

Table 5.5.3.1 Cumulative Abstinence Duration – PRAMA

	Acamprosate N = 136	Placebo N = 136
Mean Cumulative Abstinence Duration (CAD), days	224 (range 15-360)	162 (range 7- 364)
Mean±SE Corrected Cumulative Abstinence Duration (CCAD) (% days abstinent) ¹	62%±3 (range 4-100)	45%±3 (range 2-100)

¹CAD divided by 360

From In-text Table 8.7.2.7.1.1 and datasets PR_EFFPT + PR_POP

The time-to-relapse analysis (Kaplan-Meier) performed by the sponsor also yielded a statistically significant result. Results are shown in the table below.

Kaplan-Meier Estimates of Time to First Drink (in Days) During Treatment Phase (Discontinuations Treated as Failures) –PRAMA

Time to First Drink (days)	Acamprosate N = 136	Placebo N = 136	P-value (log-rank test)
25 th Percentile	25.0	15.5	<0.001
50 th Percentile	134.5	45.0	
75 th Percentile	NA	170.0	

From Sponsor's In-Text Table 8.7.2.7.2.1

5.5.3.2 Reviewer's Analysis

The sponsor's analysis clearly goes beyond the level of precision of the data. The distribution of CAD in the dataset shows the clear digit preferences resulting from arbitrarily assigning periods of time to drinking or abstinence. In an attempt to identify an analysis that does not go beyond the actual information available, I conducted two different explorations of the data. I evaluated the numbers of patients in each treatment arm who were assessed as abstinent at each of the on-treatment visits (data for the follow-up visits does not appear to have been provided), and I did a responder analysis comparing the numbers of subjects who were assessed as abstinent for the entire study. Note that the first analysis resembles CAD, in that it acknowledges that periods of abstinence are clinically significant even if they are interrupted by periods of drinking. The second analysis is the most conservative, and may represent a higher standard of success than is clinically appropriate.

5.5.3.2.1 Non-Continuous Abstinence

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

5.5.3.2.1.1 Abstinance defined as visit where drinking behavior was coded as abstinent

The table below illustrates the distribution of “abstinent visits” across treatment groups. For this analysis, the dataset PR_EFFVS was combined with PR_POP (to obtain treatment assignments). Visits coded as “abstinent” under the column STDCANEW. This column contained a categorical description of the drinking level.

Table 5.5.3.2.1.1 Number of Visits at Which Subjects’ Drinking Level was Assessed as Abstinent--PRAMA

# abstinent visits	Acamprosate N = 136		Placebo N = 136	
	N	%	N	%
0	26	19%	37	27%
1	13	10%	26	19%
2	13	10%	16	12%
3	16	12%	13	10%
4	10	7%	11	8%
5	18	13%	16	12%
6	40	29%	17	13%

Table prepared by reviewer from datasets PR_EFFVS+PR_POP

A t-test of this data shows that they are different at a level of $p < .0003$. The finding is driven primarily by the continuously abstinent subjects (6 abstinent visits), consistent with the higher rate of dropout in the placebo group, making fewer subjects actually available for 6 visits at which drinking was assessed. However, some reassurance is derived from the observation that the difference between treatments is also apparent at the other end of the success spectrum. In the placebo group, 63 subjects (46%) had zero or one visit at which they were assessed as abstinent, as compared to 39 (29%) in the acamprosate group.

5.5.3.2.1.2 Abstinance defined as a visit where physician’s assesment was coded as “abstinance, supported”

A second analysis using this approach defined an “abstinent visit” as one at which the physician’s assessment (a multiple-choice field on the CRF) was coded as “abstinance, supported.” This indicated that the physician believed that the subject was abstinent and that all available evidence (intended to include self/family report and lab values) supported this. The distribution of visits coded as abstinent by this definition is shown below.

**APPEARS THIS WAY
ON ORIGINAL**

Table 5.5.3.2.1.2 Number of Visits at Which Subjects were Assessed as Abstinent--PRAMA

# abstinent visits	Acamprosate N = 136		Placebo N = 136	
	N	%	N	%
0	29	21%	42	31%
1	14	10%	31	23%
2	13	10%	13	10%
3	20	15%	15	11%
4	11	8%	10	7%
5	18	13%	14	10%
6	31	23%	11	8%

Table prepared by reviewer from datasets PR_EFFVS+PR_POP

A t-test shows these to be different at a p value of <0.001. Again, the difference at the higher end of the success spectrum (6 visits) may be partially explained by differential rates of dropout, but the effect is also seen at the opposite end. In the placebo group, 53% of subjects had either zero or only one visit at which they were assessed as abstinent, vs. 31% in the acamprosate group.

5.5.3.2.2 Responder analysis: Continuous abstinence

The rates of complete abstinence during the treatment period across the treatment groups are shown in the table below. For this analysis, PR_EFFPT was combined with PR_POP (to obtain treatment assignments). Subjects were coded as relapsing (yes/no); "yes," if they returned to drinking before leaving or completing the study, and "no" if the subject either completed the study without drinking or discontinued prematurely without drinking. In a second analysis, subjects were coded as relapsed if they discontinued early.

Table 5.5.3.2.2 Continuous Abstinence Throughout Treatment--PRAMA

	Acamprosate N = 136	Placebo N = 136	
Censored analysis (only relapse prior to dropout = relapse)			
Subjects with no relapse	70 (51%)	54 (40%)	P=.051
Uncensored analysis (dropout = relapse)			
Subjects with no relapse	39 (29%)	16 (12%)	P=.0004

The uncensored analysis supports the efficacy of acamprosate strongly, while the censored analysis yields a marginal result. Because it is generally accepted that subjects who drop out prematurely from an addiction treatment trial are more likely to have relapsed than to have continued relapse-free, it is likely that some (although not all) of the dropouts in whom relapse was not observed prior to dropout would have been coded as relapsing had data been available, thus strengthening the finding.

5.5.3.2.2.1 Analysis by Gender

The table below shows the number and percent of subjects coded as non-relapsing in the uncensored analysis. Because of the small number of female participants, firm conclusions cannot be drawn, but acamprosate appears to be effective in both men and women in this study.

	Total			Acamprosate			Placebo		
	N	N abstinent	% abstinent	N	N abstinent	% abstinent	N	N abstinent	% abstinent
Female	61	16	26%	34	14	41%	27	2	7%
Male	211	39	18%	102	25	25%	109	14	13%

5.5.3.2.2.2 Analysis by Center

By-center rates of continuous abstinence ranged from 0-50%. Rates of continuous abstinence across groups by center are shown in the table below. The table lists the number of subjects at each center coded as non-relapsing in the uncensored analysis, and the % of enrollees represented by this number.

Center #	Total			Acamprosate			Placebo		
	N	N abstinent	% abstinent	N	N abstinent	% abstinent	N	N abstinent	% abstinent
1	19	3	16%	9	2	22%	10	1	10%
2	18	5	28%	9	4	44%	9	1	11%
3	9	3	33%	4	2	50%	5	1	20%
4	39	8	21%	20	7	35%	19	1	5%
5	10	0	0%	6	0	0%	4	0	0%
6	64	17	27%	31	9	29%	33	8	24%
7	7	0	0%	3	0	0%	4	0	0%
8	13	0	0%	8	0	0%	5	0	0%
10	14	2	14%	6	1	17%	8	1	13%
11	30	8	27%	16	6	38%	14	2	14%
12	25	4	16%	12	3	25%	13	1	8%
13	24	5	21%	12	5	42%	12	0	0%

5.5.3.3 Conclusions Regarding Efficacy Data in Study

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

Although the sponsor's analysis of CAD and CCAD are questionable, because the reconstruction of days drinking vs. abstinent relies on more detail than was collected, the overall conclusion is supported. Both an analysis of continuous abstinence and an analysis of the pattern of visits at which the investigator assessed the subject to be abstinent support the sponsor's conclusions. Concerns about the validity of the data include the likelihood that both subject and investigator (who apparently also served as therapist) would be biased in reporting and assessment. This would be expected to occur evenly across treatment assignment, however, unless unmasking occurred. The safety results (per submitted datasets) show virtually identical rates for individual adverse event terms, including diarrhea (occurring in only 9% of either treatment group). This

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

argues against unmasking due to adverse events. However, as noted by Dr. Wang in her statistical review, the differential rate of dropout in this study does cast doubt on analyses relying on the imputation of "worst case" outcome for treatment dropouts. This method would be expected to produce results in favor of acamprosate based on missing data alone.

**APPEARS THIS WAY
ON ORIGINAL**

5.6 Protocol # ACAMP/US/96.1 (“US 96.1” or “US study”) Acamprosate in Patients with Alcohol Dependence: A Double-Blind, Placebo-Controlled Safety and Efficacy Study at Two Active Dose Levels

Conducted 5/97-1/99

5.6.1 Protocol

5.6.1.1 Objective/Rationale

The objectives of the study were to:

1. Confirm the efficacy and safety of acamprosate in U.S. alcohol-dependent patients, at a dose of 500 mg ii.p.o. b.i.d in association with “standardized, but minimal psychosocial support guided by a protocol-specific manual”
2. Explore the efficacy and safety of acamprosate 3000 mg/day
3. Explore the efficacy and safety of acamprosate when initiated between 2 and 10 days of alcohol withdrawal

5.6.1.2 Overall Design

The study was designed as a 6 month treatment (plus two month follow-up), randomized, double-blind, placebo-controlled, parallel-group, outpatient, multicenter study. Subjects were to be enrolled within 2-10 days of stopping hazardous drinking or completing medicated detox. Acamprosate therapy was to be used in conjunction with standardized “medication management” supportive psychotherapy at each visit. All of the investigators were either psychiatrists, psychologists, or internists and all were alcohol disorder specialists. The study locations were predominantly specialized departments or clinics in or associated with University hospitals.

5.6.1.3 Population and Procedures

5.6.1.3.1 Inclusion/Exclusion Criteria

The planned sample size was 460 subjects to be enrolled at 18 centers. To be eligible, subjects were required to meet the following inclusion criteria

- Alcohol dependence according to the DSM-IV criteria of the American Psychiatric Association (at least three features present in past year including tolerance and withdrawal)
- Age ≥ 18
- Randomized at 48 – 120 hours since last hazardous drinking or since completion of medicated detox (hazardous drinking defined as > 2 drinks/day for women and > 3 drinks/day for men)
- Expresses a desire to cut down or stop drinking
- Hepatic enzymes $< 3 \times \text{ULN}$ and Bili $< 1.5 \times \text{ULN}$
- “Acceptable health” in judgment of investigator and sponsor, on the basis of H&P, interview, ECG, UA, and labs
- MMSE > 22
- Available collateral informant

Subjects were to be excluded for:

- Clinically significant and symptomatic medical disorders requiring active intervention (Examples included poorly controlled diabetes, symptomatic cardiac disease, ascites, encephalopathy, portal hypertension)
- Renal insufficiency or primary renal disease
- Hepatic failure, liver transplant
- Axis I disorder requiring pharmacotherapy
- DSM-IV dependence on substances other than alcohol or nicotine
- + urine test for drugs of abuse
- Inadequate contraception
- Major GI surgery within 2 months
- Legally compelled treatment
- Active malignancy
- Investigational drug in past month
- Treatment in past month with drugs that may influence drinking outcomes (e.g. antidepressants, ReVia, disulfiram)
- Lack of fixed address or means of being contacted
- > 5 days abstinence between completion of alcohol withdrawal and randomization

Amendment #1 (6/19/97) permitted the enrollment of patients with urine drug screens positive for cannabis at screening.

Amendment #2 (7/8/97) allowed up to 10 days between last hazardous drinking or completion of detox and randomization.

5.6.1.3.2 Procedures

Eligible subjects at screening were to return for a baseline/randomization (Day 0) visit. Randomization numbers were to be assigned at Day 0. The assignment of randomization numbers proceeded in ascending order for subjects who had not undergone medical detoxification and ascending order for those who had, for the purposes of "passive stratification" by this variable. The planned sample size for each group was:

168 placebo

168 acamprosate 2000 mg/day

64 acamprosate 3000 mg/day ("exploratory" dose)

Randomization numbers (28 per site) were prepared for each site. Subjects were locally randomized in blocks of 7 with a 3:1:3 ratio. Medication assignments were:

- Placebo group: 3 placebo tablets b.i.d. ("upon arising" and "in the evening")
- Acamprosate 2000 mg group: 2 acamprosate 500 mg tablets and one placebo tablet b.i.d.
- Acamprosate 3000 mg group: 3 acamprosate 500 mg tablets b.i.d.

Treatment began at the screening visit with a single-blind placebo run-in. Subjects were to return for the baseline visit at least 48 hours after the screening visit, but no more than 5 days from the last alcohol intake or from completion of medicated detox. After completion of the

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

Screening Visit, the study consisted of 11 visits: a Baseline visit (Visit 0), 8 visits (Visits 1-8) during the Treatment Phase (at Weeks 1, 2, 4, 8, 12, 16, and 20) and 2 visits during the Follow-up Phase (at Weeks 25 and 32). Visits were to include "standardized medication management and minimal supportive therapy, with an abstinence orientation and a psychoeducational approach." The protocol called for weekly telephone calls by study personnel to supplement scheduled visits. Telephone calls were to obtain drinking data, reinforce medication compliance, and to provide support.

Subjects were to be given diaries to record alcohol consumption, medication intake, and any other comments. These were to be brought to study visit for use during the Timeline Follow Back interview to reconstruct drinking data.

Collateral informants were also to be interviewed at intervals. Where discrepancies between self- and other-report of drinking existed, the protocol called for accepting the most negative report.

An extensive algorithm for locating and determining drinking status of subjects who missed visits was included in the protocol.

Drinking was to be evaluated through Timeline Followback Interview, assisted by subject diaries, and confirmed with breathalyzer. The therapist's manual indicates that the TLFB interview was "ideally" to be conducted by the therapist, although the protocol calls only for "qualified personnel." Safety was to be evaluated by collection of spontaneously reported adverse events and periodic laboratory evaluations, vital signs, and ECGs.

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

**APPEARS THIS WAY
ON ORIGINAL**

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

Table 5.6.1.3.2: Time-and-Events Schedule, US 96.1

• PATIENT STUDY VISIT FLOW CHART •

Assessment/Event	Visit	Screening and Single Blind Placebo Phase		Acamprosate/Placebo Treatment Phase							Follow-up Phase		
		Baseline	Baseline	1	2	3	4	5	6	7	8	9	10
		Week	-0.5	1	2	4	8	12	18	20	24	25	32
Informed Consent	X												
Medical, Psych., Alcohol, & Family History	X												
Complete Physical Exam (C) or PRN Physical Checkup (✓), ECG (E)	✓, E		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Employ. & Treatment Service Utilization	X							X					X
Alcohol Dependence Scale, CINA-AD, Mini-Mental State Examination	X												
DSM-IV for Alcohol Dependence	X												X
Struct. Interview Guide for HAM-A & D, Global Assessment of Functioning	X							X					X
Treatment Goals Rating													
Timeline Follow Back, Craving Scale			X	X	X	X	X	X	X	X		X	X
Concomitant Psychosocial Therapy	X		X	X	X	X	X	X	X	X		X	X
Clinical Global Impression			X	X	X	X	X	X	X	X		X	X
Papierstein Test of Nicotine Dependence								X					X
Readiness to Change													
DRIC-2R, SF-12 Health Survey								X					X
Urinalysis; Serum Folic Acid/Vit B ₁₂	X												
Breath Alcohol Concentration (BAC)	X		X	X	X	X	X	X	X	X		X	X
Blood Chemistry ¹ , CBC (with diff) & Urine Drug Screen	X				X	X	X	X	X	X			
Acamprosate Plasma Levels ²			X										
Pregnancy Test ³	X												
Tolerance/Adverse Events			X	X	X	X	X	X	X	X		X	X
Concomitant Medication Review	X		X	X	X	X	X	X	X	X		X	X
Dispense/Collect Drinking Diary	X		X	X	X	X	X	X	X	X		X	X
Dispense Placebo (Single Blind)	X												
Dispense Acamprosate/Placebo			X	X	X	X	X	X	X	X			
Tablet Count/Compliance Review			X	X	X	X	X	X	X	X			
Provide Manual-Guided Therapy	X		X	X	X	X	X	X	X	X		X	X

¹ - Chemistry Panel, to include: Glucose, LDH, Gamma-GT, SGOT, SGPT, alkaline phosphatase, bilirubin, uric acid, serum creatinine, BUN, electrolytes (sodium, potassium, chloride, bicarbonate (measured as CO₂ content)) calcium, inorganic phosphorus, total protein and albumin.

² - Plasma acamprosate levels will also be obtained in the event of a serious adverse event, for retrospective analysis.

³ - Females of child-bearing potential only; to be repeated at any visit where a missed menstrual period is reported.

5.6.1.4 Evaluations/Endpoints

The protocol-specified primary efficacy parameters were:

- Time to first day of any drinking
- Time to first day of heavy drinking (≥ 6 drinks/day for men; ≥ 4 drinks/day for women)
- Cumulative abstinence duration
- Corrected cumulative abstinence duration (% of days in double-blind treatment period that were alcohol-free)
- Rate of complete abstinence for the study period

According to the protocol, information on daily drinking was to be “based on the patient’s Alcohol Timeline Follow Back interview, supported by the patient’s daily drinking diary, the collateral informant interview, and measurement of breath alcohol concentration... Every attempt [was to be] made to resolve inconsistencies of alcohol consumption between sources. If inconsistencies remain[ed] unresolved, then primary efficacy parameters [were to] assume the most negative outcome, as follows:

First day of any drinking was protocol-defined as the earliest drinking episode identified by the patient or collateral informant, or by a BAC $> 0.003\%$.

First day of heavy drinking was protocol-defined as the earliest heavy drinking day identified by the patient or collateral informant or by a BAC $> 0.04\%$.

Cumulative abstinence duration was protocol-defined as the minimum number of alcohol-free days between visits, reported by the patient or collateral informant or indicated by breath alcohol concentrations.

Nonabstinence was to be assumed if either the patient, the collateral informant, or the BAC ($> 0.003\%$) indicated any alcohol consumption.

All subjects noted on CRF termination page as lost to follow-up were to be considered treatment failures, and heavy drinking was to be imputed beginning on the first day they were lost to follow-up. For subjects terminating for reasons other than loss to follow-up or documented treatment failure (such as “patient decision” or “sponsor’s decision”) missing data was to be considered missing in analyses.

5.6.1.5 Statistical Plan

Treatment groups were to be compared using analysis of variance tests with treatment, center, and medicated/nonmedicated detoxification strata effects (for continuous variables) or extended Mantel-Haenszel tests stratifying over centers and medicated/nonmedicated detoxification strata (for categorical variables). CAD and CCAD were to be analyzed using rank analysis of variance with effects for treatment, center, and medicated/non-medicated detoxification strata.

5.6.2 Results

5.6.2.1 Study Conduct/Outcome

5.6.2.1.1 Subject Characteristics

A total of 741 subjects were screened for possible participation in the study. Of these, 140 (19%) failed screening and were not included. The most frequent reasons for screen failure were: failed inclusion/exclusion criteria (50%), patient decision (21%), and loss to follow-up (9%)

A total of 601 subjects were randomized to treatment at 21 centers (260 placebo, 258 acamprosate 2000 mg/day, and 83 acamprosate 3000 mg/day). The protocol stipulated that, prior to randomization, patients who had evidence of alcohol withdrawal symptoms, based on the CIWA assessment, were required to have medicated detoxification in order to be considered for the study. Overall, 10% (63 patients) of those randomized received medicated detoxification prior to randomization, with the highest percentage (12%) in the acamprosate 2000 mg treatment group and the lowest percentage (7%) in the acamprosate 3000 mg treatment group. In almost all cases, detoxification was on an outpatient basis.

5.6.2.1.1.1 Enrollment by Center

The table below illustrates the enrollment by center for Study US 96.1

Site Number	Principal Investigator(s)	Screened Patients	Randomized Patients
01	Alan J. Budney, Ph.D. Clinical Director of Substance Abuse Services Dayone-Fletcher Allen Health Care U.V.M. Department of Psychiatry South Burlington, VT	40	33
02	Raymond F. Anton, M.D. (Co-PI) Professor Medical University of South Carolina Institute of Psychiatry Charleston, SC Darlene H. Moak, M.D. (Co-PI) Assistant Professor (same location as above)	43	40
03	Donald R. Wesson, M.D. Medical and Scientific Director Friends Research Associates Berkeley, CA	43	39
04	Michael Thase, M.D. Professor of Psychiatry University of Pittsburgh Western Psychiatric Institute & Clinic Pittsburgh, PA	39	33
05	Adolf Pfefferbaum, M.D. (Co-PI) Director Neuropsychiatry Program Center for Health Sciences SRI International Menlo Park, CA Barry Rosen, M.D. (Co-PI) Medical Director Sequoia Alcohol & Drug Recovery Center Redwood City, CA	25	24

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

Site Number	Principal Investigator(s)	Screened Patients	Randomized Patients
06	John Grabowski, Ph.D. Professor, Department of Psychiatry & Behavioral Sciences Director SARC Substance Abuse Research Center University of Texas-Houston Houston, TX	52	35
07	Patrick J. McGrath, M.D. Associate Professor of Clinical Psychiatry New York State Psychiatric Institute Depression Evaluation Service New York, NY	13	12
08	Domenic A. Ciraulo, M.D. Professor & Chairman Division of Psychiatry Boston University Medical School Boston, MA	43	31
09	Robert Anthenelli, M.D. Director of Substance Abuse Programs Cincinnati VA Medical Center Cincinnati, OH	38	30
10	H. George Nurnberg, M.D. (Co-PI) University of New Mexico School of Medicine Mental Health Center Albuquerque, NM Michael P. Bogenschutz, M.D. (Co-PI) Clinical Director, Dual Diagnosis Program Assistant Professor of Psychiatry University of New Mexico School of Medicine Albuquerque, NM	27	20
11	Milton L. Bullock, M.D. Division Chief of Addiction & Alternative Medicine Hennepin Faculty Associates Addiction Medicine Program Minneapolis, MN	43	35
12	Henry Kranzler, M.D. Associate Professor University of Connecticut Health Center School of Medicine, Dept. of Psychiatry Division of Addictive Disorders Farmington, CT	43	34
13	Steven Shoptaw, Ph.D. Research Director Los Angeles Addiction Treatment Research Center Los Angeles, CA	55	40

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

Site Number	Principal Investigator(s)	Screened Patients	Randomized Patients
14	Allen Zweben, DSW (Co-PI) Associate Professor University of Wisconsin-Milwaukee School of Social Welfare Milwaukee, WI Lance Longo, M.D. (Co-PI) Sinai Samaritan Medical Center Outpatient Behavioral Health Milwaukee, WI	30	29
15	Mary E. McCaul, Ph.D. The Johns Hopkins University Clinical Research Unit 10753 Falls Rd. Pavilion 2, Suite 325 Lutherville, MD 21093	54	42
16	Stephanie O'Malley, Ph.D. Associate Professor of Psychiatry Yale University School of Medicine Substance Abuse Treatment Unit New Haven, CT	28	25
17	Barbara J. Mason, Ph.D. Associate Professor Director of Alcohol Disorders Research Unit University of Miami, School Of Medicine Dept. of Psychiatry Miami, FL	51	42
18	Margaret Kotz, D.O. The Cleveland Clinic Foundation Department of Psychiatry Cleveland, OH	15	10
19	Gerard Connors, Ph.D. Director of Research, Clinical Research Center Research Institute on Addictions Buffalo, NY	19	11
20	Timothy I. Mueller, M.D. Director, Residency In Psychiatry Butler Hospital Providence, RI	16	15
21	Joseph R., Volpicelli, M.D., Ph.D. (Co-PI) University of Pennsylvania Treatment Research Center Philadelphia, PA Helen Pettinati, Ph.D. (Co-PI) (Same location as above)	24	21

5.6.2.1.1.2 Subject Disposition

The table below illustrates patient disposition and reasons for premature discontinuation. Overall, a total of 292 patients (49%) completed the Treatment Phase. Completion rate during the Treatment Phase was lower in the acamprosate 2000 mg treatment group (41%) compared to the placebo (55%) and acamprosate 3000 mg treatment groups (52%). Subjects in the acamprosate 2000 mg treatment group were more likely to terminate due to Patient Decision (28%) and Loss to Follow-up (18%), compared to the other 2 groups. Otherwise, the reasons for

discontinuation of treatment were similarly distributed among the groups, notably including discontinuation for treatment failure and for adverse events.

Table 5.6.2.1.1.2 Patient Disposition – US Short-Term Supportive Efficacy Study

	Statistic	ACAMP 1998/2000 mg/day	ACAMP 3000 mg/day	Placebo
Number of Patients Randomized	N	258	83	260
Number of Patients Who Completed Treatment Phase	n (%)	106 (41%)	43 (52%)	143 (55%)
Number of Patients Who Discontinued Treatment Phase	n (%)	152 (59%)	40 (48%)	117 (45%)
Reasons for Discontinuation:				
Adverse event	n (%)	10 (4%)	3 (4%)	7 (3%)
Lost-to-follow-up	n (%)	47 (18%)	10 (12%)	33 (13%)
Treatment failure	n (%)	13 (5%)	4 (5%)	13 (5%)
Death	n (%)	0	0	0
Protocol Violation	n (%)	4 (2%)	0	3 (1%)
Other	n (%)	78 (30%)	23 (28%)	61 (23%)

Data Source: Table 8.7.3.1.1

Sponsor's In-Text Table 8.4.4.1:1 Percentages are based on the number of patients randomized.

5.6.2.1.1.3 Demographics

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

Most patients in this study were male (65% to 72% across treatment groups) and the mean age ranged from 43.6 to 44.9 years.

With respect to alcohol use histories, the mean duration of alcohol dependence ranged from 12.5 years (acamprosate 3000 mg group) to 13 years (acamprosate 2000 mg group). Most subjects (61%-73%) drank 5 or more standard drinks per drinking day (on average) prior to treatment. The rate of very heavy drinking (>10 drinks/drinking day) did not differ across treatment groups (29%-30%). In contrast to the European populations, only 29% of the patients had previously undergone treatment or detoxification for alcoholism, and only 10% had been treated 3 or more times. The groups were similar with respect to the number of patients with 0-1 previous detoxes (81% in acamprosate 2000 mg group, 85% in acamprosate 3000 mg group, and 85% in placebo group). Slightly fewer (6%) in the acamprosate 3000 mg group had undergone multiple (3 or more) previous detoxes (vs 10% in acamprosate 2000 mg group and 12% in placebo group). As noted above, 10% of the total population underwent detoxification prior to randomization (12% in acamprosate 2000 mg, 7% in acamprosate 3000 mg and 10% in placebo group). Approximately half of the subjects were abstinent at baseline (52% in acamprosate 2000 mg group and 49% in each other group).

Table 5.6.2.1.1.3.1 Demographic Characteristics at Baseline, ITT Population – Study US/96.1

Characteristic	Statistic	ACAMP 2000 mg/day (N=253)	ACAMP 3000 mg/day (N=82)	Placebo (N=257)
Gender	N	253	82	257
Males	n (%)	176 (70%)	59 (72%)	166 (65%)
Females	n (%)	77 (30%)	23 (28%)	91 (35%)
Age (years)	N	253	82	257
	Mean (SE)	44.9 (0.7)	43.6 (1.0)	44.4 (0.6)
	Min., Max.	23, 72	21, 66	22, 69
Age Distribution (years)	N	253	82	257
16-39	n (%)	82 (32%)	27 (33%)	88 (34%)
40-59	n (%)	143 (57%)	50 (61%)	139 (54%)
≥ 60	n (%)	28 (11%)	5 (6%)	30 (12%)
Weight (kg)	N	252	82	257
	Mean (SE)	80.7 (1.0)	80.9 (1.9)	78.9 (1.0)
	Min, Max	51, 134	48, 136	46, 134
Marital Status	N	253	82	257
Married	n (%)	117 (46%)	34 (41%)	133 (52%)
Not Married	n (%)	136 (54%)	48 (59%)	124 (48%)
Detoxification Prior to Randomization	N	253	82	257
Yes	n (%)	31 (12%)	6 (7%)	25 (10%)
No	n (%)	222 (88%)	76 (93%)	232 (90%)
Abstinent at Baseline	N	253	82	257
Yes	n (%)	132 (52%)	40 (49%)	127 (49%)
No	n (%)	121 (48%)	42 (51%)	130 (51%)
Duration of Alcohol Dependence/Abuse (years)	N	253	82	257
	Mean (SE)	13.0 (0.6)	12.5 (1.0)	12.6 (0.5)
	Min., Max.	1, 42	1, 40	1, 41
<10	n (%)	101 (40%)	30 (37%)	107 (42%)
≥10	n (%)	152 (60%)	52 (63%)	150 (58%)
Average Standard Drinks per day in Recent Past	N	253	82	257
<5	n (%)	62 (25%)	32 (39%)	71 (28%)
5-10	n (%)	115 (45%)	25 (30%)	111 (43%)
>10	n (%)	76 (30%)	25 (30%)	75 (29%)
Prior treatments or detoxes for Alcoholism	N	253	82	257
0	n (%)	171 (68%)	59 (72%)	192 (75%)
1	n (%)	35 (14%)	11 (13%)	27 (11%)
2	n (%)	21 (8%)	7 (9%)	8 (3%)
3	n (%)	7 (3%)	2 (2%)	16 (6%)
>3	n (%)	19 (8%)	3 (4%)	14 (5%)

Data Source: Table 8.7.3.2.1, Table 8.7.3.3.1

Sponsor's In-Text Table 8.4.4.1:2: Percentages are based on the number of patients in the ITT population with an assessment.

Not noted in the table above, about 75% of the sample had a history of illicit substance abuse. The most commonly reported drug use was marijuana. Patients in the acamprosate 2000 mg

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

group, 3000 mg group, and placebo group, reported a mean number of years of marijuana use, respectively, of 8.6, 10.1, and 7.7 years and of cocaine use, respectively, of 4.5, 4.9, and 4.7 years. At Baseline, 8% of the acamprosate 2000 mg group, 17% of the acamprosate 3000 mg group, and 6% of the placebo group had positive urine tests for marijuana. Approximately half the population had a history of cocaine use and 10% had a history of heroin use. Because the study recruited for alcoholics seeking treatment, these findings with respect to polysubstance abuse among alcoholics are likely to be representative of the American alcoholic population.

5.6.2.1.1.3.1 Treatment Goals

Subjects were also asked to identify a goal of treatment at baseline, and were given multiple-choice options ranging from “no goal” to “total abstinence.” The table below illustrates the treatment goals of the different treatment groups. Overall, 72% aspired to total abstinence (including goal of “total abstinence” and “total abstinence, but I realize a slip is possible.” Treatment goals were similarly distributed across the treatment groups.

Table 5.6.2.1.1.3.2 Treatment Goals at Baseline

	Total N = 601		2000 mg/day N = 258		3000 mg/day N = 83		Placebo N = 260	
	N	%	N	%	N	%	N	%
No goal	1	0%	1	0%	0	0%	0	0%
Regular use but quantity controlled	33	5%	15	6%	4	5%	14	5%
Temporary abstinence	9	1%	4	2%	1	1%	4	2%
Occasional use	128	21%	56	22%	19	23%	53	20%
Total abstinence, but I realize a slip is possible	186	31%	81	31%	32	39%	73	28%
Total abstinence	244	41%	101	39%	27	33%	116	45%

5.6.2.1.2 Dosing Information

Medication compliance was generally high across all three treatment groups. The table below illustrates exposure and compliance across treatment groups. Overall compliance ranged from 89% in the two acamprosate groups to 93% in the placebo group. Among completers, compliance ranged from 92% in the acamprosate 2000 mg group to 96% in the acamprosate 3000 mg group. The number of patients who were 75%-120% compliant ranged from 80% (acamprosate 300 mg) to 89% (placebo).

**APPEARS THIS WAY
ON ORIGINAL**

Duration of Exposure and Medication Compliance – US Short-Term Supportive Efficacy Study – ITT Population

	Statistic	ACAMP 1998/2000 mg/day (N=253)	ACAMP 3000 mg/day (N=82)	Placebo (N=257)
Duration of Exposure (weeks)	Mean	15.97	17.05	17.98
	SE	0.59	1.01	0.58
	Median	14.14	23.14	24.14
	Min., Max.	0.1, 32.9	1.7, 28.1	0.1, 32.9
Exposure by Duration Category (weeks)	n	253	82	257
0- <4	n (%)	37 (15%)	9 (11%)	34 (13%)
4- <8	n (%)	33 (13%)	10 (12%)	25 (10%)
8- <13	n (%)	31 (12%)	12 (15%)	23 (9%)
13- <26	n (%)	122 (48%)	41 (50%)	146 (57%)
≥26	n (%)	30 (12%)	10 (12%)	29 (11%)
Medication Compliance (%)	Mean	88.96	88.51	92.55
	SE	1.16	1.96	1.86
	Median	95	96	98
	Min., Max.	3.8, 133.3	30.6, 110.7	21.3, 500.0
Number of patients who were ≥75% compliant	n (%)	218 (86%)	66 (80%)	229 (89%)
Data Source: Table 8.7.3.4.1.				

Sponsor's In-Text Table 8.7.4.6:1

Note: Percentages for ≥75% compliant are based on the number of patients for whom compliance was calculated. Otherwise, percentages are based on the number of patients in the ITT population.

5.6.3 Efficacy Results

5.6.3.1 Sponsor's Analysis

Although the protocol-specified analysis identified time to relapse as the primary outcome variable, the sponsor noted that the unexpectedly high rate of non-abstinence at randomization "required restructuring of the original analysis plan." The sponsor noted that the population studied, as well as certain aspects of study design, differed in various ways from the European studies, thus explaining the difference in outcome. These differences included:

- Abstinence was not explicitly required for admission to the study, but because patients were required to reduce their drinking to non-hazardous levels for study admission and because it was the focus of the protocol-directed behavioral therapy, it was anticipated that most patients would be abstinent at the time of randomization.
- At Baseline, patients also had to indicate their treatment goal, which could range from no goal at all to a goal of total abstinence.
- Broad admission criteria were used in ACAMP/U.S./96.1 relative to the European studies (e.g., no upper age limit, allowance for non-dependent cannabis use at enrollment, and other illicit drug use during the study).
- Standardized, manual-guided psychosocial support, consisting of brief intervention and medication compliance procedures of established efficacy to support abstinence, specific for the protocol, was given to all participants. In contrast, the majority of the Phase III European studies followed a more "naturalistic" approach, with variable non-structured psychosocial therapy, reflective of the individual practice techniques of the participating site.

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

- Other design features of the U.S. study which were not typical of the European studies included:
 - daily drinking diaries, maintained by the patients and reviewed with the therapist at each visit in conjunction with returned study medication;
 - specially designed “reminder” blister packaging of study medication;
 - advertising to recruit study participants from outside the existent clinical practice of the participating site;
 - weekly telephone contacts with study participants to supplement the monthly visits to the site;
 - contacts with a close friend or relative specified by the patient to evaluate the patient’s progress; and
 - mandatory follow-up algorithms for missed visits or missed telephone contacts, which included frequent attempts to contact the patient or collateral informant via phone and certified mail.

A variety of subpopulations were identified by the sponsor in an attempt to select the subjects who were most similar to those studied in the successful European trials. These subpopulations were as follows:

Population	Definition	Acamprosate 2000 mg N (% of randomized)	Acamprosate 3000 mg N (% of randomized)	Placebo N (% of randomized)
All randomized		258	83	260
Safety Population (SAF)	All randomized patients who took at least one dose of double-blind study medication	258 (100%)	83 (100%)	260 (100%)
Intent-to-Treat Population (ITT)	All randomized patients who took at least one dose of double-blind study medication and for whom some post-baseline efficacy data were recorded, including TLFB, collateral informant interview, or discontinuation due to treatment failure	253 (98%)	82 (99%)	257 (99%)
Efficacy Evaluable Population (EFF)	All randomized patients who took double-blind study medication for at least 7 days, returned for at least one post-baseline visit, did not have a positive urine test for a drug of abuse at any time after randomization, and were at least 75% compliant for the duration of the treatment phase	177 (69%)	56 (67%)	198 (76%)
Motivated ITT Population	All patients in the ITT population who had a treatment goal of complete abstinence	100 (39%)	26 (31%)	115 (44%)
Motivated EFF Population	All patients in the EFF population who had a treatment goal of complete abstinence	71 (28%)	15 (18%)	86 (33%)

It should be carefully noted that the Motivated EFF population comprises only 29% of the randomized population.

5.6.3.1.1 [Corrected] Cumulative Abstinence Duration

The “revised” “primary efficacy variable” identified by the sponsor was the corrected cumulative abstinence duration.

According to Section 10.7.12 of the application,

“Corrected cumulative abstinence duration was defined as the percentage of days during the study that the patient did not consume alcohol and was calculated as 100 times the number of abstinent days divided by the censored/uncensored study duration.

“The number of abstinent days was calculated at each monthly visit, and the overall number of abstinent days was obtained by summing across these visits. At each monthly visit, the number of abstinent days was identified from the Timeline Follow Back (TLFB) calendar, supported by the collateral informant interview and breath alcohol concentration (BAC). When there were unresolved inconsistencies between these data sources, the minimum number of abstinent days reported by any of these sources was used for that visit. Drinking status (drinking or not drinking on each day) for any missing data on the TLFB prior to discontinuations or loss to follow-up was assigned the average of the previous 7 days of nonmissing data as follows: the number of days with missing data was multiplied by the percent of the previous 7 days that were non-abstinent.

“If a patient completed the treatment phase, then the denominator for CCAD was the total treatment duration. For patients whose discontinuation was determined (by blinded expert reviewers involved in clinical alcohol research) to be “associated with” alcohol use, the denominator for CCAD was the anticipated duration of the treatment phase (the “uncensored” duration). The anticipated duration was calculated as the actual time on treatment plus the anticipated time required to complete all remaining visits per the protocol schedule.

“If a patient discontinued the treatment phase and the discontinuation was determined to be “not associated with” alcohol use, then the denominator for CCAD was the actual time the patient participated in the treatment phase (the “censored” duration).

“In addition to the analysis of CCAD as a continuous variable, CCAD was also analyzed categorically as good response (CCAD ≥ 90), partial response (CCAD $>10 - <90$), and poor response (CCAD ≤ 10).”

**APPEARS THIS WAY
ON ORIGINAL**

Sponsor's Analysis: Corrected Cumulative Abstinence Duration (CCAD) (%) – US/96.1

All Efficacy Populations

Population	Statistic	ACAMP 2000 mg/day	Placebo	Effect size*
Intent-to-Treat	N	253	256	0%
	Mean (SE)	56.1 (2.1)	54.3 (2.2)	
	Median	59	59	
Efficacy Evaluable	n	177	198	8.3%
	Mean (SE)	59.5 (2.5)	56.4 (2.4)	
	Median	65	60	
Motivated Intent-to-Treat	n	100	115	21.9%
	Mean (SE)	66.1 (3.4)	60.7 (3.3)	
	Median	78	64	
Motivated Efficacy Evaluable	n	71	86	27.5%
	Mean (SE)	70.2 (4.1)	62.7 (3.8)	
	Median	88	69	

Data Source: Table 8.7.3.5.1

Sponsor's In-Text Table 8.4.4.1:3

*Effect size = {[median (ACAMP 2000 mg/day) – median (placebo)] / median (placebo)} * 100.

5.6.3.2 Reviewer's Analysis

Unlike the European studies reviewed above, Study US/96.1 used a systematic approach to reconstruction of drinking data that has been widely accepted within the alcohol research community as a valid instrument. This allows the analysis of data at the level of days of drinking vs. abstinence. Therefore, the use of the cumulative abstinence duration analysis with this dataset seems appropriate. Because the 3000 mg dose was only "exploratory" and the size of the treatment group was 1/3 that of the other groups, I have focused my analysis on the pairwise comparison between placebo and the 2000 mg/day dose, as well as a pairwise comparison between placebo and the pooled acamprosate groups.

As noted by the sponsor, the protocol-specified primary analyses (abstinence survival and categorical analysis of complete abstinence) were doomed to failure in this population, due to the high rate of non-abstinence at randomization. In addition, as noted by the sponsor, the population in this study differed in various ways from the populations in the successful European pivotal studies. The sponsor chose to emphasize, therefore, analysis of non-continuous abstinence (percent days abstinent, as defined by the somewhat complex algorithm described above, called here CCAD), but was unable to show superiority of acamprosate over placebo using the CCAD outcome.

A series of exploratory analyses using differently-defined populations were undertaken, and on this basis, the sponsor claims that acamprosate can be shown to be superior to placebo. However, it should be noted that any number of populations could be defined. In the analysis below, I have defined various populations in an attempt to explore the ways that the US population differed from the European population. I have used the sponsor's defined CCAD on treatment as the outcome, although a more conservative analysis might have been to choose the number of days abstinent, either untransformed, or divided by 180 to yield a CCAD (rather than

using the censored treatment durations as calculated by the sponsor). As noted below, no population I defined demonstrated superiority of acamprosate over placebo, even for the somewhat less conservative sponsor-calculated CCAD; therefore no “worst case” analysis was needed.

The fundamental differences between the US population and the population in the European studies included:

- Abstinence at baseline
- High level of motivation (assumed for some studies, although required for entry in others)
- Low prevalence of polysubstance abuse

In defining the “motivated efficacy evaluable” subset, the sponsor excluded any subjects with a positive urine tox during treatment (86 subjects tested positive at any point during the study; however test results are reported for less than the full sample), as well as subjects who selected (from a multiple-choice list) any treatment goal other than “total abstinence.” This addresses the two of the differences between the US and European populations. However, in addition, the sponsor excluded subjects unless they “took study medication for at least 7 days, returned for at least one post-baseline visit, did not have a positive urine test for a drug of abuse at any time after randomization, and were at least 75% compliant for the duration of the treatment phase.” These post-randomization variables go beyond an effort to select a subgroup most similar to the European subjects. It must be noted that the European studies, no matter what the population, were analyzed on an ITT basis, and did not exclude from analysis subjects with missing data or low compliance.

5.6.3.2.1 Reviewer-defined populations

Several reviewer-defined populations were identified for analysis, chosen to address the three differences noted above between the US and European populations

5.6.3.2.1.1 Baseline Abstinent

The dataset identified subjects who were abstinent for 5 days at randomization and subjects who were abstinent for 7 days. To yield a larger sample, I chose the former.

5.6.3.2.1.2 Motivated

Of the choices offered for treatment goal, both “total abstinence” and “total abstinence, but I realize a slip is possible” represent treatment goals of abstinence. One simply reflects a more realistic view. Therefore, to construct a “motivated” population for analysis, I selected subjects with either of these two self-identified goals. To construct a population intended to resemble the population of the European studies with respect to motivation, I chose those subjects who identified either of these two options as a treatment goal.

5.6.3.2.1.3 Non-poly-substance abusing (“pure alcoholics”)

Several options were available for defining this population. Subjects were coded as to whether the investigator felt they met criteria for a DSM-IV diagnosis of substance dependence on

marijuana, psychedelics, opiates, stimulants, sedatives, cocaine, or heroin. Not surprisingly, as such a diagnosis was an exclusionary criterion, no subjects in the ITT study population were flagged as meeting criteria.

In addition, each subject was assigned a value for a calculated "Illicit Drug Use Index." The IDUS was 0 if the patient never used marijuana, psychedelics, opiates, stimulants, sedatives, cocaine, and heroin. If patient ever used any of these illicit medications, variable was derived as: (no. of years of marijuana use * 1 * marijuana frequency weight) + (no. of years of psychedelics use * 2 * psychedelics frequency weight) + (no. of years of opiate use * 3 * opiates frequency weight) + (no. of years of stimulants use * 5 * stimulants frequency weight) + (no. of years of sedatives use * 6 * sedatives frequency weight) + (no. of years of cocaine use * 7 * cocaine frequency weight) + (no. of years of heroin use * 24 * heroin frequency weight). I selected subjects with an IDUS of 0 for the "no history of illicit drugs" population. Only 20% of the randomized subjects are included in this population, ranging from 18% of the placebo group to 24% of the acamprosate 3000 mg group. For comparison, only 54 patients in the PRAMA study (20%) were listed as having "any/potential abuse."

Acknowledging that a history of use of illicit drugs may not reflect current use, I selected a population with no use of any of the illicit drugs queried for (see list in paragraph above) in the past year. This population included 39% of the randomized subjects, ranging from 34% in the acamprosate 2000 mg group to 44% in the placebo group. Because marijuana use at baseline was not grounds for exclusion, I also selected a population which had used no drugs other than marijuana in the past year. This included 80% of the randomized population, ranging from 73% of the acamprosate 2000 mg group to 88% of the acamprosate 3000 mg group.

Next, recognizing that active drug use may be more relevant than drug use history, I selected a population that did not have any positive urine tox screens during the study. It should be noted that study visits were as infrequent as monthly during portions of the study, and therefore the urine tox screens may not have identified all who were actively using illicit drugs while in the study. Furthermore, nothing can be predicted about the results of urine tox screens that were not done because subjects dropped out of the study. Therefore, selecting subjects who lacked urine tox evidence of drug use does not necessarily select a population that did not use drugs during the study or was not prone to do so after study discontinuation. In addition, urine tox data is only included for 525 subjects (226 acamprosate 2000 mg, 72 acamprosate 3000 mg, and 227 placebo). Only 83 had documented positive tests, yielding 439 (73% of randomized subjects) for whom tox data was available and showed no illicit drugs.

Finally, I identified the subset of patients who were both abstinent at randomization and motivated, and the subset that were abstinent, motivated, and had no illicit drug use (other than marijuana) in the past year.

The populations so identified were distributed as follows:

Table 5.6.3.2.1.3.1 Reviewer-Defined Sub-populations

	Total (% of 601 Randomized)	Acamprosate 2000mg (% of 258 Randomized)	Acamprosate 3000 mg (% of 83 Randomized)	Placebo (% of 260 Randomized)
ITT (sponsor's)	592 (99%)	253 (98%)	82 (99%)	257 (99%)
Goal of abstinence/abstinent + slip	430 (72%)	182 (71%)	59 (71%)	189 (73%)
Abstinent >5 days before randomization	167 (28%)	81 (31%)	18 (10%)	68 (26%)
No history of illicit drugs (IDUS = 0)	121 (20%)	54 (21%)	20 (24%)	47 (18%)
No illicit drugs past year	232 (39%)	87 (34%)	30 (36%)	115 (44%)
No illicit drugs other than marijuana in past year	479 (80%)	189 (73%)	73 (88%)	217 (83%)
No positive urine tox during study*	439 (73%)	186 (72%)	58 (70%)	195 (75%)
Abstinent at baseline AND Goal of abstinence/abstinence + slip	143 (24%)	70 (27%)	16 (19%)	57 (22%)
Abstinent at baseline AND Goal of abstinence/abstinence + slip AND no illicit drugs other than marijuana in past year	111 (18%)	48 (19%)	15 (18%)	48 (18%)

* urine tox data is only included for 525 subjects (226 acamprosate 2000 mg, 72 acamprosate 3000 mg, and 227 placebo) . Only 83 had documented positive tests.

Again, it is important to note the small size of the resulting populations.

5.6.3.2.2 Non-Continuous Abstinence

This analysis uses the reported corrected cumulative abstinence duration as a measure of non-continuous abstinence, defined as described in Section 5.6.3.1.1 above. From dataset US_CAD, CCAD during treatment (CCADTX, defined above in section on sponsor's analysis) was analyzed by treatment group. Treatment assignment was obtained through merging with dataset US_POP.

5.6.3.2.2.1 Mean Percent Days Abstinent (CCAD)

The table below shows CCAD for the various reviewer-defined subsets of subjects. Note that the N's differ from the table above because of missing values.

**APPEARS THIS WAY
ON ORIGINAL**

Table 5.6.3.2.2.1 Corrected Cumulative Abstinence Duration in Reviewer-Defined Populations

Population	Acamprosate 2000 mg	Acamprosate pooled groups	Placebo
ITT			
N	253	335	256
CCAD mean ± SE	46%±2.2	47%±1.9	51%±2.2
CCAD median	39%	45%	52%
Goal of abstinence/abstinent + slip			
N	174	228	179
CCAD mean ± SE	51%±2.7	50%±2.4	51%±2.7
CCAD median	49%	49%	52%
Abstinent >5 days before randomization			
N	81	99	67
CCAD mean ± SE	60%±3.8	62%±3.4	70%±4.2
CCAD median	67%	72%	84%
No history of illicit drugs (IDUS = 0)			
N	54		47
CCAD mean ± SE	53% ±4.7		55%±5.1
CCAD median	51%		59%
No illicit drugs past year			
N	87	117	115
CCAD mean ± SE	48%±3.8	52%±3.3	53%±3.3
CCAD median	49%	52%	59%
No illicit drugs other than marijuana in past year			
N			
CCAD mean ± SE	189	262	217
CCAD median	48%±2.6	49%±2.2	51%±2.4
	46%	47%	56%
No positive urine tox during study			
N	186		195
CCAD mean ± SE	49%±2.5		56%±2.4
CCAD median	46%		59%
Abstinent at baseline AND Goal of abstinence/abstinence + slip			
N	65	79	53
CCAD mean ± SE	45%±4.3	47%±3.9	52%±4.7
CCAD median	41%	44%	53%
Abstinent at baseline AND Goal of abstinence/abstinence + slip AND no illicit drugs other than marijuana in past year			
N	48	63	48
CCAD mean ± SE	65%±4.7	68%±4.1	71%±4.7
CCAD median	75%	81%	84%

Note: N's differ from table 5.6.3.2.1.3.1 because of missing values

None of these comparisons yield statistically significant differences.

5.6.3.2.2.2 Categorical Analysis of >90% Days Abstinent

The sponsor performed a categorical analysis of CCAD, counting those subjects with a “good response” (CCADTX ≥90%). The table below presents the sponsor’s calculations for the Motivated ITT and Motivated Efficacy Evaluable populations (sponsor-defined) and replicates this analysis for the reviewer-defined subsets deemed most relevant.

Table 5.6.3.2.2.2 Subjects with “good response” (CCADTX ≥90%)

	Acamprosate 2000 mg		Acamprosate pooled		Placebo	
	n/N	%	n/N	%	n/N	%
ITT population†	45/253	18%	66/335	20%	54/287	18%
Sponsor-defined Motivated ITT population*	35/100	35%	49/126	39%	39/115	34%
Sponsor-defined Motivated Efficacy Evaluable population*	34/71	48%	43/86	50%	31/86	36%
Reviewer-defined Motivated population†	37/174	21%	48/190	25%	43/179	24%
Reviewer-defined Abstinent/Motivated population†	8/65	12%	12/79	15%	12/53	23%
Reviewer-defined Abstinent/Motivated/No illicit drugs (other than marijuana) †	6/48	13%	9/63	14%	9/49	18%
Reviewer-defined Abstinent/Motivated/No positive urine tox†	7/53	13%	11/66	17%	8/39	21%

*From Sponsor’s In-text Table 6.15, vol 99,

† reviewer’s analysis

Clearly, no reviewer-defined population shows superior response in acamprosate-treated subjects; only the “Motivated Efficacy Evaluable” population, among the sponsor’s subpopulations, shows an effect of acamprosate. It should be remembered that this subset is defined by a number of post-randomization variables including compliance, and is therefore a less persuasive analysis than the ITT analysis or analyses of subpopulations defined by pre-randomization variables.

5.6.3.2.3 Continuous Response

5.6.3.2.3.1 Complete Abstinence

Only 33 subjects (6% of the ITT population) were assessed as completely abstinent at all 10 on-treatment visits. These included 8 (3%) in the acamprosate 2000 mg arm, 5 (6%) in the acamprosate 3000 mg arm, and 20 (8%) in the placebo arm.

Considering only the subset that began the study abstinent, 19 (11%) were continuously abstinent through all visits. Notably, this included 14 subjects in the placebo group (21% of abstinent subset of placebo group), 3 in the acamprosate 2000 mg group and 2 in the acamprosate 3000 mg group. Clearly, these numbers (even those in the ITT subset) are too small to allow meaningful comparison.

5.6.3.2.3.2 Abstinence from sustained heavy drinking

Acknowledging that continuous complete abstinence from alcohol was achieved by so few subjects as to render treatment group comparisons meaningless, I analyzed the data using another measure that was applied by the sponsor. Subjects were coded as to whether or not they had “relapsed.” The flag for relapse was attached “if the patient relapsed into having at least 5 drinks a day for 5 of the next 7 days.”

Not surprisingly, continuous “success” by this criterion was less uncommon. In the ITT population, 22% were coded as having a relapse, 20% had no data listed and 57% were coded as no relapse. These were divided across treatment groups in the various reviewer-defined populations as follows:

	Total	Acamprosate 2000 N =	Acamprosate pooled N = 335	Placebo N = 257
ITT				
Relapse	132	51/253 (20%)	70/335 (21%)	62/257 (24%)
No relapse	339	152/253 (60%)	198/335 (59%)	141/257 (55%)
No data	121	50/253 (20%)	67/335 (20%)	54/257 (21%)
Abstinent Subject				
Relapse	30	20/81 (25%)	22/99 (22%)	8/68 (12%)
No relapse	137	61/81 (75%)	77/99 (78%)	60/68 (88%)
Motivated Subject				
Relapse	120	51/182 (28%)	68/241 (28%)	52/189 (28%)
No Relapse	310	131/182 (72%)	173/241 (72%)	137/189 (72%)
No drugs (except marijuana) past year				
Relapse	127	51/191 (27%)	71/264 (27%)	56/221 (25%)
No relapse	358	140/191 (73%)	193/264 (73%)	165/221 (75%)
Abstinent, motivated, no drugs (except marijuana) past year				
Relapse	17	17/56 (30%)	26/78 (33%)	6/49 (12%)
No Relapse	95	39/56 (70%)	52/78 (67%)	43/49 (88%)
Sponsor's Motivated Efficacy Evaluable				
Relapse	37	13/71 (18%)	17/86 (20%)	20/86 (23%)
No Relapse	135	58/71 (82%)	69/86 (80%)	66/86 (77%)

Table prepared by reviewer from datasets US_RELAP, US_POP

It should be apparent that no treatment effect of acamprosate may be discerned from this data. It may be argued that setting so low a standard for success allows much of the placebo group to be classified as successful, thus obscuring any treatment differences that might occur.

All subsets based on pre-randomization variables are consistent in this finding. Again, only the sponsor's "motivated efficacy evaluable" population shows a trend toward better outcomes in the acamprosate groups than placebo group. Reservations about the definition of this population (particularly with respect to the use of post-randomization variables such as compliance) cannot be dismissed, particularly in view of the lack of evidence of acamprosate effect on several different measures in several different reviewer-defined populations.

5.6.3.3 Conclusions Regarding Efficacy Data in Study

Leaving aside entirely the issue of the sponsor replacing the protocol-specified outcome variable, this study nevertheless offers no evidence to support the effectiveness of acamprosate in the treatment of alcoholism. Subjects treated with acamprosate reported no more non-drinking days than subjects treated with placebo. Whether analyzed with emphasize on cumulative abstinence duration, categorical response of 90% days abstinent, total abstinence, or even the mere absence of a full-blown relapse, acamprosate treated subjects fared no better than placebo treated subjects and on some measures, seemed to fare numerically worse. This finding was borne out in subset analyses designed to address the major demographic differences between the European and American populations. Level of motivation, abstinence at randomization, recent illicit drug use, and illness severity were considered separately and together, but no reviewer-defined subset could be identified in which a treatment effect of acamprosate was apparent. For this reason (as well as because of the inclusion of post-randomization variables in the definition), the sponsor's "motivated efficacy evaluable" subset, in which acamprosate treatment effect may be discerned, must be viewed with extreme caution.

There is, in summary, no satisfying explanation based on population differences to explain the failure of study US96.1 to demonstrate an effect of acamprosate on increasing abstinent time in alcoholics.

5.7 Other Efficacy Studies

The application also contains study reports for 9 additional placebo-controlled studies, including 3 with a duration of treatment of 1 year and 6 shorter-term studies. The design and population features of these studies are illustrated in the table below:

**APPEARS THIS WAY
ON ORIGINAL**

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

Table 5.7 Other Controlled Clinical Studies Related to Claims of Effectiveness

Study #, (Common Name) Principal Investigator, Country	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
Supportive Studies								
AOTA/89.4 (Poldrugo) F. Poldrugo, Italy (Oct., 1989 to July, 1992)	Pro, MC (7), R, DB, PC, PG (2: acamp vs placebo) with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#1580)	1998* (1332)	2 tabs tid	122 ADS (65)	ND (42.9)	84/38 (69/31)	ND
		Placebo, tabs (#1579)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	124 ADS (47)	ND (44.9)	95/29 (77/23S)	ND
AOTA/90.1 (Tempesta) E. Tempesta, Italy (Oct., 1989 to April, 1993)	Pro, MC (18), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#3250)	1998	2 tabs tid	164 ADS (124)	ND (45.9)	139/25 (84.8/15.2)	ND
		Placebo, tabs (#3247)	6 tabs	2 tabs tid	166 ADS (122)	ND (46.0)	134/32 (80.7/19.3)	ND
AOTA/NL91.1 AOTA/B/90.2 (BENELUX) P. Geerlings and C. Ansoms, Belgium, The Netherlands (May, 1990 to Oct., 1992)	Pro, MC (22), R, DB, PC, PG (2: acamp vs placebo) with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#1519, 3306, 1580 and 3250)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	128 ADS (38)	19-65 (40.3)	97/31 (76/24)	ND
		Placebo, tabs (#1518, 3305, 1579 and 3247)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	134 ADS (32)	21-63 (41.7)	102/32 (76/24)	ND
AD 04 089 (Ladewig) D. Ladewig, Switzerland (Aug., 1989 to Jan., 1991)	Pro, MC (3), R, DB, PC, PG (2: acamp vs placebo) with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#1580)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	29 ADS (19)	28-68 (47.7)	25/4 (86/14)	ND
		Placebo, tabs (#1579)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	32 ADS (21)	31-70 (46.9)	22/10 (69/31)	ND
AD 10 089, (Lesch) O. Lesch, Austria (Dec., 1989 to March, 1993)	Pro, MC (5), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days)	Acamp, tabs, 333 mg (#1624)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	224 ADS (94)	22-64 (41.9)	168/56 (75/25)	ND
		Placebo, tabs (#1623)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	224 ADS (85)	15-70 (42.0)	185/39 (82.6/17.4)	ND
AOTA/P/89.1 (Barrias) J.C. Barrias, Portugal (Nov., 1989 to	Pro, MC (9), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E	Acamp, tabs, 333 mg (#1580)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	150 ADS (86)	21-64 (39.7)	139/11 (92.7/7.3)	ND
		Placebo, tabs	6 tabs	2 tabs tid	152 ADS (83)	23-63	139/13	ND

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

Study #, (Common Name) Principal Investigator, Country	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
Oct., 1992)	study in ADS, after withdrawal from alcohol. (360 days)	(#1579)	(4 tabs)	2-1-1 tabs tid		(41.0)	(91.4/8.6)	
AA 11 088 (Besson) J. Besson, Switzerland (Jan., 1989 to Jan., 1993)	Pro, MC (3), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight and open-label use (yes/no) of Antabuse (disulfiram) as associated therapy, S/E study in ADS, after withdrawal from alcohol. (360 days)	Acamp, tabs, 333 mg (#1243 and 3249)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	61 ADS (19) ⁵	25-62 (42.6)	50/11 (82.0/18)	ND
		Placebo, tabs (#1242 and 3247)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	57 ADS (19)	26-62 (42.6)	43/14 (75.4/24.6)	ND
AOTA/E/91.1 (ADISA) A. Gual, Spain (May, 1993 to Oct., 1994)	Pro, MC (11), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS from onset of alcohol withdrawal. (180 days)	Acamp, tabs, 333 mg (#3306)	1998	2 tabs tid	148 ADS (96)	21-61 (41.4)	119/29 (80/20)	ND
		Placebo, tabs (#3305)	6 tabs	2 tabs tid	148 ADS (90)	22-64 (40.6)	117/31 (79/21)	ND
Long-term Studies								
AD 10 089, (Lesch) O. Lesch, Austria (Dec., 1989 to March, 1993)	Pro, MC (5), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days)	Acamp, tabs, 333 mg (#1624)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	224 ADS (94)	22-64 (41.9)	168/56 (75/25)	ND
		Placebo, tabs (#1623)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	224 ADS (85)	15-70 (42.0)	185/39 (82.6/17.4)	ND
AOTA/P/89.1 (Barrias) J.C. Barrias, Portugal (Nov., 1989 to Oct., 1992)	Pro, MC (9), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days)	Acamp, tabs, 333 mg (#1580)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	150 ADS (86)	21-64 (39.7)	139/11 (92.7/7.3)	ND
		Placebo, tabs (#1579)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	152 ADS (83)	23-63 (41.0)	139/13 (91.4/8.6)	ND
AA 11 088 (Besson) J. Besson, Switzerland (Jan., 1989 to Jan., 1993)	Pro, MC (3), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight and open-label use (yes/no)	Acamp, tabs, 333 mg (#1243 and 3249)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	61 ADS (19) ⁶	25-62 (42.6)	50/11 (82.0/18)	ND
		Placebo, tabs	6 tabs	2 tabs tid		26-62	43/14	

⁵ In this study, 24 patients (20 male, 4 female) in the acamprosate treatment group and 24 patients (17 male, 7 female) in the placebo group also received Antabuse®.

⁶ In this study, 24 patients (20 male, 4 female) in the acamprosate treatment group and 24 patients (17 male, 7 female) in the placebo group also received Antabuse®.

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

Study #, (Common Name) Principal Investigator, Country	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
	of Antabuse (disulfiram) as associated therapy, S/E study in ADS, after withdrawal from alcohol. (360 days)	(#1242 and 3247)	(4 tabs)	2-1-1 tabs tid	57 ADS (19)	(42.6)	(75.4/24.6)	ND
Non-Supportive Study								
AOTA/LP90/N001 (UKMAS) J. Chick, United King. (June, 1990 to July, 1993)	Pro, MC (20), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS, after withdrawal from alcohol. A no-treatment period of ≥7 days was to occur between end of alcohol withdrawal and randomization. (24 weeks)	Acamp, tabs, 333 mg (#1624)	1998	2 tabs tid	289 ADS (100)	ND (42.8)	252/37 (87.2/12.8)	ND
		Placebo, tabs (#1623)	6 tabs	2 tabs tid	292 ADS (103)	ND (43.8)	233/59 (79.8/20.2)	ND

From Sponsor's Table 3.4.1

The following abbreviations are used throughout:

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

5.7.1 Short-term studies: features

The same basic study design was used in each of the European Short-Term Supportive studies: namely, each study was a multicenter, randomized, double blind parallel group comparison of acamprosate versus placebo. An objective of each study, except the ADISA study, was to evaluate the efficacy and safety (tolerance) of acamprosate versus placebo as therapy to maintain abstinence in the weaned alcoholic over a pre-specified double blind treatment phase. A second objective of each study, again with the exception of the ADISA study, was to determine whether efficacy was maintained over an observation period following the double blind treatment phase. The ADISA study started study medication concurrent with onset of alcohol withdrawal therapy and did not have a follow-up phase.

In general, the studies also had similar outcome parameters, as shown in the table below. Except in the UKMAS study, CAD was identified as a primary efficacy parameter. In the UKMAS study, CAD was identified as a secondary efficacy parameter. Time to first relapse or continuous abstinence was defined as a primary efficacy parameter for the Tempesta, UKMAS, and ADISA studies; it was identified as a secondary efficacy parameter in the Poldrugo, BENELUX, and Ladewig studies.

Most of the studies used the adverse event checklist as a means for recording both spontaneously reported adverse events and events elicited by review of the questionnaire.

Table 5.7.1 Primary Efficacy Parameters for the European Short-Term Supportive Efficacy Studies

Parameter	Poldrugo	Tempesta	BENELUX	Ladewig	UKMAS	ADISA
Cumulative Abstinence Duration (CAD)	1	1	1	1	2	1
Relapse rate at each visit	1		1	1	1	
Time to first relapse or continuous abstinence	2	1	2	2	1	1
Number of abstinent days after the last relapse						1
Abstinence by visit		1				
Attendance at each visit					1	
Gamma GT/MCV/relapse criterion	2	2	2	2	2	
ASAT/ALAT		2	2		2	
Compound gamma GT/relapse criterion	2					
Desialotransferrin/relapse criterion			2			
Frequency of alcohol consumed	2	2	2			
Quantity of alcohol consumed	2	2	2	2		
Physician's clinical global impression	2	2	2	2		2
Physician's treatment success rate	2				2	2
Physician's evolution of the overall alcohol dependence				2		
Alcohol craving using the visual analogue scale					2	2
Patient's subjective improvement rating					2	2
Psychological dependence						2

Data Source: European Short-Term Supportive study reports.

Sponsor's In-Text Table 8.4.3:1 Note: 1= primary efficacy parameter; 2 = secondary efficacy parameter.

Each of the controlled European short-term supportive efficacy studies followed the same ITT principle. Any randomized patient who had taken at least one dose of study medication was eligible for analysis. All patients who terminated treatment prior to the end of treatment were assumed to be treatment failures.

Detailed descriptions of these studies (taken primarily from sponsor's integrated summary of efficacy, as primary data was not provided, and from final study reports) are included in the appendix (Section 10).

5.7.2 Long-term studies: features

The 3 controlled European Long-Term Supportive efficacy studies include the Lesch, Barrias, and Besson studies, all of which had a 1 year treatment phase duration. These studies were conducted in 3 different European countries (Austria, Portugal, and Switzerland, respectively)

and involved 868 randomized alcohol-dependent outpatients (435 to acamprosate, 433 to placebo). The same basic study design was used for each of the 3 controlled European Long-Term Supportive studies: namely, each study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison of acamprosate and placebo. The primary objective of each of the 3 studies was to compare the efficacy and safety of acamprosate and placebo in maintaining abstinence over a 1-year treatment period in the weaned alcoholic. A secondary objective of each study was to determine whether efficacy was maintained over an observation period following the 12-month double-blind treatment period. In the Besson study, patients were allowed to elect to take disulfiram, in addition to study medication, and there are some analyses of the treatment combination

CAD and relapse rate at each visit were identified as the primary efficacy parameters in all 3 studies.

As with the other European studies, the majority of the long-term supportive studies used a 43 or 44 item checklist on which to record spontaneously adverse events. In addition, the checklist was reviewed with the patient to solicit other treatment-emergent symptoms.

Detailed descriptions of these studies (taken primarily from sponsor's integrated summary of efficacy, as primary data was not provided) are included in the appendix (Section 10).

5.7.3 European Non-Pivotal Studies: Results

Only UKMAS, the single study which failed to provide any evidence of acamprosate's efficacy, used daily drinking diaries to collect drinking data. Most studies appear to have relied on investigators and subjects to reconstruct long periods (often 3 months or more) of drinking history in a non-systematic fashion. In addition, UKMAS involved study visits occurring every three weeks, while other studies had as few as three on-treatment study visits over six months. Therefore, the CAD and CCAD measures must again be viewed with some skepticism. To provide a more conservative measure of outcome, I identified, wherever possible, the rates of complete abstinence throughout treatment for each study. The CCAD results and complete abstinence rates are summarized in the table below, along with comments on other aspects of the studies.

Continuous abstinence rates were higher for acamprosate than for placebo in all studies except UKMAS. However, the comparison was statistically significant (by the method used in the final report of the particular study) only for the studies indicated with an asterisk in the table below.

**APPEARS THIS WAY
ON ORIGINAL**

Summary of Results of Non-Pivotal European Studies

Study Name Duration N	CCAD (% days abstinent during treatment period)		Continuous Abstinence (% of subjects reaching end of treatment period without drinking)		Other	Comments
	Acamprosate	Placebo	Acamprosate	Placebo		
Poldrugo 180 days N = 246	72%	59%*	47%	26%*		Only three on-treatment visits
Tempesta 180 days N = 330	66%	54%*	47%	31%*		
Benelux 180 days N = 262	35%	24%*	15%	10%	Inconsistent results in abstinence-by-visit	Low completion rate; ?unblinding due to AE's; two different protocols combined for analysis
ADISA 180 days N = 288	52%	41%*	35%	26%		Treatment initiated during outpatient detox; GI symptoms may have unblinded
Ladewig 180 days N = 61	47%	26%*	17%	3%	N.S. results in abstinence by visit	Very small study; Only 3 on-treatment visits; GI symptoms may have unblinded
UKMAS 168 days N = 581	46%	48%	12%	11%		Low completion rate; Used a daily drinking diary card that was collected at each visit; Visits occurred q 3 weeks
Lesch 1 year N = 448	39%	30%*	18%	7%*		Disulfiram permitted but little-used; Only 5 on-treatment visits over 1 year; GI symptoms in 20% acamprosate vs 12% placebo
Barrias 1 year N = 302	49%	36%*	35%	20%*	Inconsistent results in abstinence by visit	
Besson 1 year N = 110	40%	21%*	25%	5%*	Inconsistent results in abstinence by visit	Small study; Low completion rate; ~40% used concomitant disulfiram

Table prepared by reviewer from Final Study Reports. CCAD not reported was calculated as CAD/180.

*Significant by analysis reported in Final Study Report

The highly conservative “continuous abstinence” standard showed statistically significant results in favor of acamprosate in only two of the short-term studies; however, in all studies except UKMAS, the rate of complete abstinence was higher in the acamprosate group than in the placebo group. The three long-term (1 year) studies did show statistically significant results in favor of acamprosate (based on the analyses in the respective final study reports) in continuous abstinence, adding support to the findings of the 1-year Paille and PRAMA studies, although it must be noted that one study (Besson) was very small and had a low completion rate and was further complicated by permitted concomitant disulfiram, and that another (Lesch) had only 5 study visits over a 1-year period.

5.8 Efficacy Conclusions

Taken together, the three European pivotal studies provide evidence of the efficacy of acamprosate in the maintenance of abstinence in recently detoxified alcoholics. The non-pivotal European studies provide further support.

The single U.S. study failed to support the efficacy of acamprosate, and this discrepancy was addressed in a meeting of the Psychopharmacologic Drugs Advisory Committee on May 10, 2002. The recommendation of the Committee was to accept the validity of the European studies (pending inspection), and to regard the American study as a failure, providing neither evidence of *lack* of efficacy, nor evidence of efficacy in any particular subgroup. The constrained setting in which evidence of efficacy has been demonstrated in European studies (i.e., only in patients who had completed an inpatient detox) was noted.

5.8.1 Overall Efficacy Findings

The non-systematic approach to the collection of alcohol use data should be recalled.⁷ Because of this non-systematic approach to the collection of the drinking behavior data, reconstruction of day-by-day abstinence goes beyond the level of sensitivity of the measure. Calculation of “cumulative abstinence time” overstates the precision of the data. Indeed, it is not known how many days the subjects were drinking and how many they were abstinent. Thus it seems inappropriate to generate conclusions based on such calculations.

What appears to be known with somewhat greater certainty is how many patients attended all visits and reported at each visit that they had abstained since the beginning of the trial. This number is not high, and it may be an overestimate, as it is not clear that data were collected by study personnel (rather than treatment personnel), offering the possibility of demand characteristics influencing subjects to deny drinking. However, these characteristics may be assumed to apply equally across treatment groups. Therefore, although we cannot be confident

⁷ In Pelc-II, the investigator was asked to record “average frequency of alcohol consumption” as well as an estimate of intensity (drinks per drinking day). However, for the purposes of analysis, this data was transformed to a binary outcome (abstinent/non-abstinent) and that value was imputed for all days in the two week interval.

In Paille, the investigator was asked, “after considering all the elements at his disposition” to record “estimated number of days of non-abstinence in the cours of the last month” (as well as drinks/drinking day). No systematic method (e.g. time-line-follow-back) was employed to reconstruct 1-2 months’ worth of information.

In PRAMA, drinking behavior was recorded as “abstinent since last visit” or “not abstinent since last visit.”

that the absolute proportion of abstinent subjects is accurate, it is reasonable to assume the relative proportions across treatment groups are a fair representation of the treatment effect.

Because the treatment periods varied among the studies, it is not surprising that there are very different proportions of subjects remaining in the completely abstinent subset. However, the subjects meeting this criteria are listed below:

Table 5.8.1 Continuous Abstinence in European Pivotal Trials

	Duration of treatment	Treatment		
		Placebo	Acamprosate 1332 mg/day	Acamprosate 1998 mg/day
Pelc-II ¹	90 days	9 (15%)	26 (41%)	26 (41%)
Paille ²	360 days	20 (11%)	34 (18%)	33 (19%)
PRAMA ³	48 weeks (336 days)	16 (12%)	N/A	39 (29%)
PRAMA + Paille		36 (12%)		72 (23%)

¹The values listed here are the proportions of subjects listed as having a "Time to first relapse" of >90 days. (Statistical Report Table 5.6, vol 76, page 30)

²The values listed here are the proportions of subjects listed as continuously abstinent through 340 days. This number was used in the analysis by the sponsor to allow for the uncertainty of scheduling the 360-day visit. The additional 6 months of off-treatment follow-up are not considered here

³The values listed here are the subjects coded as not relapsing in the uncensored analysis

This conservative analysis shows that acamprosate, at a dose of 1998 mg/day, is superior to placebo in preventing relapse to alcohol use in detoxified alcoholics. Taken together, these studies provide substantial evidence of efficacy of the drug in the intended indication. A variety of other analyses (largely less conservative and relying on more assumptions and imputation of data) undertaken by the sponsor further strengthen this conclusion. Analyses relying on non-continuous abstinence (number of visits at which subjects were assessed as abstinent) undertaken by the reviewer also confirm the finding and support the conclusion that, compared to placebo, acamprosate increases the cumulative time assessed as abstinent for a year after detoxification.

5.8.2 Discussion

The choice of analysis for the European pivotal trials is somewhat arbitrary, as there were often no prospectively defined analytic approaches, and an integration of the data requires selection of a common endpoint appropriate to all studies. However, the sponsor's approach of calculating the number and percent of the days in the study during which subjects were abstinent is clearly unsatisfactory, relying on arbitrary transformations of clinical global impressions into continuous data measured in days. Manipulations of this highly imputed data are fundamentally meaningless.

Restricting ourselves to what is known—the assessment of abstinence or non-abstinence at each visit, it is possible to compare groups on either continuous or non-continuous abstinence. Either analysis supports the efficacy of acamprosate.

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

The only problematic issue in this dataset is the negative finding in the American study, which, unlike the European study, used a systematic approach to reconstructing drinking behavior day by day, and is amenable to analysis to determine number or percent of days abstinent. The resulting value for the acamprosate-treated group (46% days abstinent) is lower than the strikingly consistent result in the sponsor-calculated CCADs for the European studies (~62%), but this is possibly attributed to the greater precision of the data collection method, allowing capture of more non-abstinent days. Arguing against this, the value for the placebo-treated group, however, is somewhat higher than in the European studies (51% vs 38-48%).

The most plausible explanation offered for the failure of the US study to demonstrate efficacy of acamprosate is that the ancillary treatment offered in the study (both the psychosocial component and any therapeutic benefit of the data collection process) produced a favorable response in the subjects that left little room for a contribution of medication to the effect. Indeed, using the sponsor's own calculations of percent days abstinent, the placebo response was highest in the US study. It cannot be overlooked, however, that it was higher than the percent days abstinent in the acamprosate treated group. Unfortunately, this makes it difficult to simply dismiss Study US96.1. The Psychopharmacologic Drugs Advisory Committee was asked to consider the discrepant data, and to determine whether the European studies were sufficiently credible to support approval in the face of the failure of the American trial. In addition, the Committee was asked to consider whether the data supported conclusions regarding any subset most likely to benefit from acamprosate. The recommendation of the Committee was to accept the validity of the European studies (pending inspection), and to regard the American study as a failure, providing neither evidence of *lack* of efficacy, nor evidence of efficacy in any particular subgroup. The constrained setting in which evidence of efficacy has been demonstrated in European studies (i.e., only in patients who had completed an inpatient detox) was noted.

**APPEARS THIS WAY
ON ORIGINAL**

6 Integrated Review of Safety

The safety data was reviewed by Drs. Michael J. Sevka and Charles Cooper. A complete integrated review of safety could not be performed due to deficiencies in the organization of the safety data submitted. The tentative conclusions and identification of deficiencies with recommendations for their resolution are found in Dr. Sevka's and Dr. Cooper's reviews.

6.1 Safety Findings and Limitations of Data

It is difficult to summarize with confidence even the number of exposed patients and duration, adequacy of monitoring and follow-up, as studies varied considerably in the methods of ascertainment of safety findings. Only three studies of approximately 6 months (US 96.1, UKMAS, and ADISA) and two studies of approximately one year (PRAMA and Paille) collected spontaneously-reported adverse events. These studies enrolled 1275 subjects randomized to acamprosate (1063 at the proposed recommended dose or higher).

All other studies used a 43-item checklist for collection of adverse events and any AE not included on the list was recorded as "other." If the event led to discontinuation, it was included on the CRF and was captured in a retrospective review of CRFs. Therefore, most serious AEs for these studies are also captured.

It is not clear whether deaths and SAEs are also captured for Phase 1 and 2 studies, or for the extensive Phase 4 European studies.

Because overall group N's cannot be determined with confidence for the various groupings of reports, no rates can be calculated to compare the incidence of serious side effects to the rates in the placebo groups.

In general, the most common side effect that appears to be clearly drug-related within individual studies (where N's can be readily ascertained) is diarrhea. Reports of pruritis and transient hypotension are also notable in literature.

The safety testing in the development program appears to have given little attention to evaluating cardiac conduction effects of acamprosate. Only two clinical trials recorded ECG's at any point during treatment. Cardiac effects may require additional evaluation if data are not available from earlier studies. Laboratory parameters assessed also varied considerably across studies, and certain parameters were assessed in only a small number of subjects.

The overall safety database is large, but as noted, the ascertainment of safety findings was inconsistent and, by current standards, incomplete. Furthermore, subjects over age 65 were routinely excluded. Polysubstance abusers were not included in most studies, but are prevalent in the target population in the U.S. Few women were included. Renal impairment was also grounds for exclusion in most trials. Safety issues in these subpopulations may arise after marketing.

6.2 Other Studies Relevant to Labeling

6.2.1.1 AOTA/F/91.6 (ASATIM: Acamprosate, Alcohol Withdrawal and Drug Interactions):
Controlled Study On Drug Interactions And Clinical As Well As Biological Tolerance
Of Acamprosate When Administered Over A Period Of 15 Days At A Daily Dose Of 6
Tablets Or 1998 Mg/Day, Prescribed In Conjunction With The Usual Drugs For
Alcohol Withdrawal, D. Barrucand, France, 12/91-6/92.

The ASATIM study was an open, multicenter (29 centers), controlled, parallel study to evaluate side effects and drug interactions resulting from administration of acamprosate together with drugs commonly prescribed (in France in the early 1990's) during the treatment of the acute detoxification phase to prevent alcohol withdrawal syndrome. A secondary objective was to study the influence of acamprosate on various biological parameters during the period of acute alcohol withdrawal. Alcohol dependent males and females received 666 mg acamprosate tid from Day 1 to Day 15, alone or together with one of the following: Atrium (150 mg febarbamate, 105 mg difebarbamate, 45 mg phenobarbitone), 300 mg/day, Equanil (meprobamate) 500 mg/day, or Seresta (oxazepam) 20 mg/day as starting doses, titrated prn by investigator. In addition, the protocol indicated that, for subjects assigned to acamprosate alone, "should specific detoxification therapy be required during the 15 day treatment period, then Atrium, Equanil, or Seresta was permitted in addition to acamprosate at the dosage required for patients assigned to [other treatments], and this additional medication should be continued until day 15. Assignment to treatment condition was at investigator discretion. During the study AEs, ECGs, clinical laboratory evaluations, and physical examinations were assessed periodically.

A total of 591 patients (males: 491 patients; females: 100 patients) were enrolled, of whom 536 patients completed the study. The predominant reason for withdrawal was refusal to continue (33 of 55 patients). The patients' mean age was 40.5 years and the mean weight was 68.0 kg. The patients were not to have started weaning more than 48 hours prior to entry into the study. As noted above, assignment to treatment arm was at investigator discretion, and in practice virtually all sites offered a single treatments to all participants. Those enrolling subjects into more than one treatment arm all enrolled subjects into *one* detox med condition and the acamprosate alone condition, and all enrolled all subjects but one into the same arm (i.e., Center 7 enrolled 1 Atrium +acamprosate subject and 18 acamprosate-alone subjects; Center 30 enrolled 6 Equanil subjects and 1 acamprosate-alone). In total, 201 subjects were assigned to Atrium + acamprosate at 10 centers, 139 were assigned to Equanil at 7 *different* centers, 123 were assigned to Seresta at 9 *yet different* centers, and 128 were assigned to acamprosate, at 7 centers. The study report gives no indication of how many subjects assigned to receive acamprosate alone actually received other detox meds in addition.

Study results showed that the a higher percentage of the acamprosate-only group reported any adverse events than the other groups, particularly after day 3. To some extent, this is explained by a higher rate of withdrawal-related complaints. This finding suggests that the addition of sedatives for detox does not worsen the safety profile of acamprosate. However, the rate of early discontinuation paints a different picture. Although dropout due to adverse event was low (1% in Equanil and Seresta groups vs. 2% in Atrium group and 3% in acamprosate-only), another 6% of the total study population "refused to continue" for reasons left uncharacterized. This included 4% in each of the Equanil and Atrium groups, 5% in the acamprosate-only group, and fully 10% in the acamprosate + Seresta group. This suggests that the combination of

acamprosate + oxazepam may be poorly accepted. This is a notable result because, of the sedative drugs studied, only oxazepam is commonly used in the United States for the treatment of alcohol withdrawal.

Therefore, it is difficult to conclude with confidence that 'L

3—the wording currently proposed for use in labeling.

7 Dosing, Regimen, and Administration Issues

The proposed dose for marketing is two 333 mg tablets, t.i.d. Lower doses were studied earlier in the development plan but the application did not contain sufficient data demonstrating superiority of lower doses (e.g. 1332 mg/day) over placebo to recommend this dose. Further exploration of the 3 g/day dose is recommended.

The majority of the studies included in the safety database used t.i.d. dosing with meals. Because the effect of food on acamprosate kinetics is to lower systemic exposure, the administration of the drug at other times might alter the tolerability of the regimen. In the U.S. study, drug was administered apart from meals, and the rate of adverse events was noted to be higher. This may be a function of the study's closer monitoring of patients compared with the European studies, and represent a bias of ascertainment rather than a true dose-response for adverse events. However, it seems prudent to recommend the tested regimen (t.i.d. with meals) in labeling.

8 Use in Special Populations

8.1 Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Analysis of efficacy by gender was conducted for the three European pivotal trials. It does not appear that analysis by gender was undertaken for the "supportive" studies, or (understandably) for the U.S. trial. Women were not extensively represented in the clinical program. Because of the small number of female participants, firm conclusions cannot be drawn, but acamprosate appears to be effective in both men and women.

Safety analysis by gender, based on the sponsor's integrated summary of safety and therefore subject to revision when the data is resubmitted, shows few treatment-by-gender interactions in favor of placebo. The exception is diarrhea, which seemed to be more prevalent in the female subjects on acamprosate (27%, vs 20% in males) while the rates in placebo groups (~12%) were similar across genders.

8.2 Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Subjects over 65 were excluded from the European studies per protocol (although some appear to have been included). Only 6% of subjects (129/2287) in the integrated safety database were ≥60 years old. Therefore, exposure in this demographic group was small and may represent an area for further exploration. The older subjects showed trends toward greater treatment group difference (in favor of placebo) in the rates of adverse events reported in several body systems, particularly the GI system. However, group N's are small (~60 people) and therefore the data must be interpreted with caution.

Information about the race of subjects was collected only in the U.S. study; therefore it is impossible to draw conclusions about effects of race on efficacy. For the small group of black subjects (52/601), larger treatment group differences in favor of placebo (compared to caucasian subjects) were noted in reports of SGOT increased and hyperglycemia. Additional safety information in a broader population representative of U.S. alcoholics may be indicated.

8.3 Evaluation of Pediatric Program

Pediatric data has not been submitted. Lipha has requested a partial waiver of the requirement for pediatric studies, noting that the product is unlikely to be used in a substantial number of patients under age 12. Lipha has requested a deferral of submission of data on pediatric patients 12 and over and plans to submit a pediatric development plan after approval of the application for use in adults. This strategy is acceptable.

8.4 Comments on Data Available or Needed in Other Populations

Use in pregnancy is possible, but no information is available on the safety of such use. Preclinical findings are equivocal and will require some additional assays for complete evaluation. The use of alcohol in pregnancy is of known risk to the fetus. Therefore, it is anticipated that at least some clinicians will assess the potential benefits (abstinence from alcohol) as outweighing the risk. Specific evaluation of pregnancy outcomes may therefore be valuable.

Studies in hepatic impairment are included in the NDA and do not indicate a need for dose modification.

Studies in renal impairment suggest dramatic accumulation is possible in severely renally impaired patients. Further study may be needed; the drug should not be recommended for use in this population is recommended at this time. Dose reduction is to be recommended for patients with moderate-mild renal impairment.

9 Conclusions and Recommendations

9.1 Conclusions

Acamprosate has been demonstrated to be superior to placebo in maintaining abstinence from alcohol in recently-detoxified alcoholics. The effect, though modest in longer-term studies, is significant whether one compares the number of subjects surviving without relapse to the end of the study, or the number of on-study visits at which subjects are assessed by the investigator as abstinent. However, the evaluation of acamprosate's safety profile has been complicated by inconsistencies in the safety database.

9.2 Recommendations

Based on the clinical efficacy data, the application is approvable. However, resubmission of the safety datasets with clarification of the inconsistencies is required to facilitate review of the safety profile. Because it is not yet clear whether the safety profile is acceptable, non-approval is recommended.

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

The sponsor should be informed of the following deficiencies in the presentation of the safety data and accompanying suggestions for their correction to facilitate safety review:

1. It is not clear that overall exposure is adequate to meet ICH guidelines for a chronically-administered new molecular entity. Piecing together various tables of short-term and long-term studies from the ISS, reviewers concluded that 71 patients have been exposed to acamprosate 1998/2000 mg for 52 weeks or more, yet other patients are known to have been exposed up to and more than 48 weeks. The sponsor should be asked to examine the database for the number of patients exposed to acamprosate for 48 weeks or more at the 1998/2000 mg/day dose and their compliance with study treatment to be certain that there has been adequate exposure for 1 year in accordance ICH guidelines.
2. The sponsor has used an arbitrary cut-off which excludes events which occurred 10 days post-treatment. The sponsor should be asked to examine their databases for AEs and SAEs occurring up to 30 days after last exposure to study treatment. Characterizing such events is important because of acamprosate's relatively long half-life, and because its CNS activity may be assumed to be mediated through actions at receptors which may persist long after plasma levels are no longer detectable. Therefore, even the half-life is not a good estimate of the duration of action. It will be of significant interest from a safety perspective to know what AE's (such as suicide, suicidal ideation, etc.) may have occurred upon withdrawal of the drug (i.e., after discontinuation).

All AE's, SAE's, and deaths which were formerly categorized as having occurred in the "follow-up" phase, should be included in the safety analysis. This should include all known AE's for patients who participated in these clinical trials. It would be appropriate to include the following analyses: 1. an analysis of all such AE's separately in a "follow-up" analysis 2. an analysis of all AE's which occurred during "follow-up" combined with those occurring during "treatment phase" 3. AE's which only occurred during "treatment phase."

In those situations where there is no recorded date of the adverse event, separate analyses should be conducted in which such AE's are included first in the on-therapy analysis, in the follow-up phase analysis, and in the combined analysis.

The inclusion of such an analysis (all AE's, SAE's, and deaths which occurred during the "treatment phase" and "follow-up" phase) will allow the FDA the ability to account for ALL such events.

3. The current NDA safety analysis cannot be confirmed by FDA reviewers because there is no clear variable in the adverse event data set indicating which AE's/ SAE's/deaths/dropouts due to AE's were included in the analysis and which were not. An ISS safety population variable does exist but it is not clear why many patients were not included in this population. The sponsor should be advised that a full detailed accounting of all AE's/SAE's/Deaths, and dropouts due to AE's should be included in the ISS.

The present submission only includes narratives for those SAE's, deaths, and dropouts due to AE's which were included in the sponsor's chosen analysis, but not all such events.

Narratives should be supplied for all patients who withdrew due to AE's, SAE's, and/or deaths for all patients who participated in these studies. This includes all such events which occurred at any time (before, during, or after drug exposure). When it is not clear as to whether a specific adverse event resulted in withdrawal from the study, it should be assumed that such adverse event did result in withdrawal from the study.

4. There is lack of apparent consistency of the capture of the outcome of death. Two patients (Barrias-63; UKMAS-484) were not counted in the paper version of the ISS with an outcome of death even though both died within 10 days of last exposure to study treatment. The sponsor should be asked to explain how this came about, re-examine their databases and identify any other such cases. Furthermore, it is unclear if deaths from all clinical trials, including those not included among the "Group I" studies have been captured. Given the very large exposure in Phase 4 open-label trials, it is important to clarify whether these exposed patients were included in the overall database from which deaths were collected.
5. There is conflicting information in this NDA as to how and when a particular AE was categorized as being a "Serious Adverse Event." For instance, in the data table of contents "define.pdf" which is included for the dataset SS_AES (adverse event dataset), there is a variable called "AESER." This variable is described in this file in the following way:

"Variable has a value of 1 to indicate if Adverse Event is Serious Adverse Event.
Note: primarily applicable to records from US 96.1 study. It should be mostly missing for records from the other 12 studies."

However, upon review of the adverse event dataset, it is evident that there are 71 adverse events from numerous studies other than US96.1 in which this variable is assigned (SAE "flagged"). These studies include the following: Pelc II, Poldrugo, Lesch, Ladewig, Besson, Barrias. The majority of AE's for patients in these studies do not have an assignment for this variable. It is unclear why some, but not all AE's from these studies received a designation for this variable. It appears that the decision to apply this variable is inconsistent and therefore, subject to bias.

The value of "0" has been assigned to this variable in some cases, while in many other cases it is blank. Missing records (no assignment of a value to this variable) were present in data from both the "other 12 studies" referred to in the data definition, and from the US96.1 study, for which an assignment of serious/non-serious could presumably have been made for each event. Notably, for the study US96.1, there are listings for 686 adverse events which do not have an assignment for this variable.

Furthermore, the description included in the ISS which defines "Serious Adverse Event" raises concern. This definition is as follows:

"Serious adverse events were only identified in the database for the US 96.1 study. In order to identify an SAE according to the current FDA definition (i.e., an event which is fatal, life-threatening, results in or prolongs hospitalization, disability/incapacity, or a congenital anomaly/birth defect) and any event of

C:\Data\My Documents\Acamprosate\21431.doc

cancer or overdose, a review of all study reports for the double-blind, placebo-controlled studies, was undertaken. Events meeting the FDA's criteria for an SAE were identified using subject narratives, descriptions of concurrent illnesses as reason for withdrawal, and AE listings. In addition, for studies with spontaneously reported AEs (US 96.1, UKMAS, ADISA, PRAMA, and Paille) SAEs 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.”

It is not clear whether this described process resulted in the assignment of a result for the variable “AESER” (flagging as SAE) or some other variable. It is also not clear why this methodology appears to have been only applied selectively.

6. In addition to lack of clarity regarding the flagging of SAE’s in the datasets, there is some concern about whether all SAEs have, in fact, been captured. 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 number. Examples of additional search terms which should be used include but are not limited to: *fatality, fatal, death, died, arrest, coma, life-threatening, suicidal, depression, psychosis, arrhythmia, gast/gastro, bleed, abdominal pain, diarrhea, vomiting, syncope, fall, paralysis, stroke, convulsion, seizure, renal/kidney failure/dysfunction, hepatic/liver failure/dysfunction, hepatitis, anaphylaxis, agranulocytosis, aplastic anemia, neutropenia, rash, pruritis, exfoliation, Stevens-Johnson, toxic epidermal necrolysis, rhabdomyolysis, tumor, birth defect, congenital anomaly*. The sponsor should be asked to re-examine their databases from non-US studies, using these descriptors or part of descriptor terms as search terms, determine if the AEs fit the definition of a SAE, and analyze them according to short-term and long-term groups.

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 SAE’s but were flagged as TEAE’s 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 SAE’s. Examination of those who were flagged as TEAE’s 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. The sponsor should be asked to re-examine their AE’s and flagging of SAE’s and reconcile discrepancies.

7. The datasets which were submitted by the sponsor are cluttered with large numbers of non-used variables and redundant variables which makes FDA review of the data difficult. There is no unique patient identifier facilitating the merging of various datasets. Attempts at merging datasets using multiple variables, including study number and patient ID have yielded results which do not match those reported in the NDA report. Future submissions should assign a unique identifying number for each patient in the NDA and this should be included in all datasets such that merging of datasets can be done with some degree of accuracy. Datasets should also include treatment assignment in every table (so that merging to determine treatment assignment is not necessary), data definition tables should be provided with the column names in the same order as the dataset, with a comprehensive explanation of each data element, including explanation of the derivation for derived elements.
8. In the text of the Integrated Summary of Safety, a particular source of confusion is the continually shifting number of subjects included in various analyses. For every grouping (e.g. Group I studies capturing all spontaneous AE's, all studies evaluating a particular laboratory parameter, all studies for which deaths were fully captured), a separate presentation of the denominators should be provided so that rates may be calculated. Rates should be presented overall, by treatment group, and by gender, age, and race across treatment groups. The continually changing denominator requires that for every table, analysis, etc., the specific studies included in the grouping and the resultant N's for each group must be presented with each analysis.
9. Review of the coding of verbatim terms under preferred COSTART terms shows that the coding may not be appropriate or consistent and raises concern over the reliability of the database. The sponsor should be asked to re-examine their coding of AE's and to reconcile discrepancies.

The following are examples:

- Reports of high blood pressure have been subsumed in *hypertension* and then in the nervous system instead of cardiovascular system. Although the COSTART system provides for inclusion the nervous system as a body system, it seems more appropriate to link systemic hypertension to the cardiovascular system.
- Verbatim terms denoting relapse have been coded to *alcohol intolerance*. Consideration should be given to re-coding them to *drug dependence* and further to the nervous system as provided by the COSTART system rather to the nutritional and metabolic body system. Alternatively, because of the context in which relapse is observed in these studies coding to *treatment failure* might also be considered.
- Verbatim terms describing positive urine toxicology results have been coded as *drug dependence*. The sponsor should clarify why positive urine toxicology results have been included as adverse events (perhaps to detect compensatory increases in other drug use in the face of alcohol cessation). Consideration should be given to coding isolated toxicology results separately from other instances of *drug dependence*.
- Specific joint pain terms are subsumed in *pain* and then in body as a whole and should be subsumed in *arthralgia*;

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

- Verbatim terms related to suicide are not consistently coded – for example, in the SS_AEs database subject 32 (study 4) has a verbatim term of *suicide (strangulation)* and is coded to the terms *death* and *suicide attempt*; but subjects 203 and 236 (study 10) have a verbatim term of *suicide* but are coded only to *suicide attempt* and not to *death* yet both have *death* listed as an outcome. A similar comparison can be made for subject 106 (study 3) and subject 29 (study 3). Completed suicides should be consistently coded to both *death* and *suicide attempt*.
- Two different sets of abbreviations for body system were used. This complicates the generation of adverse event tables organized by body system. The dataset should use only one set of abbreviations.

In the resubmission, the sponsor should provide a thesaurus, listing each preferred term and all verbatim terms subsumed under that term. This thesaurus should be reviewed by an experienced and medically knowledgeable individual and gross errors should be corrected prior to submission (bruising coded as *hemorrhage* rather than *ecchymosis*, e.g.). Inconsistencies in coding should be rectified, such as obvious site-specific differences in the handling of reports of upper respiratory infection (e.g. infection vs. flu syndrome vs. various other terms).

10. Discrepancies exist between various files within the safety data files. Examination of the various electronic databases for this NDA revealed discrepancies between some of the AE databases regarding patient inclusion. For example dataset SS_AECPT is the file that contains data found in either dataset SS_SPT (Dataset for spontaneously reported AEs) or dataset SS_QPT (Dataset for checklist reported AEs). Examination of the combined dataset for the partial term, *suicid*, yields 12 unique patients (9 – acamprosate treated; 3 – placebo treated) with all 12 coming from studies reporting AEs spontaneously and none from studies reporting AEs by checklist, yet narratives are available for suicide deaths from checklist-reporting studies. Similarly, examination of the checklist derived database does not yield any cases with the partial term, *suicid*.

In another example, datasets submitted on 2/11/02 were to have been derived from datasets submitted on 1/18/02, but containing only one report per patient of any given term. When compared with the original datasets which contained all reports from all patients for all terms, the number of unique terms was different between the two datasets.

The sponsor should be asked to ensure that these discrepancies are resolved prior to resubmitting the safety datasets.

11. The reasons for premature discontinuation have been categorized in such a way that some discontinuations due to adverse events or due to lack of efficacy may have been obscured in the category “other.” The “other” category combines investigator/sponsor decision, patient refusal, and miscellaneous reasons. Furthermore, “patient refusal” appears, in some cases, to have subsumed situations in which patients indicate unwillingness to continue in the study due to discomfort with side effects; such discontinuations should be classified as discontinuations due to AE’s. It also includes, in the case of the US study, “seeking alternative treatment,” which may be more appropriately categorized as “treatment failure.”

The sponsor should be asked to examine the reasons for discontinuation to evaluate the appropriateness of the coding.

10 Appendix

10.1 Labeling Review

A full labeling review was not undertaken because the description of the safety profile in the proposed label cannot be confirmed. However, preliminary comments may be conveyed to the sponsor.

In the pharmacodynamics section, description of the effects of acamprosate [] (Poenaru) should be deleted unless a case can be made for clinical relevance:

[]

The description of the [] should be deleted:

[]
cases under diazepam

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

The descriptions of the [] should also be deleted:

[]

Because subjects were tested [] substantially prior to Tmax for acamprosate, the results of this study do not seem applicable to the clinical situation (further complicated by the observation that Cmax at steady state is nearly 4x that after a single 666 mg dose). The lack of an additive effect of acamprosate (prior to Tmax after a single dose) on the impairment seen in extremely intoxicated subjects [] is of uncertain clinical significance.

In the clinical trials section, this text is recommended as replacement for the current descriptions:

The efficacy of BRANDNAME in the maintenance of abstinence was
[] three clinical studies involving a total of 998 []
patients who were administered at least one dose of the BRANDNAME or
placebo, [] to psychosocial therapy.
Each trial was a double-blind, placebo-controlled trial in []
[] alcohol-dependent patients who had undergone inpatient detoxification
and were abstinent from alcohol on the day of randomization []
90 days to 360 days. BRANDNAME, [] proved superior
to placebo in maintaining abstinence, as indicated by a greater percentage of
[] subjects being assessed as continuously abstinent throughout
treatment []

[]

In the Drug Interactions section, this text should be deleted (see Section 6.2.1.1, above):

[]

In the Dosage and Administration section, it is recommended that the text include the phrase
"with meals," as all studies but the US96.1 study administered medication with meals; therefore
the safety profile primarily represents the experience of subjects using the medication at
mealtimes.

APPEARS THIS WAY
ON ORIGINAL

10.2 Individual More Detailed Study Reviews

10.2.1 AOTA/I/89.4 (Poldrugo): A Study of the Effectiveness and Tolerance of Acamprosate as an Aid to Maintenance of Abstinence in the Weaned Alcoholic in a Double-Blind Trial versus Placebo

AOTA/I/89.4 (Poldrugo) was a prospective, multicenter (7 centers), randomized, double-blind, placebo-controlled, parallel group (2) study the objective of which was to compare the efficacy and safety of acamprosate and placebo on maintaining abstinence in weaned alcohol-dependent outpatients, over a 6 month treatment period. The clinical portion of the study was conducted from October 1989 to July 1992 (treatment phase) at 7 centers in Italy, with Prof. Flavio Poldrugo, M.D., Ph.D. (Assoc. Professor of Psychiatry, Alcohol Research Center, Dept. of Psychiatry, Trieste, Italy) as overall Principal Investigator. All of the investigators were either psychiatrists and/or physicians who were alcohol specialists and the study locations were primarily alcoholism centers in city hospitals.

To be eligible, subjects were: 18 to 65 years of age with a DSM-III diagnosis of alcohol dependence $x \geq 12$ months; GGT $\geq 2x$ the upper limit of normal and MCV ≥ 95 fL. Subjects were excluded for pregnancy, inadequate contraception, medical or psychiatric illness, renal insufficiency, hypercalcemia, and unsuitable living conditions.

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

Eligible patients were randomly assigned to receive acamprosate or placebo in a ratio of 1:1. The total daily dose was adjusted according to the patient's weight (1998 mg/day for subjects >60 kg, 1332 mg/day for lighter subjects). Study medication was to be taken at meal times. The scheduled duration of treatment was 180 days. The study consisted of 7 visits (screening, baseline, 3 on-treatment visits over the first six months, and two off-treatment follow-ups over the next six months), as follows: Visit -1 (Screening visit), Visit 0 (Baseline visit), Visits 1-3 (on Day 30, 90, and 180, respectively) during the Treatment Phase and Visit 4 and 5 (on Day 270 and Day 360) of the Follow-up Phase. Throughout the study, patients were provided with psychotherapy at each investigator's discretion according to each site's usual practices, although such therapy was to be held constant during the course of the study.

The primary efficacy criteria were CAD and relapse rate at each visit. Safety evaluations were performed at each visit and consisted of a review of AEs, clinical laboratory determinations (hematology, clinical chemistry, and urinalysis), and vital signs.

A total of 256 patients were selected, of which 246 patients were randomized to receive 180 days of treatment with acamprosate (122 patients) or placebo (124 patients) and included in the ITT population. More patients in the acamprosate group (53%) completed the double-blind treatment phase than in the placebo group (38%). More placebo patients discontinued due to treatment failure (23% vs. 16% in acamprosate group) and for adverse events (13% vs 8% in acamprosate group). The reasons for discontinuation are listed in the table below.

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

Parameter	Statistic	ACAMP (N=122)	Placebo (N=124)
Number of Patients Randomized	n	122	124
Number of Patients in the ITT Population	n (%)	122 (100%)	124 (100%)
Number of Patients Who Completed the Double Blind Treatment Phase	n (%)	65 (53%)	47 (38%)
Number of Patients Who Discontinued the Double Blind Treatment Phase	n (%)	57 (47%)	77 (62%)
Reasons for Discontinuation:			
Adverse Event	n (%)	10 (8%)	16 (13%)
Lost to Follow-up	n (%)	4 (3%)	5 (4%)
Treatment Failure	n (%)	20 (16%)	29 (23%)
Death	n (%)	1 (<1%)	0
Protocol Violation	n (%)	1 (<1%)	4 (3%)
Other	n (%)	21 (17%)	23 (19%)

Data Source: Table 8.7.2.1.1

Sponsor's In-Text Table 8.4.3.1:1

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

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

Demographic characteristics and history of alcohol use at Baseline were similar across treatment groups. Seventy-three percent of patients were male (69% in the acamprosate group and 77% in the placebo group), and the mean age was 44 years (42.9 years in the acamprosate group and 44.8 in the placebo group). History of alcohol use at Baseline was similar for both treatment groups with patients having a mean duration of alcohol dependence or abuse of at least 10 years (10.0 years in the acamprosate group and 11.8 years in the placebo group). A high percentage of patients in each treatment group averaged more than 10 standard drinks per day at study entry (77% for acamprosate and 73% for placebo), and 46% of patients had at least 1 prior treatment for alcoholism (46% in the acamprosate group and 47% in the placebo group). Over twice as many subjects in the placebo group had >3 prior treatments (16% vs. 9% in the acamprosate group). Contrary to the protocol, there was 1 patient in the acamprosate group who did not have a detoxification prior to randomization and was not abstinent at Baseline.

**APPEARS THIS WAY
ON ORIGINAL**

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

Parameter	Statistic	ACAMP (N=122)	Placebo (N=124)
Gender	n	122	124
Male	n (%)	84 (69%)	95 (77%)
Female	n (%)	38 (31%)	29 (23%)
Age (years)	n	122	124
	Mean (SE)	42.9 (0.9)	44.8 (0.8)
Weight (kg)	n	122	124
	Mean (SE)	69.5 (1.1)	69.0 (1.1)
	Min, Max	42, 102	45, 105
Marital Status	n	122	124
Married	n (%)	73 (60%)	69 (56%)
Not Married	n (%)	49 (40%)	55 (44%)
Detoxification Prior to Randomization	n	122	124
Yes	n (%)	121 (>99%)	124 (100%)
No	n (%)	1 (<1%)	0
Abstinence at Baseline	n	122	124
Yes	n (%)	121 (>99%)	124 (100%)
No	n (%)	1 (<1%)	0
Duration of Alcohol Dependence/Abuse (years)	n	79	86
	Mean (SE)	10.0 (1.0)	11.8 (1.0)
Average Standard Drinks per Day at Study Entry	n	122	124
<5	n (%)	6 (5%)	7 (6%)
5-10	n (%)	22 (18%)	26 (21%)
>10	n (%)	94 (77%)	91 (73%)
Prior Treatment or Detoxes for Alcoholism	n	122	124
0	n (%)	66 (54%)	66 (53%)
1	n (%)	21 (17%)	23 (19%)
2	n (%)	16 (13%)	8 (6%)
3	n (%)	10 (8%)	7 (6%)
>3	n (%)	9 (7%)	20 (16%)

Data Source: Table 8.7.2.2.1 and 8.7.2.3.1

Sponsor's In-Text Table 8.4.3.1:2

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

Compliance was almost 100% for both groups.

The primary variables for evaluating efficacy were the cumulative abstinence duration (CAD) and the relapse rate. The CAD was defined as the total number of days of abstinence and was calculated as the sum of only those periods of complete abstinence. If any relapse was recorded at a specific visit, the total period from the previous visit was considered as relapse, although, this method was conservative and may over-estimate the length of the relapse period. In determining the period between visits, the scheduled day of assessment was taken into consideration rather than the actual day of the visit. The fraction of abstinent time during the study (corrected CAD or CCAD) was also calculated. The potential treatment duration was 180 days for all patients except those with concurrent illness who were censored.

The table below shows the results for CAD and CCAD.

Cumulative Abstinent Duration (CAD) and Corrected CAD European Short-Term Supportive Efficacy Study Poldrugo

Treatment period	CAD		CCAD	
	Days	SD	%	SD
0-180 days				
Placebo	70.40	±74.08	59	±46
Acamprosate	99.10	±79.97	72	±44
T-test	P=0.004		p=0.027	
Data Source: Poldrugo Study Report, Table 7				

Sponsor's In-Text Table 8.4.3.1:3

The two calculations for the cumulative abstinence duration show a statistically significantly longer duration of abstinence in the acamprosate treated patients.

To determine relapse rate, at each assessment visit (Days 30, 90, and 180) the investigator evaluated the patient and assigned him/her to 1 of 3 categories: abstinent, relapsed or non-attendant. The relapse rate based on the score for alcohol consumption (ranging from 0 = no alcohol to 3 = >10 drinks/day) was determined at each visit. To be rated as abstinent, patients were to have consumed no alcohol. Results are shown in the table below.

Number (%) of Patients Assessed as Abstinent, Relapsed, or Non-Attendant – European Short-Term Supportive Efficacy Study Poldrugo

Assessment Day/Treatment		Abstinent	Relapsed	Non-attendant	p-value
Day 30	Placebo	73 (58.9)	15 (12.1)	36 (29.0)	0.091 (1)
	Acamprosate	92 (75.4)	7 (5.7)	23 (18.9)	
Day 90	Placebo	49 (39.5)	10 (8.1)	65 (52.4)	0.034 (1)
	Acamprosate	67 (54.9)	8 (6.6)	47 (38.5)	<0.05 (2)
Day 180	Placebo	40 (32.3)	8 (6.5)	76 (61.3)	0.026 (1)
	Acamprosate	59 (48.4)	6 (4.9)	57 (46.7)	<0.05 (2)
Data Source: Poldrugo Study report, Table 5					

Sponsor's In-text Table 8.4.3.1:4 (1) Mantel-Haenszel Chi²

(2) Kendall-Tau-c (T value)

Statistically significant differences were reached in this 3-category variable on day 90 and day 180, but not on day 30. If patients in the relapsed and non-attendant categories are combined and considered as treatment failures, the proportion of patients abstinent compared with treatment failures show a statistically significantly higher proportion of patients on all assessment days in the acamprosate treatment group compared with the placebo treatment group.

In the survival analysis the time to the occurrence of the first relapse was estimated in each treatment group. The median survival time was 150.51 days for acamprosate and 60.97 days for

placebo ($p=0.0004$). In the acamprosate group, 47% were abstinent throughout the treatment period, vs. 26% in the placebo group.

The frequency and severity of spontaneously reported events or events recorded on the questionnaire were similar in each treatment group. Very few events were reported with a frequency $\geq 1\%$, providing reassurance that unblinding due to adverse events was unlikely to have occurred.

Follow-up Period: The 112 patients who completed the double-blind treatment entered the 180 day observation period. One hundred and one (96%) of these patients completed the observation period. At Day 360, 53 acamprosate treated patients (43%) were abstinent compared with 37 patients in the placebo group (30%). The difference between treatment groups was statistically significant ($p=0.027$).

The CAD over the entire study period (treatment phase plus follow-up phase) remained significantly longer in the acamprosate group compared to the placebo group. The CAD for acamprosate was 167.7 ± 151.1 days and 120.5 ± 146.8 days for placebo treated patients ($p = 0.014$); however, the CCAD for the entire period failed to reach statistical significance in favor of acamprosate ($p = 0.082$).

10.2.2 AOTA/I/90.1 (Tempesta): A Study of the Effectiveness and Tolerance of Calcium Acetylhomotaurinate (AOTA-Ca) as an Aid to Maintenance of Abstinence in the Weaned Alcoholic, in a Double Blind Multicenter Trial Versus Placebo

AOTA/I/90.1 (Tempesta) was a prospective, multicenter (18 centers), randomized, double-blind, placebo-controlled, parallel group (2) study the objective of which was to compare the efficacy and safety of acamprosate and placebo on maintaining abstinence in weaned alcohol-dependent outpatients, over a 6 month treatment period. The clinical portion of the study was conducted from October 1989 to April 1993 (treatment phase) at 18 detoxification centers in Italy, with Prof. Enrico Tempesta, M.D., L.D. (Assoc. Professor of Neuropharmacology; Chief, Drug and Alcohol Abuse Unit at University Hospital, Faculty of Medicine, Università Cattolica S. Cuore [U.C.S.C.], Rome, Italy) as overall Principal Investigator. All of the investigators were either psychiatrists and/or physicians who were alcohol specialists and the study locations were primarily alcohol detoxification units.

In order to be randomized into the study, male and female patients were: 18 to 65 years of age with DSM-III diagnosis of alcohol dependence, GGT $\geq 2x$ upper limit of normal, MCV ≥ 95 fL, and body weight ≥ 60 kg. Subjects were excluded for pregnancy, inadequate contraception, psychiatric or medical disorders, renal insufficiency, hypercalcemia, hyperparathyroidism, unsuitable living situation, or lack of collateral informant.

Eligible patients were randomized in a ratio of 1:1 to either 1998 mg of acamprosate or placebo per day, taken as 2 tablets of 333 mg acamprosate (or matching placebo) in the morning, at mid-day, and in the evening at meals. The scheduled treatment duration was 180 days with off treatment follow-up to day 270.

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

The study consisted of 10 visits: Visit –1 (Screening visit), Visit 0 (Baseline visit), Visits 1-6 (at Day 30, 60, 90, 120, 150, and 180, respectively) during the Treatment Phase and Visits 7 and 8 (at Day 225 and Day 270) of the Follow-up Phase. Throughout the study, patients were provided with psychotherapy at each investigator’s discretion according to each site’s usual practices, although such therapy was to be held constant during the course of the study.

Primary efficacy variables were CAD, time to first relapse/continuous abstinence, and abstinence by visit. Safety was assessed on the basis of spontaneously reported AEs and additional AEs reported in response to a 44-item checklist questionnaire at each visit. Clinical laboratory tests (hematology and clinical chemistry) were also obtained at regular intervals during the Treatment Phase.

In this study, 340 patients were screened, of which 330 were randomized to 180 days of treatment with acamprosate (164 patients) or placebo (166 patients). The number of patients who completed the double-blind treatment phase was similar between the 2 treatment groups (acamprosate, 164 patients [76%]; placebo, 122 patients [73%]). The reasons for discontinuation for the remaining 84 patients are shown in the table below. Only “other” (including patient refusal, non-compliance and “serious aggravation”) occurred more commonly in the placebo group than in the acamprosate group. Other reasons for discontinuation were evenly distributed across groups.

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

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=164)	Placebo (N=166)
Number of Patients Randomized	n	164	166
Number of Patients in the ITT Population	n (%)	164 (100%)	166 (100%)
Number of Patients Who Completed the Double Blind Treatment Phase	n (%)	124 (76%)	122 (73%)
Number of Patients Who Discontinued the Double Blind Treatment Phase	n (%)	40 (24%)	44 (27%)
Reasons for Discontinuation:			
Adverse Event	n (%)	2 (1%)	0
Lost to Follow-up	n (%)	16 (10%)	15 (9%)
Treatment Failure	n (%)	11 (7%)	11 (7%)
Death	n (%)	0	0
Protocol Violation	n (%)	0	0
Other	n (%)	11 (7%)	18 (11%)
Data Source: Table 8.7.2.1.2			

Sponsor’s In-Text Table 8.4.3.2:1 Note: Percentages are based on the number of patients randomized.
Note: Other includes refusal or inability to continue, non-compliance, and serious aggravation.

Demographic characteristics and history of alcohol use at Baseline were similar across groups. Eighty-three percent of patients were male and the mean age was 46 years. History of alcohol use at Baseline was also similar for both treatment groups. Duration of alcohol dependence or abuse averaged 11.5 years in both treatment groups and over half (55% in the acamprosate group