statistic	ACAMP 1332 mg/day (N=188)	ACAMP 1998 mg/day (N=173)	Placebo (n=177)
Gender	n	188	173	177
Male	n (%)	146 (78%)	137 (79%)	148 (84%)
Female	n (%)	42 (22%)	36 (21%)	29 (16%)
Age (years)	n	188	173	177
	Mean (SE)	43.7 (0.6)	43.3 (0.6)	42.5 (0.7)
	Min, Max	27, 68	26, 65	25, 65
Age Distribution (years)	n	188	173	177
16-39	n (%)	63 (34%)	60 (35%)	70 (40%)
40-59	n (%)	119 (63%)	106 (61%)	98 (55%)
≥60	n (%)	6 (3%)	7 (4%)	9 (5%)
Weight (kg)	n	187	173	177
	Mean (SE)	69.3 (1.0)	68.3 (1.0)	70.8 (1.0)
	Min, Max	43, 130	40, 166	48, 124
Marital Status	N/A			
Detoxification Prior to Randomization	n	188	173	177
Yes	n (%)	188 (100%)	173 (100%)	177 (100%)
No	n (%)	0	0	0
Abstinent at Baseline@	n	188	173	177
Yes	n (%)	172 (91%)	154 (89%)	169 (95%)
No	n (%)	16 (9%)	19 (11%)	8 (5%)
Duration of Alcohol Dependence/Abuse (years)	n	188	173	176
	Mean (SE)	9.8 (0.6)	10.1 (0.5)	8.6 (0.5)
	Min, Max	1, 40	1, 35	1, 30
<10	n (%)	103 (55%)	87 (50%)	99 (56%)
≥10	n (%)	85 (45%)	86 (50%)	77 (44%)
Average Standard Drinks per day at Study Entry	n	187	173	176
	Mean (SE)	15.7 (1.0)	15.0 (0.6)	16.0 (0.7)
	Min, Max	4, 167	1, 42	1, 67
<5	n (%)	3 (2%)	6 (3%)	8 (5%)
5-10	n (%)	56 (30%)	57 (33%)	35 (20%)
>10	n (%)	128 (68%)	110 (64%)	133 (76%)
Prior Treatment or Detoxes for Alcoholism	n	188	173	176
0	n (%)	99 (53%)	87 (50%)	84 (48%)
1	n (%)	57 (30%)	50 (29%)	59 (34%)
2	n (%)	19 (10%)	26 (15%)	26 (15%)
3	n (%)	10 (5%)	4 (2%)	4 (2%)
>3	n (%)	3 (2%)	6 (3%)	3 (2%)

Data Source: Table 8.7.1.2.3 and Table 8.7.1.3.3

Lipha's In-Text Table 8.7.2.3:3

@ Patients who had a positive lab evaluation for alcohol at Baseline are considered non-abstinent at Baseline.

N/A = Data not collected in this study.

6.4.2.1.3 Dosing Information

The table below illustrates exposure duration and compliance with medication across treatment groups. Mean compliance was slightly higher (88%) in the acamprosate 1998 mg/day group than in the other two groups (83%). 72%-81% of subjects were >75% compliant. Duration of exposure to study medication was shorter in the placebo group (mean 32 weeks) than in the acamprosate groups (mean 35-38 weeks). Dropout within the first 26 weeks of treatment occurred in 44% of the placebo group, vs. 28% of the acamprosate 1998 mg/day group and 37% of the acamprosate 1332 mg/day group.

Drug Exposure – Paille

Parameter	Statistic	ACAMP 1332 mg/day (N=188)	ACAMP 1998 mg/day (N=173)	Placebo (N=177)
Duration of Exposure (weeks)	n	188	173	177
	Mean (SE)	35.3 (1.4)	37.7 (1.4)	31.7 (1.5)
	Median	44	50	31
	Min, Max	1, 62	0, 59	0, 60
Exposure by Duration Category (weeks)	n	188	173	177
0 - <4	n (%)	11 (6%)	8 (5%)	9 (5%)
4 - <8	n (%)	12 (6%)	11 (6%)	18 (10%)
8 - <13	n (%)	12 (6%)	12 (7%)	14 (8%)
13 - <26	n (%)	35 (19%)	17 (10%)	36 (20%)
26 - <39	n (%)	16 (9%)	20 (12%)	23 (13%)
39 - <48	n (%)	11 (6%)	9 (5%)	9 (5%)
48 - <52	n (%)	43 (23%)	47 (27%)	28 (16%)
≥52	n (%)	48 (26%)	49 (28%)	40 (23%)
Compliance (%)	n	166	154	158
	Mean (SE)	82.6 (1.7)	88.0 (1.7)	82.8 (1.6)
	Median	89	96	87
	Min, Max	11, 153	27, 167	14, 116
Number of Patients Who Were ≥75 % Compliant	n (%)	125 (75%)	124 (81%)	113 (72%)
Data Source: Table 8.7.1.4.3				

Lipha's In-Text Table 8.7.2.5:3

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

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

6.4.3   *Efficacy Results*

6.4.3.1   Sponsor's Analysis

A patient was considered as "not abstinent" at a given visit if:

(5) Blood alcohol > 0.05 g/L; OR

(6) Number of non-abstinent days since the previous visit > 0; OR

(7) Quantity of alcohol consumed > 0; OR

(8) Relative's evaluation of abstinence = one of the following:
1 = has been drinking little and rarely

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2 = is drinking less than before the treatment

3 = is drinking as much as or more than before the treatment.

A patient was considered as "abstinent" at a given visit if:

(5)   Blood alcohol is either missing or ≤0.05 g/L; AND

(6)   Number of non-abstinent days since the previous visit = 0; AND

(7)   Quantity of alcohol consumed = 0; OR one of the values (of number and quantity) = 0 and the other value is missing; AND

(8)   Relative's evaluation of abstinence is either missing or = 0 = has not been drinking at all.

A patient's status at a given visit was considered as "unknown" if the patient was not considered "not abstinent" using the algorithm above and:

(3)   The number of non-abstinent days since the previous visit is missing; AND Quantity of alcohol is missing.

Lipha reported that the rate of complete abstinence at the end of the 1-year treatment phase was 14% for the acamprosate 1332 mg/day group, 16% for the acamprosate 1998 mg/day group, and 9% for the placebo group. The acamprosate 1998 mg/day group had a statistically significantly greater percentage of patients remain abstinent throughout the treatment phase compared to the placebo group (p=0.044), while the difference between the acamprosate 1332 mg/day group and the placebo group did not achieve statistical significance (p=0.152).

As described above, Lipha also calculated percent days abstinent and time to first drink. The mean (SE) percent days abstinent was 61.6% (2.5) for the acamprosate 1332 mg/day group, 67.6% (2.7) for the acamprosate 1998 mg/day group, and 57.5% (2.6) for the placebo group. Median percent days abstinent were 72%, 85%, and 67% for the acamprosate 1332 mg/day, acamprosate 1998 mg/day, and placebo groups, respectively. The percent days abstinent were statistically significantly greater in the acamprosate 1998 mg/day group compared to the placebo group (p=0.001), while the difference in percent days abstinent between the acamprosate 1332 mg/day group and the placebo group was not statistically significant (p=0.182). The difference between percent days abstinent for the acamprosate 1332 mg/day group and the acamprosate 1998 mg/day group was statistically significant (p=0.049). The median time to first drink calculated from the uncensored approach was 32.0 days for the acamprosate 1332 mg/day group, 57.0 days for the acamprosate 1998 mg/day group, and 29.0 days for the placebo group. Patients in the acamprosate 1998 mg/day group had a statistically significantly longer time to first drink compared to patients in the placebo group (p=0.007).

6.4.3.2   Reviewer's Analysis
Using the dataset EFFPT_PI.XPT, the number of patients who were not flagged as relapsing (RELFLAGU=0) was as shown in the table below:

Rate of Complete Abstinence Throughout Treatment – Paille
Treatment

Acamprosate 1332 mg/day	Acamprosate 1998 mg/day	Placebo
20/188 (11%)	20/173 (12%)*	10/177 (6%)

*p-value acamprosate 1998 mg/day vs placebo = .048, chi-square

This differs from the values reported by Lipha, who calculated 14% for the acamprosate 1332 mg/day group, 16% for the acamprosate 1998 mg/day group, and 9% for the placebo group. Lipha has clarified that their analysis was based on a different variable (labeled "QUANES1" in the dataset). This variable is set to reflect abstinence for any patient who completes all visits in the Treatment Phase and shows no indication of drinking at any visit. However, the variable "RELFLAGU" is set to reflect abstinence only for patients who participate in the treatment phase for a minimum of 360 days.

Lipha was asked to tabulate the duration of participation for the 20 patients who were considered continuously abstinent in their analysis but whose participation was <360 days. As shown below, the majority of patients participated for 350 days or more. The two patients with extremely early Visit 10 dates were both in the placebo group.

Days from Baseline to Visit 10	ACAMP 1332	ACAMP 1998	Placebo	Total
336			1	1
346			1	1
350		2		2
355			1	1
356		3		3
357	2		2	4
358	1	2	1	4
359	3	1		4
Grand Total	6	8	6	20

Therefore, with the exception of two patients in the placebo group, it seems appropriate to include these patients as completely abstinent.

Compared to the results calculated on the original dataset submitted to the NDA, the reviewer's analysis represents re-classification of 13 patients in the acamprosate 1332 mg/day group, 14 patients in the 1998 mg/day group, and ten patients in the placebo group from abstinent to non-abstinent. Because the original NDA analysis also relied on identifying patients with a continuous abstinence of at least 360 days, these readjudications are likely attributable to the fact that "the main evaluations for abstinence in the final study report were based solely upon the reported number of non-abstinent days and the reported quantity of alcohol consumed," while the reanalysis takes into account other sources of information.

6.4.3.3   Efficacy Conclusion – Study Paille
Based on reviewer's analysis, the Paille study provides evidence of efficacy of acamprosate in maintaining abstinence in recently-detoxified alcoholics for a period of 360 days.

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6.5 PROTOCOL # AOT 411.198 ("PRAMA"): PREVENTION OF RELAPSES IN ALCOHOLICS WITH ACAMPROSATE

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

6.5.1 Protocol

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

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

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

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

- Age 18 to 65 years

- DSM-III-R diagnosis of alcohol (5 of 9 criteria)

- History of at least 3 years of alcohol dependence in males and at least 2 years of alcohol dependence in females

- Munich Alcoholism Test (MALT) test score of at least 11 points

- A minimum of 14 consecutive days abstinence following detoxification

- Intelligence level of at least 13 points on the MWT-B questionnaire

Subjects were excluded for:
- "Controlled abstinence" of more than 4 weeks;

- Existing withdrawal symptoms;

- Existing mental disease necessitating the start of psychotropic drug therapy during the study;

- Epilepsy not due to alcoholism, severe general changes in the EEG and/or epileptic foci;

- Severe hepatic damage, particularly alcoholic hepatitis and alcoholic cirrhosis, plasma cholinesterase less than the normal;

- Hypercalcemia of all etiologies;

- A planned stay of more than 3 weeks at a specialist residential clinic for addicts or at a psychiatric clinic;

- Lack of fixed address;

- Severe drug addiction or drug dependence in the past 3 years;

- Known excretory pancreatic failure;

- Pregnancy/nursing/inadequate contraception

- Severe systemic disease (e.g., poorly controlled diabetes mellitus, noncompensated hypertension, decompensated heart failure);

- ECG-confirmed cardiac arrhythmias requiring treatment, ventricular extrasystoles;

- Creatinine >120 µmol/L or >1.4 mg/dL);

- Malignancies;

- "Pronounced organic psychological syndrome which prevented an understanding of the nature of the trial and of the questionnaires"; and

- History of gastrointestinal surgery resulting in GI narrowing

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

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

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

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

On selection day, subjects were assessed for eligibility prior to entering alcohol withdrawal

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

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

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

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

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

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

- Breathalyzer was to be administered

- Subject was to be questioned about abstinence or drinking habits

- Where possible, subjects partner/relatives were to be questioned

- GGT and MCV were to be determined (local lab); if there were no other known medical reasons, then

- GGT > 2xULN or "marked increase" was to be considered indicative of alcohol consumption

- MCV > normal laboratory value was to be considered indicative of alcohol consumption

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

6.5.1.4   Evaluations/Endpoints

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

The following data were used in this amendment to determine the patient's drinking status at each visit:

- Breathalyzer (breath test);
- Patient's self-report of drinking behavior;
- Relative's report of drinking behavior; and
- Investigator's evaluation of therapy success.

A patient was considered as "not abstinent" at a given visit if:

(1) Breathalyzer result(s) since the previous visit is positive for alcohol; OR

(2) The patient's self-report since the previous visit = 1 = not abstinent; OR

(3) The relative's report of drinking behavior = 2 = not abstinent; OR

(4) The investigator's evaluation of therapy success = one of the following:
   3 = Patient has suffered periods of recidivism since the last examination, although not all the findings given above support this.
   4 = Patient has suffered periods of recidivism since the last examination according to consistent values and reports from all the findings and evaluations given above.

A patient was considered as "abstinent" at a given visit if:

(1) Breathalyzer result(s) since the previous visit is not assessed or is negative for alcohol; AND

(2) The patient's self-report since the previous visit = 0 = abstinent; AND

(3) The relative's report of drinking behavior = one of the following:

0 = could not be questioned

1 = abstinent since the last examination; AND

(4) The investigator's evaluation of therapy success = one of the following:
1 = Patient has been abstinent since the last examination according to consistent values and reports from all the findings and evaluations given above.
2= Patient has been abstinent since the last examination, although not all the findings above support this.

A patient's status at a given visit was considered as "unknown" if the value for the investigator's evaluation of therapy success was missing and there was no indication of drinking based on the breathalyzer result, the patient's self-report, and the relative's report.

This differs from the original analysis, in that the main evaluations for abstinence in the final study report were based solely upon the investigator's evaluation of therapy success.

In addition, it differs from the analysis requested by the Division. The Division noted that, at each visit, the investigator made a judgment about the GGT and MCV values. These values could be assessed as "not abnormal," "increased due to alcohol," or "increased not due to alcohol." The Division recommended that this information be incorporated into the overall classification of abstinence vs. non-abstinence; however, Lipha argued that

> The National Institute of Alcohol Abuse and Alcoholism (NIAAA) considers these measurements as unreliable reflections of current drinking behavior because of the variable latent time between cessation of drinking and reversion of these parameters to normal, as well as the possibility that other factors may contribute to elevated values for these parameters. The patient's status is considered as "non-abstinent" if any of the other assessments used to help the investigator determine the patient's abstinence status (breathalyzer result, the patient's self-report, and the relative's report) indicate drinking

Therefore, the sponsor's analysis does not take into account GGT or MCV assessments. These assessments continue to be viewed as relevant by the reviewer, and are included in the reviewer's analysis.

6.5.2 Results
6.5.2.1 Study Conduct/Outcome
6.5.2.1.1 Subject Characteristics
A total of 272 subjects were selected for enrollment. There is no indication of how many were screened in order to enroll 272. Of these, 163 were randomized to placebo and 163 were randomized to acamprosate. Acamprosate dose was based on weight, with subjects >60 kg receiving 1998 mg/day and smaller subjects receiving 1332 mg/day. Only 44

subjects (28 of 61 women and 16 of 211 men) weighed 60 kg or less. Of these, 13 women and 11 men were randomized to acamprosate. Thus, only 24 subjects in the study received the 1332 mg/day dose

6.5.2.1.1.1 Enrollment by Center

Twelve centers, all in Germany, enrolled between 7 and 64 subjects. Enrollment by center is described in the original NDA review in Table 5.5.2.1.1.1.

6.5.2.1.1.2 Subject Disposition

The table below illustrates patient disposition and reasons for premature discontinuation, based on audited and readjudicated data submitted in this amendment. More patients in the placebo group discontinued for treatment failure and "patient decision," compared to the acamprosate group. Overall, completion was higher in the acamprosate group (54% vs. 38%).

Patient Disposition During Treatment Phase – PRAMA

	Statistic	ACAMP (N=136)	Placebo (N=136)
Number of Patients Randomized	n	137	138
Number of Patients in the ITT Population	n (%)	136 (>99%)	136 (>99%)
Number of Patients Who Completed Treatment Phase	n (%)	74 (54%)	53 (38%)
Number of Patients Who Discontinued Treatment Phase	n (%)	62 (45%)	83 (60%)
Reasons for Discontinuation:			
Adverse Event	n (%)	9 (7%)	7 (5%)
Lost to Follow-up	n (%)	26 (19%)	29 (21%)
Treatment Failure	n (%)	14 (10%)	29 (21%)
Death	n (%)	2 (1%)	1 (<1%)
Patient Decision	n (%)	11 (8%)	16 (12%)
Protocol Violation	n (%)	0	0
Other	n (%)	0	1 (<1%)
Data Source: Table 8.7.1.1.2			

Lipha's In-Text Table 8.7.2.2:3

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

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

6.5.2.1.2 Demographics

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

With respect to alcohol use histories, the mean duration of alcohol dependence was 10.4 years in both groups. Almost all subjects drank 5 or more standard drinks per drinking day prior to treatment. The rate of very heavy drinking (>10 drinks/drinking day) did not differ across treatment groups (77-80%). Most (73%) of the patients had previously undergone treatment or detoxification for alcoholism, and the groups were similar with

respect to the number of patients with 0-1 previous detoxes (49% in acamprosate group and 53% in placebo group) and the number with 3 or more previous detoxes (35% in each group). All of the patients in the study had undergone detoxification and were abstinent at baseline.

Demographic and Baseline Characteristics – PRAMA

Characteristic	Statistic	ACAMP (N=136)	Placebo (n=136)
Gender	n	136	136
Male	n (%)	102 (75%)	109 (80%)
Female	n (%)	34 (25%)	27 (20%)
Age (years)	n	136	136
	Mean (SE)	41.9 (0.7)	40.5 (0.7)
	Min, Max	21, 58	21, 65
Age Distribution (years)	n	136	136
16-39	n (%)	54 (40%)	69 (51%)
40-59	n (%)	82 (60%)	64 (47%)
≥60	n (%)	0	3 (2%)
Weight (kg)	n	136	136
	Mean (SE)	72.4 (1.0)	73.9 (1.1)
	Min, Max	46, 130	41, 107
Marital Status	n	136	136
Married	n (%)	58 (43%)	67 (49%)
Not married	n (%)	78 (57%)	69 (51%)
Detoxification Prior to Randomization	n	136	136
Yes	n (%)	136 (100%)	136 (100%)
No	n (%)	0	0
Abstinent at Baseline	n	136	136
Yes	n (%)	136 (100%)	136 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)	n	136	136
	Mean (SE)	10.4 (0.5)	10.4 (0.6)
	Min, Max	2, 30	2, 30
<10	n (%)	61 (45%)	67 (49%)
≥10	n (%)	75 (55%)	69 (51%)
Average Standard Drinks per Day at Study Entry	n	136	136
	Mean (SE)	18.8 (1.0)	18.7 (0.8)
	Min, Max	3, 67	1, 45
<5	n (%)	3 (2%)	6 (4%)
5-10	n (%)	28 (21%)	21 (15%)
>10	n (%)	105 (77%)	109 (80%)
Prior Treatment or Detoxes for Alcoholism	n	136	136
0	n (%)	33 (24%)	40 (29%)
1	n (%)	34 (25%)	32 (24%)
2	n (%)	22 (16%)	17 (13%)
3	n (%)	13 (10%)	13 (10%)
>3	n (%)	34 (25%)	34 (25%)
Data Source: Table 8.7.1.2.2 and Table 8.7.1.3.2			

Lipha's In-Text Table 8.7.2.3:2

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

6.5.2.1.3 Dosing Information

The table below illustrates exposure duration and compliance with medication across treatment groups. Mean compliance was over 80% in each group, and 68-71% of subjects were >75% compliant. Groups were similar with respect to compliance. Duration of exposure to study medication was shorter in the placebo group (mean 26 weeks) than in the acamprosate group (mean 32 weeks). Less than half of patients in the placebo group (44%) completed at least 26 weeks of treatment, whereas 59% of the patients in the acamprosate group completed at least 26 weeks of treatment.

Drug Exposure –PRAMA

Parameter	Statistic	ACAMP (N=136)	Placebo (N=136)
Duration of Exposure (weeks)	n	136	136
	Mean (SE)	32.2 (1.7)	26.0 (1.8)
	Median	40	18
	Min, Max	0, 61	0, 65
Exposure by Duration Category (weeks)	n	136	136
0 - <4	n (%)	19 (14%)	24 (18%)
4 - <8	n (%)	8 (6%)	10 (7%)
8 - <13	n (%)	7 (5%)	21 (15%)
13 - <26	n (%)	21 (15%)	21 (15%)
26 - <39	n (%)	12 (9%)	7 (5%)
39 - <48	n (%)	15 (11%)	10 (7%)
48 - <52	n (%)	40 (29%)	31 (23%)
≥52	n (%)	14 (10%)	12 (9%)
Compliance (%)	n	118	109
	Mean (SE)	81.6 (1.7)	80.9 (2.3)
	Median	87	89
	Min, Max	20, 128	5, 173
Number of Patients Who Were ≥75% Compliant	n (%)	84 (71%)	74 (68%)
Data Source: Table 8.7.1.4.2			

Lipha's In-Text Table 8.7.2.5:2Note: ACAMP = Acamprosate 1332 mg/day for patients ≤60 kg or Acamprosate 1998 mg/day for patients >60 kg.

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

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

6.5.3 Efficacy Results

6.5.3.1 Sponsor's Analysis

The following data were used in this amendment to determine the patient's drinking status at each visit:

- Breathalyzer (breath test);
- Patient's self-report of drinking behavior;
- Relative's report of drinking behavior; and
- Investigator's evaluation of therapy success.

A patient was considered as "not abstinent" at a given visit if:

(5) Breathalyzer result(s) since the previous visit is positive for alcohol; OR

(6) The patient's self-report since the previous visit = 1 = not abstinent; OR

(7) The relative's report of drinking behavior = 2 = not abstinent; OR

(8) The investigator's evaluation of therapy success = one of the following:
  3 = Patient has suffered periods of recidivism since the last examination, although not all the findings given above support this.
  4 = Patient has suffered periods of recidivism since the last examination according to consistent values and reports from all the findings and evaluations given above.

A patient was considered as "abstinent" at a given visit if:

(5) Breathalyzer result(s) since the previous visit is not assessed or is negative for alcohol; AND

(6) The patient's self-report since the previous visit = 0 = abstinent; AND

(7) The relative's report of drinking behavior = one of the following:

0 = could not be questioned

1 = abstinent since the last examination; AND

(8) The investigator's evaluation of therapy success = one of the following:
1 = Patient has been abstinent since the last examination according to consistent values and reports from all the findings and evaluations given above.
2= Patient has been abstinent since the last examination, although not all the findings above support this.

A patient's status at a given visit was considered as "unknown" if the value for the investigator's evaluation of therapy success was missing and there was no indication of drinking based on the breathalyzer result, the patient's self-report, and the relative's report.

6.5.3.1.1.1 Rate of Complete Abstinence
By the end of the 48-week treatment phase, 28% of the patients in the acamprosate group remained abstinent compared to 13% of the patients in the placebo group. The difference in rates was statistically significant (p=0.002).

6.5.3.1.1.2 Secondary Analyses
The mean (SE) percent days abstinent was 61.8% (3.2) for the acamprosate group and 45.6% (3.2) for the placebo group. Median percent days abstinent were 74% and 38% in the acamprosate and placebo groups, respectively. The treatment group difference for percent days abstinent was statistically significant (p<0.001). The median time to first drink calculated from the uncensored approach was 134.5 days in the acamprosate group vs 45.0 days in the placebo group(p<0.001).

6.5.3.2 Reviewer's Analysis
The dataset EFFPT_PR.XLS was used to identify those patients who were considered

non-relapsed (RELFLAGU=0). These numbers corresponded with the number of patients identified as abstinent in the sponsor's ISE. However, Lipha's rejection of the use of MCV and GGT as informative was not persuasive. Lipha asserts that the time course of responsiveness of these values, and the possibility that they might be influenced by other factors, argues against incorporating the investigator assessments of the lab values into the classification of patients as abstinent or non-abstinent. However, the PRAMA study involved very widely-spaced visits; after the first three months, visits occurred quarterly. A patient who had normal values at one visit and abnormal values, assessed *by the investigator* as "increased due to alcohol," particularly when the option of "increased not due to alcohol" was available to the investigator, may very logically be assumed to have resumed drinking. Other causes of elevated MCV and GGT are certainly possible, but in a population of alcoholics, it seems illogical to attribute a developing abnormality to other causes.

Therefore, the database EFFVS_PR.XPT was examined to identify those subjects, classified as abstinent in the EFFPT_PR.XPT dataset, in whom one or both laboratory values were assessed as "abnormal due to alcohol" *after previously being assessed as normal.* Patients with consistently abnormal values were not re-classified. Patients who had only one visit at which a lab value was considered "not abnormal" among a series of visits assessed as abnormal were also not reclassified if the value subsequently was again assessed as abnormal. Altogether, nine patients had the emergence of lab values assessed as "abnormal due to alcohol" in the setting of previous normal values. These included 6 on acamprosate (2 on 1332 mg/day and 4 on 1998 mg/day) and 3 on placebo.

Rate of Complete Abstinence - PRAMA
Sponsor's vs. Reviewer's Classification

	1332 mg/day	1998 mg/day	All Acamprosate	Placebo	p-value
Sponsor's Classification	7	31	38/136 (28%)	17/136 (13%)	
Reviewer's Classification	5	27	32/136 (23%)	14/136 (10%)	p <.0001

Therefore, even taking into account the investigator assessment of lab values, the number of abstinent patients in the acamprosate group remains statistically significantly higher than the number in the placebo group.

Compared with the data submitted in the original NDA, this represents reclassification of 8 patients in the acamprosate group by the sponsor and 12 by the reviewer from abstinent to non-abstinent. In the placebo group, the sponsor's analysis includes one patient reclassified from non-abstinent to abstinent. The reviewer's analysis yields a total decrease of 2 abstinent patients from the original analysis.

6.5.3.3 Efficacy Conclusion – Study PRAMA
Based on reviewer's analysis, the PRAMA study provides evidence of efficacy of

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acamprosate in maintaining abstinence in recently-detoxified alcoholics for a period of 48 weeks.

6.6   EFFICACY BY GENDER – PIVOTAL STUDIES

The population studied was primarily male. Altogether, 195 of the 998 patients (20%) included in the three pivotal trials were women. In each study, the rate of complete abstinence was lower in the placebo group for women than for men. However, response to acamprosate was variable across studies, with women demonstrating higher rates of abstinence than men in the PRAMA study and lower rates in the Pelc-II and Paille studies. Exploration of baseline severity suggests overall higher severity of illness at baseline in male subjects. Therefore, differential response is not readily explained by this variable. The small numbers in the female groups preclude extensive interpretation of the findings. However, notably, in every study, the acamprosate groups demonstrated numerically higher rates of abstinence than the placebo groups in both male and female subjects.

In the table below, the numbers of patients classified as RELFLAGU=0 are displayed by gender. The numbers differ slightly from the efficacy results shown above because the reviewer's adjustment for lab values was not applied in this analysis.

	Total		Acamprosate dose					
			1332 mg/day		1998 mg/day		Placebo	
	N	%	N	%	N	%	N	%
Pelc-II								
Female	4/27	15%	2/12	17%	2/8	25%	0/7	0%
Male	54/161	34%	24/51	47%	22/55	40%	8/15	15%
Paille								
Female	8/107	7%	3/42	7%	4/36	11%	1/29	3%
Male	42/431	10%	17/146	12%	16/137	12%	9/148	6%
PRAMA								
Female	16/61	26%	5/13	38%	9/21	43%	2/27	7%
Male	39/211	18%	2/11	18%	22/91	24%	15/109	14%
Overall								
Female	28/195	14%	10/67	15%	15/65	23%	3/63	5%
Male	135/803	17%	43/208	21%	60/283	21%	32/312	10%

7   INTEGRATED REVIEW OF SAFETY

7.1   METHODS AND FINDINGS

Using the paper and electronic NDA submissions of 9/5/2003 (response to ECG issue) and 12/19/03 (full response to NA letter), and responses to specific reviewer questions, treatment emergent adverse events identified from the acamprosate development program were reviewed.

The sponsor provided case report forms (CRFs) and summaries for all deaths, discontinuations due to adverse events, and serious adverse events in the Group I studies.

No case report forms were available for either the Group II or Group III studies. When available, related CRFs for Group IV patients experiencing treatment-emergent SAEs were provided. For Group II-IV studies, narratives for patients experiencing treatment-emergent SAEs either were based on information in the CRF (if available) and, at times, related Adverse Event forms or, when available, were copied from the study report or brief summaries.

To verify the accuracy of the primary data summarized by the sponsor, case report forms (CRFs), narrative summaries, and electronic data sets were compared for all deaths in the Group I studies, and a random sample of deaths in non-Group I studies and SAEs throughout the development program. To evaluate the adverse event (AE) coding procedures, investigator verbatim terms with the corresponding preferred terms assigned by the sponsor were compared using the provided thesaurus. Narratives for all deaths, SAEs, and events of a suicidal nature were reviewed and clinical details for selected events were summarized. The sponsor's analyses of laboratory values and EKG findings were reviewed and summarized. The provided datasets were employed to conduct additional analysis, where possible, of laboratory values and adverse events.

Because of differences in the level of detail available for different safety measures across the studies, each safety parameter was assessed in a slightly different group of studies. Analysis of deaths and SAEs includes all Group I studies included in the table of efficacy studies, plus an additional Group I study which was terminated for lack of enrollment and for which data on deaths and SAEs (only) was submitted as part of the safety update. Additionally, deaths and SAEs from four additional Group IV studies was submitted as part of the safety update and are included in these analyses. The data on discontinuation due to adverse events, common adverse events, laboratory values, vital signs, and ECG data are drawn from a subset of studies, as described in each section.

The overall N for each of the safety assessments is tabulated below.

	Acamprosate	Placebo
Deaths	7502	2406
SAEs	6090	2295
Common AEs	2019	1706
Lab values	200 – 1700+	<200 – 1400+
Vital signs	1160	925
EKGs	248	112

7.1.1   Deaths
Overall, the mortality rate was similar in the acamprosate-treated subjects in the various study groupings and in the placebo-treated subjects in the Group I studies. Causes of death were primarly those expected in this study population, including traumatic injury, suicide, gastrointestinal hemorrhage, and complications of alcoholic liver disease.

7.1.1.1 Deaths in Group I Studies

Lipha reported 21 deaths classified as "treatment emergent" in the Group I studies. Mortality risk was similar in the acamprosate and placebo treatment groups in the Group I studies. Two of 440 subjects in the acamprosate 1332 mg/day group (0.45%), ten of 1749 subjects in the acamprosate 1998 mg/2000 mg/day group (0.57%), and 9 of 1962 subjects in the placebo group (0.47%) died within 30 days of treatment discontinuation. There were no deaths among the 83 subjects treated with 3000 mg/day in the US 96.1 study, the only study to include this dose level. Causes of death did not differ across groups, as shown in the table below. Terms are sponsor's preferred terms, recoded as noted after review of CRF's and narratives. As shown in the table below, many deaths appear to have been related to either alcohol use (accidental injuries, motor vehicle accidents) or the medical consequences of alcoholism (esophageal bleed, cirrhosis, hepatic failure). No percentages are calculated as all are <1%.

Table 4.2.1: Causes of Death in Group I Studies

| BODY SYSTEM | TERM | Acamprosate Dose | | Placebo |
		1332 mg/day N = 440	1998 mg/ 2000 mg/ day N = 1749	N = 1962
BODY	ACCIDENTAL INJURY[a]	1	2	2
	MOTOR VEHICLE ACCIDENT	0	1	1
	DEATH[b]	0	1	1
	SUDDEN DEATH[c]	0	1	0
	SUICIDE ATTEMPT	0	3	2
CV	CARDIAC HYPERTROPHY[d]	0	0	1
	MESENTERIC OCCLUSION	0	1	0
	MYOCARDIAL INFARCT	0	0	1
DIG	CIRRHOSIS[e]	0	1	0
	GASTROINTESTINAL HEMORRHAGE	1	0	0
	HEPATIC FAILURE	0	0	1
TOTAL		2	10	9

[a] sponsor's preferred term for one case was subdural hematoma; cause on review of CRF and narrative appears to be accidental fall (UKMAS 297)

[b] unknown cause (Lesch 183)

[c] both probably cardiac (per review of verbatim terms)

[d] sponsor's preferred term was HYPERTROPHY (BODY); recoded after review of CRF and narrative to to Cardiac Hypertrophy (CV), "death was attributed to left ventricular hypertrophy, probably on the basis of alcohol-related cardiomyopathy" (Barrias 3072)

[e] sponsor's preferred terms were "death" and "shock"; recoded to cirrhosis as cause of death based on review of CRF and narrative; cirrhosis listed as AE but not as cause of death (Poldrugo 1)

7.1.1.2 Deaths in Non-Group I Studies

There were no deaths in the Group II Clinical Pharmacology studies. Three deaths occurred in the Group III Early Clinical Experience studies, all of them in one study

(Lhuintre). Two of the subjects were receiving placebo and one was receiving acamprosate 1332 mg/day. The causes of death were similar to those in the Group I data, as shown in the table below, and are not unexpected for the population.

Deaths in Group III Early Clinical Experience Studies

Treatment Group	Patient ID	Gender	Age	COSTART Preferred Term for Cause of Death
ACAMP 1332	1111	Male	57	Cirrhosis of liver
Placebo	2120	Male	46	Accidental injury
Placebo	3322	Male	71	Cerebrovascular accident

(Sponsor's In-Text Table 8.8.10.3:1)

In the Group IV Phase 4 Open-label studies, including those submitted with the safety update, were primarily 6 months in duration, and comprise a safety population of 4247 patients. Twenty-one deaths occurred in acamprosate-treated patients during these studies, representing a mortality risk of 0.49%, similar to the Group I studies. The causes of death are entirely consistent with the data from the Group I studies and are expected in the clinical population.

BODY SYSTEM	TERM	Acamprosate Dose	
		1332 mg/day	1998 mg/ 2000 mg/day
BODY	ACCIDENTAL INJURY	2[a]	
	DEATH[b]	1	
	HOMICIDE		1
	MOTOR VEHICLE ACCIDENT		1
	SUDDEN DEATH[c]	1	
	SUICIDE	1[a]	3
	SURGICAL PROCEDURE	1[a]	1[d]
CV	MYOCARDIAL INFARCT		1
DIG	CIRRHOSIS	1[a]	1
	GASTROINTESTINAL CARCINOMA	1	
	GASTROINTESTINAL HEMORRHAGE		2
	HEPATOCELLULAR CARCINOMA	1	1
RESP	ASTHMA		1

[a] For deaths occurring in MERAM study, no CRFs or further information available

[b] Died in hospital in context of multiple admissions for alcohol-related problems

[c] No cause identified on autopsy

[d] Failed portocaval shunt placement

7.1.2 Other Serious Adverse Events

At the time of the initial NDA review, the safety reviewers identified inconsistencies in the identification of serious adverse events in the dataset. The original safety review by Dr. Michael Sevka indicated that:

> 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.

> 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.

Specific examples of clearly serious events not flagged as SAEs were cited. As part of the re-audit and re-compilation of the ISS and safety database, Lipha reexamined the data to identify all SAEs and treatment-emergent serious adverse events. Serious adverse events were defined as events which were fatal, life-threatening, resulted in or prolonged hospitalization, disability/incapacity, or a congenital anomaly/birth defect. In addition, any event of cancer or overdose was included. A search through the database for a variety of text strings (see appendix) was undertaken to identify any heretofore unidentified events meeting criteria for SAEs. Each identified event was reviewed by a medically knowledgeable individual to determine whether the event met criteria for SAE.

In the ISS of the original NDA, adverse events were considered treatment-emergent if they occurred on or after the first day of study medication and within 10 days after last exposure to study treatment. At FDA request, the database was examined to capture events occurring up to 30 days after treatment discontinuation. However, not all studies consistently captured start and stop dates of treatment. Events occurring after treatment discontinuation with only partial information about start date available were considered treatment-emergent if the earliest possible date, based on available date information, was up to 30 days after last exposure to study treatment. Events occurring after treatment discontinuation with no available information for the start date were not considered treatment-emergent.

Narratives and CRFs for SAEs in Group I studies were submitted. However, the majority

of narratives generally contained little more than patient ID, gender, age, SAE, duration of treatment, investigator's attribution to treatment, and discontinuation status; diagnostic work –up and laboratory values were seldom included. For Group II-IV studies, narratives were developed from CRFs where available, or were copied/written from study reports. In some cases, little information was available.

In the Group I studies, 561 events were reported in 364 patients (69 in the acamprosate 1332 mg/day group, 147 in the acamprosate 1998/2000 mg/day group, and 143 in the placebo group), 1 SAE was reported in the Group II studies (acamprosate 1998 mg/day), 22 in the Group III studies (2 treated with acamprosate 1500 mg/day, 11 in the acamprosate 1332 mg/day group, and 9 treated with placebo), and 177 in the open-label Group IV studies submitted with the NDA and an additional 247 in the safety update.

7.1.2.1   Serious Adverse Events in Group I Studies

In the Group I studies, 561 treatment-emergent serious adverse events (TESAEs) were reported in 364 patients. Of these, 216 were acamprosate-treated patients (10% of 2275 exposed patients) and 59 were placebo-treated patients (3% of exposed patients).

The table below shows preferred terms for TESAEs reported in the Group I studies. There was only one specific SAE that occurred at a frequency of 1% or greater in these studies: alcohol consumption/relapse. This preferred term was assigned to events in which the verbatim description involved the return to uncontrolled drinking. Typically, events of this type meet the criterion for seriousness on the basis of the patient being rehospitalized for alcoholism treatment; a few were assessed as serious due to seizures reported in the context of alcohol relapse. Note that fatal events were coded both to the specific term *and* to "death."

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Treatment-Emergent Serious Adverse Events in Group I Studies

BODY SYSTEM	PREFERRED TERM	1332 mg/day N = 440		1998 mg/ 2000 mg/day N = 1749		3000 mg/day N = 83		Placebo N = 1962	
		N	%	N	%	N	%	N	%
BODY	ABDOMINAL PAIN	0	0.0%	2	0.1%	0	0.0%	2	0.1%
	ABSCESS	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	ACCIDENTAL INJURY	3	0.7%	6	0.3%	0	0.0%	5	0.3%
	ASCITES	1	0.2%	2	0.1%	0	0.0%	0	0.0%
	ASTHENIA	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	CARCINOMA	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	CELLULITIS	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	CHEST PAIN	0	0.0%	1	0.1%	0	0.0%	2	0.1%
	CYST	0	0.0%	1	0.1%	0	0.0%	1	0.1%
	DEATH	3	0.7%	8	0.5%	0	0.0%	7	0.4%
	DRUG INTERACTION	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	FEVER	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	FRACTURE	2	0.5%	5	0.3%	0	0.0%	6	0.3%
	HERNIA	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	INFECTION	0	0.0%	1	0.1%	0	0.0%	1	0.1%
	INFECTION PARASITIC	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	INTENTIONAL INJURY	2	0.5%	2	0.1%	0	0.0%	1	0.1%
	INTENTIONAL OVERDOSE	3	0.7%	9	0.5%	0	0.0%	6	0.3%
	LAB TEST ABNORMAL	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	MOTOR VEHICLE ACCIDENT	1	0.2%	3	0.2%	0	0.0%	3	0.2%
	NEOPLASM	0	0.0%	0	0.0%	0	0.0%	2	0.1%
	PROCEDURE	4	0.9%	10	0.6%	0	0.0%	12	0.6%
	SEPSIS	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	SUDDEN DEATH	0	0.0%	1	0.1%	0	0.0%	2	0.1%
	SUICIDE ATTEMPT	5	1.1%	16	0.9%	0	0.0%	8	0.4%
CV	ANGINA PECTORIS	0	0.0%	3	0.2%	0	0.0%	0	0.0%
	ARRHYTHMIA	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	ARTERIOSCLEROSIS	0	0.0%	2	0.1%	0	0.0%	0	0.0%
	ATRIAL FLUTTER	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	CARDIOMYOPATHY	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	DEEP THROMBOPHLEBITIS	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	HEART ARREST	0	0.0%	1	0.1%	0	0.0%	1	0.1%
	HEART FAILURE	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	HEMORRHAGE	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	MESENTERIC OCCLUSION	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	MYOCARDIAL INFARCT	1	0.2%	3	0.2%	0	0.0%	2	0.1%
	SHOCK	0	0.0%	1	0.1%	0	0.0%	0	0.0%

BODY SYSTEM	PREFERRED TERM	Acamprosate Dose							
		1332 mg/day N = 440		1998 mg/ 2000 mg/day N = 1749		3000 mg/day N = 83		Placebo N = 1962	
CV	SYNCOPE	1	0.2%	6	0.3%	0	0.0%	2	0.1%
	TACHYCARDIA VENTRICULAR	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	VARICOSE VEIN	1	0.2%	1	0.1%	0	0.0%	0	0.0%
	VASCULAR DISORDER	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	VENTRICULAR HYPERTROPHY	0	0.0%	0	0.0%	0	0.0%	1	0.1%
DIG	CARCINOMA OF LIVER	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	CIRRHOSIS OF LIVER	0	0.0%	2	0.1%	0	0.0%	1	0.1%
	DIARRHEA	0	0.0%	1	0.1%	0	0.0%	1	0.1%
	GASTROENTERITIS	0	0.0%	2	0.1%	0	0.0%	0	0.0%
	GASTROINTESTINAL CARCINOMA	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	GASTROINTESTINAL DISORDER	0	0.0%	1	0.1%	0	0.0%	2	0.1%
	GASTROINTESTINAL HEMORRHAGE	2	0.5%	3	0.2%	0	0.0%	1	0.1%
	HEMATEMESIS	2	0.5%	0	0.0%	0	0.0%	4	0.2%
	HEPATIC FAILURE	0	0.0%	0	0.0%	0	0.0%	2	0.1%
	LIVER DAMAGE	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	LIVER FUNCTION TESTS ABNORMAL	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	PANCREATITIS	0	0.0%	1	0.1%	0	0.0%	0	0.0%
HAL	BLOOD DYSCRASIA	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	RUPTURE OF SPLEEN	0	0.0%	1	0.1%	0	0.0%	0	0.0%
MAN	ACIDOSIS	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	DIABETES MELLITUS	1	0.2%	2	0.1%	0	0.0%	1	0.1%
	EDEMA	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	HYPERGLYCEMIA	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	HYPERLIPEMIA	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	HYPOGLYCEMIA	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	HYPOKALEMIA	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	KETOSIS	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	PERIPHERAL EDEMA	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	THIRST	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	WATER INTOXICATION	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	WEIGHT LOSS	0	0.0%	1	0.1%	0	0.0%	0	0.0%
MS	ARTHRALGIA	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	ARTHRITIS	0	0.0%	0	0.0%	0	0.0%	2	0.1%
	BONE DISORDER	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	JOINT DISORDER	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	MYALGIA	0	0.0%	0	0.0%	0	0.0%	1	0.1%

NER	AGITATION	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	ALCOHOL CONSUMPTION/ RELAPSE	43	9.8%	57	3.3%	2	2.4%	68	3.5%
	ANXIETY	1	0.2%	3	0.2%	1	1.2%	0	0.0%
	ATAXIA	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	COMA	0	0.0%	2	0.1%	0	0.0%	1	0.1%
	CONFUSION	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	CONVULSION	2	0.5%	8	0.5%	0	0.0%	4	0.2%
	DELIRIUM	0	0.0%	0	0.0%	0	0.0%	3	0.2%
	DEPRESSION	8	1.8%	17	1.0%	0	0.0%	15	0.8%
	ENCEPHALOPATHY	0	0.0%	1	0.1%	0	0.0%	2	0.1%
	GRAND MAL CONVULSION	0	0.0%	1	0.1%	0	0.0%	3	0.2%
	HEPATIC COMA	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	HOSTILITY	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	HYPERTENSION	1	0.2%	0	0.0%	0	0.0%	1	0.1%
	INTRACRANIAL HEMORRHAGE	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	NEURALGIA	0	0.0%	1	0.1%	0	0.0%	1	0.1%
	NEUROSIS	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	PARANOID REACTION	0	0.0%	1	0.1%	0	0.0%	1	0.1%
	PERSONALITY DISORDER	2	0.5%	2	0.1%	0	0.0%	1	0.1%
	PSYCHOSIS	1	0.2%	1	0.1%	0	0.0%	1	0.1%
	SOMNOLENCE	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	SUBDURAL HEMATOMA	1	0.2%	1	0.1%	0	0.0%	0	0.0%
	SUICIDAL IDEATION	2	0.5%	6	0.3%	0	0.0%	2	0.1%
	SUICIDAL TENDENCY	1	0.2%	1	0.1%	0	0.0%	0	0.0%
	THINKING ABNORMAL	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	VASODILATATION	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	WITHDRAWAL SYNDROME	0	0.0%	6	0.3%	1	1.2%	3	0.2%
RES	ASTHMA	1	0.2%	0	0.0%	1	1.2%	0	0.0%
	CARCINOMA OF LARYNX	0	0.0%	1	0.1%	0	0.0%	1	0.1%
	EPISTAXIS	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	LUNG EDEMA	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	PLEURAL DISORDER	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	PNEUMONIA	0	0.0%	2	0.1%	0	0.0%	0	0.0%
	PNEUMOTHORAX	0	0.0%	0	0.0%	0	0.0%	1	0.1%
	RESPIRATORY DISORDER	0	0.0%	0	0.0%	0	0.0%	1	0.1%
SKIN	RASH	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	SKIN CARCINOMA	0	0.0%	1	0.1%	0	0.0%	0	0.0%
SS	DEAFNESS	0	0.0%	0	0.0%	0	0.0%	1	0.1%

UG	ABORTION	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	BREAST CARCINOMA	0	0.0%	1	0.1%	0	0.0%	1	0.1%
	BREAST NEOPLASM	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	KIDNEY FUNCTION ABNORMAL	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	POLYURIA	0	0.0%	1	0.1%	0	0.0%	0	0.0%
	PROSTATIC DISORDER	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	UNINTENDED PREGNANCY	0	0.0%	3	0.2%	0	0.0%	1	0.1%

Table generated by reviewer from dataset SS_AES.XPT

The list of preferred terms/verbatim terms identified as TESAEs in the dataset SS_AES was reviewed, and for terms of particular interest, the narratives and case report forms were examined to determine whether the cases were suggestive of drug relatedness. A brief listing of pertinent cases is shown below. For other cases coded to terms of interest such as seizure, convulsion, diarrhea, and pancreatitis, the events had clear alternate explanations, in many cases, alcohol intake.

Study/Pt#/NDA Pt ID		Term of Interest	Comment
Poldrugo 1 (200001)	64 yo M Acamprosate 1998 mg	Kidney function abnormal	Occurred in setting of hepatorenal syndrome in patient with advanced alcoholic liver disease
Lesch 194 (300194)	46 yo M Acamprosate 1998 mg	Blood dyscrasia/Rash	Pt. hospitalized 10 days after 30 day visit and was LTFU. ~5 months later site learned of hospitalization for "exanthem and hematologic disorder." Neither narrative nor CRF gives additional information
Besson 1026 (501026)	38 yo F Acamprosate 1332 mg	Asthma	Pt with h/o asthma reported having several "asthmatic crises" in first 30 days of tx; also experienced severe pruritis. Reported at next visit (>4 mos later) having been hospitalized for asthma. Medication d/c (@ unknown date)
UKMAS 686 (1100686)	59 yo M Acamprosate 1998 mg	Thirst/polydipsia	Patient experienced polydipsia/polyuria after 3 wks on study med. Hospitalized and diagnosed with diabetes.
Paille 108 (1500108)	33 yo M Placebo	Water intoxication	Intentional ingestion of large quantity of water in context of psychiatric illness requiring hospitalization
Paille 375 (1500375)	42 yo M Placebo	Ventricular tachycardia	Hospitalized for alcohol relapse and onset of Vtach at approximately study day 100. Etiology not determined.

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7.1.2.2   Treatment-Emergent Serious Adverse Events in Non-Group I Studies
The 33 completed Group II Clinical Pharmacology studies involved 522 subjects, all but 51 of whom were normal healthy, predominantly male, volunteers. Because these studies did not specifically identify treatment-emergent serious adverse events (TESAEs), all study reports and available patient information on adverse events (subject narratives, descriptions of concurrent illnesses as reason for withdrawal, and AE listings, as available) were reviewed by Lipha in order to identify TESAEs according to the current FDA definition. Only one TESAE was identified, a grand mal seizure occurring on day 18 of study drug administration in a patient treated with acamprosate 1998 mg/day. Relationship to study drug is uncertain.

The 6 Group III Early Clinical Experience studies involved a combined patient population of 924. A review of all 6 study reports was undertaken by Lipha and events meeting the FDA's criteria for a SAE were identified using subject narratives, descriptions of concurrent illnesses as reasons for withdrawal and adverse event listings, as available. In these studies, serious adverse events (SAEs) were not specifically identified in the study reports and it was also sometimes impossible for Lipha to determine whether an SAE was or was not treatment-emergent (TESAE).

There were no SAEs identified in available materials from four of the six studies. In the Hillemand I study, 3 events in the patient population of 83 (40 acamprosate, 43 placebo) were considered by the medical monitor to fulfill criteria for TESAEs. For the Lhuintre study, 19 events, including 3 deaths, were thought to represent serious adverse events, occurring in the patient population of 569 (279 acamprosate, 290 placebo). Narratives for these patients were submitted, based on information in study reports, but no case report forms are available for these patients. These 22 events included similar terms to those reported in the controlled studies, including hospitalizations for alcoholism treatment and complications of alcoholism (traumatic injuries, cirrhosis, hematemesis). One case of jaundice and fever was reported in a patient treated with acamprosate, occurring approximately two months after the last treatment visit (no other information available). Other terms of potential importance, "cardiopathy" [sic—narrative indicates arrhythmia, present at study entry] and "allergic skin eruption with severe erythema," were reported in placebo-treated subjects.

Tabulations of adverse events (non-serious) for the Clinical Pharmacology studies and Group IV studies include various line listing for "exfoliative dermatitis." Lipha provided additional information upon request about these cases, and none was suggestive of a severe dermatologic event such as Stevens-Johnson syndrome. Typically, cases described peeling/flaking skin and appeared to have been correctly judged non-serious.

The 10 Group IV Phase IV open-label studies included in the NDA submission enrolled 3773 alcohol-dependent patients. Information on other serious adverse events occurring during the conduct of these 10 studies was obtained by Lipha via review of the study reports and statistical addenda and individual case report forms, where available (all studies except MERAM Phase IV), with final judgment made by the medical monitors. For the MERAM Phase IV study, no individual patient information was available except for the mention of 4 deaths occurring during this early study, which involved 860 alcohol-dependent patients. Sufficient information was available for the remaining 9 studies to identify events. The

5/28/04 Safety Update included data on SAEs from four additional Phase IV studies. All were open-label, but one included a "supportive treatment" control arm (no acamprosate). In these four studies, 582 patients were treated with acamprosate and 211 were treated with supportive therapy, without acamprosate. Therefore, the acamprosate-treated population denominator for SAEs in the Group IV studies is 3499. Overall, 345 patients experienced serious adverse events. Listings reveal terms similar to those seen in the Group I-III studies, including primarily traumatic injuries, psychiatric symptoms, and complications of alcoholism. In many cases, little detail is available. In the safety update studies, a substantial number of the events meeting seriousness criteria represented hospitalizations for alcoholism treatment in the context of relapse. Narratives for SAEs in the Group IV studies were reviewed and the following events coded to terms of potential importance, not clearly explained by alcohol consumption or pre-existing alcohol-related comorbidities, were identified:

Study/Pt#		Term of Interest	Comment
ASATIM 58	44 yo M	thrombocytopenia, thrombocytopenic purpura	Noted on study day 2. No BL platelets drawn. Plts 19,000 at study termination, purpura resolved by 1 wk after tx d/c
ASATIM 162	46 yo F	thrombocytopenia	Noted on BL labs, pt transferred to general hospital and d/c from study on day 2, no f/u
ASATIM 304		acute pancreatitis	Study day 8, meds d/c'd, resolved within 72 hrs
INTEGRAL 41/15	46 yo M	acute pancreatitis	Onset after two weeks of treatment. Acamprosate d/c, restarted and d/c'd again by 3rd day of hospitalization, pt d/c'd from study, no f/u.
A.P.D.T. 61	44 yo M	acute pancreatitis	Onset after ~3 wks on study despite abstinence; pt hospitalized; no f/u information
NEAT Portugal 1/35	46 yo M	pancreatitis	Hospitalized for 8 days after 3 weeks of treatment; acamprosate "partially discontinued," resumed approximately 6 weeks after the event. Pt LTFU, no further information.
NEAT UK	29 yo M	pancreatitis	Hospitalized for abdominal pain after ~3.5 months on study; dx pancreatitis; acamprosate continued, event resolved.
NEAT UK	42 yo M	hemiplegia	Transient symptoms lasting approximately 24 hours, onset after approximately 2 weeks of treatment.
INTEGRAL pt 9/7	43 yo M	hemiparesis	Onset after 4 wks of tx, resolved 1 day after study drug d/c'd but did

Study/Pt#		Term of Interest	Comment
			not recur when study drug reintroduced
INTEGRAL 23/12	40 yo F	allergic reaction, angioneurotic edema	hospitalized for 4 days after 3 weeks on study drug for "allergic skin reaction, dyspnea, and wheezing." Rehospitalized 4 weeks later for urticaria ("Quincke's edema"), which resolved after 1 week of treatment. Acamprosate treatment continued throughout. Concomitant meds = propranolol, levothyroxine, tiapride, carbamazepine, lorazepam, promethazine.
INTEGRAL 36/3	35 yo F	angioneurotic edema ("Quincke's edema")	hospitalized for Quincke's edema 1 day after resuming acamprosate, which she had stopped taking for approximately 2 weeks during a relapse (after approximately 10 weeks of treatment). Acamprosate d/c, no f/u available. Concomitant meds = trimipramine, carbamazepine, chlormethiazole, paracetamol
NEAT Austria 9/16	38 yo F	asthma	Patient required hospitalization for asthma twice while on study drug: after approximately 6 wks on study and approximately 6 weeks later.
NEAT Belgium 19/1	38 yo F	asthma	Required three weeks of hospitalization for asthmatic bronchitis after approximately 4 months on study
NEAT Belgium 21/15	60 yo M	bronchitis and dyspnea	Hospitalized for bronchitis after approximately 10 weeks on study
INTEGRAL 73/1	31 yo M	"Signs of hepatitis in blood chemistry"	Pt hospitalized after ~10 wks study drug for diagnostic workup of asymptomatic "signs of hepatitis in his blood chemistry." Hepatitis was not diagnosed; study drug d/c'd.
A.R.E.S. 678	53 yo M	jaundice	Hospitalized after ~2 months on study for jaundice attributed to gallstones. Study medication d/c'd x ~6 weeks during hospitalization.
NEAT Portugal 4/5	27 yo M	decreased prothrombin time	Hospitalized after one month on study for decreased prothrombin time; in context of alcohol relapse

Study/Pt#		Term of Interest	Comment
			and poor compliance with study medication; elevated GGT and transaminases noted. Medication continued and condition improved.
NEAT Switzerland 8/4	40 yo M	Glomerulonephritis	Pt with normal creatinine at BL was rehospitalized for "psychosocial problems" approximately 2.5 months after enrollment. Had discontinued study medication ~one month earlier. Lab tests during hospitalization revealed elevated creatinine (129-162 μmol/L), decreased creatinine clearance (54 ml/min), and proteinuria. Biopsy revealed mesangio-proliferative and sclerosing glomerulonephritis, but nephrologist assessed it as being present for at least 6-12 months prior to diagnosis.
A.R.E.S. 204	38 yo F	Paroxysmal atrial tachycardia	Onset after ~2 months on study, hospitalized x 3 days; reported retrospectively at 3 month visit, medication continued, event resolved.
A.R.E.S. 609	57 yo M	Uncontrollable epistaxis	Hospitalized x 1 month after ~ 2 wks on study for uncontrollable epistaxis; attributed to concomitant med (ticlopidine).

7.1.2.3 Serious Adverse Events from Pharmacovigilance Program

Lipha has had responsibility for pharmacovigilance for acamprosate since 1995 and has post-marketing information from that time forward. Lipha estimates that the sales during this period account for [ ] treatment months," but the number of individual patients exposed is difficult to estimate, as treatment periods vary from several months to several years. In post-marketing pharmacovigilance covering the period January 31, 1995 through February 28, 2003, there have been 482 events reported concerning 294 patients who were presumed to be taking acamprosate. Of these 294 patients with spontaneously reported events, 95 patients were reported to have experienced 194 serious adverse events (40.6% of all events). The remainder were non-serious events. Of the total events reported, the most common were "suicide attempt"/"intentional overdose" (3%), "death" (2%), "drug interaction" (1%), "hepatitis" (1%), "hyponatremia" (1%) and "convulsion" (1%). (In this revised ISS, all overdoses were considered to be "intentional" even if there was no information to support this and all such events were also coded to "suicide attempt"). Five

cases of "allergic reaction" were reported. In several cases, coadministered medications included Atrium, a combination of febarbamate, difebarbamate, and phenobarbital, known to be associated with allergic reactions. One case of fatal Stevens-Johnson syndrome and one case of erythema multiforme were reported. The Stevens-Johnson case was a 49 year-old man who was taking acamprosate 1998 mg/day along with Atrium. No details of the clinical findings were available. The sponsor notes that phenobarbital is associated with bullous eruptions. In the erythema multiforme case, a 40 year-old male developed an erythema multiforme-like dermatitis 48 hours after initiating acamprosate 1332 mg/day and Atrium. No other information is available. Three cases of acute renal failure were reported. In one case, acute renal failure occurred 15 days after an intentional overdose with 15 tablets of acamprosate. Another case, described as poorly documented, describes onset of acute renal insufficiency after one week of acamprosate treatment. In the third case, chronology was not described.

The safety update covering the period March 1, 2003 to January 31, 2004 provides reports of 33 adverse events occurring in 21 patients. Nine of these events (27%) occurring in 6 patients were assessed as serious. One additional case of fatal Stevens Johnson Syndrome/Toxic Epidermal Necrolysis was reported. In this case, a 40 year-old woman treated with acamprosate, omeprazole, prednisolone, spironolactone, folic acid, and potassium for six weeks prior to the event, and paracetamol beginning 4 days before the event, experienced toxic epidermal necrolysis and died of septic shock. The report notes the association of omeprazole and prednisolone with TEN. Other events assessed as serious included blurred vision (present at baseline; reason for seriousness assessment unclear); hepatitis (2 cases); one case of febrile neutropenia and one case of neutropenia/thrombocytopenia/anemia (both possibly attributed to concomitant medications).

7.1.3   Dropouts and Other Significant Adverse Events
7.1.3.1   Overall Profile of Dropouts
In analyzing discontinuations due to adverse events, Dr. Sevka noted, in review of CRFs, instances when adverse events were reported in association with premature discontinuation for a given patient, but the reason given for discontinuation was, "patient decision," or "other." Lipha was asked to re-examine reasons for patient discontinuation throughout the safety database and to re-categorize discontinuations appropriately, giving particular attention to those which might have been more properly attributed to an adverse event. The operational approach to this readjudication is described in the appendix of this review.

In this analysis, withdrawals due to adverse events subsume the following descriptors used on the various CRF's, as well as patients identified as terminating for "other" reasons who, upon medical review by Lipha, were determined to have had an adverse event as the explanation for early discontinuation:

- Abnormal Laboratory Results;
- Adverse Event;
- Adverse Event/Illness;
- Adverse Events;
- Concomitant Illness;
- Concurrent Illness;
- Intercurrent Med/Psych/Surg Event;
- Severe AE.

The sponsor's submission presents information on the incidence of withdrawals due to adverse events in the 13 Group I studies, according to 2 major categories: Controlled Short-Term studies and Controlled Long-Term studies. Treatment arms these studies included 1332 mg/day (in some studies), 1998 mg/day (some studies featuring dose adjustment based on weight), and placebo. The U.S. study included a 2000 mg/day arm, which is pooled with the 1998 mg/day groups from other studies in analysis. Only the U.S. study included a 3000 mg/day arm.

7.1.3.2   Discontinuation Due To Adverse Events In Controlled Short-Term Studies
A total of 2564 alcohol-dependent patients constitute the Safety Population from these 8 studies, with 135 patients assigned to acamprosate 1332 mg/day, 1128 patients to acamprosate 1998/2000 mg/day, 83 patients to acamprosate 3000 mg/day and 1218 patients to placebo. The primary focus of the sponsor's presentation is on comparisons of the 1998/2000 mg/day acamprosate treatment group versus placebo. Data from the acamprosate 3000 mg/day and/or 1332 mg/day groups are considered collectively in the sponsor's tables as part of the so-called "pooled acamprosate group". The pooled acamprosate group consists of all patients from the 3 acamprosate dosage groups (1346 patients).

Overall, 8% of patients treated with acamprosate (either 1998/2000 mg/day group or acamprosate pooled group) discontinued due to adverse events. In the smaller acamprosate treatment groups, these percentages were 7% for the 1332 mg/day group (10 of 135 patients) and 6% for the 3000 mg/day group (5 of 83 patients).

The table below (Lipha's In-Text Table 8.8.8.1.1:1) summarizes the incidence of TEAEs leading to withdrawal by COSTART body system and preferred term for the acamprosate 1998/2000 mg/day, pooled acamprosate and placebo groups. All COSTART preferred term events reported by more than one patient are included.

Withdrawals due to Treatment-Emergent Adverse Events Occurring in More Than One
Patient in Any Treatment Group –Safety Population of Controlled Short-Term Studies[see note]

COSTART Body System/Preferred Term	Statistic	ACAMP 1998/2000 mg/day	ACAMP Pooled	Placebo
Number of patients	N	1128	1346	1218
Number (%) of patients with an adverse event leading to withdrawal	N (%)	91 (8%)	106 (8%)	75 (6%)
Body as a Whole	N (%)	26 (2%)	30 (2%)	28 (2%)
Abdominal pain	N (%)	7 (<1%)	9 (<1%)	15 (1%)
Asthenia	N (%)	0	0	3 (<1%)
Suicide attempt	N (%)	5 (<1%)	6 (<1%)	2 (<1%)
Intentional overdose	N (%)	4 (<1%)	4 (<1%)	2 (<1%)
Allergic reaction	N (%)	0	0	2 (<1%)
Fracture	N (%)	0	0	2 (<1%)
Procedure	N (%)	0	0	2 (<1%)
Headache	N (%)	8 (<1%)	9 (<1%)	1 (<1%)
Pain	N (%)	3 (<1%)	3 (<1%)	0
Cardiovascular System	N (%)	9 (<1%)	9 (<1%)	4 (<1%)
Syncope	N (%)	2 (<1%)	2 (<1%)	1 (<1%)
Digestive System	N (%)	31 (3%)	38 (3%)	22 (2%)
Diarrhea	N (%)	19 (2%)	22 (2%)	8 (<1%)
Nausea	N (%)	10 (<1%)	10 (<1%)	5 (<1%)
Vomiting	N (%)	6 (<1%)	7 (<1%)	5 (<1%)
Gastrointestinal disorder	N (%)	0	0	2 (<1%)
Hematemesis	N (%)	0	0	2 (<1%)
Melena	N (%)	0	0	2 (<1%)
Flatulence	N (%)	2 (<1%)	2 (<1%)	1 (<1%)
Constipation	N (%)	1 (<1%)	2 (<1%)	0
Metabolic and Nutritional Disorders	N (%)	4 (<1%)	5 (<1%)	1 (<1%)
Peripheral edema	N (%)	2 (<1%)	2 (<1%)	1 (<1%)
Nervous System	N (%)	32 (3%)	40 (3%)	30 (2%)
Depression	N (%)	11 (<1%)	13 (<1%)	7 (<1%)
Alcohol consumption/relapse	N (%)	5 (<1%)	5 (<1%)	2 (<1%)
Hypertension	N (%)	2 (<1%)	2 (<1%)	3 (<1%)
Paranoid reaction	N (%)	1 (<1%)	1 (<1%)	2 (<1%)
Paresthesia	N (%)	1 (<1%)	1 (<1%)	2 (<1%)
Dizziness	N (%)	0	0	2 (<1%)
Grand mal convulsion	N (%)	0	0	2 (<1%)
Libido decreased	N (%)	0	0	2 (<1%)
Vertigo	N (%)	0	0	2 (<1%)
Anxiety	N (%)	4 (<1%)	5 (<1%)	1 (<1%)
Suicidal ideation	N (%)	3 (<1%)	3 (<1%)	1 (<1%)
Convulsion	N (%)	2 (<1%)	2 (<1%)	1 (<1%)
Personality disorder	N (%)	2 (<1%)	2 (<1%)	1 (<1%)
Psychosis	N (%)	1 (<1%)	2 (<1%)	1 (<1%)
Somnolence	N (%)	4 (<1%)	4 (<1%)	0
Insomnia	N (%)	0	2 (<1%)	0
Skin and Appendages	N (%)	5 (<1%)	5 (<1%)	4 (<1%)
Rash	N (%)	2 (<1%)	2 (<1%)	3 (<1%)
Pruritus	N (%)	3 (<1%)	3 (<1%)	2 (<1%)
Urogenital System	N (%)	7 (<1%)	8 (<1%)	3 (<1%)
Unintended pregnancy	N (%)	2 (<1%)	2 (<1%)	1 (<1%)
Impotence	N (%)	1 (<1%)	2 (<1%)	0

(Lipha's In-text Table 8.8.8.1.1:1) Data Source: Table 8.8.7.0.0, Volume 17 See Notes, next page

Note: Studies included in this table (and the original NDA volume number of the respective study reports) are:
ADISA (Vol. 93-96), BENELUX (Vol. 90-92), Ladewig (Vol. 97-98), Pelc II (Vol. 76-78), Poldrugo (Vol. 84-85),
Tempesta (Vol. 86-87), UKMAS (Vol. 88-89) and US 96.1 (Vol. 99-198). Study summaries are in original
NDA Vol. 63, Section 8.4.

Note: Data for the acamprosate 1332 mg/day group (N=135) and the acamprosate 3000 mg/day group (N=83) are not included in this in-
text table, but can be found in Table 8.8.7.0.0, Volume 17.

Note: Adverse events included in this table led to study drug discontinuation and were considered either a primary or secondary reason
(US 96.1 only) for discontinuation.

Note: Patients are counted only once within each body system and preferred term.

Note: Adverse events were coded using the COSTART dictionary.

Note: Some patients who withdrew due to adverse events had CRF reasons for discontinuation other than "Adverse Event" (often
"treatment failure" or "patient refusal"), but they are included in this table.

The numbers of patients discontinuing for a particular AE are low across groups. Diarrhea
and nausea stand out as more common in drug-treated than placebo-treated patients and seem
reasonably attributable to acamprosate. Despite low numbers, it is notable that terms such as
suicide, intentional overdose, and depression were also cited more commonly as a reason for
discontinuation among acamprosate-treated than placebo-treated patients.

7.1.3.3   Discontinuation Due To Adverse Events In Controlled Long-Term Studies

The Safety Population for these collective studies consists of 1670 patients (305 in the
acamprosate 1332 mg/day group, 621 in the acamprosate 1998 mg/day group and 744 in the
placebo group). The pooled acamprosate group consists of all patients from the 2
acamprosate dosage groups (926 patients). Consistent with the data from the short-term
studies, 7% of patients in the acamprosate groups (1998 mg/day group or pooled group), 8%
of the patients in the acamprosate 1332 mg/day group, and 7% of the patients in the placebo
group discontinued due to adverse events. Reasons for discontinuation were similar to those
cited in the short-term studies. Again, the numbers of patients discontinuing for a particular
AE are low across groups. Diarrhea was more common in drug-treated than placebo-treated
patients. Suicide was again cited more commonly as a reason for discontinuation among
acamprosate-treated than placebo-treated patients (2 patients in 1998 mg/day group vs. 0 in
placebo group), but depression was not.

7.1.3.4   Discontinuation Due To Adverse Events In Non-Group I Studies

Lipha also presented information on withdrawals due to adverse events in the Group II
Clinical Pharmacology studies, the Group III Early Clinical Experience studies and the
Group IV Phase IV open-label studies. All information concerning these patients comes from
review of study reports and individual patient records, when available. Narrative summaries
and case report forms were not submitted.

According to Lipha's report, among the 522 subjects who were enrolled across the 33 Group
II clinical pharmacology studies, a total of 7 subjects withdrew due to a TEAE during the
treatment phase of the respective study. None of these events were serious. Six of the 7
subjects were on acamprosate at the time of withdrawal, at doses ranging from 800 mg to
3000 mg/day. Three of these subjects had infectious illnesses ("infection", "pharyngitis" and
"fever"); one subject had severe headache (acamprosate 1600 mg/day) and one subject had
severe vomiting (acamprosate 3000 mg/day). One subject had metatarsal pain and edema of
the area, while receiving acamprosate 1998 mg/day + diazepam. The 7th subject was

receiving only diazepam and discontinued for "circulatory disturbances".

Minimal information was available on subject disposition in the Group III, Early Clinical Experience, studies. These studies include **Hillemand I, Hillemand II, Lhuintre, Poinso, Pelc I and Roussaux** and involve 924 patients in total. Withdrawals due to a treatment-emergent adverse event could be determined from information contained in the study reports of only 4 of the 6 Group III studies (Hillemand I, Hillemand II, Lhuintre and Poinso). A total of 693 patients were enrolled in these 4 studies, of whom 42 patients withdrew due to an adverse event or concurrent illness (acamprosate, 22 patients; placebo, 20 patients). For Pelc I, there was no individual patient information available in the study report and no specific information on patient disposition. For Hillemand I and Hillemand II, brief narratives were available for all enrolled patients. By-patient data were available for Lhuintre. For the Roussaux study, only a publication was available and there was no information on patient discontinuation for adverse events. Adverse events associated with premature discontinuation were tabulated by Lipha. In summary, reasons for discontinuation were similar to those seen in the Group I studies and no event was a more common reason for discontinuation among acamprosate-treated than placebo-treated patients.

For the Group IV, Phase 4 open-label studies, 2% of the 3773 patients withdrew prematurely for reasons coded as adverse event or intercurrent illness, according to summaries of patient disposition included in the individual study reports and compiled by Lipha. However, no individual patient information is available to identify specific terms associated with discontinuation due to adverse events.

7.1.3.5   Time Course of Discontinuations Due to Adverse Events

Lipha analyzed the data to determine the time course of discontinuations due to adverse events. Because not all studies captured the necessary information, the analysis of time dependence of dropout associated with adverse events is based on only those Group I studies which consistently captured adverse event start and stop dates. All the information derives from events which were spontaneously reported.

The studies include:

	Acamprosate 1332	Acamprosate 1998/2000	Acamprosate 3000	Acamprosate pooled	Placebo
Controlled Short-Term Studies (3 of 8)					
ADISA	N/A	147	N/A	148	148
UKMAS	N/A	289	N/A	289	292
US 96.1	N/A	258	83	341	260
Total short-term	N/A	694	83	777	700
Controlled Long-Term (3 of 5)					
Barrias	48	102	N/A	150	152
Paille	188	173	N/A	361	177
PRAMA	24	112	N/A	136	136
Total long-term	260	387	N/A	647	465
Total	260	1081	83	1424	1165

For this analysis, Lipha defined the following treatment exposure categories: 0-<4 weeks, 4-<8 weeks, 8-<13 weeks, and ≥13 weeks for the Short-Term studies (planned duration 26 weeks or less), and 0-<4 weeks, 4-<8 weeks, 8-<13 weeks, 13-<26 weeks, 26-<39 weeks, and ≥39 weeks for the Long-Term studies (planned duration 48 weeks to 52 weeks). Events were counted in the time interval during which they had their onset. Patients were counted at most once within each COSTART body system, COSTART adverse event preferred term, and time interval. Patients were counted in the denominator if they were present during the time interval. Events with missing start dates were not included.

Overall, the incidence of premature patient withdrawal because of TEAEs in the Short-Term studies ranged from 3% to 5% during the interval 0-<4 weeks, and, thereafter, was 2% to 4% for the remaining study intervals assessed. For the Long-Term studies, the incidence of TEAEs resulting in patient withdrawal ranged from 2% to 3% during the interval 0-<4 weeks, <1% to 1% during 4-<8 weeks and 8-<13 weeks, <1 to 2% during the interval 13 to <26 weeks, <1 to 1% during the interval 26 to <39 weeks and 0 to <1% during the remainder of the study period (≥39 weeks up to 51 weeks). Lipha summarized the incidence of dropout related to adverse events for selected body systems and for selected COSTART terms in In-Text Tables 8.8.8.2.1:1 and 8.8.8.2.1:2 (ISS page 278-281)

Because the overall incidence of early terminations for treatment-emergent adverse events was low, patterns do not clearly emerge as function of treatment exposure. However, in the Short-Term studies, the more common events leading to treatment discontinuation tended to occur during the first 4 weeks on study and then decreased during the next 4 weeks and stabilized thereafter. This was particularly true for the acamprosate treatment groups. After 8 weeks, there were very few terminations for any events. This pattern was less noticeable for placebo-group patients in the Short-Term studies and both groups in the Long-Term studies,

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possibly because of the low overall incidence of events leading to early termination.

In summary, the data suggest that subjects who drop out due to adverse events do so relatively early in treatment.

7.1.3.6 Events of a Suicidal Nature

During the initial NDA safety review, the reviewers noted a number of events with terms suggestive of suicidality, but were unable to comprehensively retrieve all such events. In the action letter, the Division noted:

> Verbatim terms related to suicide were not coded correctly and consistently. Re-code all such events so that all suicide attempts are identified and all completed suicides are included both as suicide attempt and death. Perform a separate analysis of any suicide, suicidal ideation, or intentional overdose that may have occurred during treatment, and upon withdrawal of the drug.

At FDA request, Lipha reviewed all of the existing safety information to identify events of a suicidal nature, using the process described below:

> A new coding guideline has been developed to ensure that events related to suicide (e.g., suicide attempts, suicidal ideation) have been coded appropriately:
>
> To address concerns regarding descriptions related to suicide attempts or suicidal ideation, all investigator descriptions which include mention of the word "suicide" or a method of suicide (e.g., "hanging", "asphyxiation", "intentional overdose"[2], etc.), have been coded to a preferred term that indicates a suicidal nature.
>
> This method of coding has been used even when the default coding with COSTART dictionary indicates that another preferred term should be used (e.g., the reported term of "suicidal tendency" codes to "depression" in the COSTART dictionary).
>
> All successful suicides have been coded to both "death" and "suicide attempt."

In the 7 Controlled Short-Term studies that collected spontaneously-reported adverse events, there were 19 patients (1.4% of 1317 patients) in the pooled acamprosate group with at least one event of a suicidal nature (including 10 with "suicidal ideation" and 9 coded to "suicide attempt") compared to 6 patients (0.5% of 1186 patients) in the placebo group (2 patients with "suicidal ideation" and 4 patients with events coded to "suicide attempt"). Of the 19 patients in the acamprosate group, 3 were in the acamprosate 1332 mg/day group, 15 were in the acamprosate 1998/2000 mg/day group and 1 was in the acamprosate 3000 mg/day group. In addition, there was one death by suicide in a placebo patient in the Ladewig study. The Ladewig study did not collect spontaneously reported adverse events and is therefore not included in the overall denominator, however, this patient was included by Lipha in the numerator. An additional 12-week placebo-controlled study, A.P.D.T., which was terminated prematurely due to slow enrollment after 25 patients had been randomized to acamprosate and 24 to placebo, was included in the safety update. In this study, one patient (treated with acamprosate) made a suicide attempt. When this study is included, the rate in the short-term studies is 1.5%; the placebo rate remains unchanged at 0.5%.

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[2] When it was not known whether an overdose was intentional, the overdose has been coded as intentional and a suicide attempt.

In the 4 Controlled Long-Term studies which recorded spontaneously reported adverse events, there were 17 patients (2.4% of 702 patients) in the pooled acamprosate group with at least one event of a suicidal nature (including 1 with "suicidal tendency", 3 with "suicidal ideation" and 13 coded to "suicide attempt"), with 2 deaths from suicide. Of these 17 patients, 7 were in the acamprosate 1332 mg/day group and 10 were in the acamprosate 1998/2000 mg/day group. In the placebo group, there were 4 patients (0.8% of 520 patients) with at least one event of a suicidal nature (including 3 with "intentional overdose" and 4 coded to "suicide attempt"), with 1 death from suicide. There was an additional death of an acamprosate-treated patient (by overdose on antidepressant medication) reported in the remaining Long-Term study (**Lesch**).

Notably, the higher rate of events of a suicidal nature is not driven by one study. Events of a suicidal nature occurred in 9 of the 14 controlled studies (13 Group I studies and the additional study submitted in the safety update). The rate of suicidal events was higher in acamprosate-treated patients than in placebo-treated patients in all studies except Pelc-II. In four studies, all suicidal events reported were in acamprosate-treated patients. In the Barrias and Besson studies, there were no suicidal events in the placebo group, while 1-2 events were reported in the acamprosate group(s), giving the studies a rate of events of a suicidal nature of roughly 2% (Barrias, 1.96%; Besson, 2.27%) vs. 0% in the placebo group. In the ADPT study, two suicide attempts were reported by one of the 25 patients randomized to acamprosate, while no events of a suicidal nature were reported in the 24 patients randomized to placebo (4% vs 0%).

The table below illustrates the number of events of a suicidal nature and the proportion of randomized patients reporting such events, by study. In the last column, a ratio of the pooled acamprosate rate to the placebo rate is calculated (where possible; i.e. where the placebo rate was not zero).

	Acamprosate Pooled			Placebo			Ratio
	n	N	%	n	N	%	
Barrias	2	150	1.33%	0	152	0.00%	#DIV/0!
Besson	1	55	1.82%	0	55	0.00%	#DIV/0!
Ladewig	0	29	0.00%	1	32	3.13%	0
Lesch	1	224	0.45%	0	224	0.00%	#DIV/0!
PRAMA	4	136	2.94%	1	136	0.74%	4.0
Paille	10	361	2.77%	3	177	1.69%	1.6
Pelc II	3	126	2.38%	2	62	3.23%	0.7
UKMAS	10	289	3.46%	3	292	1.03%	3.4
US 96.1	5	341	1.47%	1	260	0.38%	3.8

In the Lesch and Ladewig studies, where spontaneous adverse events were not captured and therefore terms such as "suicidal ideation" or attempts at suicide deemed non-serious were not likely to be recorded, one completed suicide occurred in each study and was reported as a death. In the Lesch study, the patient was acamprosate-treated, while in the Ladewig study,

the patient was placebo treated.

To further explore the apparent drug-relatedness of these suicidal events, the database was examined to identify any patients who experienced treatment emergent depression meeting criteria for seriousness and reported as TESAEs (typically because hospitalization was required). If the placebo group had an over-representation of such patients, this might balance out the presence of fewer patients with frank suicidality. Depression reported as a TESAE occurred in 25 patients treated with acamprosate and 15 treated with placebo. Counting only once those patients in which both "depression" and "suicide" were reported, twelve patients in each treatment arm (acamprosate pooled vs placebo) had *only* a TESAE of depression and no report of suicidality. The majority of these subjects were in a single study, Paille, in which 6 acamprosate-treated and 10 placebo-treated patients had an SAE of depression but did not have an AE of a suicidal nature. Therefore, taking together both events of a suicidal nature and AEs of depression meeting criteria for seriousness, the apparent association with acamprosate is maintained. Notably, in the only study in which suicidality was more common in acamprosate-treated than placebo-treated patients, Pelc-II, the addition of these patients who experienced serious depression renders the rates of concerning affective events identical in both groups (5%). However, in the Paille study, when these patients are considered, the rate is higher in the placebo group than in the acamprosate group (4% vs 7%).

As shown in the table below, taking together serious and non-serious events of a suicidal nature, and events coded as "depression" which met criteria for seriousness, 2.4% of the 2019 acamprosate-treated patients and 1.3% of the 1706 placebo-treated patients for whom this information was available had very concerning affective symptoms emerge during treatment.

Table 7.1.3.6 Affective Symptoms of Concern

	Acamprosate		Placebo	
Long-term Studies	N = 702		N = 520	
	N	%	N	%
Suicide + Suicidal Ideation	17	2.4%	4	0.8%
Suicidal Events + Serious Depression	25	3.5	17	2.6%
Short-term Studies	N = 1317		N = 1186	
	N	%	N	%
Suicide + Suicidal Ideation	19	1.4%	6	0.5%
Suicidal Events + Serious Depression	23	1.7%	8	0.7%
Overall	N = 2019		N = 1706	
	N	%	N	%
Suicide + Suicidal Ideation	36	1.8%	10	0.6%
Suicidal Events + Serious Depression	48	2.4%	22	1.3%

Lipha examined the prevalence of pre-existing suicidal ideation among the subjects reporting events of a suicidal nature, and found that roughly half the subjects, across treatments, had a prior history of suicidal thinking (in those studies where this information was collected).

However, because suicidal ideation is common in the population under study, this is not surprising and offers no particular insight into the role of study drug in treatment-emergent suicidal events.

Lipha examined time-dependency in those studies (noted above in section 7.1.3.5) in which start and stop dates for adverse events were captured. Patterns of incidence rates cannot be discerned because of the low number of events, but overall, events appear to be distributed across the range of treatment intervals.

There were no events of a suicidal nature in the Group II Clinical Pharmacology studies.

In the 6 Group III Early Clinical Experience studies, there were 3 cases (2 in placebo-treated patients and 1 in acamprosate-treated patient) among 922 patients treated for periods of 3-6 months with acamprosate, 1332 mg/day or placebo.

In the 14 Group IV Phase IV Open-Label studies (NDA submission + Safety Update submission), which involved 4355 alcohol-dependent patients, treated primarily with acamprosate 1998 mg/day (>60 kg) or 1332 mg/day (<60 kg) for 6 months, and 211 patients treated with supportive therapy, there were 40 acamprosate-treated patients (0.9%) who had 45 adverse events of a suicidal nature.

Only one study had a comparator arm. In this study, ARES, 422 recently-detoxified patients were randomized to treatment with usual supportive therapy with or without open-label acamprosate. In this study, both arms had a very high rate of events of a suicidal nature, with 6 of 211 acamprosate-treated patients (2.8%) and 7 of 211 supportive therapy-treated patients (3.3%) reporting adverse events of a suicidal nature.

In the pharmacovigilance database, 15 of the 515 reported events (3%) were coded as being of a suicidal or possibly suicidal nature. Three of the suicidal events were fatal.

Review of narratives for the cases throughout the database reveals that the events, typically, are correctly coded as being suicidal in nature. The prevalence of "depression" further emphasizes the predisposition of this population to depression and suicide.

Lipha concluded that the low rates of events of a suicidal nature in the controlled trials and in pharmacovigilance argued against a role of acamprosate in promoting suicide. Although the absolute rates of suicide were low in the Group I studies, the rates were consistently higher in acamprosate-treated than in placebo-treated patients in both short-term and long-term studies, with the acamprosate-treated group experiencing three times the rate of events of a suicidal nature compared to the placebo group. However, there were comparable rates of suicidal events in the ADES study in the acamprosate and control groups. Nevertheless, it is difficult to rule out an association between acamprosate and suicidal ideation and/or behavior. This possibility should be clearly described in labeling, and physicians should be instructed to monitor patients for the emergence of suicidal thinking.

7.1.4   Other Adverse Events of Interest

Because of animal findings of renal effects, increased water consumption, and increased

body weight, the safety dataset was queried to identify any adverse events related to these findings. Search terms included *renal, kidney, thirst, polydipsia, hyponatremia, weight gain.* No drug-related events suggestive of renal effects were noted. One event coded to polydipsia occurred in the setting of newly-diagnosed diabetes. Weight gain was observed more frequently in acamprosate-treated than in placebo-treated patients (see discussion under vital signs).

The normalized lab data was also examined to determine the number of subjects experiencing post-baseline low sodium values. Because the data was normalized to the ULN, a cutoff of 80% of the ULN was chosen to represent the LLN. Patients who showed a decline from baseline in serum sodium, and had post-baseline values below 80% of the ULN, were evenly distributed across treatment groups, at approximately 6-7% of patients for whom change from baseline values were available.

7.1.5   Common Adverse Events

7.1.5.1   Approach to Eliciting Adverse Events in the Development Program

During the initial IND review, materials submitted by Lipha identified studies which had collected adverse events using a checklist, and others which collected spontaneously-reported adverse events. Based on this categorization, the original safety reviewers raised the concern that only the studies which captured spontaneously-reported adverse events had been able to appropriately characterize the adverse event profile of acamprosate, and that when these studies were considered alone, the size of the safety database was no longer considered adequate. Lipha, in this resubmission, has clarified the procedures used for capture of adverse events in the studies included in the primary safety database. Their explanation is shown below:

In the Group I studies, adverse events were collected in the following manner:

- Five studies (Short-Term studies ADISA, UKMAS, US 96.1 and Long-Term studies Paille and PRAMA) collected information on adverse events (AEs) exclusively by spontaneous report. These studies involved 2287 patients (1274 randomly assigned to acamprosate and 1013 randomly assigned to placebo).

- For the remaining 8 studies,[3] a pre-specified worksheet was used as a convenience to investigators and consisted of events known to be associated either with alcohol withdrawal (e.g., waking in middle of night, difficulty concentrating) or with acamprosate use, based on the Group III early clinical experience studies (e.g., diarrhea). However, it also included fields for capturing other events, which were to be specified. These 8 studies can be broken down into 2 subgroups, as follows:

  - Six of the 8 studies (Short-Term studies BENELUX, Pelc II, Poldrugo and Tempesta and Long-Term studies Barrias and Besson) instructed investigators to solicit spontaneously reported adverse events first. Such events either corresponded to an item on the worksheet or were recorded (and specified) under the "other" category. After recording the spontaneous AEs on the case report form (CRF), investigators were then instructed to review events on the pre-specified worksheet with the patient. In all 6 studies, the CRF had a separate column for indicating which events were reported spontaneously and another column for events that were subsequently elicited by review of the worksheet. These 6 studies involved 1438 patients (745 assigned to acamprosate and 693 assigned to placebo), in effect, captured both spontaneous and worksheet events.

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[3] These were referred to in the original NDA ISS as "checklist studies".

Events reported in the "spontaneous" column in these studies are included in tabular displays identified as "...Spontaneously Reported Adverse Events". Events acknowledged during the subsequent review of the worksheet are reported separately in tables identified as "...Worksheet Review Reported Treatment Emergent Adverse Events".

− Two of the 8 studies (Short-Term study Ladewig and Long-Term study Lesch) did not require reporting of spontaneous events prior to review of the worksheet, although they also allowed for additional events to be specified by a field for "other problems", which could then be specified. These 2 studies involved 509 patients (253 assigned to acamprosate and 256 assigned to placebo).

Events from these studies are presented only in tables identified as "...Worksheet Review Reported Treatment Emergent Adverse Events".

− Information regarding adverse event severity was available for all 8 studies, utilizing various numerical scores. For purposes of summarization in the revised ISS, the data translation of these numerical scores is as follows:
  - "Mild" = Score of either 0^4 or 1;
  - "Moderate" = Score of 2;
  - "Severe" = Score of either 3 or 4.
− Information regarding relationship to study medication was available for all 8 studies. For purposes of summarization in the revised ISS, the data translation is as follows:
  - "Not related" = "not correlated";
  - "Related" = "possible", "probable", and "certain".

The revised ISS database reflects the above changes.

In summary, 11 of the 13 Group I studies, involving 3725 patients (2019 assigned to acamprosate and 1706 assigned to placebo), did capture spontaneously reported adverse events first, without the prompting of the investigator. In tabular displays of spontaneously reported adverse event data, the Short-Term study tables, therefore, include all Short-Term except for Ladewig. The Long-Term study tables include all Long-Term studies in this sub-group except for Lesch.

In addition, for the 8 studies using adverse event worksheets, all text descriptions captured under the adverse event category of "other" or "other problems" have been coded, as appropriate, and have been included in all tables presenting data from these studies[5].

7.1.5.2   Appropriateness of Adverse Event Categorization and Preferred Terms

Audit of the safety datasets by the original safety reviewer, Dr. Michael Sevka, identified many inconsistencies and errors in the adverse event coding. Accordingly, in response to FDA request, "All adverse events, including post-marketing events reported to the French Pharmacovigilance system, have been re-coded at one time using COSTART body systems and preferred terms. A standard abbreviation for body systems has been applied to all events."

A thesaurus of preferred terms and the verbatim terms subsumed thereunder was provided with the resubmission. Per Lipha, prior to analysis using the re-coded terms, a thesaurus containing COSTART body system, preferred term, and investigator description of all events was reviewed by at least one medically knowledgeable individual. At Agency request, certain non-COSTART terms were used to subsume events that were not adequately captured by the standard COSTART coding. The most salient example is the use of the preferred term "alcohol consumption/relapse," which does not exist in the COSTART coding system.

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[4] Except when "0" means "not present" (Ladewig and Lesch studies) or "absent" (Barrias and Besson studies).

[5] In the original NDA and ISS, these "other" events were in the database as "reaction unevaluable".

The thesaurus was reviewed and showed that the coding was, overall, appropriate. Some similar verbatim terms were arbitrarily coded to different preferred terms (e.g. nervousness vs. anxiety), while some verbatim descriptions were coded to preferred terms which, while accurate, did not capture the significance of the event (e.g. "car accident (broken arm)" coded to "motor vehicle accident" and to "fracture," but not to "accidental injury"). In these circumstances, like terms were combined and are noted in the table below. The term "hypertension" was subsumed under the body system "NER." This is permissible under COSTART but seems inappropriate; these events were reclassified to the cardiovascular system. In addition, it appears that, for the U.S. study at least, elevations in SGOT and SGPT were coded to "SGOT increased" or "SGPT increased," while elevations in GGT were coded to "liver function tests abnormal." In the majority of cases, these events co-occurred and gave the impression of a higher rate of laboratory abnormality than actually existed. In the tables below, separate listings for SGOT and SGPT were deleted as the patients are also represented in the "liver function tests abnormal" rate.

7.1.5.3   Selection of Adverse Event Tables for Characterizing the Adverse Event Profile

Various groupings were used for adverse event presentation by Lipha. Adverse event tables were prepared summarizing spontaneously reported adverse events in controlled trials, separated by short-term vs. long-term, and checklist-elicited adverse events (again separated by trial duration). Tables summarizing the safety experience of non-Group I studies were also prepared.

In selecting the appropriate tables for characterizing the adverse event profile, I considered the intensity of monitoring among the trials. The long term trials and some of the short-term trials included very widely-spaced inter-visit intervals, some as long as 90 days apart. Some of the short-term trials featured closer monitoring, with the most intense monitoring included in the US 96.1 trial and the Pelc-II trial. The table below illustrates the variability across studies with respect to the frequency of on-treatment visits for safety assessment.

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Study name	Duration	Number & Timing of On-treatment Visits
Short-term		
Pelc-II	90 days	7: 8, 15, 30, 45, 60, 75, 90
US 96.1	24 weeks	8: 7, 14, 28, 56, 84, 112, 140, 168
UKMAS	24 weeks	7: 14, 21, 35, 60, 90, 120, 150, 175
ADISA	6 months	6: 8, 30, 60, 90, 135, 180
Tempesta	6 months	6: 30, 60, 90, 120, 150, 180
Benelux	6 months	5: 30, 60, 90, 135, 180
Ladewig	6 months	3: 30, 90, 180
Poldrugo	6 months	3: 30, 90, 180
Long-term		
Paille	360 days	9: 30, 60, 90, 120, 150, 180, 240, 300, 360
PRAMA	48 weeks	6: 28, 56, 84, 168, 252, 336
Lesch	360 days	5: 30, 90, 180, 270, 360
Barrias	360 days	5: 30, 90, 180, 270, 360
Besson	360 days	5: 30, 90, 180, 270, 360

(table constructed by reviewer from study descriptions)

Because of the intensity of monitoring, the greater data quality assurance, and the relevance of the population, the safety profile of acamprosate described in the US 96.1 study is likely to be the most representative and applicable to the target population. Furthermore, only the US 96.1 study included a 3000 mg/day treatment arm. In the discussion below, the overall data are compared to the results of the US trial to confirm that the adverse event experience in study US 96.1 is representative, and appropriate for inclusion in labeling.

Lipha's tables display incidence of adverse events in the acamprosate 1998/2000 mg/day group, the placebo group, and the "pooled acamprosate" group (comprised of the acamprosate 1998/2000 mg/day group combined with the 1332 mg/day group, and, for the short-term studies, the 83 subjects treated with acamprosate 3000 mg/day in study US 96.1. These data tables preclude evaluation of dose-response in the integrated dataset. Lipha has noted that the 3000 mg/day group had a higher overall rate of all adverse events and cautions that the small sample size mitigates against interpretation of this finding as evidence of dose response; alternatively, it might be an epiphenomenon of the closer monitoring in the only study in which the 3000 mg/day dose was used. Therefore, I have chosen to evaluate the common adverse events in the US study separately, and compare the overall profile to the data from the non-US studies.

In the US study, the most common adverse events were gastrointestinal. Diarrhea was reported by 18% of the placebo group, 33% of the 2000 mg/day group, and 40% of the 3000 mg/day group, showing dose dependency. Although other events were more common in subjects treated with active drug compared to subjects treated with placebo, dose dependency was not evident for other AEs. Other events occuring more commonly among acamprosate-treated subjects were flatulence, and, for the 3000 mg/day group only, insomnia, accidental injury, and hyperglycemia. Most adverse events occurred at similar rates in treatment and placebo groups.

The table below shows adverse events occurring in at least 3% of either active treatment group, at a rate greater than that seen in the placebo group.

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