

FDA
Psychopharmacologic Drugs
Advisory Committee
May 10, 2002

Briefing Document for
Acamprosate 333 mg Tablets
April 3, 2002

Lipha Pharmaceuticals, Inc.
An Associate of Merck KGaA
Darmstadt, Germany

AVAILABLE FOR PUBLIC DISCLOSURE
WITHOUT REDACTION

TABLE OF CONTENTS

LIST OF TABLES	6
LIST OF FIGURES	12
1. EXECUTIVE SUMMARY.....	13
1.0 INTENDED USE.....	13
1.1 MARKETING HISTORY	13
1.2 MECHANISM OF ACTION AND RELEVANT PRECLINICAL PHARMACOLOGY	14
1.2.1 Preclinical ADME and Toxicology.....	16
1.3 RELEVANT CLINICAL PHARMACOLOGY AND PHARMCOKINETICS	18
1.4 ALCOHOLISM AND CURRENT THERAPY	22
1.5 ANALYSIS OF EFFICACY OF ACAMPROSATE	23
1.5.1 Evidence of Efficacy from Controlled Clinical Trials	23
1.5.2 Evidence of Generalizability of Acamprosate Effect across Studies and Populations.....	26
1.6 ANALYSIS OF SAFETY OF ACAMPROSATE	28
1.6.1 Relevant Safety Information from Clinical Trials.....	28
1.6.2 Post-Marketing Safety Information.....	32
1.7 RISK-BENEFIT SUMMATION	33
1.7.1 Summary of Benefits.....	33
1.7.2 Summary of Risks	36
1.8 CONCLUSIONS.....	38
2. INTRODUCTION AND OVERVIEW.....	41
2.0 INTENDED USE	41
2.1 FOREIGN MARKETING HISTORY	41
2.2 SCIENTIFIC RATIONALE AND POTENTIAL CLINICAL BENEFIT	42
3. MECHANISM OF ACTION AND PRECLINICAL SUMMARY.....	47
3.0 DESCRIPTION OF ACAMPROSATE.....	47
3.1 SUMMARY OF RELEVANT PRECLINICAL INFORMATION.....	49
3.1.1 Nonclinical Pharmacology Overview	49
3.1.2 Overview of Nonclinical Pharmacokinetics.....	53

3.1.3	Overview of Nonclinical Toxicology.....	54
4.	CLINICAL RESULTS.....	57
4.0	CLINICAL DEVELOPMENT SUMMARY	57
4.0.1	European Development Program	57
4.0.2	US Development Program	60
4.1	CLINICAL PHARMACOLOGY OVERVIEW	60
4.1.1	Human Pharmacokinetics.....	60
4.1.1.1	Overall Program.....	60
4.1.1.2	Pharmacokinetic properties of acamprosate.....	61
4.1.1.3	Main drug-drug interaction findings	65
4.1.1.4	Main bioavailability-bioequivalence findings.....	65
4.1.1.5	Overall Conclusions Regarding Pharmacokinetic Studies.....	66
4.1.2	Clinical Pharmacology Summary.....	67
4.1.2.1	Summary of CNS Effects.....	67
4.2	ENDPOINTS IN ALCOHOL TRIALS	70
4.3	EARLY CLINICAL EXPERIENCE.....	71
4.4	EVIDENCE FROM CONTROLLED CLINICAL STUDIES OF THE EFFICACY OF ACAMPROSATE IN MAINTAINING ABSTINENCE FROM ALCOHOL.....	75
4.4.1	Introduction	75
4.4.2	Overview	76
4.4.2.1	General Considerations	76
4.4.2.2	Pivotal Efficacy Studies	81
4.4.2.3	Supportive Studies for Efficacy	81
4.4.2.4	Overview of Efficacy Parameters	82
4.4.3	Pivotal Efficacy Studies	85
4.4.3.1	Study Design and Summary.....	85
4.4.3.2	Patient Disposition	94
4.4.3.3	Demographic and Baseline Characteristics.....	98
4.4.3.4	Drug Exposure.....	105
4.4.3.5	Primary Efficacy Parameters.....	109
4.4.3.5.1	Corrected Cumulative Abstinence Duration (CCAD)	109
4.4.3.5.2	Time to First Drink	111
4.4.3.5.3	Rate of Complete Abstinence	117
4.4.3.6	Secondary Efficacy Parameters.....	119
4.4.3.6.1	Frequency of Alcohol Consumption.....	119
4.4.3.6.2	Quantity of Alcohol Consumption.....	124
4.4.3.6.3	Pattern of Alcohol Consumption.....	130
4.4.3.6.4	Overall Clinical Assessment.....	134
4.4.3.6.5	Study Retention.....	142
4.4.3.6.6	Alcohol Craving.....	144
4.4.3.6.7	Patient Global Impression of Improvement.....	145

4.4.3.7 Overall Summary of Primary and Secondary Efficacy Parameters for the Pivotal Efficacy Studies	147
4.4.4 Controlled Clinical Studies. European Short-Term Supportive Efficacy Studies	151
4.4.4.1 Controlled European Short-Term Supportive Efficacy Studies	151
4.4.4.2 Study Design and Summary	151
4.4.4.3 Patient Disposition	155
4.4.4.4 Demographic and Baseline Characteristics	162
4.4.4.5 Drug Exposure	176
4.4.4.6 Primary Efficacy Parameters	183
4.4.4.6.1 Corrected Cumulative Abstinence Duration	183
4.4.4.6.2 Time to First Drink	187
4.4.4.6.3 Rate of Complete Abstinence	197
4.4.4.6.4 Summary for Primary Efficacy Parameters for the European Short-Term Supportive Efficacy Studies	199
4.4.4.7 Summary of Results on Secondary Efficacy Parameters	201
4.4.5 Controlled Clinical Studies. US Short-Term Supportive Efficacy Study	204
4.4.5.1 Controlled US Short-Term Supportive Study	204
4.4.5.2 Study Design and Summary	204
4.4.5.3 Patient Disposition	211
4.4.5.4 Demographic and Baseline Characteristics	213
4.4.5.5 Medication Exposure	217
4.4.5.6 Primary Efficacy Parameters	219
4.4.5.7 Secondary Efficacy Analysis	222
4.4.5.8 Summary of Original Analyses	229
4.4.5.9 Summary of Primary and Secondary Efficacy Parameters for the US Short-Term Supportive Efficacy Study	230
4.4.6 Controlled Clinical Studies. European Long-Term Supportive Efficacy Studies	233
4.4.6.1 Controlled European Long-Term Supportive Efficacy Studies	233
4.4.6.2 Study Design and Summary	233
4.4.6.3 Patient Disposition	236
4.4.6.4 Demographic and Baseline Characteristics	241
4.4.6.5 Drug Exposure	246
4.4.6.6 Primary Efficacy Parameters	249
4.4.6.6.1 Corrected Cumulative Abstinence Duration	250
4.4.6.6.2 Time to First Drink	252
4.4.6.6.3 Rate of Complete Abstinence	257
4.4.6.7 Secondary Efficacy Parameters	259
4.4.6.7.1 Frequency of Alcohol Consumption	260
4.4.6.7.2 Quantity of alcohol consumption	263
4.4.6.7.3 Overall Clinical Assessment	266
4.4.6.7.4 Alcohol Craving (Visual Analog Scale or VAS)	269
4.4.6.7.5 Summary of Primary and Secondary Efficacy Parameters for European Long-Term Supportive Efficacy Studies	270
4.4.7 Overall Summary of All Supportive Studies	271

4.4.8	Summary of Meta-Analyses.....	274
4.5	SUMMARY OF SAFETY INFORMATION	277
4.5.1	Safety Summary from US 96.1	277
4.5.2	Safety Summary from Group I Studies	289
4.5.3	Additional Safety Information from Clinical Trials.....	297
4.6	SUMMARY OF EVIDENCE OF EFFICACY AND SAFETY FROM GROUP I CONTROLLED CLINICAL TRIALS	299
4.6.1	Summary of Efficacy	299
4.6.2	Summary of Safety Information.....	301
5.	OVERALL CONCLUSIONS.....	305
6.	REFERENCES.....	307

LIST OF TABLES

Table 1	Geometric Mean And 95% Confidence Interval Limits Of Selected Pharmacokinetic Parameters After Multiple Oral Administration Of 666 mg t.i.d. Acamprosate	63
Table 2.	Mean (%CV), Minimum, And Maximum Values Of Selected Pharmacokinetic Parameters After Intravenous Administration Of 333 mg Acamprosate.....	63
Table 3.	Studies in Alcohol-Dependent Patients Included in the Integrated Summary of Efficacy – Intent-to-Treat Population.....	80
Table 4.	Primary Efficacy Parameters of the Integrated Efficacy Analysis Assessed by Studies in Alcohol-Dependent Patients	84
Table 5.	Patient Disposition During Treatment Phase – Pivotal Efficacy Studies Pelc II, PRAMA, and Paille Combined	94
Table 6.	Patient Disposition During Treatment Phase – Pivotal Efficacy Study Pelc II	95
Table 7.	Patient Disposition During Treatment Phase – Pivotal Efficacy Study PRAMA.....	96
Table 8.	Patient Disposition During Treatment Phase and Follow-up Phase – Pivotal Efficacy Study Paille.....	98
Table 9.	Demographic and Baseline Characteristics – Pivotal Efficacy Study Pelc II	100
Table 10.	Demographic and Baseline Characteristics – Pivotal Efficacy Study PRAMA.....	102
Table 10a.	Demographic and Baseline Characteristics – Pivotal Efficacy Study Paille.....	104
Table 11.	Drug Exposure – Pivotal Efficacy Study Pelc II.....	106
Table 12.	Drug Exposure – Pivotal Efficacy Study PRAMA	107
Table 13.	Drug Exposure – Pivotal Efficacy Study Paille	108
Table 14.	Percentage of Abstinent Days on Study. Corrected Cumulative Abstinence Duration (CCAD) During Treatment Phase – Pivotal Efficacy Studies Pelc II, PRAMA, and Paille.....	110
Table 15.	Kaplan-Meier Estimates of Time to First Drink (in Days) During Treatment Phase (Discontinuations Treated as Failures) – Pivotal Efficacy Studies Pelc II, PRAMA, and Paille.....	113
Table 16.	Rate of Complete Abstinence During Treatment Phase – Pivotal Efficacy Studies Pelc II, PRAMA, and Paille.....	117

Table 17.	Frequency of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study Pelc II	121
Table 18.	Frequency of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study PRAMA.....	123
Table 19.	Quantity of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study Pelc II	125
Table 20.	Quantity of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study PRAMA.....	127
Table 21.	Quantity of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study Paille.....	129
Table 22.	Pattern of Alcohol Consumption During Entire Study Phase – Pivotal Efficacy Study Paille.....	132
Table 23.	Clinical Global Impression Improvement During Treatment Phase – Pivotal Efficacy Study Pelc II	136
Table 24.	Investigator’s Global Assessment of Success/Failure During Treatment Phase – Pivotal Efficacy Study PRAMA	138
Table 25.	Clinical Global Impression Severity During Treatment Phase – Pivotal Efficacy Study Paille.....	140
Table 26.	Days on Study During Treatment Phase – Pivotal Efficacy Studies Pelc II, PRAMA, and Paille	143
Table 27.	Patient Global Impression of Improvement at the Last Visit – Pivotal Efficacy Study Pelc II	147
Table 28.	Summary of Conduct of Study Information for the European Short-Term Supportive Studies.....	152
Table 29.	Primary and Secondary Efficacy Parameters for the European Short-Term Supportive Efficacy Studies	154
Table 30.	Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Studies Combined	156
Table 31.	Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study Poldrugo.....	157
Table 32.	Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study Tempesta.....	158
Table 33.	Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study BENELUX.....	159
Table 34.	Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study Ladewig	160
Table 35.	Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study UKMAS.....	161

Table 36.	Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study ADISA	162
Table 37.	Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study Poldrugo.....	165
Table 38.	Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study Tempesta.....	167
Table 39.	Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study BENELUX.....	169
Table 40.	Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study Ladewig	171
Table 41.	Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study UKMAS.....	173
Table 42.	Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study ADISA	175
Table 43.	Drug Exposure – European Short-Term Supportive Efficacy Study Poldrugo	177
Table 44.	Drug Exposure – European Short-Term Supportive Efficacy Study Tempesta	178
Table 45.	Drug Exposure – European Short-Term Supportive Efficacy Study BENELUX	179
Table 46.	Drug Exposure – European Short-Term Supportive Efficacy Study Ladewig.....	180
Table 47.	Drug Exposure – European Short-Term Supportive Efficacy Study UKMAS	181
Table 48.	Drug Exposure – European Short-Term Supportive Efficacy Study ADISA.....	182
Table 49.	CAD and CCAD During Treatment Phase – European Short-Term Supportive Studies.....	184
Table 50.	Cumulative Percentage of Abstinent Patients at Day 90 (or 84) and Day 180 (or 168) During Treatment Phase – European Short-Term Supportive Efficacy Studies.....	189
Table 51.	Cumulative Percentage of Patients in Abstinence During Treatment Phase (\pm SE) – European Short-Term Supportive Efficacy Study Poldrugo	190
Table 52.	Cumulative Percentage of Patients Continuously Abstinent During Entire Study Phase (\pm SE) – European Short-Term Supportive Efficacy Study Poldrugo.....	191

Table 53. Cumulative Percentage of Patients in Abstinence During Treatment Phase (\pm SE) – European Short-Term Supportive Efficacy Study Tempesta	192
Table 54. Cumulative Percentage of Patients Continuously Abstinent During Entire Study Phase (\pm SE) European Short-Term Supportive Efficacy Study Tempesta	192
Table 55. Time to First Relapse During Treatment Phase – European Short-Term Supportive Efficacy Study BENELUX.....	193
Table 56. Cumulative Percentage of Patients Continuously Abstinent During Treatment Phase – European Short-Term Supportive Efficacy Study Ladewig.....	194
Table 57. Cumulative Percentage of Patients in Abstinence During Treatment Phase – European Short-Term Supportive Efficacy Study UKMAS.....	195
Table 58. Cumulative Percentage of Patients in Abstinence During Treatment Phase – European Short-Term Supportive Efficacy Study ADISA.....	196
Table 59. Rate of Complete Abstinence During Treatment Phase – European Short-Term Supportive Efficacy Studies	198
Table 60. Patient Disposition – US Short-Term Supportive Efficacy Study	212
Table 61. Populations Studied – US Short-Term Supportive Efficacy Study.....	212
Table 62. Demographic Characteristics at Baseline – US Short-Term Supportive Efficacy Study – ITT Population	215
Table 63. Duration of Exposure and Medication Compliance – US Short-Term Supportive Efficacy Study – ITT Population.....	218
Table 64. Corrected Cumulative Abstinence Duration (CCAD) (%) and Effect Size – US Short-Term Supportive Efficacy Study – All Efficacy Populations.....	220
Table 65. Corrected Cumulative Abstinence Duration (CCAD) (%). Treatment Group Comparisons and Adjusted Means – US Short-Term Supportive Efficacy Study – All Efficacy Populations	221
Table 66. CCAD (%) Categorized as Good Response and Effect Size – US Short-Term Supportive Efficacy Study – All Efficacy Populations	223
Table 67. Rate of Complete Abstinence During the Last Visit Interval and Effect Size – US Short-Term Supportive Efficacy Study – All Efficacy Populations.....	224
Table 68. Percent of Alcoholic Drinks Consumed per Week Relative to Baseline – US Short-Term Supportive Efficacy Study –All Efficacy Populations	228
Table 69. Summary of Originally Planned Efficacy Analyses – ITT Population – US Short-Term Supportive Efficacy Study.....	230

Table 70	Summary of Conduct of Study Information for the European Long-Term Supportive Studies.....	233
Table 71	Primary and Secondary Efficacy Parameters for the European Long-Term Supportive Efficacy Studies	236
Table 72.	Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Studies Combined	237
Table 73.	Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Study Lesch.....	238
Table 74.	Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Study Barrias.....	239
Table 75.	Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Study Besson.....	240
Table 76.	Demographic and Baseline Characteristics – European Long-Term Supportive Efficacy Study Lesch.....	242
Table 77.	Demographic and Baseline Characteristics – European Long-Term Supportive Efficacy Study Barrias.....	244
Table 78.	Demographic and Baseline Characteristics – European Long-Term Supportive Efficacy Study Besson.....	245
Table 79.	Exposure and Compliance to Study Medication – European Long-Term Supportive Efficacy Study Lesch.....	247
Table 80.	Exposure and Compliance to Study Medication – European Long-Term Supportive Efficacy Study Barrias.....	248
Table 81.	Exposure and Compliance to Study Medication – European Long-Term Supportive Efficacy Study Besson.....	249
Table 82.	CAD and CCAD – During the Double-Blind Treatment Phase – European Long-Term Supportive Efficacy Studies Lesch, Barrias, and Besson	251
Table 83.	Cumulative Percentage of Patients in Continuous Abstinence at Day 180 and Day 360 During Treatment Phase – European Long-Term Supportive Efficacy Studies Lesch, Barrias, and Besson.....	253
Table 84.	Cumulative Proportion of Patients Continually Abstinent During Treatment Phase – European Long-Term Supportive Efficacy Study Lesch	254
Table 85.	Cumulative Proportion of Patients Continually Abstinent During Treatment Phase – European Long-Term Supportive Efficacy Study Barrias	255
Table 86.	Cumulative Proportion of Patients Continually Abstinent During Treatment Phase – European Long-Term Supportive Efficacy Study Besson	256

Table 87.	Rate of Complete Abstinence During Treatment Phase – European Long-Term Supportive Efficacy Studies Lesch, Barrias, and Besson	257
Table 88.	Frequency of Alcohol Consumption During Treatment Phase – European Long-Term Supportive Efficacy Study Lesch	261
Table 89.	Frequency of Alcohol Consumption During Treatment Phase – European Long-Term Supportive Efficacy Study Barrias	263
Table 90.	Quantity of Alcohol Consumption During Treatment Phase – European Long-Term Supportive Efficacy Study Lesch	265
Table 91.	Quantity of Alcohol Consumption During Treatment Phase – European Long-Term Supportive Efficacy Study Barrias	266
Table 92.	Final Clinical Global Impression of Response to Treatment – European Long-Term Supportive Efficacy Study Besson	269
Table 93.	By-Patient* Listing of Premature Study Terminations Due to an Adverse Event as Primary Reason – US Short-Term Supportive Efficacy Study	279
Table 94.	Incidence of Most Frequent ($\geq 5\%$ of Patients in a Treatment Group) Treatment Emergent Adverse Events (Safety Population) in US 96.1	282
Table 95.	Incidence of Most Frequent ($\geq 5\%$ of Patients in a Treatment Group) Treatment Emergent Adverse Events in Patients with Positive Drug Screens During the Treatment Phase	284
Table 96.	Additional Serum Chemistry Tests (Safety Population) in US 96.1	287
Table 97.	Deaths that Occurred During Treatment Phase in the Controlled Double-Blind Group I Studies*	292

LIST OF FIGURES

Figure 1.	Acamprosate structure, relative to other key amino acids	48
Figure 2.	Pharmacokinetic profile of multiple doses of acamprosate, using linear scale (left) and semi-log scale (right).....	62
Figure 3.	Changes in C_{max} and AUC with increasing single dose or multiple doses of acamprosate.....	64
Figure 4.	Kaplan-Meier Estimate of Time to First Drink During Treatment Phase – Pivotal Efficacy Study Pelc II.....	114
Figure 5.	Kaplan-Meier Estimate of Time to First Drink During Treatment Phase – Pivotal Efficacy Study PRAMA	115
Figure 6.	Kaplan-Meier Estimate of Time to First Drink During Treatment Phase – Pivotal Efficacy Study Paille	116

1. EXECUTIVE SUMMARY

1.0 INTENDED USE

Calcium acetylhomotaurinate (acamprosate, Campral®)^a, a new chemical entity formulated as a 333 mg (and 500 mg) oral enteric-coated tablet, is indicated for the maintenance of long-term abstinence from alcohol in patients with alcohol dependence who have been withdrawn from alcohol and want to maintain their abstinence. Treatment with acamprosate is intended as part of a comprehensive management program that includes psychosocial support. Recommended treatment duration is one year.

1.1 MARKETING HISTORY

Acamprosate is a synthetic molecule, originally identified by Laboratoires Meram (Meram s.a., Paris, France) and subsequently licensed to Lipha s.a. (Lyon, France) for worldwide development. It was authorized for marketing in France in 1987 (as Aotal®) and has been commercially available there since 1989, in the 333 mg tablet strength.

Acamprosate tablets have been in clinical use for more than 10 years for the indication of maintaining abstinence in alcohol-dependent patients, in conjunction with counseling. Acamprosate tablets are currently approved for marketing in 39 countries and are commercially available in 24 countries, including the United Kingdom and the majority of countries in Europe and Scandinavia, Australia, South Africa, and countries in Eastern Europe and Central and South America. Acamprosate tablets have been under Investigational New Drug study in the United States since 1997 by Lipha Pharmaceuticals, Inc., Lipha s.a.'s U.S. subsidiary.

Currently, more than 1 million patients with alcohol dependence have been treated with acamprosate.

^a In this Briefing Document, the following names are synonymous with "acamprosate": calcium acetaminopropane-sulfonate, calcium acetylamino-propane-sulphonate, calcium acetylhomotaurinate, calcium-N-acetylhomotaurine, Campral®, AOTAL®, AOTA-Ca, Ca-AOTA.

1.2 MECHANISM OF ACTION AND RELEVANT PRECLINICAL PHARMACOLOGY

In 4 rat models of alcohol dependence, acamprosate significantly reduced voluntary alcohol consumption, with an evident dose-response relationship. The compound was active both after oral and parenteral administration, with a minimum orally active dose in the rat of 25 mg/kg. The effects of acamprosate on alcohol consumption were considerably less in alcohol-naïve rats than in rats subjected to forced alcoholization, indicating that acamprosate interfered with mechanisms central to alcohol dependence.

While a possible explanation for the observed reduction in alcohol consumption was that acamprosate potentiated alcohol toxicity, thereby inducing aversion, such an effect was not observed. Acamprosate, in fact, reduced the toxicity of ethanol and acetaldehyde, attenuated the ethanol withdrawal syndrome, and had no major effect on ethanol kinetics, indicating that acamprosate did not have a disulfiram-like action.

The mechanism of action of acamprosate has not been definitively elucidated, but appears to be unique. Two potential mechanisms, which are not mutually exclusive, have been proposed: 1) an interaction with the GABAergic system, although the effects of acamprosate do not appear to be comparable to either sodium valproate, phenobarbital, or benzodiazepines; 2) an interaction with glutamate and its receptors, particularly the NMDA receptor complex. Results of studies suggest that acamprosate interacts with the NMDA receptor, but appears to exert a modulatory effect rather than being a direct antagonist at this site. A GABAergic action, even modest, can combine with excitatory amino acid antagonism resulting in a decrease in the neuronal hyperexcitability that is described in the post-withdrawal period after chronic alcoholization.

Overall, in pre-clinical studies cited in this NDA, acamprosate exhibited very few pharmacological effects outside of its primary activity of decreasing voluntary alcohol consumption. It could not be categorized into any known pharmacological class. Specifically, acamprosate did not have any muscle relaxant, hypnotic, or anxiolytic effects, thereby distinguishing it from benzodiazepines and barbiturates. There was no evidence of antidepressant, neuroleptic, anticonvulsant, or central analgesic effects.

(Some peripheral analgesic activity was attributed to the calcium moiety of the molecule). Acamprosate inhibited manifestations of cerebral anoxia induced by gallamine triiodoethylate and attenuated acetylpyridine-induced trembling and kainic acid-induced shaking. In states of intense drug-induced agitation (amphetamine/chlordiazepoxide combination, morphine, or harmaline), acamprosate antagonized hyperactivity. At high doses, acamprosate was inhibitory to the serotonergic system when the latter was stimulated, but was agonistic when the serotonergic system activity was low.

Potential interactions between acamprosate and drugs likely to be prescribed for, and during, the maintenance of abstinence from alcohol were investigated for a number of categories of medications, including, among others:

- **anticonvulsants** (phenobarbital, sodium valproate, diazepam),
- **antidepressants** (imipramine [a tricyclic], and fluvoxamine [a serotonin-reuptake inhibitor]),
- **anxiolytics** (dipotassium clorazepate, diazepam, meprobamate, Atrium® [mixture of febarbamate, difebarbamate, and phenobarbital]),
- **neuroleptics** (haloperidol, sulpiride, tiapride, and chlorpromazine),
- **hypnotics** (butabarbital), and
- **hepatic metabolism inhibitors** (disulfiram).

Acamprosate---administered orally to mice and rats at doses of 100, 200, or 400 mg/kg---showed no significant interactions with any of the compounds tested.

The effect of acamprosate on liver metabolizing enzymes was determined *in vitro* using human hepatic microsomes or hepatocytes. The inhibitory properties of acamprosate were determined in hepatic microsomes using cytochrome P450 (CYP) specific substrates for CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. Acamprosate was coincubated with the substrates at a concentration of 10 and 100 µM. The induction properties of acamprosate were studied using freshly isolated human hepatocyte cultures. Acamprosate (10 and 100 µM) was coincubated with specific substrates for CYP1A2 and

3A4, two CYPs known to be inducible *in vivo*. Acamprosate produced no inhibition or induction of any of the enzymes studied.

The dependence potential of acamprosate was evaluated in rhesus monkeys experienced in intravenous self-administration of cocaine and pentobarbital and in rhesus monkeys trained to discriminate between d-amphetamine or pentobarbital and saline. In addition, acamprosate was tested in pigeons trained to discriminate pentobarbital from saline. In all of these tests, acamprosate lacked both reinforcing properties as well as stimulus discrimination properties, indicating that the compound had little or no abuse potential.

1.2.1 Preclinical ADME and Toxicology

The pharmacokinetics of acamprosate were investigated in rat, rabbit, and dog following single oral and intravenous administration and in mouse, rat, and dog following repeated oral administration. The dosages employed covered both pharmacologically active doses and the higher doses used in toxicity studies. Acamprosate labelled with ³⁵S was used to determine the fate of acetylhomotaurine and ⁴⁵Ca-labelled acamprosate was used to determine the fate of calcium. ¹⁴C-labelled acamprosate was also used in the pharmacokinetic studies.

These studies indicated that gastrointestinal absorption of acamprosate was about 12-20% in rat, 35% in dog, and 55% in rabbit. Pharmacokinetics were not affected by repeated administration in animals. Acamprosate was not metabolized in any of the species studied. In rat and dog, acamprosate was extensively distributed throughout tissues, although concentrations within individual tissues were low. High concentrations (over 95% of the total amount) observed in the gastrointestinal tract were attributed to unabsorbed drug. Low concentrations were detected in the brain of rat. In rat, acamprosate was shown to cross the placental barrier. Acamprosate was not protein bound. Following absorption acamprosate was largely excreted via the urine in man and animals. Small amounts were excreted in the milk of lactating rats.

Single dose toxicity studies in mice, rats, and rabbits demonstrated that acamprosate had a low order of toxicity by the parenteral route and was virtually non-toxic after oral

administration. The toxicity exhibited by acamprosate was essentially due to the calcium component. Derivatives of acamprosate were also practically free of toxicity.

In mouse and rat treated for up to 13 weeks with acamprosate in the diet at doses between 500 and 2000 mg/kg/day, no major signs of toxicity were evident. In both species, alterations in water intake and electrolyte imbalances were observed at the highest doses. In dogs treated for 4 weeks and monkeys treated for 7 days, doses of acamprosate up to 100 mg/kg/day produced no treatment-related signs apart from gastrointestinal disturbances presenting as loose feces. When administered intravenously to dogs at doses of 25 to 200 mg/kg/day, acamprosate demonstrated no significant toxicity.

The chronic oral toxicity of acamprosate was assessed in rat and dog treated for 26 weeks with doses up to 2400 mg/kg/day and 1000 mg/kg/day, respectively. The rat study included a 6-week recovery period. The dose levels used in these studies were considered to be the maximum tolerated doses for these species. In rats, acamprosate was well-tolerated at doses of 320 and 960 mg/kg/day with only metabolic imbalances observed. At 2400 mg/kg/day there was a high incidence of mortality, severe metabolic imbalances and a variety of soft tissue calcifications, cardiac, gastric and renal lesions. In dog, there was a dose-related incidence of diarrhea at 500 and 1000 mg/kg/day and a dose-related increase in urinary calcium in all acamprosate treated groups.

The signs of toxicity observed in both subchronic and chronic studies were attributed to the calcium component of acamprosate.

The carcinogenic potential of acamprosate was examined in mice and rats following oral administration in the diet for 91 and 104 weeks, respectively. In mice, acamprosate was well-tolerated at the highest dose administered (400 mg/kg/day) with no evidence of any carcinogenic effect. In the rat, treatment of males with the high dose (400 mg/kg/day) resulted in a slight reduction in body weight gain and a slightly higher white cell count. There was an increased incidence of some common rat endocrine tumors (pancreatic islet cell adenoma, thyroid C-cell adenoma, and pheochromocytoma) at the high dose, in slight excess of historic controls for the pancreatic and thyroid adenomas only. It is considered that---because acamprosate is a calcium salt---the increased incidence of

adrenal pheochromocytomas, thyroid C-cell tumors, and renal pelvic mineralization may be associated with changes in calcium absorption or metabolism. There is an indication that hypercalcemia may result in cellular proliferation in the adrenal and thyroid glands. This would suggest that these tumors were induced as a result of physiological or pharmacological effects of acamprosate rather than a direct carcinogenic effect. There was no evidence of an increased incidence of other tumor types.

Acamprosate did not present any mutagenic or clastogenic activity in any of the test systems studies, including the Ames test, gene mutation, chromosomal aberrations, or micronucleus test.

No effects on fertility were observed in mice. The administration of acamprosate to rats at doses up to 1000 mg/kg/day elicited no apparent effect on mating performance, pregnancy rate, litter size, or the incidence of fetal malformations. There was no obvious effect on survival of the F1 generation to maturity, reproductive capacity, or ability to rear offspring to weaning.

Acamprosate exhibited no teratogenic effects in rats (2000 mg/kg/day) and rabbits (1600 mg/kg/day) when administered during the period of organogenesis. In addition, acamprosate had no effect on peri- or post-natal development in rats and rabbits.

In vivo, acamprosate produced no signs of neurotoxicity in the posterior cingulate/retrosplenial cortex of rats treated with a single oral dose of 2000 mg/kg. In addition, an *in vitro* study demonstrated that acamprosate was neuroprotective against glutamate-induced neurotoxicity in cultures of fetal neocortical neurons exposed to ethanol.

1.3 RELEVANT CLINICAL PHARMACOLOGY AND PHARMCOKINETICS

Acamprosate is absorbed orally at a slow rate and with variable bioavailability. After single dose administration of two 333 mg tablets, peak concentrations are reached 4.5 hours after dosing with the current formulation. After repeated administration 3 times daily, absorption is rate-limited and only 2 peak concentrations are observed. After oral

administration of two 333 mg acamprosate tablets 3 times daily (t.i.d.) for 8 days, the geometric mean C_{\max} was 353 ng/mL and the area under the curve over 24 hours was 5904 ng.h/mL. After administration of a single dose of two 333 mg tablets, food decreased C_{\max} and AUC by 42 and 23%, respectively.

After oral administration of two 333 mg acamprosate tablets t.i.d. for 18 days, the apparent volume of distribution (V_{ss}/F) and the apparent clearance (CL/F) were 11,420 L and 288 L/h respectively, resulting in a terminal half-life at steady-state of 33 hours. The variability between subjects is large, ranging from 53% on clearance to 108% on volume of central compartment.

Upon multiple dosing with acamprosate tablets, 666 mg t.i.d. for 8 days, steady-state is reached after 5 days of treatment. Compared to a single 666 mg dose in the same subjects, the apparent clearance (CL/F) increases upon multiple dosing by 41%.

Of the administered dose of oral acamprosate, a large proportion is eliminated unchanged in the feces, probably representing unabsorbed drug. The majority of absorbed drug is eliminated unchanged in the urine (11% of the dose). Acamprosate is not metabolized. Plasma protein binding of acamprosate is negligible.

The pharmacokinetics of acamprosate are not influenced by gender.

The renal clearance of acamprosate ranged from approximately 10 to 20 L/h, indicating tubular secretion. In subjects with varying degrees of renal impairment, clearance of acamprosate decreases proportionally to creatinine clearance.

In 2 studies of patients classified according to the Childs-Pugh classification as having mild or moderate hepatic impairment (either on the basis of chronic alcoholism or other etiologies), there was no difference in pharmacokinetics of acamprosate compared to healthy subjects (*Haug, Miguet*).

Multiple-dose interaction studies have been performed in healthy volunteers which showed that concomitant acamprosate had no effect on the pharmacokinetics of ethanol, diazepam or its metabolite nordiazepam, imipramine or its metabolite desipramine, or

naltrexone and its metabolite 6- β -naltrexol. The pharmacokinetics of acamprosate were not influenced by the concomitant administration of alcohol, disulfiram, or diazepam. There was increased bioavailability of acamprosate when naltrexone was concomitantly administered, the clinical significance of which is currently unknown. All co-administrations were well tolerated. Multiple dose co-administration of disulfiram had no effect on the overall safety profile of acamprosate (adverse event reports, vital signs, ECGs, or clinical laboratory evaluations) either in the normal healthy volunteer study (*Dewland V*) or in a controlled clinical trial (*Besson*) where patients were stratified for voluntary coadministration of disulfiram.

In placebo-controlled clinical pharmacology studies comparing acamprosate and diazepam effects in healthy volunteers, there were no systematic differences between acamprosate and placebo in EEG tracings, whereas diazepam produced significantly different effects from both acamprosate and placebo. With acamprosate, inhibitory and sedative effects were either absent or far less pronounced than with diazepam. Cognitive function, as assessed by calculation tests, was clearly impaired with diazepam, but only slightly with acamprosate and placebo. Diazepam was associated with significantly more adverse events (dizziness, giddiness, tiredness, balance disturbances) than acamprosate or placebo. Acamprosate had a significantly higher incidence of headache than did diazepam or placebo.

Studies comparing the effects of single doses of acamprosate (666 mg) and diazepam (10 mg) vs placebo, with and without co-administered alcohol, on performance relevant to driving in normal, healthy volunteers showed there was a significant decrease in perceptive and reactive performance with diazepam, compared to no adverse effects of either acamprosate or placebo on performances relevant to driving. The co-administration of alcohol with acamprosate did not modify or increase the reductions in performance caused by alcohol alone. In contrast, diazepam plus alcohol resulted in more marked performance deterioration than with alcohol alone. It was concluded that reduction in the ability to drive as occurs with alcohol ingestion would not be further affected by acamprosate administration.

Two completed studies have compared the effects of multiple doses of acamprosate or naltrexone versus placebo on various cognitive activities in normal healthy volunteers. One of these, in a 3-period crossover design with drugs given over 9 days, compared effects of acamprosate (666 mg t.i.d.) or naltrexone (50 mg/day) versus placebo on various psychomotor skills before or after coadministration of ethanol. Neither acamprosate nor naltrexone alone significantly modified the pharmacodynamic parameters (electrophysiological, bodysway, and subjective self-rating scales) investigated in the trial. For the driving simulator, both active drugs significantly decreased driving speed. Following alcohol intake, testing of these same variables largely showed the effects of alcohol. It was concluded that there were no significantly different interactions between either acamprosate and alcohol or naltrexone and alcohol. The effects measured were often confounded with the effects of alcohol given alone, but when effects of the 2 active treatments were different from placebo, they tended to be characterized by changes in a direction opposite to those induced by alcohol alone. Both drugs were well tolerated, even with concomitant alcohol intake. However, acamprosate seemed to be better tolerated than naltrexone, as reflected by fewer spontaneous adverse event reports.

A 3-way crossover pharmacokinetic/pharmacodynamic interaction study in normal, healthy volunteers confined to a Clinical Research Unit, compared multiple doses (7 days) of acamprosate (1000 mg b.i.d.) and naltrexone (50 mg/day), alone and in combination, on various standardized assessments of cognitive function. Despite a pharmacokinetic interaction (increase in the rate and extent of absorption of acamprosate with naltrexone coadministration), there were no performance deficits associated with the combined treatment condition relative to naltrexone alone or acamprosate alone on any cognitive assessments. In fact, negative or positive changes in performance from baseline associated with administration of either drug alone were consistently normalized back to baseline levels with co-administration.

1.4 ALCOHOLISM AND CURRENT THERAPY

Alcoholism is more than a physical disease. It is an addictive behavior with complex biological, psychological, and social dimensions. The multidimensional nature of the disease is reflected in the array of treatment approaches, which include individual and group psychotherapy, behavioral and cognitive therapy, drug therapy, self-help groups, half-way houses, family therapy, expressive therapy, relaxation techniques, and even social skills training. Treatment providers include self-help and 12-step sponsors and group leaders, social and mental health workers, psychologists and addiction specialists, psychiatric nurses, psychiatrists, internists and general practitioners, and others.

In general, current management of alcohol dependence begins with alcohol withdrawal, either by means of a brief period of weaning (detoxification), during which the patient is given medication to more safely and comfortably withdraw from alcohol either as an outpatient or inpatient (the common approach in Europe even in the absence of physiological evidence of alcohol withdrawal symptoms) or by means of intensive group or individual counseling. However, few professionals consider treatment during this period alone to be sufficient overall management. The more difficult task is to help the patient be motivated and maintain long-term abstinence following the acute alcohol withdrawal period.

The current New Drug Application refers to this post-withdrawal period. The duration of active medical and psychological support during this time depends on the treatment program, but periods of 3 to 12 months or more are usual, with long term less intensive follow-up over many years.

Until recently, the long-term management of alcohol dependence had been limited almost entirely to various types of counseling. Only psychological and psychosocial approaches had been shown to be moderately successful, with rates of remission estimated by some to be similar to those achieved in treatment of other chronic medical conditions.^[1] However, the wide-spread nature of alcohol dependence (in the United States, it is estimated that there are more than 8.1 million alcohol-dependent individuals) and its cost,

complexity, familial and societal impacts, and long-term aspects makes the search for additional, supplemental therapeutic options imperative.

Currently, there are only 2 pharmaceutical agents available in the United States FDA-approved for treatment of alcohol dependence: the aversive agent disulfiram and the opioid antagonist naltrexone.

Acamprosate represents another possible and promising pharmacotherapeutic adjunct to the overall management of the alcohol-dependent patient after withdrawal from alcohol. Its development has paralleled the ever-increasing understanding of the neurobiology of alcohol dependence. Alcohol withdrawal in alcohol dependent individuals results in well-described disturbances of neurotransmitters in the central nervous system. Acamprosate was developed as a new psychotropic drug to influence this neurotransmitter imbalance, with the specific indication of maintaining long-term abstinence in the treatment-seeking alcohol-dependent patient, after withdrawal or weaning from alcohol. Studies presented in this NDA support its effectiveness and safety when used in conjunction with psychosocial supportive treatment. Acamprosate is not intended for the treatment of alcohol withdrawal or alcohol abuse.

1.5 ANALYSIS OF EFFICACY OF ACAMPROSATE

1.5.1 Evidence of Efficacy from Controlled Clinical Trials

- Across 3 pivotal efficacy studies in alcohol-dependent outpatients, conducted in Belgium (*Pelc II*), Germany (*PRAMA*), and France (*Paille*), a total of 623 patients on acamprosate and 375 patients on placebo were evaluated with regard to the effectiveness of acamprosate in maintaining abstinence following withdrawal from alcohol. All patients had completed alcohol-withdrawal treatment and were abstinent prior to beginning study medication. Two dose levels of acamprosate were examined in 2 of the studies (1332 mg/day and 1998 mg/day, both with t.i.d. divided dosing) and in the 3rd study, acamprosate was dosed on the basis of body weight, but most patients received 1998 mg/day. Treatment periods were 1 year in 2 of the studies and 3 months in the remaining study. Analyses of primary efficacy parameters reflective

of abstinence in these studies demonstrated that patients treated with acamprosate realized improvements in their disease that were statistically significant and clinically meaningful. Patients treated with acamprosate in these studies abstained from their first drink 2 to 3 times longer, had a complete abstinence rate (i.e., not a single drink) 2 to 3 times greater, and were abstinent 20% to 38% more days while on study than patients treated with placebo. For these primary efficacy parameters, there was also evidence of dose-relatedness of response in the 2 studies which generated these data, with patients in the 1998 mg/day group showing a stronger treatment effect than the 1332 mg/day group.

- Additional analyses of secondary parameters in these 3 studies, predominantly related to quantitative assessment of drinking behavior and global outcome, were consistent with these findings. These benefits were consistent across subgroups of patients defined by demographic characteristics, aspects of the history of alcohol use, and categories of concomitant medications frequently used in alcohol-dependent patients.
- In the two pivotal 1-year studies (*PRAMA* and *Paille*), both of which had follow-up periods, it was apparent that the benefits of treatment with acamprosate were maintained while patients continued to be followed, off treatment (but still under double-blind conditions relative to the completed treatment phase), for an additional year (*PRAMA*) or while on placebo-only for a 6-month follow-up period (*Paille*). During the follow-up period, abstinence rates in groups previously assigned to acamprosate and placebo gradually decreased, but the difference was still apparent.
- The effectiveness of acamprosate demonstrated in the 3 pivotal efficacy studies was also evaluated relative to the findings in 9 European supportive efficacy studies of similar design conducted in Austria, Belgium, Italy, Luxemburg, the Netherlands, Portugal, Spain, Switzerland, and the United Kingdom. These studies involved 2628 alcohol-dependent patients, 1302 on acamprosate and 1326 on placebo. In 8 of the 9 studies, patients underwent alcohol withdrawal therapy and were to be abstinent for at least 5 days prior to starting study medication. In the remaining trial, study medication was to be started concurrently with withdrawal therapy (ADISA).

In 5 of the 6 Short-Term (6-month) and all 3 Long-Term (1-year) supportive studies, acamprosate was also associated with more days of abstinence (and a higher percentage of abstinent time while on study), a longer period of time to the first drink, and a higher rate of complete abstinence. The single study (*UKMAS*) which failed to show a significant difference between the acamprosate and placebo groups was noteworthy for its high rate of relapse to drinking (30%) prior to initiation of study medication and the long latent period (almost one month) between the end of withdrawal therapy and initiation of study medication.

- A U.S. Phase III placebo-controlled study in alcohol-dependent patients (*US 96.1*) used a 500 mg tablet strength of acamprosate, with dosing at 1000 mg b.i.d. (with an exploratory dose group of 1500 mg b.i.d.). *US 96.1* did not require alcohol withdrawal or medicated detoxification prior to study entry and had a high rate of non-abstinence at baseline (50%), in contrast to the European studies. The planned primary analysis showed no significant difference between acamprosate and placebo in the ITT population.

However, since the patients in the US study had not begun their study treatment in an abstinent condition or with necessarily a significant level of commitment to treatment (as had patients in the European studies), effectiveness of acamprosate was examined more closely in a subset of patients in the US study who were clearly more motivated to achieve or maintain abstinence, in that they had identified, at Baseline, total abstinence as their treatment goal. This group constituted about 40% of the total *US 96.1* study population. Results of efficacy analyses among these patients in the US study who had a treatment goal of abstinence (Motivated ITT population) showed that treatment with acamprosate had a beneficial effect on cumulative abstinence duration (i.e., the summation of all abstinent periods while on study) and drinking behavior. Even more promising results were seen in the subset of these motivated patients who had a greater commitment to their own treatment as demonstrated by their adherence with the study requirements and treatment regimen (Motivated EFF population). Among patients in the Motivated ITT and Motivated EFF populations treated with acamprosate, the relative percentage of abstinent days while on study was 22% and

28% higher, respectively, than that for patients treated with placebo. In the Motivated EFF population, the rate of “good” response (abstinent at least 90% of time on study) was 33% higher for patients treated with acamprosate compared to those on placebo. Results in the subset of Motivated patients from the US study thus support the overall findings of effectiveness in the European studies.

1.5.2 Evidence of Generalizability of Acamprosate Effect across Studies and Populations

Two meta-analyses were performed in response to the FDA’s interest in: 1) how acamprosate efficacy may extend across study populations and methodologies; 2) identifying a population of alcohol dependent patients who may derive the greatest benefit from acamprosate; and 3) confirming the generalizability of these findings for US and non-US populations.

- The first meta-analysis examined the overall relative benefit of acamprosate on abstinence from alcohol across 16 randomized, double-blind, placebo-controlled clinical trials, most of which had a duration of 6 to 12 months. The data-set included the 13 trials mentioned above and 3 additional trials for which similar parameters were available. Overall, there were nearly 4500 alcohol-dependent outpatients. Acamprosate was most commonly administered at a daily dose of 1998 mg, given in 3 divided doses. The purpose of the meta-analysis was to reconcile differences in study populations and methods. No statistical modeling was used in the outcome analyses of any of the studies included in this meta-analysis. The main outcome parameter was the continuous abstinence rate at 6 months. Secondary endpoints included continuous abstinence rates at 3 and 12 months, point prevalence of abstinence at 6 and 12 months (common study end-points) and the percentage of abstinent time on study (corrected Cumulative Abstinence Duration or CCAD) at 3, 6 and 12 months. The conclusions were:
 - The relative benefit of acamprosate compared with placebo in increasing the continuous abstinence rate compared with placebo was seen at 6 months (145% relative benefit), as well as at 3 months (131%) and 12 months (195%).

- Acamprosate also significantly increased the prevalence of abstinence at months 6 and 12 (point prevalence of abstinence) compared with placebo, with a relative benefit at 6 months of 137% and at 12 months of 162%.
 - The percentage of abstinent time on study (CCAD) was significantly increased by acamprosate compared with placebo. At 3, 6, and 12 months the increases in the acamprosate group were approximately 10%, 10%, and 13%, respectively.
 - The results of this meta-analysis support a sustained long-term benefit of acamprosate across populations.
- The second meta-analysis sought to assess similar patient characteristics across these same studies, through utilization of individual data from the 4457 study participants, and the relationship of these characteristics with treatment outcome. The objective was to create a statistical model predictive of response to treatment, irrespective of a patient's national origin.

Box plots and bar charts for 7 variables (age, gender, Body Mass Index, alcohol dependence severity at Baseline, whether or not the patient lived with a partner and children, medication compliance during the first week on study, and drinking behavior during the first 2 days on study) showed that patient samples were generally comparable and overlapping across studies.

Correlation coefficients of these variables with a more precise definition of CCAD, termed “CAD-meta”, tended also to be of similar magnitude and directionality across studies, as well as between European and US populations. Furthermore, examination of CAD-meta in the European and US populations as a function of various subgroups of each variable, showed similar influences of the main predictors on outcome across these 2 populations, with similar directionality. These results attested to the comparability of the populations, irrespective of national origin.

A model utilizing these key variables was developed and tested on the entire dataset, using CAD-meta, and was shown to fit all studies. This universal model is consistent with factors thought to be clinically relevant in terms of their influence on alcoholism treatment outcome and includes 5 predictors: drinking behavior (abstinent/non-

abstinent) at the onset of treatment; initial medication compliance during the first week of treatment; baseline alcohol dependence severity; the existence of family support (i.e., living with a partner and child); and the treatment itself. The conclusions were:

- Acamprosate was less effective in patients who were non-abstinent at the onset of treatment.
- An adjusted relative benefit of acamprosate on CAD-meta of 7.56% was estimated compared with placebo using the universal model. When treatment exposure was included in the model, this estimated benefit increased to 11.71%, lending further support to the positive effects of acamprosate when taken as prescribed over the entire study period.
- There was no significant interaction between treatment and whether the study was US or European, thus supporting the generalizability of the model for predicting treatment outcome across populations and national boundaries.
- The model also has clinical relevance and may be useful in the general management of alcohol-dependent patients and in optimizing the therapeutic response to acamprosate.

1.6 ANALYSIS OF SAFETY OF ACAMPROSATE

1.6.1 Relevant Safety Information from Clinical Trials

A total of 4243 alcohol-dependent patients were randomized in double-blind, placebo-controlled studies (so-called Group I studies): 2565 patients in the short-term studies (601 patients in the US 96.1 study and 1964 patients in the European Short-Term studies) and 1678 patients in the Long-Term studies. Collectively, there were 2272 patients in this group who were randomized to acamprosate. Additional safety information has been reviewed, based on 797 subjects/patients (494 subjects received acamprosate) treated in clinical pharmacology studies (so-called Group II studies), 923 patients in early clinical experience studies (so-called Group III studies, with 482 patients having received acamprosate), and 3665 patients treated with acamprosate in post-marketing studies

(so-called Group IV studies). In total, almost 7000 patients (6913) have been exposed to acamprosate in clinical trials.

A total of 49 deaths were reported in all these study groupings combined (16 of whom were on [or had been on] placebo). The most frequently reported causes of death were suicide and accidents, which is not unexpected for a study population of alcohol-dependent patients. No relevant differences were seen between treatment groups regarding the reported causes of death.

Overall^b, a similar percentage of patients experienced a treatment-emergent serious adverse event (SAE) in the acamprosate group (range 3% to 6%^c), compared to the placebo group (range 2% to 4%). The most frequent SAEs were accidental injury, depression, and overdose (only 1 of the 7 overdoses was with acamprosate). There were no clinically relevant differences among treatment groups in the percentage of patients who experienced treatment-emergent SAEs in any of the study groupings.

Withdrawals from clinical trials due to an adverse event (AE) were slightly higher in the acamprosate group (range 8% to 12%), than in the placebo group (range 7% to 9%). The most frequently reported AE leading to withdrawal was diarrhea, responsible for withdrawal by from 1% to 3% of patients in the acamprosate group, and <1% in the placebo group. There were no clinically relevant differences among treatment groups in the percentage of patients who experienced any other individual AE leading to withdrawal in any of the study groupings. Most events leading to withdrawal were experienced by a small number of patients in a particular treatment group.

There were no important treatment group differences observed regarding the overall incidence of spontaneously reported treatment-emergent adverse events (TEAEs) in any study grouping.

^b In the discussion of adverse event incidence, only information from the Group I studies is presented, with the primary comparison being the acamprosate group at the recommended daily dose (1998/2000 mg/day) and placebo groups, unless otherwise specified.

^c Wherever ranges are given, they are derived from results of the various study groupings used in the ISS analysis.

In each study grouping the only body system with a statistically significantly higher incidence of adverse events in the acamprosate group was the Digestive System, because of an increase in the incidence of diarrhea. The difference in the incidence of diarrhea between the acamprosate groups and the placebo group, ranged from an excess of 6% (Paille, PRAMA) to 17% (US 96.1) in the acamprosate-treated patients. The difference between the acamprosate and placebo groups for most of the European studies was an excess of 8% of cases in the acamprosate group. Diarrhea was generally mild to moderate in severity and tended to disappear with continued use of acamprosate. The other Digestive System symptom which occurred significantly more often in the acamprosate groups was flatulence, with an excess incidence in the acamprosate groups of 3% to 5%, compared to the placebo group.

Based on information from the Group III early clinical experience studies it was considered that, in addition to diarrhea, acamprosate was associated with an increased incidence of pruritus and other dermatologic conditions, as well as changes in libido. However, based on the current review and integrated analyses of Group I controlled-trial data, only diarrhea and flatulence occur with a significantly greater incidence in acamprosate-treated patients, across the study groupings.

Specifically, for **dermatologic** adverse events:

- Pruritus occurred with equal incidence across acamprosate and placebo groups:
 - pooled Short-Term studies: 4% in acamprosate and 4% in placebo groups;
 - pooled Long-Term studies: 3% in acamprosate and 3% in placebo groups.
- Rashes occurred with equal incidence across acamprosate and placebo groups:
 - pooled Short-Term studies: 3% in acamprosate and 3% in placebo groups;
 - pooled Long-Term studies: 2% in acamprosate and 2% in placebo groups.
- Maculopapular rash occurred with equal incidence across acamprosate and placebo groups:
 - pooled Short-Term studies: 1% in acamprosate and <1% in placebo groups;
 - pooled Long-Term studies: <1% in acamprosate and 0% in placebo groups.

- Vesiculobullous rash occurred with equal incidence across acamprosate and placebo groups:
 - pooled Short-Term studies: <1% in acamprosate and <1% in placebo groups;
 - pooled Long-Term studies: 0% in acamprosate and 0% in placebo groups);
- Skin disorder occurred with equal incidence across acamprosate and placebo groups:
 - pooled Short-Term studies: <1% in acamprosate and <1% in placebo groups;
 - pooled Long-Term studies: 0% in acamprosate and 0% in placebo groups).
- Photosensitivity reaction^d occurred with equal incidence across acamprosate and placebo groups:
 - pooled Short-Term studies: 0% in acamprosate and <1% in placebo groups;
 - pooled Long-Term studies: <1% in acamprosate and 0% in placebo groups).

Thus, it can be concluded, based on this analysis, that there is no increased incidence of dermatologic events in acamprosate-treated patients, compared to placebo.

With regard to **libido and sexual function**, again, there were no significant treatment group differences upon review of the integrated data.

- Decreased libido occurred with equal incidence across acamprosate and placebo groups:
 - pooled short-term studies: 2% in acamprosate and 2% in placebo groups;
 - pooled long-term studies: <1% in acamprosate and <1% in placebo groups;
- Increased libido occurred with equal incidence across acamprosate and placebo groups:
 - pooled short-term studies: <1% in acamprosate and 0% in placebo groups;
 - pooled long-term studies: 0% in acamprosate and 0% in placebo groups.
- Impotence occurred with equal incidence across acamprosate and placebo groups:
 - pooled short-term studies: 1% in acamprosate and <1% in placebo groups;
 - pooled long-term studies: 1% in acamprosate and <1% in placebo groups.

^d “Photosensitivity reaction” is coded to COSTART Body as a Whole body system.

- Sexual function abnormality occurred with equal incidence across acamprosate and placebo groups:
 - pooled short-term studies: <1% in acamprosate and 0% in placebo groups;
 - pooled long-term studies: <1% in acamprosate and 0% in placebo groups.

Based on these data, it can be concluded that there are no differences between acamprosate and placebo treatment groups in effects on libido, potency, or sexual function.

Analysis of laboratory data for the Group I controlled studies showed that Baseline mean values for liver enzymes (GGT, AST, ALT) and red blood cell mean corpuscular volume (MCV) were typically above the normal range, consistent with currently drinking, alcohol-dependent subjects with some element of hepatic dysfunction. A substantial improvement was observed in all these parameters during treatment with a slightly more favorable response seen for GGT in the acamprosate groups compared to the placebo group. There were no meaningful treatment group differences detected for any other laboratory test.

Vital signs data collected in these studies, and available ECG data from Group I studies (US 96.1, UKMAS) and the majority of clinical pharmacology studies revealed no treatment group differences.

1.6.2 Post-Marketing Safety Information

As noted in the acamprosate New Drug Application, based on worldwide sales of acamprosate tablets, it is estimated that more than 1 million patients with alcohol dependence have been treated with acamprosate. Results of the regular post-marketing monitoring and safety update reports are presented in the NDA. Throughout the reporting periods for which Lipha s.a. has had responsibility, there has been no requirement to add substantive safety information to the approved Summary of Product Characteristics (SmPC), either because of new events or increased frequency of already-listed events.

1.7 RISK-BENEFIT SUMMATION

1.7.1 Summary of Benefits

- Acamprosate has a unique central action which, in preclinical studies, seems restricted to reduction in voluntary drinking of alcohol, particularly in chronically alcoholized animal models. Acamprosate is practically devoid of other central pharmacologic effects and does not interact with other CNS-active compounds generally used therapeutically in alcohol dependence. Acamprosate's mechanism of action differs from other approved drugs for chronic alcoholism: it is not an alcohol-aversive agent such as disulfiram and it is not an opioid-antagonist such as naltrexone.
- There is no preclinical or existent clinical evidence that acamprosate would be associated with abuse or dependence.
- Acamprosate is not metabolized and has negligible protein-binding. In studies with human hepatocytes, acamprosate does not induce or inhibit cytochrome enzymes. Thus, interactions with other drugs which are protein-bound or dependent on cytochrome enzymes for metabolism should not be anticipated.
- Acamprosate has demonstrated efficacy across multiple controlled clinical studies in various countries of alcohol-dependent patients who have been withdrawn from alcohol. Acamprosate treatment was associated with a higher rate of complete abstinence, a greater percentage of abstinent days while under study, and a longer time to first drink when compared to placebo. Acamprosate also reduced the quantity and frequency of alcohol consumption, even if abstinence was not maintained. These effects were seen and sustained in clinical trials lasting as long as 1 year. Acamprosate appears to be most effective in patients with moderately severe alcohol dependence, who are motivated to maintain abstinence (as manifest by abstinence at treatment onset and compliance with treatment) and who have a supportive family structure.
- Acamprosate pharmacokinetics were studied in patients with mild or moderate hepatic insufficiency. They did not differ significantly from kinetics in normal

control subjects. Thus, acamprosate can be used safely in patients with hepatic dysfunction, who are also frequently alcohol-dependent.

- Acamprosate pharmacokinetics do not differ in alcohol-dependent subjects and normal control subjects.
- Acamprosate can be safely combined with alcohol and a variety of medications used in the treatment of alcohol-dependent patients. There is no evidence of effect on acamprosate pharmacokinetics of co-administered ethanol, diazepam, imipramine, or disulfiram. Naltrexone co-administration results in increased absorption of acamprosate, which is of unknown clinical significance, but may be therapeutically advantageous, since acamprosate absorption is low and its safety margin is very high. There is no effect of acamprosate on the pharmacokinetics of ethanol, imipramine and its major metabolite, diazepam and its major metabolite, or naltrexone and its major metabolite. Acamprosate has been co-administered during withdrawal treatment of alcohol-dependent patients with either compounded mixtures of barbiturates, meprobamate, or oxazepam, and there was no evidence of adverse interactions or diminished efficacy.
- Acamprosate does not have a deleterious effect on performance related to driving and, when combined with alcohol, did not show any greater decline in such performance than seen with alcohol alone.
- Acamprosate has been demonstrated to be extremely well-tolerated and safe based on controlled clinical trials and post-marketing exposure of at least 1 million patients.

In controlled clinical trials involving more than 2000 patients exposed to acamprosate, only Digestive System events occurred with a significantly greater incidence in acamprosate-treated patients, compared to placebo-treated patients. The most frequently occurring adverse event was diarrhea, with an excess incidence of 6-17% compared to placebo. Diarrhea was generally mild to moderate in severity, however, and only infrequently (1-3% of patients) resulted in discontinuation from further clinical trial participation. Flatulence also occurred more frequently in acamprosate-treated patients, with an excess incidence of 3-5% compared to placebo.

- Acamprosate had no adverse effects on the usual safety laboratory parameters monitored during clinical trials and, in fact, in the alcohol-dependent study populations, wherein abnormal liver function was common at treatment onset, there was significant improvement in liver function tests during the study periods.
- Acamprosate has a very high safety margin, as evidenced by reports of voluntary overdoses, involving ingestion of quantities of acamprosate as high as 56 grams. When acamprosate has been taken alone (or even with alcohol) under such circumstances, patients have been either asymptomatic or had only acute diarrhea. No specific intervention has been required. In 3 cases where serum calcium has been documented and reported, serum calcium levels have been normal (all 3 cases with ingestion of approximately 30 grams of acamprosate). Thus, in this population, where associated mental illness and depression are common, acamprosate appears to pose a low risk of severe reaction or death, if taken in excessive quantities.
- Acamprosate appears to be equally effective in maintaining abstinence or modifying drinking behavior across different types of psychosocial support, based on data from Phase IV studies.

1.7.2 Summary of Risks

Acamprosate and Renal Impairment

- Acamprosate is excreted entirely by renal elimination. A kinetic study in patients with either moderate or severe renal insufficiency compared to normal volunteers showed that there is a direct relationship between decreases in creatinine clearance and decreases in acamprosate clearance (total clearance and renal clearance). It suggests that prolonged dosing with the usual therapeutic dose of acamprosate could lead to product accumulation in patients with impaired renal function, although there is no direct experience to indicate what the consequences of such an accumulation might be. No information exists at this time on what dose adjustments might be necessary in renal-impaired patients to avoid accumulation of acamprosate. In current European labeling, acamprosate is contraindicated in patients with renal insufficiency.

Acamprosate and the Alcohol Dependent Patient

In the second meta-analysis, various elements were identified which appear to be key to successful treatment outcome of alcohol dependence and which, through their understanding, can maximize the possibility of response to acamprosate. However, for any alcohol management program to be successful, there must be the commitment of the patient to meaningful change in their life and a readiness to take action to realize and sustain such a change. Currently, no available medication, including acamprosate, can substitute for this patient contribution to the multi-faceted management program of alcohol dependence.

- In the second meta-analysis, baseline alcohol dependence severity was found to have a quadratic relationship with outcome when examined in the context of the entire database. The clinical relevance of these findings is that patients with a moderate severity of alcohol dependence are most likely to benefit from acamprosate. Those with the very mildest of symptoms may be less motivated to become abstinent, whereas those with the most severe dependence may be unable to achieve this treatment effect without more intensive clinical support than could be provided by

participation in an outpatient trial with relatively infrequent visits. This should not, however, preclude the relevance of acamprosate treatment for these patients, but rather points to the need for motivation enhancement strategies for patients with the milder symptoms and more intensive, comprehensive treatment programs for those with more severe dependence.

- Acamprosate is not an aversive or alcohol detoxifying agent and was developed to prevent alcohol relapse, thereby its aim is to support abstinence following alcohol withdrawal, as part of an overall management program. Abstinence at treatment onset appears to serve as an important marker of the patient's motivation and psychological readiness to change behavior, without which no alcoholism treatment will be successful. Thus, efforts directed at enhancing patient motivation to have abstinence as a treatment goal are likely to improve the prognosis for a favorable response to acamprosate therapy. Patients who are not motivated to be abstinent are not as likely to benefit from acamprosate, whereas those who are so motivated are significantly more likely to meet their treatment objectives with acamprosate than with placebo.
- Initial medication compliance, as well as compliance with acamprosate over the prescribed treatment period, again, perhaps self-evidently, were significantly associated with treatment outcome. The corollary of this is that patients should be closely followed and monitored, particularly during treatment initiation. If difficulties with medication compliance are noted during the first weeks of treatment, prompt implementation of strategies to facilitate and stabilize compliance, such as the association of taking medication with a specific activity of daily living (e.g., taking medication at mealtime, taking medication after brushing teeth, etc.) can be recommended. Medication compliance should also be re-enforced at each follow-up visit. As the above data indicate, the better the compliance, the better the response to treatment.
- Finally, the findings that family support influences acamprosate treatment outcome suggest that medication alone cannot override negative environmental influences and

emphasizes the importance of assessing factors in the patient's life that may be contributing to a failure to respond to treatment. Living alone or with only a partner who may also be alcoholic has the potential to negatively influence the identified patient's recovery. In contrast, the existence of a family structure which includes a child may facilitate response to acamprosate treatment because of heightened motivation generated from the family's interest in a good treatment outcome and/or the patient's sense of responsibility to the family unit.

Requirement for Multiple Daily Doses of Acamprosate Tablets

Although not truly a risk, the ability to comply with a dosing schedule of 3 daily intakes over a long period of time may be viewed as a risk or disadvantage by some. However, as seen in the general discussions of the controlled clinical trials, where t.i.d. dosing was used, medication compliance was reported to be high and was, generally, better than 80% in all trials.

As noted above, medication compliance needs to be closely monitored during the initial therapy with acamprosate and if it appears to be a problem, attempts should be made to link taking of medication with other regular daily activities. From a motivational and psychological point of view, the patient should be instructed to view the taking of the medication as a reminder to himself/herself that they have taken charge of their dependence and are consciously attempting to do something about it. Rather than being burdensome to take medication 3 times a day, it could be psychologically re-enforcing and empowering.

1.8 CONCLUSIONS

As noted above, alcohol dependence is more than a physical disease. It is an addictive behavior with complex biological, psychological, and social aspects. In order to break the cycle of alcohol dependence, a high degree of involvement and commitment on the part of the patient is required. Prior to beginning a multi-faceted approach to maintaining abstinence, the patient must withdraw from alcohol.

The availability in the United States of acamprosate enteric-coated tablets, a unique centrally-acting drug, specifically developed for maintaining long-term abstinence in the alcohol-dependent patient who has discontinued alcohol intake, will add a new dimension to the therapeutic possibilities of this disease. Its effectiveness on mean values for relevant parameters related to abstinence (improvement in abstinence rate, more abstinent days, longer time to first drink, decreased alcohol consumption), although modest, are consistently seen over diverse populations, which included alcohol-dependent patients of varying severity. Those who will benefit most from acamprosate are patients with:

- moderately severe alcohol dependence,
- a commitment to remaining abstinent,
- medication compliance, both initial and continued, and
- a supportive family structure.

However, this should not preclude the relevance of acamprosate treatment for other alcohol-dependent patients. Motivation enhancement strategies can be used for patients with the milder symptoms and more intensive, comprehensive treatment programs can be developed for those with more severe dependence.

It is recommended that patients be treated with acamprosate for one year, post-alcohol withdrawal. Treatment should be continued even in the event of relapse.

A variety of psychosocial therapies can be used with acamprosate, and should not affect therapeutic response. Acamprosate can be safely used with a variety of other therapeutic agents commonly employed as part of supportive care for the alcohol-dependent patient who has discontinued or is discontinuing alcohol use.

Acamprosate is not metabolized and is not protein bound. It is eliminated by renal excretion. It can be used in patients with mild or moderate hepatic impairment. It should not be used in patients with renal insufficiency, unless dosage can be adjusted. Acamprosate has a high safety margin, and even single doses as great as 56 grams have been ingested without significant symptomatology. Acamprosate does not appear to have abuse or dependence potential.

2. INTRODUCTION AND OVERVIEW

2.0 INTENDED USE

Calcium acetylhomotaurinate (acamprosate, Campral®)^e, a new chemical entity formulated as a 333 mg (and 500 mg) oral enteric-coated tablet, is indicated for the maintenance of long-term abstinence from alcohol in patients with alcohol dependence who have been withdrawn from alcohol and want to maintain their abstinence. Treatment with acamprosate is intended as part of a comprehensive management program that includes psychosocial support. Recommended treatment duration is one year.

2.1 FOREIGN MARKETING HISTORY

Acamprosate is a synthetic molecule, originally identified by Laboratoires Meram (Meram s.a., Paris, France) and subsequently licensed to Lipha s.a. (Lyon, France) for worldwide development. It was authorized for marketing in France in 1987 (as Aotal®) and has been commercially available there since 1989, in the 333 mg tablet strength. Based on data from more than 10 placebo-controlled clinical trials of acamprosate's efficacy and safety in alcohol-dependent patients conducted throughout Europe by Lipha s.a., acamprosate (333 mg tablets) has since been approved in 38 additional countries for the indication of maintaining abstinence from alcohol, post-withdrawal, in conjunction with counseling. Acamprosate is commercially available in 24 countries, listed below:

^e In this Briefing Document, the following names are synonymous with "acamprosate": calcium acetylamino-propane-sulphonate, calcium acetylaminopropane-sulfonate, calcium acetylaminopropane-sulphonate, calcium acetylhomotaurinate, calcium-N-acetylhomotaurine, Campral®, AOTAL®, AOTA-Ca, Ca-AOTA.

ARGENTINA	FRANCE	POLAND
AUSTRALIA	GERMANY	PORTUGAL
AUSTRIA	HUNGARY	SLOVAKIA
BELGIUM	IRELAND	SOUTH AFRICA
BRAZIL	LUXEMBURG	SPAIN
CHILE	MEXICO	SWEDEN
CZECH REPUBLIC	NETHERLANDS	SWITZERLAND
DENMARK	NORWAY	UNITED KINGDOM

It is estimated that more than 1 million patients with alcohol dependence have been treated with acamprosate since its availability as a prescription drug in France in 1989.

Acamprosate tablets have been under Investigational New Drug study in the United States since 1997.

The current New Drug Application (NDA) seeks approval for the 333 mg acamprosate tablet, with use of a total daily dose of 1998 mg, in a dosage schedule of 666 mg (2 tablets) 3 times daily.

2.2 SCIENTIFIC RATIONALE AND POTENTIAL CLINICAL BENEFIT

Alcoholism is more than a physical disease. It is an addictive behavior with complex biological, psychological, and social dimensions. The multidimensional nature of the disease is reflected in the array of treatment approaches, which include individual and group psychotherapy, behavioral and cognitive therapy, drug therapy, self-help groups, half-way houses, family therapy, expressive therapy, relaxation techniques, and even social skills training. Treatment providers include self-help and 12-step sponsors and group leaders, social and mental health workers, psychologists and addiction specialists, psychiatric nurses, psychiatrists, internists and general practitioners, and others.

In general, current management of alcohol dependence begins with alcohol withdrawal, either by means of a brief period of weaning (detoxification), during which the patient is

given medication to more safely and comfortably withdraw from alcohol either as an outpatient or inpatient (the common approach in Europe even in the absence of physiological evidence of alcohol withdrawal symptoms) or by means of intensive group or individual counseling. However, few professionals consider treatment during this period alone to be sufficient overall management. The more difficult task is to help the patient maintain abstinence following the acute alcohol withdrawal period.

The current New Drug Application refers to this post-withdrawal period. The duration of active medical and psychological support during this time depends on the treatment program, but periods of 3 to 12 months or more are usual, with long term less intensive follow-up over many years.

Until recently, the Long-Term management of alcohol dependence had been limited almost entirely to various types of counseling. Only psychological and psychosocial approaches had been shown to be moderately successful, with rates of remission estimated by some to be similar to those achieved in treatment of other chronic medical conditions. However, the wide-spread nature of alcohol dependence (in the United States, it is estimated that there are more than 8.1 million alcohol-dependent individuals) and its cost, complexity, familial and societal impacts, and Long-Term aspects makes the search for additional, supplemental therapeutic options imperative.

Currently, there are only 2 FDA-approved pharmaceutical agents available in the United States for treatment of alcohol dependence: the aversive agent disulfiram and the opioid antagonist naltrexone.

Acamprosate represents another possible and promising pharmacotherapeutic adjunct to the overall management of the alcohol-dependent patient after withdrawal from alcohol. Its development has paralleled the ever-increasing understanding of the neurobiology of alcohol dependence. Alcohol withdrawal in alcohol dependent individuals results in well-described disturbances of neurotransmitters in the central nervous system. Acamprosate was developed as a new psychotropic drug to influence this neurotransmitter imbalance, with the specific indication of maintaining abstinence in the treatment-seeking alcohol-dependent patient, after withdrawal or weaning from alcohol.

Studies presented in this NDA support its effectiveness and safety when used in conjunction with psychosocial supportive treatment, and allow the following conclusions to be drawn:

- Acamprosate has demonstrated efficacy across multiple controlled clinical studies in various countries of alcohol-dependent patients who have been withdrawn from alcohol. Acamprosate treatment was associated with a higher rate of complete abstinence, a greater percentage of abstinent days while under study, and a longer time to first drink when compared to placebo. Acamprosate also reduced the quantity and frequency of alcohol consumption, even if abstinence was not maintained. These effects were seen and sustained in clinical trials lasting as long as 1 year. Acamprosate appears to be most effective in patients with moderately severe alcohol dependence, who are motivated to maintain abstinence (as manifest by abstinence at treatment onset and compliance with treatment) and who have a supportive family structure.
- Acamprosate can be safely combined with alcohol and a variety of medications used in the treatment of alcohol-dependent patients. There is no evidence of effect on acamprosate pharmacokinetics of co-administered ethanol, diazepam, imipramine, or disulfiram. Naltrexone co-administration results in increased absorption of acamprosate, which is of unknown clinical significance, but may be therapeutically advantageous, since acamprosate absorption is low and its safety margin is very high. There is no effect of acamprosate on the pharmacokinetics of ethanol, imipramine and its major metabolite, diazepam and its major metabolite, or naltrexone and its major metabolite. Acamprosate has been co-administered during withdrawal treatment of alcohol-dependent patients with either compounded mixtures of barbiturates, meprobamate, or oxazepam, and there was no evidence of adverse interactions or diminished efficacy.
- Acamprosate pharmacokinetics were studied in patients with mild or moderate hepatic insufficiency. They did not differ significantly from kinetics in normal

control subjects. Thus, acamprosate can be used safely in patients with hepatic dysfunction, who are also frequently alcohol-dependent.

- Acamprosate pharmacokinetics do not differ in alcohol-dependent subjects and normal control subjects.
- There is no preclinical or existent clinical evidence that acamprosate would be associated with abuse or dependence.
- Acamprosate has been demonstrated to be extremely well-tolerated and safe based on controlled clinical trials and post-marketing exposure of at least 1 million patients. In controlled clinical trials involving more than 2000 patients exposed to acamprosate, only Digestive System events occurred with a significantly greater incidence in acamprosate-treated patients, compared to placebo-treated patients. The most frequently occurring adverse event was diarrhea, with an excess incidence of 6-17% compared to placebo. Diarrhea was generally mild to moderate in severity, however, and only infrequently (1-3% of patients) resulted in discontinuation from further clinical trial participation. Flatulence also occurred more frequently in acamprosate-treated patients, with an excess incidence of 3-5% compared to placebo.
- Acamprosate has a very high safety margin, as evidenced by reports of voluntary overdoses, involving ingestion of quantities of acamprosate as high as 56 grams. When acamprosate has been taken alone (or even with alcohol) under such circumstances, patients have been either asymptomatic or had only acute diarrhea. No specific intervention has been required. In 3 cases where serum calcium has been documented and reported, serum calcium levels have been normal (all 3 cases with ingestion of approximately 30 grams of acamprosate). Thus, in the alcohol-dependent population, where associated mental illness and depression are common, acamprosate appears to pose a low risk of severe reaction or death, if taken in excessive quantities.
- Acamprosate appears to be equally effective in maintaining abstinence or modifying drinking behavior across different types of psychosocial support.

3. MECHANISM OF ACTION AND PRECLINICAL SUMMARY

3.0 DESCRIPTION OF ACAMPROSATE

Acamprosate, calcium acetylhomotaurinate (calcium 3-acetylaminopropane sulfonate), a new chemical entity, is a synthetic homotaurine derivative, which was discovered to reduce voluntary alcohol intake in experimental models of alcohol dependence. Overall, acamprosate has very few pharmacological effects outside of this primary activity. The actions observed in the central nervous system are insufficient to categorize acamprosate in any known pharmacological class.

At present, the state of alcohol dependence is believed to result in disturbance of the fundamental balance in the brain between the inhibitory transmitter GABA and the excitatory transmitter glutamate.

In the central nervous system, certain amino acids, classified as either excitatory or inhibitory, are putative neurotransmitters or neuromodulators. Homotaurine (3-aminopropanesulfonic acid) is a higher homologue of the naturally occurring amino acid, taurine, both of which have structural similarities to the neurotransmitter, γ -amino butyric acid (GABA) (Figure 1). Taurine and GABA are considered to be inhibitory, centrally active amino acids. GABA was identified in the early 1980s as being involved in the CNS actions of alcohol and withdrawal from alcohol. Administration of GABA antagonists potentiates the convulsions of ethanol withdrawal, whereas the agonists or substances that increase GABA levels antagonize alcohol-withdrawal convulsions ^[2,3]. Cerebellar GABA concentrations have also been shown to decrease after chronic alcoholization.^[4] Homotaurine, a GABA agonist which is not naturally occurring, cannot enter the central nervous system, because of the impermeability of the blood-brain barrier to zwitterions. Acamprosate, a homotaurine derivative with modified polarity, was synthesized in order to improve the cerebral transfer of homotaurine.^[5] In addition, acamprosate has structural similarities to glycine and to the excitatory neurotransmitters, aspartate and glutamate (a precursor of GABA) (Figure 1). Based on structural considerations, interactions of acamprosate with receptors for the major amino acid

transmitters, GABA (GABA-A receptors, inhibitory) and glutamate (NMDA receptors, excitatory) have been sought.

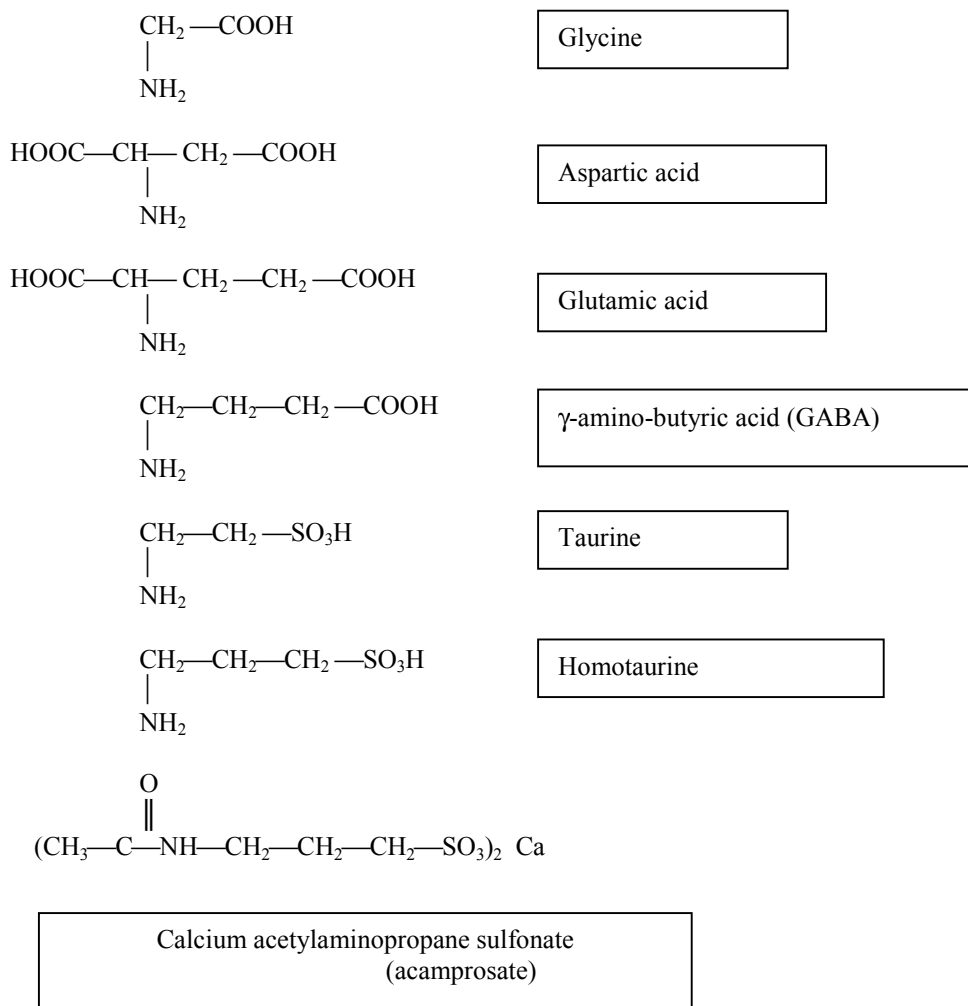


Figure 1. Acamprosate structure, relative to other key amino acids

Although the precise mechanism of action of acamprosate is still under active investigation, at the cellular level, acamprosate has actions which, generally, but not exclusively, suppress neuronal hyperexcitation. In vitro, acamprosate displaced GABA bound to GABA A and GABA B receptors and in vivo reduced the cerebellar cGMP level, increased the number of GABA uptake sites and transporter affinity, thereby speeding uptake by various cerebral structures. These effects suggest a GABAergic type of activity, although electrophysiological evidence appears to rule out any direct acute interaction of acamprosate with GABA A receptors and there is no evidence of an

anxiolytic or hypnotic activity of acamprosate. Other studies on excitatory amino acid transmission indicate that acamprosate antagonizes the excitatory action of glutamate-like amino acids and attenuates excitatory neurotransmission by increasing glutamate uptake in vitro and in vivo. The most recent evidence suggests that the major central mechanism of acamprosate is via modulation of the NMDA receptor.^[6,7] Here, acamprosate may act as a "partial co-agonist", enhancing activation of the receptor at low levels of activation by endogenous activators, but inhibiting activation when levels of endogenous activators are high (as in alcohol withdrawal).^[8,9] At the molecular level an allosteric interaction with a polyamine binding site on the NMDA receptor complex is the current best explanation for this action of acamprosate.

In summary, acamprosate appears to restore the fundamental balance in the brain between the inhibitory and excitatory transmitters, which is thought to be disturbed in chronic alcoholism. Through normalization of function of glutamate receptors of the NMDA receptor subtype, acamprosate may both reduce cravings, which occur during abstinence from alcohol, and reduce the reinstatement of dependence if relapse occurs.

3.1 SUMMARY OF RELEVANT PRECLINICAL INFORMATION

3.1.1 Nonclinical Pharmacology Overview

Nonclinical pharmacology studies have been conducted to determine the pharmacodynamics and mechanism of action of acamprosate, and safety pharmacology studies have been conducted to determine the general pharmacological effects of acamprosate. In addition, pharmacodynamic studies, mechanism of action studies, and safety pharmacology studies have been conducted with the derivatives of acamprosate, homotaurine and sodium acetylhomotaurinate as well as with calcium chloride. The interaction of acamprosate with a variety of other drugs and the potential for the development of dependence has also been determined.

The initial preclinical studies of acamprosate demonstrated a dose-related inhibition of voluntary alcohol intake in rats, with no effect on alcohol consumption of the related compounds sodium acetylhomotaurinate, calcium acetyltaurinate, calcium homotaurine,

or calcium chloride.^[10,11] In 4 rat models of alcohol dependence, acamprosate significantly reduced voluntary alcohol consumption, with an evident dose-response relationship. The compound was active both after oral and intraperitoneal (i.p.) administration. The minimum orally active dose in the rat was 25 mg/kg. The effects of acamprosate on alcohol consumption were considerably less in naive rats than in rats subjected to forced alcoholization, indicating that acamprosate interfered with mechanisms central to alcohol dependence.

In more recent experimental studies by several different teams, acamprosate decreased voluntary alcohol intake (but not other fluid or food intake) in rat models of alcohol dependence ^[12,13] indicating that the compound has a specific effect on alcohol dependence. Further animal studies have shown that acamprosate does not substitute for alcohol nor act as an ethanol antagonist.^[14] Acamprosate, in fact, reduced the toxicity of ethanol and acetaldehyde, attenuated the ethanol withdrawal syndrome and had no major effect on ethanol kinetics, indicating that acamprosate did not have a disulfiram-like action.

Acamprosate seems to suppress negative reinforcement associated with removal of alcohol from the brain, and so may act as an "anti-craving" agent during abstinence. Another emerging possibility is that chronic acamprosate treatment slows the neurochemical adaptive mechanisms elicited by ethanol, which would otherwise lead to the induction of physiological dependence. Acamprosate, given during abstinence, might therefore inhibit the reinstatement of this type of dependence if any relapse into drinking occurred. The proposed molecular mechanism at the NMDA receptor is compatible with both these hypotheses.^[15]

Mechanism of action studies demonstrated that, *in vitro*, acamprosate displaced GABA bound to GABA_A and GABA_B receptors and *in vivo* reduced the cerebellar cGMP level, increased the number of GABA uptake sites, modified transporter affinity, and the speed of uptake by various cerebral structures. In addition, acamprosate prolonged survival time in response to a lethal dose of pentetrazole or bicuculline. These results suggest that acamprosate crosses the blood-brain barrier and exerts a GABAergic type of activity.

Further investigations on excitatory amino acid transmission indicated that acamprosate antagonized the excitatory action of glutamate-like amino acids and attenuated excitatory neurotransmission by increasing glutamate uptake *in vitro* and *in vivo*. Acamprosate may act as a partial agonist at the NMDA receptor complex, although its activity is shifted towards inhibition during alcohol dependence.

The mechanism of action of acamprosate has not been definitively elucidated. However, two potential mechanisms have been proposed. The first is an interaction with the GABAergic system, although the effects of acamprosate do not appear to be comparable to either sodium valproate, phenobarbital, or benzodiazepines. The second is an interaction with glutamate and its receptors, particularly the NMDA receptor complex. Results of studies suggest that acamprosate interacts with the NMDA receptor, but appears to exert a modulatory effect rather than being a direct antagonist at this site. A GABAergic action, even modest, can combine with excitatory amino acid antagonism resulting in a decrease of neuronal hyperexcitability that is described in the post-withdrawal period after chronic alcoholization.

In safety pharmacology studies, acamprosate was devoid of any general effects on spontaneous activity or food and water consumption. It did, however, antagonize hyperactivity induced by an amphetamine/chlordiazepoxide combination, morphine, or harmaline in the mouse. Acamprosate, therefore, exerted a slight sedative effect in states of intense agitation. A hypothermic effect was noted at a dose of 220 mg/kg, probably related to the calcium moiety of the molecule.

Various tests demonstrated that acamprosate was free of muscle relaxant, hypnotic, or anxiolytic effects, therefore distinguishing the actions of acamprosate from the benzodiazepines and barbiturates.

In standard tests used to investigate antidepressant activity, acamprosate potentiated yohimbine toxicity, antagonized reserpine-induced hypothermia, had no effect on reserpine-induced ptosis, attenuated oxotremorine-induced hypothermia, did not modify apomorphine-induced stereotypy or hypothermia, and did not increase agitation time during forced swimming and tail suspension tests. These results demonstrated that

acamprosate did not possess any antidepressant activity. The few positive responses obtained in these tests may be explained by a slight beta-adrenergic activity.

Acamprosate was devoid of any neuroleptic effector dopaminergic activity. Moreover, it did not exhibit any anticonvulsant activity since it exerted no effect on picrotoxin- or strychnine-induced convulsions or on sodium gamma-hydroxybutyrate cortical hypersynchronization (“petit mal” model).

Acamprosate effectively inhibited manifestations of cerebral anoxia induced by gallamine triiodoethylate. It also attenuated acetylpyridine-induced trembling as well as the kainic acid-induced shaking syndrome.

Acamprosate interacted with the serotonergic system in a complex fashion. At high doses it appeared to be inhibitory when the serotonergic system was stimulated, but was agonistic when the activity in the serotonin system was low.

Acamprosate has no central analgesic activity, although it does exert a peripheral effect, as demonstrated in the phenylbenzoquinone writhing test, apparently due to the calcium moiety.

The cardiovascular activity of acamprosate was minimal in that it did not affect blood pressure or heart rate in the normotensive rat, but did reduce blood pressure in the hypertensive rat at high doses. Acamprosate, administered intravenously at doses up to 100 mg/kg, exerted little effect on cardiovascular, respiratory and gastrointestinal parameters in the dog.

Acamprosate had no anti-inflammatory or spasmolytic activity. Weak anti-allergic activity was detected at high doses, which was confirmed by a slight *in vitro* antihistamine effect. The effect, however, was not comparable to the actions of known antihistamines.

Potential interactions between acamprosate and drugs likely to be prescribed for, and during, the maintenance of alcohol deprivation were investigated for a number of categories of medications including anticonvulsants, antidepressants, anxiolytics, neuroleptics, hypnotics, and hepatic metabolism inhibitors. Acamprosate, administered

orally to mice and rats at doses of 100, 200, or 400 mg/kg, showed no significant interactions with any of the compounds tested.

The dependence potential of acamprosate was evaluated in rhesus monkeys experienced in self-administration of cocaine and pentobarbital and in rhesus monkeys trained to discriminate between d-amphetamine or pentobarbital from saline. In addition, acamprosate was tested in pigeons trained to discriminate pentobarbital from saline. In these tests, acamprosate lacked both reinforcing properties and stimulus discrimination properties, indicating that the compound had little or no abuse potential.

Overall, acamprosate had very few pharmacological effects outside of its primary activity. The actions observed in the central nervous system were insufficient to categorize acamprosate in any known pharmacological class.

3.1.2 Overview of Nonclinical Pharmacokinetics

The pharmacokinetics of acamprosate were investigated in rat, rabbit, and dog following single oral and intravenous administration and in mouse, rat, and dog following repeated oral administration. The dosages employed covered both pharmacologically active doses and the higher doses used in toxicity studies. Acamprosate labeled with ^{35}S was used to determine the fate of acetylhomotaurine and ^{45}Ca -labelled acamprosate was used to determine the fate of calcium. ^{14}C -labelled acamprosate was also used in the pharmacokinetic studies.

These studies confirmed that acamprosate was rapidly absorbed through the gastrointestinal tract, but to a limited extent. Slight differences in absorption and bioavailability of acamprosate were found among the rat, rabbit, and dog models.

There was a constant relationship between absorption and the oral dose administered in rats, but not in dogs where the non-linearity was attributed to saturation of absorption mechanisms. The bioavailability of acamprosate after oral administration did not exceed 16% in rats. In dogs, the bioavailability after oral administration of acamprosate at a dose of 25 mg/kg was 60%, but at a dose of 400 mg/kg was only 13%. In rabbits, the absorption was above 50% of the administered dose. The plasma kinetics of acamprosate

were unchanged after repeated doses of acamprosate, demonstrating no accumulation. In plasma, acamprosate did not bind to circulating plasma proteins.

It was shown that acamprosate was widely distributed in rats and dogs, despite low concentrations within individual tissues. It was also observed that the levels of radioactivity in the liver and kidney exceeded those found in plasma, while in other tissues the radioactivity level was lower than that observed in plasma. Acamprosate was able to cross the placental barrier during the period of organogenesis and was found in the milk of lactating rats.

Samples of pooled urine and feces from rats, dogs, and rabbits were analyzed by HPLC and demonstrated only a single radiocomponent identical to acamprosate. These findings suggested that acamprosate was not metabolized. In addition, acamprosate produced no inhibition or induction of hepatic metabolizing enzymes in human hepatic microsomes or cell cultures.

Several studies in rats, dogs, and rabbits showed rapid excretion after oral and intravenous administration of acamprosate. Acamprosate was eliminated from plasma by the kidneys within the first 120 hours after oral administration. The probable mechanism of excretion is through glomerular filtration. The presence of acamprosate in feces after oral administration was attributed to unabsorbed acamprosate; however, a very small biliary excretion may also occur.

3.1.3 Overview of Nonclinical Toxicology

Single dose toxicity studies in mice, rats, and rabbits demonstrated that acamprosate had a low order of toxicity by the parenteral route and was virtually non-toxic after oral administration. The toxicity exhibited by acamprosate was essentially due to the calcium component. Derivatives of acamprosate were similarly practically free of toxicity.

In mouse and rat treated for up to 13 weeks with acamprosate in the diet at doses between 500 and 2000 mg/kg/day, no major signs of toxicity were evident. In both species, alterations in water intake and electrolyte imbalances were observed at the highest doses. In dogs treated for 4 weeks and monkeys treated for 7 days, doses of acamprosate up to

100 mg/kg/day produced no treatment-related signs apart from gastrointestinal disturbances presenting as loose feces. When administered intravenously to dogs at doses of 25 to 200 mg/kg/day, acamprosate demonstrated no significant toxicity.

The chronic oral toxicity of acamprosate was assessed in rat and dog treated for 26 weeks with doses up to 2400 mg/kg/day and 1000 mg/kg/day, respectively. The rat study included a 6-week recovery period. The dose levels used in these studies were considered to be the maximum tolerated doses for these species. In rats, acamprosate was well tolerated at doses of 320 and 960 mg/kg/day with only metabolic imbalances observed. At 2400 mg/kg/day there was a high incidence of mortality, severe metabolic imbalances and a variety of soft tissue calcifications, cardiac, gastric and renal lesions. In dog, there was a dose-related incidence of diarrhea at 500 and 1000 mg/kg/day and a dose-related increase in urinary calcium in all acamprosate treated groups.

The signs of toxicity observed in both subchronic and chronic studies were attributed to the calcium component of acamprosate.

The carcinogenic potential of acamprosate was examined in mice and rats following oral administration in the diet for 91 and 104 weeks, respectively. In mice, acamprosate was well tolerated at the highest dose administered (400 mg/kg/day) with no evidence of any carcinogenic effect. In the rat, treatment of males with the high dose (400 mg/kg/day) resulted in a slight reduction in body weight gain and a slightly higher white cell count. There was an increased incidence of some endocrine tumors (pancreatic islet cell, thyroid C-cell, and pheochromocytoma) at the high dose, and minor renal calcium content leading to changes in calcium metabolism. This would suggest that these tumors were induced as a result of physiological or pharmacological effects of acamprosate rather than a direct carcinogenic effect. There was no evidence of an increased incidence of other tumor types.

Acamprosate did not present any mutagenic or clastogenic activity in any of the test systems studied, including the Ames test, gene mutation, chromosomal aberrations, or micronucleus test.

No effects on fertility were observed in mice. The administration of acamprosate to rats at doses up to 1000 mg/kg/day elicited no apparent effect on mating performance, pregnancy rate, litter size, or the incidence of fetal malformations. There was no obvious effect on survival of the F1 generation to maturity, reproductive capacity, or ability to rear offspring to weaning.

Acamprosate exhibited no teratogenic effects in rats (2000 mg/kg/day) and rabbits (1600 mg/kg/day) when administered during the period of organogenesis. In addition, acamprosate had no effect on peri- or post-natal development in rats and rabbits.

In vivo, acamprosate produced no signs of neurotoxicity in the posterior cingulate/retrosplenial cortex of rats treated with a single oral dose of 2000 mg/kg. In addition, an *in vitro* study demonstrated that acamprosate was neuroprotective against glutamate-induced neurotoxicity in cultures of fetal neocortical neurons exposed to ethanol.

4. CLINICAL RESULTS

In this section of the Briefing Document, the following topics will be presented:

- A brief summary of the completed worldwide and US clinical development programs;
- An overview of the human pharmacokinetic and clinical pharmacology study results;
- A summary of the early clinical experience studies and acamprosate dose selection;
- An integrated summary of the efficacy data from the randomized clinical trials for the:
 - Pivotal Efficacy Studies,
 - European Short-Term Supportive Efficacy Studies,
 - US Short-Term Supportive Efficacy Study (*US 96.1*),
 - European Long-Term Supportive Efficacy Studies,
 - Summary of Meta-Analyses Presented in NDA;
- A brief summary of all safety data, with emphasis on US 96.1.

4.0 CLINICAL DEVELOPMENT SUMMARY

4.0.1 European Development Program

The clinical development of acamprosate and the clinical evidence for acamprosate's efficacy in alcohol dependence began in France in 1982 with several small safety/dose-response and Phase II studies conducted by Laboratoires Meram in normal volunteers^f and in alcohol-dependent patients, following their withdrawal from alcohol¹⁶. Under the direction of Laboratoires Meram, a single multicenter, placebo-controlled, clinical efficacy trial involving 569 alcohol-dependent patients was also performed in France

^f Italicized names appearing in parentheses are the clinical study report "common" names, as used in the New Drug Application. When the "official" clinical study report identifier is used (often a letter/number combination), these names will appear afterward in parentheses

(*Lhuintre*)¹⁷. These studies, conducted during the period 1982-1988, largely looked at changes in gamma-glutamyltranspeptidase (γ -GT or GGT), elevated at study onset, as confirmatory of abstinence.^g

The results of this limited clinical program led to the granting on July 24, 1987 of a marketing authorization in France to Laboratoires Meram for acamprosate, 333 mg tablets, under the trade name Aotal®, for the indication of maintaining abstinence in alcohol-dependent patients. Initially, the total daily dosage was 1332 mg (given in divided dose, three times daily) for a treatment period of up to 3 months. Subsequently the French Ministry of Health requested an additional clinical study to compare the efficacy and safety of 2 dose levels of acamprosate, 1332 mg/day and 1998 mg/day, in alcohol dependent patients who had undergone detoxification therapy (*Paille*).

Thereafter—and subsequent to the licensing of acamprosate by Lipha s.a. from Laboratoires Meram for worldwide development in 1986—a comprehensive preclinical and clinical European development program was undertaken by Lipha s.a. to support further registration and marketing authorizations for acamprosate. In addition to an extensive clinical pharmacology program, 13 large studies were conducted by Lipha s.a. throughout Europe^h during the period 1988 to 1993, involving a total of 2430 patients who received acamprosate and 1601 patients who received placebo.

Twelve of the 13 studies were randomized, multicenter, double-blind, placebo-controlled, parallel group, Phase III studies in alcohol-dependent patients who had been withdrawn from alcohol.ⁱ In these studies, acamprosate was administered primarily at a total daily dose of 1998 mg/day (two 333 mg tablets t.i.d.). In 11 of the 12 studies, patients receiving acamprosate had significantly greater cumulative abstinence duration, higher complete abstinence rates and a longer time to first drink, compared to placebo-treated patients. In addition to the meaningful effects on drinking behavior, acamprosate was

^g In the NDA, these studies are collectively referred to as Group III Early Clinical Experience studies.

^h Studies were conducted in Austria, Belgium, France, Germany, Italy, Luxemburg, the Netherlands, Portugal, Switzerland, and the United Kingdom. Subsequently, studies were also conducted in Spain and Sweden.

ⁱ Eleven of these 12 studies are included among the Group I double-blind, placebo-controlled clinical studies in this NDA. The 12th study is listed with the Group III, early clinical experience studies.

well-tolerated, without any clinically significant drug-related adverse experiences. The only drug-related adverse events that were more prevalent in acamprosate-treated patients were mild gastrointestinal effects, consisting of loose stools or diarrhea.

The remaining (13th) study was a large French, Phase IV, open-label, parallel group study (*ASATIM*), which assessed possible drug interactions and clinical and biological tolerance of acamprosate during the initial period of alcohol withdrawal in alcohol dependent patients.

Based on these additional data, the marketing authorization for Aotal® in France was renewed in 1995, with revisions in the total daily dose and administration recommendations. Dosage was on the basis of body weight, with a total daily dose of 1998 mg (patients >60 kg body weight) or 1332 mg (patients ≤60 kg body weight), given in divided dose, 3 times daily. The approved treatment period was extended up to 1 year. Since 1995, acamprosate (as both Aotal® and Campral®) has been marketed by Lipha s.a. in France. These data also resulted in marketing approvals for the countries involved in the multistate application process as well as additional countries over the ensuing years, as previously noted, based on national applications. The predominant trade name for acamprosate is Campral®^j.

Since these registration-oriented clinical trials have been completed, there have been additional double-blind studies completed (*ADISA*, *Borg*), as well as multinational, Phase IV open-label studies involving more than 2000 alcohol-dependent outpatients, participating in a range of psychosocial treatment programs^k. These studies demonstrated marked improvement in drinking behavior and abstinence in study participants that did not vary as a function of psychosocial program.

In addition, a clinical pharmacology program, consisting of 26 studies involving 388 subjects (349 healthy volunteer subjects and 39 patients), has been carried out.

^j Other less common trade names include Aotal (France), Campral EC (Ireland, the United Kingdom), Sobrial (Dominican Republic, South Africa), and Zulex (Spain).

^k In the NDA, these studies are designated as Group IV, Phase IV studies. One of these studies (MERAM Ph. IV) was conducted by Laboratoires Meram in France and the remaining studies (Austria, Belgium, France; Germany, Portugal, Switzerland, and the United Kingdom) were conducted by Lipha s.a.

Finally, in order to explore alternative dosing schedules, Lipha s.a. developed a 500 mg tablet, identically formulated to the 333 mg tablet. Acamprosate, 500 mg, was the initial focus of the U.S. Phase III development program.

4.0.2 US Development Program

The intent of the US clinical development program was to confirm the European experience with acamprosate in US alcohol-dependent patients. At the first meeting of the sponsor and FDA, we proposed that the clinical efficacy database for the NDA would consist of the following:

- data from 2 of the completed European randomized, placebo-controlled studies of acamprosate, 1998 mg/day (333 mg tablets), serving as the 2 “adequate and well-controlled” trials;
- data from the US placebo-controlled efficacy and safety trial (but using the 500 mg dosage strength tablets and 2 dose levels: 1000 mg twice daily and 1500 mg twice daily)¹;
- data from the remaining 10+ European randomized, placebo-controlled trials considered as “supportive”.

4.1 CLINICAL PHARMACOLOGY OVERVIEW

4.1.1 Human Pharmacokinetics

4.1.1.1 Overall Program

The overall clinical pharmacology program of acamprosate consists of 26 studies which have involved 388 subjects (349 healthy volunteer subjects and 39 patients). Six subjects only received placebo. Of these 26 studies, 22 have been conducted in healthy volunteers and 4 in various patient groups, including 9 patients with alcohol dependence, 12 patients with renal impairment, and 18 patients with hepatic impairment.

A primary objective of the clinical pharmacology studies was to assess the tolerability of acamprosate in healthy subjects, as well as in alcoholic patients. The absorption, the

¹ The 3000 mg/day group was considered “exploratory”.

distribution and the metabolism, and the elimination of acamprosate were assessed as well, when administered either as a tablet or as a solution (orally or intravenously). Doses ranged up to 2664 mg for oral doses and up to 2132.5 mg of acamprosate for intravenous doses.

Two studies evaluated the dose proportionality of rising doses of acamprosate administered as oral solutions, both as single doses and multiple doses.

Four studies investigated the relative bioavailability of the different formulations of acamprosate: 2 studies compared the initial tablet formulation to an oral solution; 2 studies assessed the relative bioavailability of the current formulation against the initial formulation. One study evaluated the absolute bioavailability of the initial acamprosate tablet formulation.

One study assessed the effects of gender on the pharmacokinetics of acamprosate.

The effects of renal impairment on the pharmacokinetics of acamprosate were studied in patients with moderate or severe impairment.

The effects of hepatic impairment on the pharmacokinetics of acamprosate were studied in patients with moderate or severe impairment.

Four studies addressed the potential for pharmacokinetic or pharmacodynamic interactions of acamprosate with other drugs and two studies addressed the potential for interaction with alcohol.

In the sections to follow, the summary findings of these studies are presented.

4.1.1.2 Pharmacokinetic properties of acamprosate

- Acamprosate is absorbed orally at a slow rate and with variable bioavailability. After single dose administration of two 333 mg tablets, peak concentrations are reached 4.5 hours after dosing with the current formulation (*Fourtillan III*). After repeated administration 3 times daily, absorption is rate-limited and only 2 peak concentrations are observed. After oral administration of two 333 mg acamprosate tablets 3 times daily (t.i.d.) for 8 days, the geometric mean C_{\max} was 353 ng/mL and the area under

the curve over 24 hours was 5904 ng.h/mL. After administration of a single dose of two 333 mg tablets, food decreased C_{\max} and AUC by 42 and 23%, respectively (*Fourtillan IV*).

- After oral administration of two 333 mg acamprosate tablets t.i.d. for 18 days, the apparent volume of distribution (V_{ss}/F) and the apparent clearance (CL/F) were 11,420 L and 288 L/h respectively, resulting in a terminal half-life at steady-state of 33 hours. The variability between subjects is large, ranging from 53% on clearance to 108% on volume of central compartment. The pharmacokinetic profile of acamprosate, administered to healthy subjects at the dose of 666mg t.i.d., is represented in Figure 2, below (*Fourtillan V*, *EMF II*):

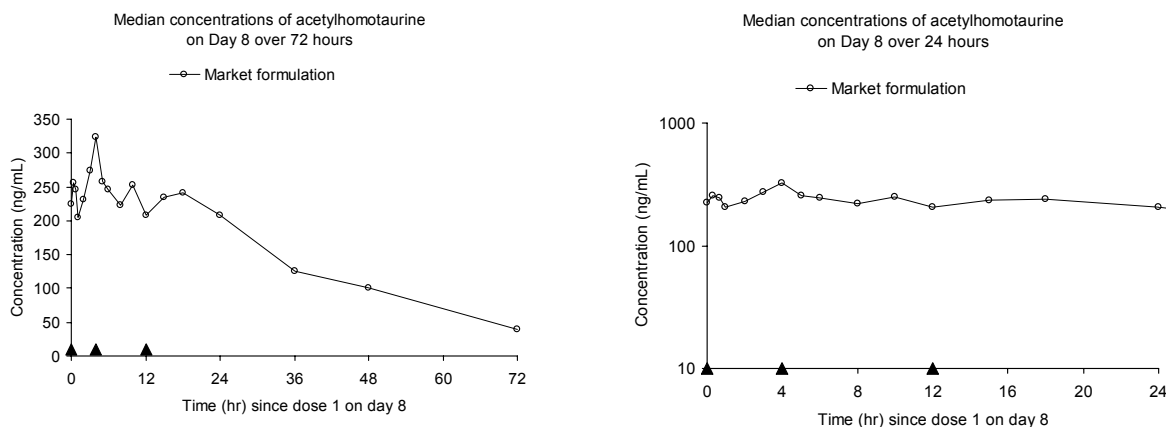


Figure 2. Pharmacokinetic profile of multiple doses of acamprosate, using linear scale (left) and semi-log scale (right)
(Data Source. EMFFR2001/003/00, Study AD1044H)

A summary of the main pharmacokinetic parameters for the currently marketed tablet following multiple oral administration is presented below in Table 1.

Table 1 Geometric Mean And 95% Confidence Interval Limits Of Selected Pharmacokinetic Parameters After Multiple Oral Administration Of 666 mg t.i.d. Acamprosate

Acamprosate 666 mg t.i.d.	C_{max}	T_{max}^*	$t_{1/2}$	AUC_{τ}	$AUC_{0-\infty}$
	(ng.ml ⁻¹)	(h)	(h)	(ng.h.ml ⁻¹)	(ng.h.ml ⁻¹)
Geometric Mean	352.6	4.5	18.1	5771.7	11960.4
95% Conf. Interval Limits	286.9- 433.3	0-18	11.3- 24.9	4565.1 - 7297.3	9580.8 – 14931.0
*: Median Min- T_{max} values Source: EMF II study report in NDA					

A summary of the main pharmacokinetic parameters following single intravenous administration is presented below in Table 2.

Table 2. Mean (%CV), Minimum, And Maximum Values Of Selected Pharmacokinetic Parameters After Intravenous Administration Of 333 mg Acamprosate

Acamprosate 333 mg IV infusion	$AUC_{0-\infty}$	$t_{1/2}$	Vd	Cl_t	Cl_r
	(ng.h.ml ⁻¹)	(h)	(l)	(l.h ⁻¹)	(l.h ⁻¹)
Mean	24875.5	5.7	109.5	13.82	14.43
CV %	18	49	38	20	20
N	12	12	12	12	12
Min.	17016.8	2.9	50.7	10.82	10.49
Max.	30764.0	13.5	212.2	19.57	20.18
Source: Caplain study report in NDA					

- After single (*Dewland II*) administration of oral acamprosate solution at increasing doses, there was a linear correlation between acamprosate exposure and plasma peak up to 2664 mg. But after repeated dosing (*Theodor II*), exposure and plasma peak do not increase linearly with the dose: C_{max} and AUC increase less than proportionally at multiple doses above 800 mg bid, as represented in Figure 3, below.

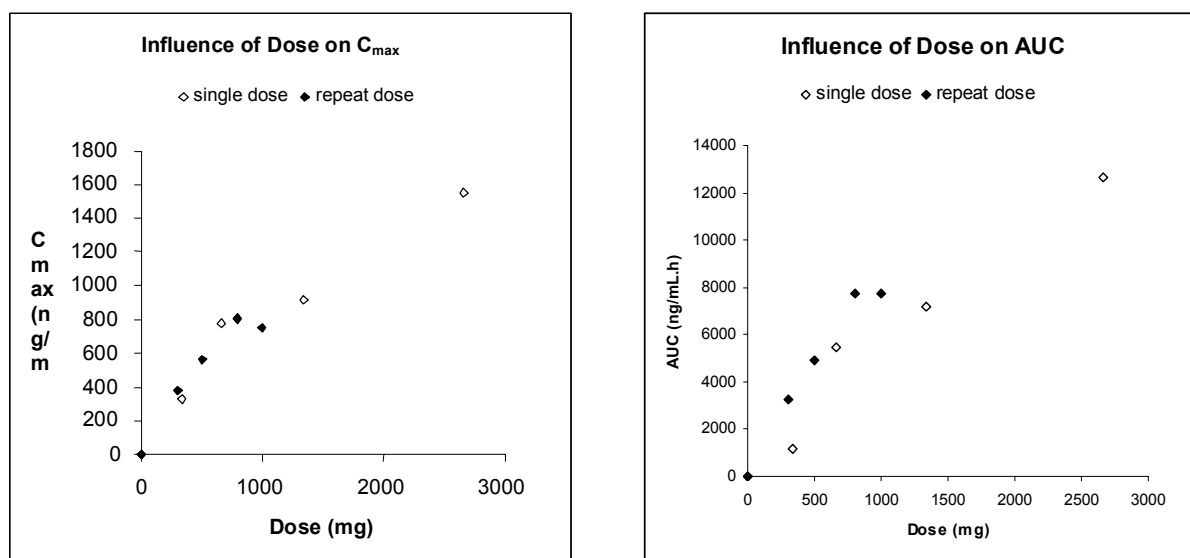


Figure 3. Changes in C_{max} and AUC with increasing single dose or multiple doses of acamprosate
(Data Source. Theodor II and Dewland II Study Reports)

- Upon multiple dosing with acamprosate tablets, 666 mg t.i.d. for 8 days, steady-state is reached after 5 days of treatment. Compared to a single 666 mg dose in the same subjects, the apparent clearance (CL/F) increases upon multiple dosing by 41% (*Fourtillan V*).
- Of the administered dose of oral acamprosate, a large proportion is eliminated unchanged in the feces, probably representing unabsorbed drug (*Scott*). The majority of absorbed drug is eliminated unchanged in the urine (11% of the dose) (*Scott*). Acamprosate is not metabolized (*Scott*). Plasma protein binding of acamprosate is negligible (*Chasseaud*).
- The pharmacokinetics of acamprosate are not influenced by gender (*Dewland IV*).
- The renal clearance of acamprosate ranged from approximately 10 to 20 L/h, indicating tubular secretion (*Caplain*). In subjects with varying degrees of renal impairment, clearance of acamprosate decreases proportionally to creatinine clearance (*Sennesael*).

- In patients with hepatic impairment (either on the basis of chronic alcoholism or other etiologies), there was no difference in pharmacokinetics of acamprosate compared to healthy subjects (*Miguet, Haug*).

4.1.1.3 Main drug-drug interaction findings

- Concomitant acamprosate had no effect on the pharmacokinetics of ethanol, diazepam or its metabolite nordiazepam (*Decourt I*), imipramine or its metabolite desipramine (*Decourt II*), or naltrexone and its metabolite 6- β -naltrexol (*Dixon*).
- The pharmacokinetics of acamprosate were not influenced by the concomitant administration of alcohol (*Dewland III, Lückert*), disulfiram (*Dewland V*), or diazepam (*Decourt I*). There was increased bioavailability of acamprosate when naltrexone was concomitantly administered.
- All co-administrations were well tolerated.

4.1.1.4 Main bioavailability-bioequivalence findings

- The absolute bioavailability of acamprosate is approximately 11% (*Fourtillan I*).
- Bioequivalence could be established for $AUC_{0-\infty}$, but not for C_{max} after single dose administration of 666 mg tablets of the clinical development formulation (reference) and the currently marketed formulation (test) (*Fourtillan III, EMF I*). A period effect in that study precludes, however, a definitive conclusion regarding single-dose bioequivalence. An additional reason for the lack of bioequivalence with the single-dose study may be high variability in the pharmacokinetics of acamprosate with oral administration, as assessed with population PK modeling (*EMF III and EMF IV*). After administration of 666 mg t.i.d. of the same formulations to steady-state (*Fourtillan V, EMF II*), the formulations were bioequivalent (confidence intervals of the ratios within 0.8 to 1.25) with respect to $AUC_{0-\tau}$, AUC_{0-last} and $AUC_{0-\infty}$ and C_{max} . Therefore, the test (currently marketed) formulation of acamprosate is considered to be bioequivalent to the reference (clinical development) formulation with chronic administration.

4.1.1.5 Overall Conclusions Regarding Pharmacokinetic Studies

It can be concluded that oral acamprosate enteric-coated tablets have low (about 11%) bioavailability though plasma concentrations are measurable for 48 hours. The current marketed formulation of acamprosate tablets is bioequivalent to the drug development reference formulation with respect to both C_{max} and AUC at steady-state and with respect to $AUC_{0-\infty}$ with a single dose. The rate of oral absorption appears to decrease with higher doses, with second and third doses of the day (compared to the first dose), and with steady-state (compared to single-dose) administration.

Acamprosate is not protein bound, it is not metabolized, and it is eliminated almost entirely by the kidneys, with tubular secretion.

With increasing intravenous doses or oral solutions, concentration-related pharmacokinetic parameters increase in a linear manner, although there may be subproportional increase at higher oral solution doses (≥ 800 mg b.i.d.).

There is no apparent influence of gender on acamprosate kinetics. Food appears to decrease the absorption of a single dose of acamprosate, but this is probably inconsequential for a product that is administered chronically and according to a schedule of multiple daily doses.

Pharmacokinetics of acamprosate are similar in alcohol-dependent and normal subjects. There is no influence of hepatic insufficiency on acamprosate kinetics and no influence of ethanol on the product's disposition. Likewise, there is no effect of acamprosate on ethanol kinetics.

Kidney impairment significantly affects acamprosate kinetics, with a direct correlation between decrease in creatinine clearance and decrease in acamprosate clearance (renal and total). Consequently, it is not advisable to use acamprosate in patients with severe renal impairment.

Finally, from various drug interaction studies completed to date, it can be concluded that: 1) there is no influence of ethanol on acamprosate pharmacokinetics or of acamprosate on the pharmacokinetics of ethanol; 2) there is no pharmacokinetic interaction of

acamprosate and disulfiram or of acamprosate and diazepam; 3) there is no influence of acamprosate on imipramine pharmacokinetics; 4) there is no effect of acamprosate on the pharmacokinetics of naltrexone, but naltrexone appears to increase the absorption of acamprosate.

4.1.2 Clinical Pharmacology Summary

4.1.2.1 Summary of CNS Effects

The initial pharmacodynamic program was conducted in Europe during the period 1986-1989.

Two studies were performed to determine whether or not acamprosate exhibited adverse central nervous system activity.

1. Acamprosate administered alone for 14 days at a dose of 1332 mg/day did not modify EEG or sleep histograms in normal healthy volunteers. However, when co-administered with alcohol, it tended to normalize sleep abnormalities induced by alcohol alone (*Poenaru*). At the dosage employed, administration and withdrawal of acamprosate did not cause any clinically observable effects in the healthy volunteers participating in the study.
2. The second study compared the CNS effects of single doses of acamprosate (400 mg and 800 mg) with those of placebo and diazepam (10 mg) in normal healthy volunteers (*Hermann*). Acamprosate did not appear to influence CNS activity and there were no systematic differences between acamprosate and placebo in EEG tracings, whereas diazepam produced significantly different effects from both acamprosate and placebo. With acamprosate, inhibitory and sedative effects were either absent or far less pronounced than with diazepam. Cognitive function, as assessed by calculation tests, was clearly impaired with diazepam, but only slightly with acamprosate and placebo—largely as a function of testing time. Diazepam was associated with significantly more adverse events (dizziness, giddiness, tiredness, balance disturbances) than acamprosate or placebo. Acamprosate had a significantly higher incidence of headache than did diazepam or placebo.

Two studies on performance relevant to driving compared the effects of single doses of acamprosate (666 mg), diazepam (10 mg), and placebo in healthy volunteers, without (*Moser I*) or with alcohol coadministration (*Moser II*). A third study (*Macher II*) compared the effects of multiple doses of acamprosate or naltrexone or placebo, without or with alcohol coadministration, on various pharmacodynamic parameters, including simulated driving.

1. In the first of these studies, there was a significant decrease in perceptive and reactive performance with diazepam, compared to no adverse effects of either acamprosate or placebo on performances relevant to driving (*Moser I*). Side effects were much more frequent and severe with diazepam, compared to acamprosate or placebo.
2. When 40% alcohol was coadministered, sufficient to result in breath alcohol levels of approximately 0.59 parts per thousand, no additional effects of acamprosate to those caused by alcohol alone were detected (*Moser II*). There was no indication that a reduction in the ability to drive should be expected with alcohol ingestion during treatment with acamprosate beyond the effect normally expected with alcohol. Based on degree of change in various tests, diazepam plus alcohol resulted in more marked performance deterioration than did acamprosate plus alcohol or placebo plus alcohol.
3. In *Macher II*, multiple oral doses of acamprosate (666 mg t.i.d.) or naltrexone (50 mg/day) versus placebo, given over 9 days, were given to healthy volunteers, either with or without alcohol coadministration during the testing sessions. Neither acamprosate nor naltrexone significantly modified the pharmacodynamic parameters (electro-physiological, body sway, and subjective self-rating scales) investigated in the trial. For the driving simulator, both active drugs significantly decreased driving speed. Following alcohol intake, testing of these same variables largely showed the effects of alcohol. It was concluded that there were no significantly different interactions between either acamprosate or naltrexone and alcohol. The effects measured were often confounded with the effects of alcohol given alone, but when effects of the 2 active treatments were different from placebo, they tended to be characterized by changes in a direction opposite to those induced by alcohol alone. Both drugs were well tolerated, even with concomitant alcohol intake. However,

acamprosate seemed to be better tolerated than naltrexone, as reflected by fewer spontaneous adverse event reports.

US 97.1 compared pharmacokinetic and pharmacodynamic responses after 7 day treatment periods of multiple oral doses of acamprosate (1000 mg b.i.d.) and naltrexone (50 mg/day), alone or co-administered, in normal, healthy male and female subjects in a 3-way crossover design. There was a statistically significant pharmacokinetic interaction during coadministration, with naltrexone increasing the rate and extent of absorption of acamprosate, as indicated by the 33% increase in acamprosate C_{max} , the 25% increase in the AUC_{0-T} and the shorter T_{max} values. Although these differences were statistically significant, their clinical relevance remains to be determined. Naltrexone did not affect the elimination half-life of acamprosate. Acamprosate had no effects on the pharmacokinetic parameters of naltrexone or its major metabolite 6- β -naltrexol. Cognitive function testing showed changes on several measures with administration of naltrexone alone, but these changes were reversed when acamprosate was coadministered. Acamprosate impaired performance on a single measure, but the degree of change was reduced with coadministration of naltrexone. It was concluded that the 2 drugs do not interact pharmacodynamically, in the sense that impairments with the combination are greater than would be expected from a summation of their individual effects. Instead, wherever either drug was identified to have some negative effects on performance or mood, co-dosing consistently reduced these effects.

A placebo-controlled study of the CNS effects of intravenous acamprosate (15 mg/kg) on localized magnetic resonance (MR) spectroscopy was performed, which showed decreases in the spectral region of N-acetylaspartate and glutamate for a period of 20 to 90 minutes, post-acamprosate infusion (*Macher I*). These findings are consistent with the purported anti-excitatory and anti-glutamatergic effects of acamprosate. Inability to detect radiolabeled acamprosate in cerebral tissue was attributed to levels in brain which did not attain the MR's threshold of detection.

Finally, a 26 week intensively monitored study compared the effects of acamprosate and placebo on markers of alcohol relapse in 10 alcohol-dependent patients (*Borg*). The best correlations between self-reported drinking and laboratory assessments appeared to be

with carbohydrate-deficient transferrin (CDT) values >20 and urinary 5-HTOL/5-HIAA ratios >20. In the study, the 5 subjects on placebo and the 5 subjects on acamprosate, had comparable cumulative abstinence durations. Acamprosate was well-tolerated.

4.2 ENDPOINTS IN ALCOHOL TRIALS

It is worth noting that it is more difficult to meticulously define a dose-response curve for therapeutic agents in a disease such as alcohol dependence, which lacks clear-cut, universally accepted biological or physiologic endpoints which can be accurately monitored. In the absence of frank evidence of immediate past ethanol use (such as intoxication, or positive breath or blood alcohol levels), surrogate biologic markers indicative or suggestive of recent drinking (e.g., elevations of γ -glutamyl transferase [GGT], carbohydrate deficient transferrin [CDT] levels) or of chronic excessive drinking (e.g., elevations of mean corpuscular volume [MCV] of red blood cells, elevated liver enzymes, including gamma-glutamyl transferase [GGT]) have been used and continue to be assessed, but largely as supportive evidence. In such instances, declines in previously elevated values are considered to represent improvement, whereas increases or increases after an earlier decrease, suggest resumption of drinking. Many studies have also relied on patient's self-reports of drinking, sometimes corroborated by an additional person familiar with the patient and his/her habits and activities. In addition, the clinician's global assessment of the patient's improvement has been used as an endpoint. Often, however, it is a combination of these assessments which allows judgment to be made as to whether or not the patient is continuing to drink and whether or not there has been improvement.

More recently (and applicable to the Group I studies in this NDA) various assessments related to abstinence have been used to study the effectiveness of therapeutic agents. To be reliable, all such parameters depend on patients beginning study participation from a platform of abstinence. These include survival analysis techniques, with censoring of data at the time of first drink or at evidence of relapse to heavy drinking. In addition, the endpoint of cumulative abstinence duration (CAD), representing a summation of abstinent periods either in absolute terms or relative to the amount of time on study

(corrected cumulative abstinence duration or CCAD), has also been used to assess the effectiveness of therapeutic agents. Cumulative abstinence duration (and its variations) has greater practical application as an endpoint, since it permits a “slip” to drinking, a not uncommon event in the process of recovery. In contrast, survival analysis--particularly to first drink--is a more strict and rigid endpoint, and may result in an unfair assessment of the actual benefits of a therapeutic agent.

4.3 EARLY CLINICAL EXPERIENCE

During the period 1982 to 1988, the first clinical explorations of the effectiveness of acamprosate in patients with alcohol dependence were ongoing in Europe. Simultaneously, preclinical studies and clinical pharmacology and pharmacokinetic studies of acamprosate were being performed, which contributed to considerations of what might be an effective and safe clinical dose and dosing schedule and, additionally, a well-tolerated pharmaceutical presentation of acamprosate.

When considering how the clinical dose selection of acamprosate developed, several aspects of acamprosate's pharmacokinetic profile need to be recalled. First, clinical pharmacokinetic studies of oral tablet bioavailability have consistently shown that oral acamprosate tablets have a relative bioavailability of 50-60% compared to oral solutions of acamprosate and an absolute bioavailability of approximately 11%. The divided dose schedule appears to have been utilized from the beginning, most likely because of the low bioavailability of individual oral doses and the lack of evidence from preclinical studies of significant end-organ toxicity. It should also be recalled that there is no evidence that acamprosate is metabolized either from animal (mouse, rat, dog, rabbit) or human studies. Furthermore, there does not appear to be a dose-limiting toxicity in animals that can be related to the acetylhomotaurinate portion of the acamprosate molecule, and most toxicity has been attributed to the calcium portion of the molecule.^m Finally, in rat models of alcohol dependence, acamprosate significantly reduced voluntary alcohol consumption,

^m From the clinical point of view, the amount of calcium per tablet is 10% of the tablet weight (thus 33 mg per tablet) and given the low absorption of acamprosate tablets, it does not appear that considerations of calcium content are important in dose selection.

with evidence of a dose-response relationship, with the lowest effective dose of 25 mg/kg.

One of the early pharmacokinetic studies (*Boismare*) explored multiple doses of acamprosate capsules given 3 times daily in equal divided doses, with total daily doses ranging from 750 mg to 3000 mg. Normal healthy volunteers received each dose level for 3 days. An increase in frequency (but not severity) of gastrointestinal side-effects was noted with total daily doses of acamprosate above 1500 mg/day. In this early study, it was also suggested that formulation of acamprosate with an enteric coating might improve the side-effect profile. A 2nd dose-tolerance pharmacokinetic study, also in normal healthy volunteers, was performed with single doses of oral solutions of acamprosate: 333 mg, 666 mg, 1332 mg, and 2664 mg (*Dewland II*). There were no clinically significant changes in the electrocardiographic (ECG) findings, vital signs, or safety laboratory parameters. A rising dose pharmacokinetic study in normal subjects performed in 1988 of multiple doses of enteric-coated acamprosate tablets, given twice daily (total daily doses of 1332, 2664, 3996, and 5328 mg), suggested an increase in adverse events (diarrhea) at or above a total daily dose of 2662 mg (*Dewland I*). There were no clinically significant changes in vital signs, ECG findings, safety laboratory assessments, psychometric testing, or self-assessment of mood change. In a single dose rising dose intravenous study of acamprosate (10, 20, and 30 mg/kg versus placebo) given to normal healthy subjects, a clinically significant decrease in heart rate was noted at the 2 higher dose levels.

During the initial development of acamprosate, effects of acamprosate on GGT and MCV were used as evidence of effects of the drug on drinking. To be eligible for study participation, potential candidates had to have elevated values for these parameters, as well as evidence of current excessive drinking and alcohol dependence. It is also important to point out that, after initial assessment, all patients underwent inpatient weaning from alcohol, prior to randomization to study medication. In all these early studies (as well as ones to follow), the treatment goal was maintenance of abstinence from alcohol and not controlled drinking. Patients began study participation from a

baseline platform of abstinence which permitted more accurate assessment of changes from baseline as either reflective of resumption of drinking or maintenance of abstinence.

Three studies summarized in this section comprised part of the initial development of acamprosate by Laboratoires Meram (*Hillemand I*, *Hillemand II*, *Poinso*) and involved relatively small numbers of alcohol-dependent patients, receiving dosages of acamprosate in capsule form. The initial efficacy study performed in 80 alcohol-dependent patients who had completed inpatient alcohol withdrawal (*Hillemand I*) used the 250 mg capsule, at daily doses of 250 mg/10 kg (most likely based on preclinical considerations which showed that the lowest effective dose on voluntary alcohol consumption in rat models of alcohol dependence was 25 mg/kg). Almost twice as many patients in the acamprosate group (61%) remained abstinent compared to the placebo group (32%) during the 3 month study. Most patients had received a daily dose of 1500 mg (range 1000 to 2250 mg/day).

An open-label study looked at the safety and efficacy of a lower daily dose of 750 mg (250 mg t.i.d.) over a 3 month treatment period and concluded that this dose was ineffective in maintaining abstinence (*Hillemand II*). A second open-label, randomized 30 patient study looked at 3 daily doses levels: 750 mg/day, 1000 mg/day, and 1500 mg/day, administered to alcohol-dependent patients who had undergone outpatient alcohol withdrawal (*Poinso*). In this study, there was evidence of a dose-response in patients deemed “successes”, with 750 mg/day confirmed as ineffective and 1500 mg/day somewhat better than 1000 mg/day, although with more side-effects, particularly gastric pains and asthenia. This study gave further impetus to development of an enteric-coated tablet.

These studies demonstrated that 750 mg/day, given in divided doses, appeared to be less effective than higher doses (essentially, up to 1500 mg/day) and also suggested a dose-relatedness to efficacy. These early studies also showed a dose-relatedness to gastrointestinal side effects which resulted in formulation of acamprosate as an enteric coated tablet.

Using the reformulated tablet, the initial Phase III multicenter efficacy study in 569 weaned alcohol-dependent patients conducted by Laboratoires Meram (*Lhuintre*) used a total daily dose of acamprosate (1332 mg/day), a dose less than the 1500 mg/day maximum of the earlier studies. This study used endpoints of changes in MCV and GGT levels to confirm efficacy on maintaining abstinence. It was concluded that acamprosate showed consistently better effects on efficacy parameters than placebo, even when they were not statistically significant. Acamprosate was well-tolerated, with only diarrhea being more frequent than in placebo-treated patients.

The first approved dosing instructions in France were based on this study and schedule: 1332 mg/day in 3 divided doses for a 3-month treatment period.

However, thereafter, additional studies were conducted with the 333 mg enteric-coated acamprosate tablet at a higher daily dose, based on weight. Patients weighing 60 kg or more received 1998 mg/day (2 tablets t.i.d.) and patients weighing less than 60 kg received 1332 mg/day (2-1-1)(*Pelc I*). Patients were also treated for a longer period of time (6 months). This culminated in the overall clinical development program of Lipha s.a. (comprised of the Group I randomized, double-blind, placebo-controlled studies in alcohol-dependent patients reported herein), where dosing schedules were largely based on the schedule used in *Pelc I*, but for treatment periods as long as 1 year.

The data from these studies resulted in the current European dosing recommendations for acamprosate: namely, 1998 mg/day for patients weighing >60 kg and 1332 mg/day for patients weighing <60 kg, for a treatment period of 1 year. Although dosing is based on body weight categories, there is no clear evidence that dosing on a weight basis is necessary. In fact, overall, only about 10% of the study populations were in the <60 kg category, and, therefore, in fact, the majority of patients have been treated with 1998 mg acamprosate/day.

4.4 EVIDENCE FROM CONTROLLED CLINICAL STUDIES OF THE EFFICACY OF ACAMPROSATE IN MAINTAINING ABSTINENCE FROM ALCOHOL

4.4.1 Introduction

Thirteen controlled clinical studies related to claims of acamprosate's effectiveness in maintaining abstinence from alcohol are presented in this section and are referred to as "Group I studies". Study results have been published for 12 of the studies.

All Group I studies were double-blind, placebo-controlled studies in alcohol-dependent patients (almost entirely outpatients). These include 3 pivotal studies (*Pelc II*, *PRAMA*, and *Paille*) and 10 supportive studies, 7 of which are considered "Short-Term", because the duration of the Treatment Phase (i.e., the protocol-designated time period on randomized study medication) was ≤ 6 months, and 3 of which are considered "Long-Term", because the duration of the Treatment Phase was approximately 1 year. Among the supportive Short-Term studies, the US Phase III study, ACAMP/US/96.1 (*US 96.1*) is given greater emphasis because it involves a U.S. population and also because of the greater available detail and relevance of safety information.

All Group I studies (except for *ADISA* and *US 96.1*) were initiated prior to July 1, 1991, the date when the EC Guidelines on Good Clinical Practice (GCP) came into force. It is understood that these earlier studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, that all the study subjects were adequately informed of the study before freely giving their consent to participate, and that local requirements for GCP were fulfilled. All studies commencing thereafter were conducted under guidelines of Good Clinical Practice. All Group I studies were conducted in Europe except for the US study, *US 96.1*, which was conducted under a US IND.

In all Group I studies except for *US 96.1*, acamprosate was administered as 333 mg tablets, generally at a total daily dose of 1998 mg/day, given in 3 equal divided doses. In *US 96.1*, the identically formulated 500 mg tablet strength of acamprosate was employed,

at a main daily dose of 2000 mg/day, given in 2 equal divided doses (a smaller arm explored a daily dose of 3000 mg, given in 2 equal doses).ⁿ

The 3 pivotal studies demonstrate that treatment of alcohol-dependent patients with acamprosate is associated with:

- A highly statistically significant reduction ($p \leq 0.001$ for all 3 studies) in the percentage of days abstinent from alcohol, as indicated by between-group differences (acamprosate minus placebo) in medians of 20% to 38%;
- A highly statistically significant ($p \leq 0.005$ for all 3 studies) differences in the time to first drink, as indicated by a median time to first drink 2 to 3 times that of placebo;
- A statistically significant ($p \leq 0.028$ for all 3 studies) difference in the rate of complete abstinence, as indicated by rates 2 to 3 times that of placebo.

Results from the analyses of these parameters in the European Short-Term studies, selected sub-populations from the US Short-Term study, and European Long-Term studies support the results of the primary parameters in the pivotal efficacy studies.

In addition, the benefits of treatment with acamprosate in alcohol-dependent patients were consistent across various subgroups defined by demographic characteristics, aspects of history of alcohol use, and concomitant medication use.

4.4.2 Overview

4.4.2.1 General Considerations

All 13 Group I studies were multicenter, randomized, double-blind, and placebo-controlled (parallel-group) and involved alcohol-dependent outpatients. The studies were conducted under the direction of alcoholism specialists, who were frequently associated with a facility specializing in alcoholism or other addictive behaviors, and who had either backgrounds in internal medicine, psychiatry, or psychology. In the majority of studies,

ⁿ For discussion purposes and in tables, the 1998 mg/day and 2000 mg/day are considered to represent the same dosing level.

patients received “weaning treatment” (detoxification) for alcohol withdrawal prior to being randomized.

The blinded study medication was subsequently introduced to evaluate the maintenance of abstinence, according to the following dose schedules:

- In 2 of the controlled studies (the pivotal studies *Paille* and *Pelc II*), patients were randomized to 3 parallel, equal-sized treatment groups (2 dose levels of acamprosate and placebo). Acamprosate was given at a total daily dose of either 1998 mg (2x333 mg t.i.d.) or 1332 mg (2-1-1x333 mg acamprosate t.i.d. plus 0-1-1xmatching placebo t.i.d.).
- In 7 of the studies (including *PRAMA*, the 3rd pivotal study), acamprosate dosing was on the basis of body weight. For patients weighing >60 kg, the total daily acamprosate dose was 1998 mg, given as 2x333 mg tablets t.i.d., with meals. For patients weighing ≤60 kg, the total daily dose was 1332 mg, given as 2-1-1x333 mg tablets t.i.d., with meals.
- In the 3 remaining European studies, all patients received a total daily acamprosate dose of 1998 mg, given as 2x333 mg tablets t.i.d., with meals.
- In US 96.1 (the only double-blind study using 500 mg tablets), there were 3 parallel treatment groups (2 dose levels of acamprosate - 2000 mg/day and 3000 mg/day -and placebo). Patients received either 2x500 mg acamprosate tablets b.i.d. plus 1 placebo tablet b.i.d. or 3x500 mg b.i.d. or 3 placebo tablets b.i.d. However, the randomization in this study was unequal (3:3:1 for the placebo:2000 mg acamprosate: 3000 mg acamprosate, respectively) and the 3000 mg group was considered “exploratory”.

In all the studies except US 96.1, whatever psychosocial support was normally used for alcohol-dependent patients in treatment at each respective study center was continued. There was no effort to standardize such support, but rather the desire was to simulate actual medical/psychiatric practice through a “naturalistic” design. In contrast, in US 96.1 standardized psychosocial support was provided which was manual-guided, consisting of brief intervention and medication compliance procedures specific for the study. In all

13 studies, concomitant participation in self-help groups, including 12-step programs such as Alcoholics Anonymous, was also permitted.

All studies used standardized assessment scales of alcohol severity or dependence, although these varied somewhat from study to study.

In general, the selection criteria were similar. Patients had to have a history of alcohol dependency of 1 year or more with dependence of the chronic or episodic type as defined by the DSM-III/III-R or DSM-IV criteria. A GGT value twice the upper limit of laboratory normal and/or a defined increased MCV value were frequently additional selection criteria in the European studies. At the Selection visit in the European studies, patients had to agree to undergo alcohol weaning therapy in order to be abstinent for at least 5 days before being randomized to double-blind study medication at the Baseline visit. Patients entered into the study immediately after termination of the weaning period, following inpatient detoxification in most cases. Exceptions to this were 2 European studies (*UKMAS* and *ADISA*), and the US study US 96.1:

- In *UKMAS*, although most patients underwent detoxification, study drug was introduced much later following alcohol withdrawal and was started subsequent to a period of no medication (so-called “stabilization” period). Accordingly, many patients had already resumed drinking by randomization time.
- In *ADISA*, the objective of the study was to start randomized double-blind study medication concurrently with onset of alcohol withdrawal and detoxification.
- In US 96.1, in contrast, patients did not routinely undergo medicated detoxification; rather, only if they manifested clinical symptoms of alcohol withdrawal, based on Clinical Institute Withdrawal Assessment (CIWA) criteria. In addition, there was no clear study requirement for abstinence. Thus, a significant proportion of patients in the US study were still drinking at study onset and the great majority did not undergo medicated detoxification or alcohol withdrawal.

The exclusion criteria tended to be similar for all the European studies. Patients with renal failure or severe hepatic failure were excluded. Prohibited medication usually

included drugs which might influence GGT (since it was often an evaluation criterion), consisting of barbiturates, meprobamate, valproic acid, carbamazepine, clonidine and, usually, disulfiram (the Besson study permitted its use). Limited use of the phenothiazine thioridazine and often a single nominated antidepressant and benzodiazepine were frequently allowed in the European studies. In the US study, no such additional medication was allowed. The European studies did not permit illicit substance use either at screening or during the Treatment Phase, whereas US 96.1 was more inclusive and allowed for non-dependent cannabis use at Baseline and permitted patients to remain on-study even if subsequent illicit drug screening was positive. All studies excluded patients with severe concomitant psychiatric illness (major depression, psychosis).

Outcome criteria were also, generally, quite similar and assessed drinking behavior, as described in greater detail in the next section.

Compliance to taking the assigned medication was assessed by tablet counts of returned study medication at each visit and clinical evaluations. In 2 studies (PRAMA and US 96.1), biological samples (urine for PRAMA, blood for US 96.1) were collected to determine the presence or absence of acamprosate. Compliance with the study requirements, including timely adherence to the study visit schedule, was also used as an index of successful outcome in some studies.

As anticipated, because of the high dropout rate in these studies of alcohol-dependent subjects, the patient sample at final visit was substantially smaller than the randomized patient sample and precluded an “on treatment” analysis. In all individual study analyses, the primary analysis of efficacy has been on an “intention to treat” basis, with any patient receiving 1 or more doses of study medication included in the analysis. In almost all instances, non-attendance or lost to follow-up was considered to represent treatment failure/relapse.

A brief overview of the clinical studies included in this integrated presentation of efficacy is provided in Table 3. This table includes the number of patients per treatment group in the Intent-to-Treat (ITT) population by study type. Each study is identified in the table

by its study number and a “Common Name”. Throughout the remainder of this Briefing Document, studies are referenced by their common name.

Table 3. Studies in Alcohol-Dependent Patients Included in the Integrated Summary of Efficacy – Intent-to-Treat Population

		Daily Acamprosate Dose						Treatment Duration ¹
Study # (Common Name) (Country)	Total Patients	1332 mg	1998/ 2000 mg	3000 mg	Total	Placebo	Dosing Regimen	
GROUP I STUDIES. PLACEBO-CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS								
Controlled Pivotal Efficacy Studies								
AOTA/B/90.3 (<i>Pelc II</i>) (Belgium/ France)	188	63	63		126	62	2×333 mg t.i.d. or 2-1-1×333 mg t.i.d	90 days (13 weeks)
AOT 411.198 (<i>PRAMA</i>) (Germany)	272	24*	112*		136	136	<60 kg: 2-1-1×333 mg t.i.d. ≥60 kg: 2×333 mg t.i.d.	48 weeks
544 (<i>Paille</i>) (France)	538	188	173		361	177	2×333 mg t.i.d. or 2-1-1×333 mg t.i.d	360 days (51 weeks)
TOTAL	998	251 24*	236 112*		623	375		
European Controlled Short-Term Supportive Studies								
AOTA/I/89.4 (Poldrugo) (Italy)	246	31*	91*		122	124	≤60 kg: 2-1-1×333 mg t.i.d. >60 kg: 2×333 mg t.i.d.	180 days (26 weeks)
AOTA/I/90.1 (Tempesta) (Italy)	330		164		164	166	2×333 mg t.i.d.	180 days (26 weeks)
AOTA/LP90/N001 (UKMAS) (United Kingdom)	581		289		289	292	2×333 mg t.i.d.	24 weeks
AOTA/NL/91.1; AOTA/B/90.2 (BENELUX) (Belgium, The Netherlands, and Luxemborg)	262	32*	96*		128	134	≤60 kg: 2-1-1×333 mg t.i.d. >60 kg: 2×333 mg t.i.d.	180 days (26 weeks)
AOTA/E/91.1 (ADISA) (Spain)	288		141		141	147	2×333 mg t.i.d.	180 days (26 weeks)
AD 04089 (Ladewig) (Switzerland)	61	9*	20*		29	32	≤60 kg: 2-1-1×333 mg t.i.d. >60 kg: 2×333 mg t.i.d.	180 days (26 weeks)
TOTAL	1768	0 72*	594 207*		873	895		
US Controlled Short-Term Supportive Study								
ACAMP/US/96.1 (US 96.1) (United States)	592		253	82	335	257	2×500 mg b.i.d. or 3×500 mg b.i.d	6 months (24 weeks)
European Controlled Long-Term Supportive Studies								
AD 10 089 (Lesch) (Austria)	448	34*	190*		224	224	≤60 kg: 2-1-1×333 mg t.i.d. >60 kg: 2×333 mg t.i.d.	360 days (51 weeks)
AOTA/P/89.1 (Barrias) (Portugal)	302	48*	102*		150	152	≤60 kg: 2-1-1×333 mg t.i.d. >60 kg: 2×333 mg t.i.d.	360 days (51 weeks)
AA 11 088 (Besson) (Switzerland)	110	11*	44*		55	55	≤60 kg: 2-1-1×333 mg t.i.d. >60 kg: 2×333 mg t.i.d.	360 days (51 weeks)
TOTAL	860	0 93*	0 336*		429	431		

Note: Patients from PRAMA, Poldrugo, BENELUX, Ladewig, Lesch, Barrias, and Besson (denoted by “*”) were categorized, post-randomization, on the basis of body weight (≤60 kg or >60 kg). Patients with a body weight ≤60 kg who were randomized to the acamprosate group received 1332 mg acamprosate daily. Patients with a body weight >60 mg who were randomized to the acamprosate group received 1998 mg acamprosate daily.

4.4.2.2 Pivotal Efficacy Studies

The Briefing Document focuses on Treatment Phase data from 3 pivotal efficacy studies conducted in European alcohol-dependent patients: 1 Short-Term Phase II study (*Pelc II*, [Belgium/France]) and 2 Long-Term studies (Phase III *PRAMA* [Germany] and Phase II *Paille* [France]). In the subsequent sections, the studies will be presented first in an integrated fashion and then each of the studies will be discussed sequentially.

All 3 studies were conducted during the period 1989-1992. Two of the studies (*Paille* and *Pelc II*) were the first studies designed to determine if there were efficacy and/or tolerance differences between acamprosate dosages of 1332 mg/day and 1998 mg/day. Additionally, although most of the European studies had an off-treatment, observational follow-up phase, the *Paille* study was the only European study to have a single-blind (patient) follow-up phase, where patients continued on “study drug” for an additional 6 months, but were actually receiving placebo.

These studies were selected as the pivotal studies for the following reasons:

- Observational findings from these studies are robust and provide sufficient evidence of the effectiveness of acamprosate, including some evidence of dose-response;
- These adequate and well-controlled studies are representative of the other Phase II and Phase III studies of acamprosate in design, execution, and results and allow for some examination of a dose-response effect;
- The studies provide therapeutic experience over a wide range of time (90 to 360 days);
- Regulatory considerations.

4.4.2.3 Supportive Studies for Efficacy

Efficacy data from 9 additional Phase III studies conducted in Europe are considered supportive: 8 of the studies were part of the original European registration submission and were conducted during the period 1989-1993. The 9th study (*ADISA*) was conducted in Spain from 1993-1994. Six of the studies are Short-Term studies (*Poldrugo* [Italy], *Tempesta* [Italy], *UKMAS* [United Kingdom], *BENELUX* [Belgium, the Netherlands,

Luxemborg], *ADISA* [Spain], and *Ladewig* [Switzerland]) and the remaining 3 are Long-Term studies (*Lesch* [Austria], *Barrias* [Portugal], *Besson* [Switzerland]).

In addition, efficacy data from the recently completed Phase III US study (*US 96.1*), conducted from 1997-1999, with particular emphasis on the subpopulation defined as the Motivated Efficacy Evaluable population, are considered supportive and are presented separately from the European supportive studies.

4.4.2.4 Overview of Efficacy Parameters

Each Group I study utilized a slightly different set of primary and secondary efficacy parameters, although all were related to measures of drinking behavior or hematologic and biochemical parameters reflecting such behavior.

In general, drinking behavior relied on self-report of drinking between study visits, often corroborated by a second party, such as a relative or significant other, and verified by breath, blood, or urine alcohol measurements. Drinking diaries were not used in the European studies (with the exception of UKMAS which recorded number of abstinent days). Accordingly, in the individual study report analyses, if there was any reported drinking within an inter-visit interval, the entire interval was considered non-abstinent. In addition to UKMAS, the other exception to this general rule was for US 96.1, where patients maintained a daily drinking diary, using standard drinks, so that more precise feedback on number of drinking days and quantity of drinking was obtained.

The majority of the individual study reports provide data on Cumulative Abstinence Duration or CAD. CAD represents a summation of abstinent periods while on study, reported in days, and, in contrast to measures such as complete abstinence rate or time to first drink, allows for a “slip” or “lapse” from abstinence, with recovery. From a statistical point of view, CAD allows for analysis of more of the period of study participation without censoring of data. It is also more reflective of a patient’s actual experience in recovery and is a more practical measure of success than a parameter such as time to first drink, which utilizes survival analysis.

However, in order to compare such a parameter across studies of different duration, a variation of CAD, termed “corrected cumulative abstinence duration” or CCAD, has also been created. This takes into account the duration of time on study and, in its most conservative form uses as its denominator the entire planned-for study duration and not the actual time on study. In general, this has been the way CCAD, if reported, has been calculated in individual study reports.

For purposes of the Briefing Document, the primary efficacy parameters used in the integrated analysis of efficacy are:

- CCAD;
- Time to first drink; and
- Rate of complete abstinence.

Unless otherwise noted, discussion of these parameters will refer to these parameters defined over the Treatment Phase only. Primary efficacy parameter results will be presented for the pivotal as well as the supportive studies.

CCAD is the percentage of abstinent time while on study and is defined as:

$$\text{CCAD} = \frac{\text{Total number of days of abstinence} \times 100}{\text{Total potential duration of exposure to treatment.}}$$

Time to first drink is the number of days from the start of double-blind study medication to the first consumption of any alcohol.

The **rate of complete abstinence** is expressed as the percentage of patients who completed the study without consuming any alcohol relative to the number of patients treated.

Table 4 lists the studies for which the primary efficacy parameters are discussed.

Table 4. Primary Efficacy Parameters of the Integrated Efficacy Analysis Assessed by Studies in Alcohol-Dependent Patients

Clinical Study Type and Common Name	Primary Efficacy Parameters in the ISE		
	Time to first drink	CCAD	Rate of complete abstinence
Controlled Pivotal Efficacy Studies			
Pelc II	✓	✓	✓
PRAMA	✓	✓	✓
Paille	✓	✓	✓
European Controlled Short-Term Supportive Efficacy Studies			
Poldrugo	✓	✓	✓
Tempesta	✓	✓	✓
BENELUX	✓	✓	✓
Ladewig	✓	✓	✓
UKMAS	✓		✓
ADISA	✓		✓
US Controlled Short-Term Supportive Efficacy Study			
US 96.1		✓	
European Controlled Long-Term Supportive Efficacy Studies			
Lesch	✓	✓	✓
Barrias	✓	✓	✓
Besson	✓	✓	✓

Note: CCAD = Corrected cumulative abstinence duration.

In general, secondary efficacy parameters will be presented in detail only for the pivotal efficacy studies and will be summarized for the supportive studies. The following parameters are considered secondary efficacy parameters for purposes of the integrated analysis:

- Frequency of alcohol consumption;
- Quantity of alcohol consumption;
- Pattern of alcohol consumption;
- Overall clinical assessment;
- Study retention;
- Alcohol craving; and
- Patient global impression of improvement.

4.4.3 Pivotal Efficacy Studies

4.4.3.1 Study Design and Summary

Each of the pivotal efficacy studies of acamprosate was a randomized, double-blind, placebo-controlled, multicenter study conducted under the supervision of specialists in alcoholism at centers in France, Germany, and Belgium which specialized primarily in alcohol-related illness. All 3 studies were initiated in 1989-1990.

Enrolled patients were adult alcohol-dependent outpatients who had at least a 12-month history of alcohol dependence (ranging from a minimum of 12 months [*Pelc II* and *Paille*] to 2 or 3 years [*PRAMA*]) and who were abstinent from alcohol for at least 5 days after undergoing detoxification (minimum of 5 days in *Pelc II*, minimum of 14 consecutive days and maximum of 28 days in *PRAMA*, and 7 to 30 days in *Paille*) before receiving study medication.

Patients in the *Pelc II* and *Paille* studies were randomly assigned to treatment with either acamprosate 1332 mg/day, acamprosate 1998 mg/day, or placebo. Patients in the *PRAMA* study were randomly assigned to treatment with acamprosate (1332 mg/day for patients ≤60 kg or 1998 mg/day for patients >60 kg) or placebo.

The treatment durations for the pivotal efficacy studies were 90 days (*Pelc II*), 360 days (*Paille*), and 48 weeks (*PRAMA*). Patients in these studies were to receive psychotherapy or other psychosocial therapy at the discretion of the investigator.

Pelc II

This Phase II, double-blind, randomized, placebo-controlled study of acamprosate was conducted by Lipha s.a. at 11 sites in Belgium and 1 site in France between 1990 and 1992. A report of this study has been published.^[18] The objective of the study was to compare the efficacy and safety of 2 dose levels of acamprosate versus placebo in maintaining abstinence over a 90-day treatment period in the weaned alcoholic. The selection of patients was made among alcohol-dependent patients who were about to start withdrawal or “weaning” from alcohol (inpatient acute detoxification) and who would

then be followed in the study as outpatients. Study medication was initiated after alcohol withdrawal had been completed and patients were abstinent for at least 5 days.

Inclusion criteria for the study included the following:

- Age 18 to 65 years;
- Weight ≥ 60 kg;
- Diagnosed with chronic or episodic alcohol dependence ,as defined by the DSM-III Classification of the American Psychiatric Association;
- Provided written informed consent;
- Consented to alcohol weaning therapy;
- Were abstinent for at least 5 days before entering the study; and
- Had at least a 12-month history of alcohol dependence.

Patients meeting any of the following criteria were excluded from study participation:

- Pregnant women or premenopausal women not practicing contraception;
- Psychiatric disorders which might necessitate specific drug treatment;
- Systemic disease (inadequately controlled diabetes mellitus, hypertension or cardiac failure, septicemia, active tuberculosis, or neoplastic disease);
- Epilepsy unrelated to alcoholism;
- Renal insufficiency (serum creatinine >120 $\mu\text{mol/L}$);
- Hypercalcemia of all etiologies;
- Any condition which was incompatible with the study;
- Prior treatment with acamprosate; and
- Patients who were not willing to collaborate with the alcohol weaning therapy.

Eligible patients were randomized to receive 1 of the following treatments in a ratio of 1:1:1: placebo (2 tablets matching acamprosate taken in the morning, mid-day, and evening); acamprosate 1332 mg/day (2 tablets acamprosate 333 mg in the morning, 1 tablet acamprosate 333 mg plus 1 tablet of placebo at mid-day and in the evening); acamprosate 1998 mg/day (2 tablets acamprosate 333 mg in the morning, mid-day, and in the evening). Study medication was to be taken during meal times. The scheduled

duration of treatment was 90 days. Throughout the study, patients were provided with psychotherapy at the investigator's discretion according to the site's usual practices.

Patients were initially assessed (Day of Selection) to determine whether they conformed with all of the inclusion and exclusion criteria including the CAGE ^[19] and the Michigan Alcoholism Screening Test (MAST) ^[20] questionnaires. Provided the patient met the inclusion criteria, the patient was reassessed and the Baseline parameters for measuring efficacy and safety were determined (Day 0). Subsequent assessments were made on Days 8, 15, 30, 45, 60, 75, and 90. Patients relapsing during treatment could continue or be admitted to a hospital to be weaned off alcohol while continuing their blinded study medication. Subsequently, they were returned to their outpatient status if their detoxification period was less than 14 days. There was no follow-up period in this study.

The defined primary efficacy parameters for the study were:

- CAD, defined as the total number of days of complete abstinence;
- CCAD, in percent, defined as the (total number of days of complete abstinence/total potential duration of treatment)X100; and
- Relapse rate (the complement of complete abstinence rate).

The secondary efficacy parameters were the:

- Time to first relapse (defined as the time to first drink);
- Total number of patients attending throughout the 90 day study and patients lost to follow-up;
- Frequency and quantity of alcohol consumption, based on self-report; and
- Physician's and patient's global clinical impression.

The primary population for efficacy analyses was all patients randomized who received at least 1 dose of study medication.

PRAMA

This Phase III, double-blind, randomized, placebo-controlled study of acamprosate was conducted by Lipha s.a. in 12 psychiatric clinics in Germany between 1990 and 1992.

Several reports of this study have been published.^[21-23] The objectives of the study were to:

- Evaluate the efficacy and tolerance of acamprosate versus placebo as therapy to maintain abstinence in the weaned alcoholic over a 48-week treatment period; and
- Determine whether efficacy is maintained over a 48-week observation period following the 48-week double-blind treatment period.

The selection of patients was made among alcohol-dependent patients who were about to start alcohol withdrawal therapy (inpatient acute detoxification) and who would then be followed in the study as outpatients. Randomization occurred following completion of detoxification and a minimum of 14 days of continuous abstinence (but no more than 28 days).

Inclusion criteria for the study included the following:

- Age 18 to 65 years;
- History of at least 3 years of alcohol dependence in males and at least 2 years of alcohol dependence in females;
- Diagnosed with alcohol dependence according to ICD9 ^[24], as defined by the DSM-III-R Classification of the American Psychiatric Association with at least 5 of the 9 features present in the DSM-III-R Classification;
- Munich Alcoholism Test (MALT) test score of at least 11 points ^[25];
- A minimum of 14 consecutive days abstinence following detoxification;
- Intelligence level of at least 13 points on the MWT-B questionnaire; and
- Provided written informed consent.

Exclusion criteria for the study included the following:

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

- Epilepsy not due to alcoholism, severe general changes in the EEG and/or epileptic foci;
- Severe hepatic damage, particularly alcoholic hepatitis and alcoholic cirrhosis, plasma cholinesterase less than the normal;
- Hypercalcemia of all etiologies;
- A planned stay at a specialist residential clinic for addicts or at a psychiatric clinic;
- Patients with no fixed abode;
- Severe drug addiction or drug dependence in the past 3 years;
- Known excretory pancreatic failure;
- Pregnant women or women of childbearing potential not using contraceptive measures, or women who are breastfeeding;
- Severe systemic disease (e.g., poorly controlled diabetes mellitus, noncompensated hypertension, decompensated heart failure);
- ECG-confirmed cardiac arrhythmias requiring treatment, ventricular extrasystoles;
- Kidney failure (plasma creatinine >120 µmol/L or >1.4 mg/dL);
- Malignancies;
- Refusal of patient to take part in the study;
- Patients with a pronounced organic psychological syndrome which prevents an understanding of the nature of the trial and of the questionnaires; and
- Patients who have undergone gastrointestinal surgery (except appendectomy).

Eligible patients were randomly assigned to receive acamprosate or placebo in a ratio of 1:1. The total daily dose was thereafter adjusted according to the patient's weight. Patients with a body weight ≥ 60 kg were to receive 1998 mg of acamprosate or placebo per day, taken as 2 tablets of 333 mg acamprosate (or placebo) in the morning, at mid-day, and in the evening. Patients with a body weight <60 kg were to receive 1332 mg of acamprosate or placebo per day, taken as 2 tablets of 333 mg acamprosate (or placebo) in the morning, and 1 tablet of 333 mg acamprosate (or placebo) at mid-day and in the

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

On the Day of Selection, patients were initially assessed to determine whether they conformed to the inclusion and exclusion criteria. Patients had to successfully complete the detoxification process and remain abstinent for at least 14 days before being assessed for the Baseline parameters. Provided the patient met the inclusion criteria, the patient was reassessed and Baseline parameters for measuring efficacy and safety were made at Weeks 4, 8, 12, 24, 36, and 48. Patients relapsing during treatment could continue with their study medication or, if the severity of the relapse necessitated, undergo detoxification and subsequently restart study medication. Psychotherapy was permitted during the weaning period and also the 48-week double-blind treatment. At Day 0, the severity of the patient's alcohol dependence was measured using the Göttinger Dependence Scale (GABS) [26].

The primary efficacy parameter for the study was the time to first relapse (defined as the time to first drink). Drinking behavior was based on patient self-report with corroboration by a 2nd party, when possible.

The secondary efficacy parameters for the study were:

- CAD, defined as the total number of days of complete abstinence;
- CCAD, defined as the (total number of days of complete abstinence/total potential duration of treatment)*100;
- Clinical global impression (CGI) of the investigator;
- Frequency of relapses per patient; and
- Craving for alcohol by visual analog scale (VAS).

For this study, the primary population for the analysis of efficacy was all patients randomized who received at least 1 dose of study medication.

Paille

This Phase II, randomized, double-blind, placebo-controlled study of acamprosate was conducted by Laboratoires Meram in 31 centers in France from 1989 to 1992 as a pivotal dose-response study and has been the subject of several publications.^[27-29] The objectives of the study were to:

- Compare the safety and efficacy of 2 dose levels of acamprosate versus placebo in maintaining abstinence over a 12-month double-blind treatment period in patients withdrawn from alcohol; and
- Subsequent to the double-blind treatment period, observe the outcome over the succeeding 6-month follow-up period while patients received placebo (single-blind).

The selection of patients was made among alcohol-dependent patients who were about to start withdrawal treatment (either on an inpatient basis or as outpatients) who would then be followed through the study as outpatients. Patients were to be included provided they had clearly stated their desire to maintain abstinence.

Inclusion criteria for the study included the following:

- Age 18 to 65 years;
- Alcohol dependence of the chronic or episodic type as defined by the DSM-III (R) Classification of the American Psychiatric Association;
- Had consented to alcohol weaning therapy;
- Were abstinent before being randomized into the study (7 to 30 days after the start of withdrawal);
- Had at least a 12-month history of alcohol dependency;
- Had a GGT value $\geq 2 \times \text{ULN}$ and/or an MCV value $>98 \mu\text{m}^3$;
- Had provided written informed consent.

Exclusion criteria for the study included the following:

- Pregnant women or premenopausal women not practicing contraception or breast-feeding women;
- Psychiatric disorders which might necessitate specific drug treatment;

- Systemic disease (inadequately controlled diabetes mellitus, hypertension or cardiac failure, septicemia, active tuberculosis, or neoplastic disease);
- Epilepsy unrelated to alcoholism;
- Renal insufficiency (serum creatinine >120 µmol/L);
- Hypercalcemia of all etiologies;
- Patients previously treated with acamprosate;
- Patients who had attempted more than 3 withdrawals during the 2 years prior to inclusion in the study;
- Patients who had been included in a therapeutic trial during the previous 6 months;
- Patients who were incapable of completing their self assessment form;
- Patients with no fixed address, patients residing in an alcohol treatment facility or patients who were not living with a non-alcohol-dependent spouse, friend or acquaintance, capable of providing information on the patient's dependence on alcohol;
- Patients who were unlikely to comply with treatment over an 18-month period;
- Obvious lack of cooperation during the withdrawal treatment; and
- Incompatible medication.

Eligible patients were randomly assigned to receive either acamprosate 1332 mg/day, acamprosate 1998 mg/day, or placebo in a ratio of 1:1:1. Patients assigned to acamprosate 1332 mg/day were to receive 2 tablets of 333 mg acamprosate in the morning, 1 tablet each of acamprosate 333 mg and placebo at mid-day and the evening. Patients assigned to acamprosate 1998 mg/day were to receive 2 tablets of 333 mg acamprosate in the morning, mid-day, and evening. Patients assigned to placebo were to receive 2 tablets of placebo in the morning, mid-day, and evening. The planned duration of exposure to double-blind study medication was 12 months. Throughout the study, patients were provided with psychotherapy at the investigator's discretion according to the site's usual practices.

Prior to withdrawal from alcohol, patients were evaluated for their eligibility for the study during an assessment period which lasted from 1 week to 1 month. Patients then underwent alcohol withdrawal either as inpatients or outpatients. At the end of the withdrawal period (following 7 to 30 days of abstinence) and on Day 0 of the double-blind study treatment, the patient's eligibility was confirmed by repetition of the clinical evaluation and laboratory tests. Evaluations were carried out on a monthly basis for 6 months and bimonthly thereafter and were either comprehensive visits, with clinical and laboratory assessments (Days 90, 180, 360, and 540) or follow-up evaluations (Days 30, 60, 120, 150, 240, 300, 420, and 480).

The primary efficacy parameters for the study were:

- CAD, defined as the total number of days of complete abstinence;
- CCAD, defined as the (total number of days of complete abstinence/total potential duration of treatment)*100;
- Number of days of continuous abstinence from the start of treatment;
- Number of days of continuous abstinence or controlled drinking (40 g alcohol/day or less); and
- Total treatment period with continuous attendance.

The secondary efficacy parameters for the study were:

- Classification of the patient's drinking pattern into categories of "Abstinent", "Controlled", "Uncontrolled", or "Treatment Failure";
- "Success" at Day 180 and Day 360 (defined as reported abstinence at Day 180 and Day 360; "partial success" was defined as abstinence at either visit);
- Clinical global impression (CGI) of the severity of the illness and the overall improvement; and
- Summary of therapeutic results regardless of adverse effects.

The primary population for the analysis of efficacy was all patients randomized who received at least 1 dose of study medication.

4.4.3.2 Patient Disposition

A summary of patient disposition across the 3 pivotal efficacy studies is presented in Table 5.

Collectively in these 3 studies, a total of 623 patients were treated with acamprosate (251 with 1332 mg/day, 236 with 1998 mg/day, and 136 with a weight-adjusted dose)^o and 375 were treated with placebo. These patients comprise the ITT population.

The percentage of patients completing the Treatment Phase of the pivotal efficacy studies was greater for patients treated with acamprosate compared to placebo (54% vs. 39%).

The percentage of patients discontinuing for each reason was similar between the acamprosate and placebo groups with the exception of the reason “Other” (which included “patient refusal” and “noncompliance”). Twice as many patients in the placebo group (22%) discontinued the study for the reason “Other” compared to patients treated with acamprosate (10%).

Table 5. Patient Disposition During Treatment Phase – Pivotal Efficacy Studies Pelc II, PRAMA, and Paille Combined

Parameter	Statistic	ACAMP	Placebo
Number of Patients Randomized	n (%)	624 (100%)	377 (100%)
Number of Patients in the ITT Population	n (%)	623 (>99%)	375 (>99%)
Number of Patients Who Completed Treatment Phase	n (%)	335 (54%)	147 (39%)
Number of Patients Who Discontinued Treatment Phase	n (%)	288 (46%)	228 (60%)
Reasons for Discontinuation:			
Adverse Event	n (%)	37 (6%)	22 (6%)
Lost to Follow-up	n (%)	87 (14%)	69 (18%)
Treatment Failure	n (%)	93 (15%)	50 (13%)
Death	n (%)	6 (1%)	3 (1%)
Protocol Violation	n (%)	1 (<1%)	3 (1%)
Other	n (%)	64 (10%)	81 (21%)
Data Source: NDA Table 8.7.1.1.1, Table 8.7.1.1.2, and Table 8.7.1.1.3.			

Note: The ACAMP column includes all patients assigned to the acamprosate groups, regardless of dose.

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

^o Of the PRAMA patients randomized to acamprosate, 24 received 1332 mg/day and 112 received 1998 mg/day, based on body weight criteria.

Pelc II

For the Pelc II study, a total of 188 patients were randomized (63 patients to acamprosate 1998 mg/day, 63 to acamprosate 1332 mg/day, and 62 to placebo). All 188 patients took at least 1 dose of study medication and comprise the ITT population. The percentage of patients who completed the 90-day treatment period was greater for acamprosate groups compared to the placebo group (70%, 68%, and 52% for the acamprosate 1332 mg/day, acamprosate 1998 mg/day, and placebo groups, respectively). Apart from the reason of “lost to follow-up”, which resulted in a larger percentage of patients in the placebo group discontinuing (24% vs. 10% and 13% for the acamprosate 1332 mg/day and 1998 mg/day groups, respectively), the reasons for discontinuation were similar among treatment groups.

No deaths occurred during the Treatment Phase.

**Table 6. Patient Disposition During Treatment Phase – Pivotal Efficacy Study
Pelc II**

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

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

PRAMA

In the PRAMA study, a total of 275 patients were randomized (137 to acamprosate and 138 to placebo). Three of these patients were withdrawn from the study on the Day 0 visit and did not receive the first dose of study medication. Hence, a total of 272 patients (136 in each group) received study medication and comprise the ITT population. A majority of the patients (82%) randomized to acamprosate were scheduled to receive a dose of 1998 mg/day, based on body weight. A greater percentage of patients in the acamprosate group completed the 48-week Treatment Phase compared to the placebo group (53% vs. 38%, respectively). A greater percentage of patients in the placebo group (32%) dropped out of the study for the reason of “Other” (which included “patient refusal” or “inability to continue”) compared to the acamprosate group (15%). Otherwise, the distribution of reasons for discontinuation was similar between the treatment groups.

There were 3 deaths during the Treatment Phase (2 in the acamprosate group and 1 in the placebo group).

Table 7. Patient Disposition During Treatment Phase – Pivotal Efficacy Study PRAMA

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

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

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

Paille

A total of 538 patients were randomized to treatment in the Paille study (188 to acamprosate 1332 mg/day, 173 to acamprosate 1998 mg/day, and 177 to placebo). The percentage of patients completing the 360-day treatment period was greater for patients in the acamprosate groups compared to the placebo group (45%, 52%, and 35% for the acamprosate 1332 mg/day, acamprosate 1998 mg/day, and placebo groups, respectively). Compared to patients in the acamprosate groups, a greater percentage of patients in the placebo group discontinued the study for the reason of “Other” (which included “patient refusal” and “noncompliance”): 13%, 10%, and 20% for the acamprosate 1332 mg/day, acamprosate 1998 mg/day, and placebo groups, respectively. Otherwise, the reasons for discontinuation of treatment were similarly distributed among the groups.

Six patients (2 in each of the 3 treatment groups) died during the Treatment Phase.

The percentage of patients completing the placebo follow-up phase was similar across the groups (82%, 83%, and 85% in the acamprosate 1332 mg/day, acamprosate 1998 mg/day, and placebo groups, respectively). A greater percentage of patients in the acamprosate 1332 mg/day group discontinued from the follow-up phase for “lost-to-follow-up” (7%) compared to the acamprosate 1998 mg/day group (2%) and the placebo group (0%). Otherwise, the reasons for discontinuation from the follow-up phase were similar across the groups.

Table 8. Patient Disposition During Treatment Phase and Follow-up Phase – Pivotal Efficacy Study Paille

Parameter	Statistic	ACAMP 1332 mg/day (N=188)	ACAMP 1998 mg/day (N=173)	Placebo (N=177)
Number of Patients Randomized	n	188	173	177
Number of Patients in the ITT Population	n (%)	188 (100%)	173 (100%)	177 (100%)
Number of Patients Who Completed Treatment Phase	n (%)	85 (45%)	90 (52%)	62 (35%)
Number of Patients Who Discontinued Treatment Phase	n (%)	103 (55%)	83 (48%)	115 (65%)
Reasons for Discontinuation from Treatment Phase				
Adverse Event	n (%)	13 (7%)	10 (6%)	12 (7%)
Lost to Follow-up	n (%)	22 (12%)	26 (15%)	27 (15%)
Treatment Failure	n (%)	42 (22%)	28 (16%)	35 (20%)
Death	n (%)	2 (1%)	2 (1%)	2 (1%)
Protocol Violation	n (%)	0	0	3 (3%)
Other	n (%)	24 (13%)	17 (10%)	36 (20%)
Number of Patients Who Entered Follow-up Phase	n	85	90	62
Number of Patients Who Completed Follow-up Phase	n (%)	70 (82%)	75 (83%)	53 (85%)
Number of Patients Who Discontinued Follow-up Phase	n (%)	15 (18%)	15 (17%)	9 (15%)
Reasons for Discontinuation from Follow-up Phase:				
Adverse Event	n (%)	2 (2%)	2 (2%)	2 (3%)
Lost to Follow-up	n (%)	6 (7%)	2 (2%)	0
Treatment Failure	n (%)	2 (2%)	4 (4%)	3 (5%)
Death	n (%)	0	0	0
Protocol Violation	n (%)	0	0	1 (2%)
Other	n (%)	3 (6%)	7 (8%)	3 (5%)
Data Source: NDA Table 8.7.1.1.3, Table 2 of Paille study report (for data from follow-up phase).				

Note: Percentages for the Treatment Phase are based on the number of patients randomized. Percentages for the Follow-up phase are based on the number of patients who entered the Follow-up phase.

4.4.3.3 Demographic and Baseline Characteristics

Demographic characteristics and aspects of alcohol history were similar across the 3 pivotal efficacy studies. The majority (80%) of the patients in these studies were male, the mean age was 42 years, and the mean weight was 71 kg.

On study entry, patients had an average of 9.7 years of alcohol dependence and 73% had been drinking more than 10 standard drinks per day (*defined for the purposes of the integrated analysis as 12 g of pure alcohol per standard drink*).

All but 2 of the 623 patients in the pivotal efficacy studies were abstinent from alcohol prior to the initiation of randomly assigned study medication and all, by virtue of the individual study entry criteria, had undergone detoxification prior to entering the study.

Pelc II

In the Pelc II study, the 3 treatment groups were similar with respect to demographic and Baseline characteristics. Most patients in this study were male (81% to 89% across treatment groups) and the mean age ranged from 40.5 to 43.3 years. There was a greater percentage of patients in the 16-39 years age category within the acamprosate 1998 mg/day group (52%) compared to the acamprosate 1332 mg/day (32%) and placebo groups (42%). Approximately one-half of patients were married (47% to 54% across treatment groups). There were no statistically significant differences among the treatment groups with respect to these demographic characteristics, except for age category ($p=0.035$).

Aspects of the patients' history of alcohol use were similar across treatment groups, as well. Patients in the study had a mean duration of alcohol dependence of 8.6 years (mean range of 7.5 to 10.1 across treatment groups) and 77% (71% to 87% across groups) drank more than 10 standard drinks (12 g of per alcohol per standard drink) per day in the recent past prior to study entry. More than half (62%) of the patients had previously undergone treatment or detoxification for alcoholism and the majority did not attend alcoholic self-help groups. All of the patients in the study had undergone detoxification and all but 2 patients (both in the placebo group) were abstinent at Baseline. There were no statistically significant treatment group differences with respect to the characteristics of alcohol history evaluated for this study.

**Table 9. Demographic and Baseline Characteristics – Pivotal Efficacy Study
Pelc II**

Characteristic	Statistic	ACAMP 1332 mg/day (N=63)	ACAMP 1998 mg/day (N=63)	Placebo (N=62)
Gender	n	63	63	62
Male	n (%)	51 (81%)	54 (86%)	55 (89%)
Female	n (%)	12 (19%)	9 (14%)	7 (11%)
Age (years)	n	63	63	62
	Mean (SE)	43.3 (1.1)	40.5 (1.0)	40.9 (1.1)
	Min, Max	21, 71	26, 59	26, 59
Age Distribution (years)	n	63	63	62
16-39	n (%)	20 (32%)	33 (52%)	26 (42%)
40-59	n (%)	40 (63%)	30 (48%)	36 (58%)
≥60	n (%)	3 (5%)	0	0
Weight (kg)	n	63	63	62
	Mean (SE)	74.0 (1.5)	71.4 (1.2)	72.1 (1.7)
	Min, Max	58, 122	52, 94	56, 137
Marital Status	n	63	63	62
Married	n (%)	30 (48%)	34 (54%)	29 (47%)
Not married	n (%)	33 (52%)	29 (46%)	33 (53%)
Detoxification Prior to Randomization	n	63	63	62
Yes	n (%)	63 (100%)	63 (100%)	62 (100%)
No	n (%)	0	0	0
Abstinent at Baseline	n	63	63	62
Yes	n (%)	63 (100%)	63 (100%)	60 (97%)
No	n (%)	0	0	2 (3%)
Duration of Alcohol Dependence/Abuse (years)	n	63	63	62
	Mean (SE)	10.1 (1.1)	8.3 (0.9)	7.5 (1.0)
	Min, Max	1, 40	1, 45	1, 35
<10	n (%)	33 (52%)	39 (62%)	42 (68%)
≥10	n (%)	30 (48%)	24 (38%)	19 (31%)
Average Standard Drinks per Day at Study Entry	n	63	63	62
<5	n (%)	1 (2%)	2 (3%)	0
5-10	n (%)	17 (27%)	16 (25%)	8 (13%)
>10	n (%)	45 (71%)	45 (71%)	54 (87%)
Prior Treatment or Detoxes for Alcoholism	n	63	63	62
0	n (%)	25 (40%)	26 (41%)	21 (34%)
1	n (%)	17 (27%)	15 (21%)	18 (29%)
2	n (%)	6 (10%)	9 (14%)	8 (13%)
3	n (%)	4 (6%)	2 (3%)	9 (15%)
>3	n (%)	11 (17%)	11 (17%)	6 (10%)
Data Source: NDA Table 8.7.1.2.1 and Table 8.7.1.3.1				

PRAMA

Demographic characteristics were similar between the 2 treatment groups in the PRAMA study. Seventy-eight percent (75% to 80% across treatment groups) of the patients were male, the average age was 41 years (40.5 to 41.9 across treatment groups), and the mean weight was 73 kg (72.4 and 73.9 across treatment groups). Forty-six percent of patients were married. There were no significant treatment group differences with respect to demographic characteristics, with the exception of weight category distribution ($p=0.037$).

Aspects of the alcohol history were similar across the treatment groups, as well. Patients in the PRAMA study had, on average, 10.4 years of alcohol dependence. At the time of study entry, 78% (77% to 80% across treatment groups) of the patients had been drinking more than 10 standard drinks (12 g of pure alcohol per standard drink) per day and 73% (71% to 76% across treatment groups) had undergone previous treatment or detoxification for alcoholism. Less than a third of the patients in the study attended alcoholic self-help groups. There were no statistically significant differences with respect to the characteristics of alcohol history evaluated for this study.

Table 10. Demographic and Baseline Characteristics – Pivotal Efficacy Study PRAMA

Characteristic	Statistic	ACAMP (N=136)	Placebo (n=136)
Gender	n	136	136
Male	n (%)	102 (75%)	109 (80%)
Female	n (%)	34 (25%)	27 (20%)
Age (years)	n	136	136
	Mean (SE)	41.9 (0.7)	40.5 (0.7)
	Min, Max	21, 58	21, 65
Age Distribution (years)	n	136	136
16-39	n (%)	54 (40%)	69 (51%)
40-59	n (%)	82 (60%)	64 (47%)
≥60	n (%)	0	3 (2%)
Weight (kg)	n	136	136
	Mean (SE)	72.4 (1.0)	73.9 (1.1)
	Min, Max	46, 130	41, 107
Marital Status	n	136	136
Married	n (%)	58 (43%)	67 (49%)
Not married	n (%)	78 (57%)	69 (51%)
Detoxification Prior to Randomization	n	136	136
Yes	n (%)	136 (100%)	136 (100%)
No	n (%)	0	0
Abstinent at Baseline	n	136	136
Yes	n (%)	136 (100%)	136 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)	n	136	136
	Mean (SE)	10.4 (0.5)	10.4 (0.6)
	Min, Max	2, 30	2, 30
<10	n (%)	61 (45%)	67 (49%)
≥10	n (%)	75 (55%)	69 (51%)
Average Standard Drinks per Day at Study Entry	n	134	136
	Mean (SE)	17.9 (0.8)	18.7 (0.8)
	Min, Max	3, 46	1, 45
<5	n (%)	3 (2%)	6 (4%)
5-10	n (%)	28 (21%)	21 (15%)
>10	n (%)	103 (77%)	109 (80%)
Prior Treatment or Detoxes for Alcoholism	n	136	136
0	n (%)	33 (24%)	40 (29%)
1	n (%)	34 (25%)	32 (24%)
2	n (%)	22 (16%)	17 (13%)
3	n (%)	13 (10%)	13 (10%)
>3	n (%)	34 (25%)	34 (25%)
Data Source: NDA Table 8.7.1.2.2 and Table 8.7.1.3.2			

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

Paille

In the Paille study, demographic characteristics were similar across the 3 treatment groups. More than 75% of the patients in each treatment group were male. The mean age was 43 years (42.5 to 43.7 across treatment groups) and the mean body weight was 69 kg (67.8 to 70.8 kg across treatment groups). There were no statistically significant treatment group differences with respect to demographic characteristics.

Characteristics of patients' alcohol history were also well-balanced across the 3 treatment groups in the Paille study. At entry into the study, 69% (64% to 76% across treatment groups) of the patients had been drinking more than 10 standard drinks (12 g of pure alcohol per standard drink) per day. No data were collected pertaining to the duration of each patient's alcohol dependence. However, 50% (47% to 52% across treatment groups) of the patients had undergone previous detoxification or treatment for alcoholism and 79% (77% to 81% across treatment groups) of the patients were rated (per Clinical Global Impression) by the investigators as "clearly ill", "seriously ill" or "extremely ill". There were no statistically significant treatment group differences with respect to the aspects of the patients' alcohol history.

Table 10a. Demographic and Baseline Characteristics – Pivotal Efficacy Study Paille

Characteristic	Statistic	ACAMP 1332 mg/day (N=188)	ACAMP 1998 mg/day (N=173)	Placebo (n=177)
Gender	n	188	173	177
Male	n (%)	146 (78%)	137 (79%)	147 (83%)
Female	n (%)	42 (22%)	36 (21%)	30 (17%)
Age (years)	n	188	173	177
	Mean (SE)	43.7 (0.6)	43.3 (0.6)	42.5 (0.7)
	Min, Max	27, 68	26, 65	25, 65
Age Distribution (years)	n	188	173	177
16-39	n (%)	63 (34%)	60 (35%)	70 (40%)
40-59	n (%)	119 (63%)	106 (61%)	98 (55%)
≥60	n (%)	6 (3%)	7 (4%)	9 (5%)
Weight (kg)	n	187	173	177
	Mean (SE)	69.3 (1.0)	67.8 (0.9)	70.8 (1.0)
	Min, Max	43, 130	40, 105	48, 124
Marital Status	NA			
Detoxification Prior to Randomization	n	188	173	177
Yes	n (%)	188 (100%)	173 (100%)	177 (100%)
No	n (%)	0	0	0
Abstinent at Baseline	n	188	173	177
Yes	n (%)	188 (100%)	173 (100%)	177 (100%)
No	n (%)	0	0	0
Duration of Alcohol Dependence/Abuse (years)	n	NA	NA	NA
	Mean (SE)			
	Min, Max			
Average Standard Drinks per day at Study Entry	n	187	173	176
	Mean (SE)	15.7 (1.0)	15.0 (0.6)	16.0 (0.7)
	Min, Max	4, 167	1, 42	1, 67
<5	n (%)	3 (2%)	6 (3%)	8 (5%)
5-10	n (%)	56 (30%)	57 (33%)	35 (20%)
>10	n (%)	128 (68%)	110 (64%)	133 (76%)
Prior Treatment or Detoxes for Alcoholism	n	188	173	176
0	n (%)	99 (53%)	87 (50%)	84 (48%)
1	n (%)	57 (30%)	50 (29%)	59 (34%)
2	n (%)	19 (10%)	26 (15%)	26 (15%)
3	n (%)	10 (5%)	4 (2%)	4 (2%)
>3	n (%)	3 (2%)	6 (3%)	3 (2%)
Data Source: NDA Table 8.7.1.2.3 and Table 8.7.1.3.3				

NA = Not Available

4.4.3.4 Drug Exposure

Summaries of study drug exposure and compliance are presented separately for each of the pivotal efficacy studies. Duration of exposure to study medication was calculated as the difference between the last date of study medication and the first date of study medication, inclusive. Compliance with study medication usage (assessed by returned tablet counts) and the percentage of patients who were 75% compliant are summarized. Statistical testing was not performed for either duration of exposure or compliance.

In all 3 of the pivotal efficacy studies, the duration of exposure for patients in the placebo group was shorter than for patients in the acamprosate groups. This result is consistent with the higher dropout rate in the placebo group compared to the acamprosate groups. There were some differences in treatment compliance between studies. However, compliance was similar between treatment groups within each of the 3 pivotal efficacy studies. The percentage of patients who were $\geq 75\%$ compliant was highest in the Pelc II study (at least 94% in all treatment groups), which might be expected since the study duration (3 months) was shorter than for the Paille and PRAMA studies (approximately 1 year, with the percentage of patients with $\geq 75\%$ compliance ranging from 68% to 81% across all groups).

Pelc II

In the Pelc II study (Table 11), mean duration of exposure to study medication for patients in the placebo group (9.4 weeks) was shorter than the duration of exposure for patients in the acamprosate 1332 mg/day group (10.6 weeks) and the acamprosate 1998 mg/day group (11.2 weeks). This finding can be attributed to more placebo patients discontinuing within the first 4 weeks. Compliance was similar for the 3 treatment groups (means values of 96.7% to 100.4% across treatment groups) and a similar percentage (94% to 100%) of patients in all treatment groups were at least 75% compliant.

Table 11. Drug Exposure – Pivotal Efficacy Study Pelc II

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

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

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

PRAMA

In the PRAMA study (Table 12), duration of exposure to study medication was shorter in the placebo group than in the acamprosate group (means of 26.1 and 32.2 weeks, respectively). Less than half of patients in the placebo group (44%) completed at least 26 weeks of treatment, whereas 59% of the patients in the acamprosate group completed at least 26 weeks of treatment. The mean compliance was similar between the groups (80.7 to 80.8), and a similar percentage of patients were at least 75% compliant (68% to 70% of patients).

Table 12. Drug Exposure – Pivotal Efficacy Study PRAMA

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

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

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

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

Paille

The mean duration of exposure to study medication in the acamprosate groups (35.3 and 37.7 weeks for acamprosate 1332 mg/day and acamprosate 1998 mg/day, respectively) was greater than in the placebo group (31.6 weeks). This result was consistent with a higher dropout rate within the first 26 weeks in the placebo group (43%) compared to the acamprosate groups (28% to 36%). Mean compliance was similar across the treatment groups, although there was a slightly greater percentage of patients with at least 75% compliance in the acamprosate 1998 mg/day group compared to the acamprosate 1332 mg/day and placebo groups (81% vs. 75% and 73%, respectively).

Table 13. Drug Exposure – Pivotal Efficacy Study Paille

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

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

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

4.4.3.5 Primary Efficacy Parameters

The primary efficacy parameters discussed in this section include:

- CCAD;
- Time to first drink; and
- Rate of complete abstinence.

Results of the analyses of the primary efficacy parameters for the pivotal studies are presented for the ITT population.

4.4.3.5.1 *Corrected Cumulative Abstinence Duration (CCAD)*

The analysis of CCAD showed that CCAD was statistically significantly greater for patients treated with acamprosate compared to patients treated with placebo in all 3 pivotal efficacy studies. Differences in median CCAD values between the acamprosate 1998 mg/day (or acamprosate in PRAMA) and placebo groups ranged from 20% (Paille study) to 38% (Pelc II study). Differences in median CCAD values between the acamprosate 1332 mg/day and placebo groups were 14% in the Paille study and 38% in the Pelc II study. Differences between the acamprosate 1332 mg/day and placebo groups were statistically significant in the Pelc II study and approached statistical significance in the Paille study. Similar results were observed for the on-treatment analysis from the PRAMA study compared to the ITT analysis. Detailed results of the CCAD analysis are presented for each study below.

For each of the pivotal efficacy studies, CCAD was calculated as:

$$\text{CCAD (\%)} = \frac{\text{Total number of days of abstinence} \times 100}{\text{Total potential duration of exposure to treatment}}$$

Corrected CAD (CCAD) results for all of the pivotal efficacy studies are summarized in Table 14.

Table 14. Percentage of Abstinent Days on Study. Corrected Cumulative Abstinence Duration (CCAD) During Treatment Phase – Pivotal Efficacy Studies Pelc II, PRAMA, and Paille

Study	Statistic	ACAMP 1332 mg/day	ACAMP 1998/2000 mg/day	Placebo	P-value ¹
Pelc II	N	63	63	62	<0.001**
	Mean (SE)	59.1 (5.2)	62.9 (4.7)	38.1 (4.8)	
	Median	67	67	29	
	Min, Max	0, 100	0, 100	0, 100	
PRAMA	N	-	136	136	<0.001**
	Mean (SE)	-	62.4 (3.3)	45.3 (3.1)	
	Median	-	75	38	
	Min, Max	-	4, 100	2, 100	
Paille	N	188	172	177	0.001**
	Mean (SE)	62.2 (2.6)	68.9 (2.7)	58.2 (2.7)	
	Median	72	86	66	
	Min, Max	0, 100	0, 100	0, 100	
Data Source: NDA Tables 8.7.1.5.1, 8.7.1.5.2, and 8.7.1.5.3					

* Significant at the 0.050 level; ** significant at the 0.010 level.

¹ P-value is from the comparison of ACAMP 1998/2000 vs. Placebo (Pelc II and Paille) or ACAMP vs. Placebo (PRAMA) based on a rank one-way ANOVA model.

Note: Results from the ACAMP group in PRAMA are presented in the ACAMP 1998/2000 mg/day column.

Pelc II

For the 3-month Pelc II study, the mean (SE) CCAD was 59.1% (5.2) for the acamprosate 1332 mg/day group, 62.9% (4.7) for the acamprosate 1998/2000 mg/day group, and 38.1% (4.8) for the placebo group. Median values were 67% for both the acamprosate 1332 mg/day and acamprosate 1998 mg/day groups, compared to 29% for the placebo group. The CCAD values for the acamprosate 1998/2000 mg/day and acamprosate 1332 mg/day groups were statistically significantly greater than the CCAD values for the placebo group ($p < 0.001$). The difference in CCAD between the 2 acamprosate groups was not statistically significant ($p = 0.738$).

PRAMA

For the 1-year PRAMA study, the mean (SE) CCAD was 62.4% (3.3) for the acamprosate group and 45.3% (3.1) for the placebo group. Median CCAD values were 75% and 38% in the acamprosate and placebo groups, respectively. The treatment group difference on CCAD was statistically significant ($p < 0.001$).

Paille

For the 1-year Paille study, the mean (SE) CCAD was 62.2% (2.6) for the acamprosate 1332 mg/day group, 68.9% (2.7) for the acamprosate 1998/2000 mg/day group, and 58.2% (2.7) for the placebo group. Median CCAD values were 72%, 86%, and 66% for the acamprosate 1332 mg/day, acamprosate 1998 mg/day, and placebo groups, respectively. The CCAD values were statistically significantly greater in the ACAMP 1998/2000 group compared to the placebo group ($p=0.001$), while the difference in CCAD between the acamprosate 1332 mg/day group and the placebo group was not statistically significant ($p=0.159$). The difference between CCAD for the acamprosate 1332 mg/day group and the acamprosate 1998/2000 mg/day group was not statistically significant ($p=0.071$).

Summary of CCAD

In summary, as shown in all 3 pivotal efficacy studies, treatment group differences with respect to CCAD between the acamprosate 1998 mg/day (or acamprosate) and placebo groups were statistically significant in favor of acamprosate. Differences in median CCAD values between the acamprosate 1998 mg/day (or acamprosate in PRAMA) and placebo groups were 38% (67% vs. 29%) in the Pelc II study, 35% (75% vs. 38%) in the PRAMA study, and 20% (86% vs. 66%) in the Paille study. There was a suggestion of a dose-response effect in that values for CCAD in the 1332 mg/day dosage group in both the Pelc II and Paille studies were intermediate between CCAD values for the placebo and acamprosate 1998 mg/day groups. The difference between acamprosate 1332 mg/day and placebo was statistically significant in Pelc II ($p<0.001$), but not in Paille. The difference between acamprosate 1332 mg/day and acamprosate 1998 mg/day was not significant in either study, although it approached significance in the Paille study ($p=0.071$).

4.4.3.5.2 Time to First Drink

Results for the analysis of time to first drink demonstrate that patients treated with acamprosate had longer durations of continuous abstinence compared to patients treated with placebo. Differences between the acamprosate 1998 mg/day (or acamprosate) and

placebo groups in the median time to first drink were 35.5 days (Pelc II study), 89.5 days (PRAMA study), and 29.0 days (Paille study). Median values of time to first drink for patients treated with acamprosate 1998 mg/day (or acamprosate) were 2.0 to 3.1 times longer than for patients treated with placebo. The treatment group differences between acamprosate 1998 mg/day (or acamprosate) and placebo were highly statistically significant ($p \leq 0.005$ for all 3 studies).

Time to first drink was analyzed using censored and uncensored approaches. For the censored approach, patients who discontinued prior to the first drink were censored at the time of discontinuation. For the uncensored approach, patients who discontinued prior to the first drink were considered to be treatment failures (relapse) at the time of discontinuation. Results from the uncensored analysis are presented in the tables. However, results from the censored approach are presented textually for comparison purposes.

Results from the uncensored survival analysis for time to first drink are presented in Table 15 for the 3 pivotal efficacy studies during the Treatment Phase.

Figures 4 (Pelc II study), 5 (PRAMA study), and 6 (Paille study) present corresponding Kaplan-Meier plots^[30] of time to first drink during the Treatment Phase.

Table 15. Kaplan-Meier Estimates of Time to First Drink (in Days) During Treatment Phase (Discontinuations Treated as Failures) – Pivotal Efficacy Studies Pelc II, PRAMA, and Paille

Study	Statistic	ACAMP 1332 mg/day	ACAMP 1998/2000 mg/day	Placebo	P-value ¹
Pelc II	N	63	63	62	<0.001**
	25 th Percentile	11.5	22.5	4.0	
	50 th Percentile	52.5	52.5	17.0	
	75 th Percentile	NA	NA	52.5	
PRAMA	N		136	136	<0.001**
	25 th Percentile	-	25.0	15.5	
	50 th Percentile	-	134.5	45.0	
	75 th Percentile	-	NA	170.0	
Paille	N	188	172	177	0.005**
	25 th Percentile	0.0	0.0	0.0	
	50 th Percentile	33.0	59.0	30.0	
	75 th Percentile	195.0	238.0	124.0	
Data Source: NDA Tables 8.7.1.6.1, 8.7.1.6.2, and 8.7.1.6.3					

* Significant at the 0.050 level; ** significant at the 0.010 level.

¹ P-value is from the comparison of ACAMP 1998/2000 vs. Placebo (Pelc II and Paille) or ACAMP vs. Placebo (*PRAMA*) based on the logrank test.

Note: Results from the ACAMP group in PRAMA are presented in the ACAMP 1998/2000 mg/day column.

Note: NA = Not available since fewer than 75% of patients reported drinking.

Pelc II

For the Pelc II study, the median time to first drink calculated from the uncensored approach was 52.5 days for the acamprosate 1332 mg/day group, 52.5 days for the acamprosate 1998/2000 mg/day group, and 17.0 days for the placebo group (see also Figure 4). These results demonstrated a prolongation of the median time to first drink for patients treated with acamprosate 1998/2000 mg/day of 3.1 times that for patients treated with placebo. The acamprosate 1998/2000 mg/day and acamprosate 1332 mg/day groups had statistically significantly longer durations of time to first drink compared to the placebo group ($p < 0.001$). As the censored analysis approach only affected 1 patient in the acamprosate 1998 mg/day group, the results of the censored approach were very similar to the uncensored results. The survival distributions for the 3 treatment groups exhibit the early (by Day 5) separation of the acamprosate groups from placebo. These separations were maintained, and slightly increased, throughout the Treatment Phase.

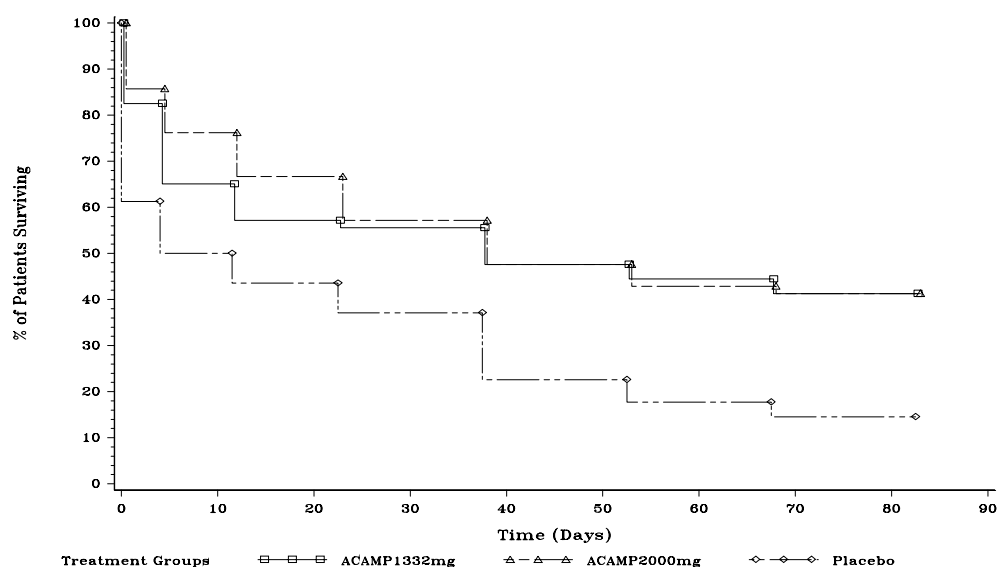


Figure 4. Kaplan-Meier Estimate of Time to First Drink During Treatment Phase – Pivotal Efficacy Study Pelc II

PRAMA

For the PRAMA study, the median continuous abstinence duration calculated from the uncensored approach was almost 3 times longer in the acamprosate group (134.5 days) compared to the placebo group (45.0 days; see also Figure 5). The difference between treatment groups was statistically significant ($p < 0.001$). A total of 69 patients (31 in acamprosate and 38 in placebo) were dropouts with censored data. The inclusion of these patients in the uncensored analysis had a similar effect on the median estimates. In both groups the median duration estimates were essentially cut in half. Results from the censored analysis showed that the median time to first drink for the acamprosate group (253.0 days) was statistically significantly longer in duration compared to the placebo group (92.0 days, logrank test $p = 0.006$). The Kaplan-Meier estimates^[30] for the ITT population demonstrate that separation between the 2 treatments was well established by Day 60, with consistency of effect afterward.

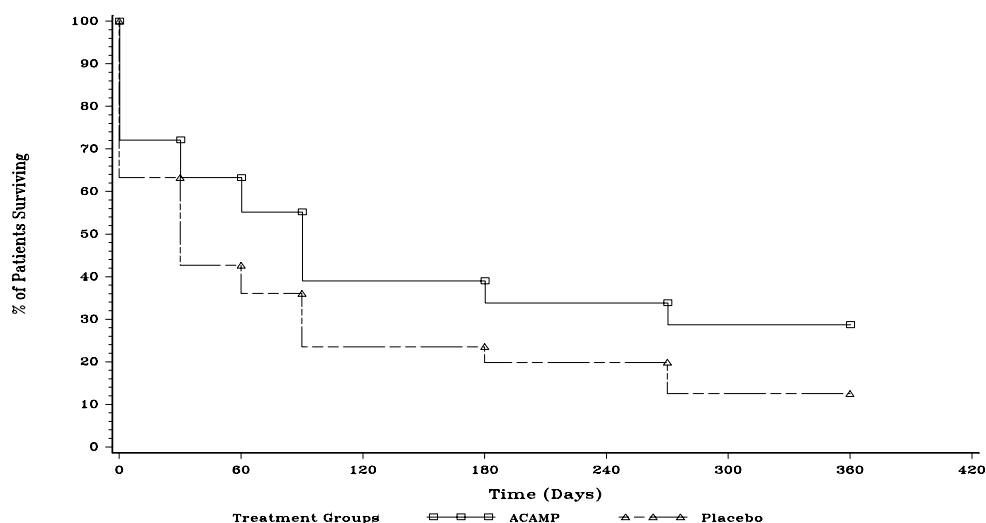


Figure 5. Kaplan-Meier Estimate of Time to First Drink During Treatment Phase – Pivotal Efficacy Study PRAMA

Paille

The median time to first drink for the Paille study calculated from the uncensored approach was 33.0 days for the acamprosate 1332 mg/day group, 59.0 days for the acamprosate 1998/2000 mg/day group, and 30.0 days for the placebo group (see also Figure 6). The median value for the acamprosate 1998/2000 mg/day group was 2.0 times that for the placebo group. Patients in the acamprosate 1998/2000 mg/day and acamprosate 1332 mg/day groups had statistically significantly longer times to first drink compared to patients in the placebo group ($p=0.005$ and $p=0.033$, respectively). There were 70 patients who dropped out and were included as events in the uncensored analysis. These patients were equally distributed across treatment groups (24 in the acamprosate 1998/2000 mg/day group, 27 in the acamprosate 1332 mg/day group, and 28 in the placebo group). Their effects on the median duration estimates were minimal as these patients were not typically early dropouts. Hence, results for the censored approach were similar to those of the uncensored approach with patients in the acamprosate 1998/2000 mg/day group having a statistically significantly longer abstinence duration than patients in the placebo group ($p=0.021$). The graphical presentation of these analyses demonstrate that separation in survival estimates between the acamprosate

1998/2000 mg/day and placebo groups occurred around 30-60 days and was maintained throughout the study.

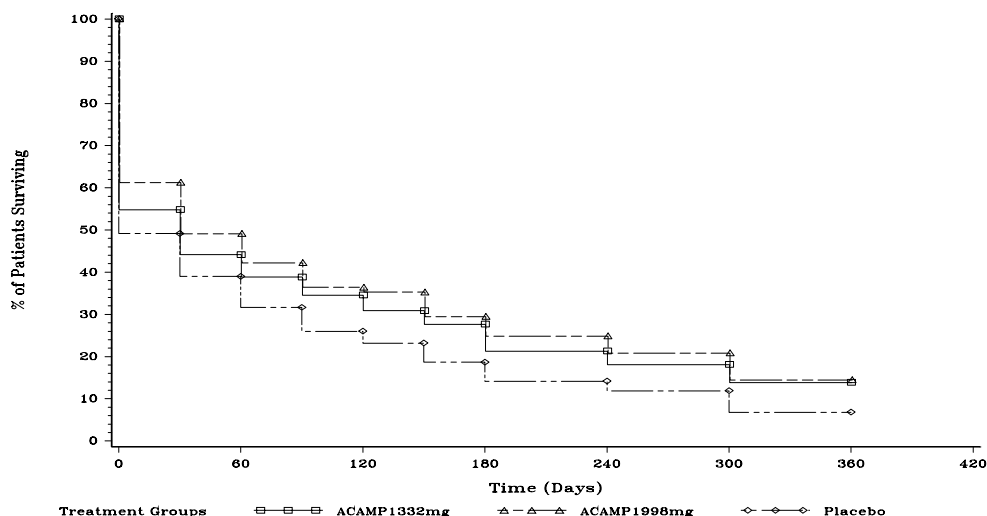


Figure 6. Kaplan-Meier Estimate of Time to First Drink During Treatment Phase – Pivotal Efficacy Study Paille

Summary of Time to First Drink

In summary, patients treated with acamprosate had longer durations of abstinence, defined as time to first drink, compared to patients treated with placebo. The results of the uncensored analyses showed highly statistically significant differences ($p \leq 0.005$ for all studies) in favor of the acamprosate 1998/2000 mg/day group (or acamprosate group in the PRAMA study) compared to the placebo group. In the Pelc II study, median time to first drink for the 1332 mg/day group was identical to the value for the 1998/2000 mg/day group, statistically significantly longer than placebo. There was also a statistically significant increase in time to first drink in the 1332 mg/day group in the Paille study, compared to placebo. In the Paille study, the median value for time to first drink was greater than that for the placebo group, but less than the value for the 1998/2000 mg/day group. However, the differences between the acamprosate groups in the Paille study were not statistically significant. The findings of the censored analyses supported these conclusions.

4.4.3.5.3 *Rate of Complete Abstinence*

The rate of complete abstinence during the Treatment Phase was higher for patients treated with acamprosate compared to patients treated with placebo. Specifically, the acamprosate 1998/2000 mg/day group (Pelc II and Paille studies) and the acamprosate group (PRAMA study) had statistically significantly greater percentages of patients remaining complete abstinent compared to patients in the placebo group (range of 8-26% higher than placebo). The rates of complete abstinence for the acamprosate 1998 mg/day (or acamprosate) group were 1.7 times to 2.7 times the rates for the placebo group. The treatment group differences between the acamprosate 1332 mg/day group and the placebo group in the Pelc II and Paille studies also favored acamprosate, supporting the results observed in the higher acamprosate dose.

Table 16 presents the rate of complete abstinence during the Treatment Phase for the pivotal efficacy studies. Statistical testing results for the comparison of the acamprosate 1998/2000 mg/day group versus the placebo group are presented. Statistical testing results for the acamprosate 1332 mg/day group versus the placebo group are presented textually.

Table 16. Rate of Complete Abstinence During Treatment Phase – Pivotal Efficacy Studies Pelc II, PRAMA, and Paille

Study	Statistic	ACAMP 1332 mg/day	ACAMP 1998/2000 mg/day	Placebo	P-value ¹
Pelc II	n / N (%)	26 / 63 (41%)	26 / 63 (41%)	9 / 62 (15%)	<0.001**
PRAMA	n / N (%)	-	39 / 136 (29%)	16 / 136 (12%)	<0.001**
Paille	n / N (%)	34 / 188 (18%)	33 / 173 (19%)	20 / 177 (11%)	0.028*
Data Source: NDA Tables 8.7.1.7.1, 8.7.1.7.2, and 8.7.1.7.3					

* Significant at the 0.050 level; ** significant at the 0.010 level.

¹ P-value is from the comparison of ACAMP 1998/2000 vs. Placebo (Pelc II and Paille) or ACAMP vs. Placebo (PRAMA) based on a chi-square test of complete abstinence vs. non-abstinent or missing.

Note: Results from the ACAMP group in PRAMA are presented in the ACAMP 1998/2000 mg/day column.

Pelc II

For the Pelc II study, the rate of complete abstinence during the 90-day Treatment Phase was 41% for the acamprosate 1332 mg/day group, 41% for the acamprosate 1998/2000 mg/day group, and 15% for the placebo group. Patients in the acamprosate 1998/2000 mg/day group had a statistically significantly greater percentage of patients remaining abstinent throughout the entire trial compared to patients in the placebo group ($p<0.001$). In addition, a statistically significantly greater percentage of patients in the acamprosate 1332 mg/day group were abstinent over the entire Treatment Phase compared to the placebo group ($p<0.001$). Differences between acamprosate treatment and placebo were evident by Day 8 and were maintained throughout the study.

PRAMA

By the end of the 48-week Treatment Phase for the PRAMA study, 29% of the patients in the acamprosate group remained abstinent compared to 12% of the patients in the placebo group. The difference in rates was statistically significant ($p<0.001$). Treatment group differences of at least 11% were demonstrated at each observation beginning at Day 30.

Paille

For the Paille study, the rate of complete abstinence at the end of the 1 year Treatment Phase was 18% for the acamprosate 1332 mg/day group, 19% for the acamprosate 1998/2000 mg/day group, and 11% for the placebo group. The acamprosate 1998/2000 mg/day group had a statistically significantly greater percentage of patients remaining abstinent throughout the entire study compared to the placebo group ($p=0.028$), while the difference between the acamprosate 1332 mg/day group and the placebo group did not achieve statistical significance ($p=0.063$).

Summary of Rate of Complete Abstinence

In summary, the rate of complete abstinence during the Treatment Phase (which means not a single drink during this period) was between 1.7 and 2.7 times higher for patients treated with acamprosate 1998/2000 mg/day (or acamprosate) compared to patients treated with placebo. Specifically, the acamprosate 1998/2000 mg/day group (Pelc II and Paille studies) and the acamprosate group (PRAMA study) had statistically significantly

($p \leq 0.028$ for all studies) greater percentages of patients remaining completely abstinent throughout the Treatment Phase of each study compared to patients in the placebo group. As might be expected, abstinence rates were higher in the 3 month Pelc II study compared to the 1 year PRAMA and Paille studies, but, as noted, differences between the active and placebo group were maintained throughout the observation period. In the Pelc II study, the complete abstinence rate in the 1332 mg/day group was the same as that of the 1998/2000 mg/day group and, accordingly, was significantly greater than the placebo group. In the Paille study, the 1332 mg/day group also had a complete abstinence rate greater than the placebo group, but this did not reach statistical significance.

4.4.3.6 Secondary Efficacy Parameters

The secondary efficacy parameters discussed in this section are:

- Frequency of alcohol consumption;
- Quantity of alcohol consumption;
- Pattern of alcohol consumption;
- Overall clinical assessment (i.e., CGI or global investigator assessment);
- Study retention;
- Alcohol craving; and
- Patient global impression of improvement.

Statistical analyses of the secondary efficacy parameters were performed using the same methods described in the original study reports, where possible. Results are presented for the ITT population by study day (visit) within each study, including the Last Visit per patient.

4.4.3.6.1 Frequency of Alcohol Consumption

Frequency of alcohol consumption was not collected in the Paille study. Results from the analysis of frequency of alcohol consumption for the other 2 studies showed that acamprosate patients had less frequent alcohol consumption compared to placebo patients

throughout the Treatment Phase. Detailed results of the analysis for the frequency of alcohol consumption are presented below.

Treatment group comparisons (statistical) were not performed for the Pelc II study.

Pelc II

Table 17 presents the frequency of alcohol consumption during the Treatment Phase for the Pelc II study.

Although patients in the Pelc II study were required to be abstinent from alcohol at the start of the study, 2 patients in the placebo group reported drinking every day at the Day 0 assessment. At all visits in the Pelc II study, the percentage of patients who were not drinking was greater in the acamprosate 1998/2000 mg/day group compared to the placebo group. At all visits except Day 75 and the Last Visit, the percentage of patients who were drinking >2 times/week or every day was lower in the acamprosate 1998/2000 mg/day group compared to the placebo group. At the Last Visit, 25% of the acamprosate 1998/2000 mg/day patients reported drinking every day, compared to 44% of placebo patients. These results, combined with a greater percentage of patients abstinent at every visit, demonstrate that patients in the acamprosate 1998/2000 mg/day group were drinking less frequently than patients in the placebo group during the Treatment Phase. Likewise, similar drinking patterns, although somewhat less consistent were demonstrated in the acamprosate 1332 mg/day group as with the acamprosate 1998/2000 mg/day group.

Table 17. Frequency of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study Pelc II

Study Day	Frequency of Alcohol Consumption	ACAMP 1332 mg/day (N=63)	ACAMP 1998/2000 mg/day (N=63)	Placebo (N=62)
Day 0	Abstinent	63 (100%)	63 (100%)	60 (97%)
	≤2 times/week	0	0	0
	>2 times/week	0	0	0
	Every day	0	0	2 (3%)
Day 8	Abstinent	51 (82%)	53 (85%)	38 (61%)
	≤2 times/week	7 (11%)	4 (6%)	11 (18%)
	>2 times/week	1 (2%)	1 (2%)	2 (3%)
	Every day	3 (5%)	4 (6%)	11 (18%)
Day 15	Abstinent	43 (72%)	49 (82%)	35 (65%)
	≤2 times/week	8 (13%)	7 (12%)	8 (15%)
	>2 times/week	3 (5%)	1 (2%)	5 (9%)
	Every day	6 (10%)	3 (5%)	6 (11%)
Day 30	Abstinent	39 (68%)	46 (79%)	29 (56%)
	≤2 times/week	4 (7%)	8 (14%)	10 (19%)
	>2 times/week	4 (7%)	2 (3%)	4 (8%)
	Every day	10 (18%)	2 (3%)	9 (17%)
Day 45	Abstinent	38 (72%)	39 (68%)	25 (53%)
	≤2 times/week	3 (6%)	7 (12%)	8 (17%)
	>2 times/week	4 (8%)	7 (12%)	6 (13%)
	Every day	8 (15%)	4 (7%)	8 (17%)
Day 60	Abstinent	34 (68%)	36 (67%)	18 (43%)
	≤2 times/week	5 (10%)	7 (13%)	9 (21%)
	>2 times/week	4 (8%)	3 (6%)	5 (12%)
	Every day	7 (14%)	8 (15%)	10 (24%)
Day 75	Abstinent	31(65%)	33 (65%)	17 (45%)
	≤2 times/week	4 (8%)	5 (10%)	7 (18%)
	>2 times/week	3 (6%)	4 (8%)	3 (8%)
	Every day	10 (21%)	9 (18%)	11 (29%)
Day 90	Abstinent	28 (61%)	32 (68%)	16 (47%)
	≤2 times/week	5 (11%)	5 (11%)	5 (15%)
	>2 times/week	5 (11%)	4 (9%)	5 (15%)
	Every day	8 (17%)	6 (13%)	8 (24%)
Last Visit	Abstinent	33 (53%)	34 (54%)	20 (32%)
	≤2 times/week	6 (10%)	8 (13%)	7 (11%)
	>2 times/week	7 (11%)	5 (8%)	8 (13%)
	Every day	16 (26%)	16 (25%)	27 (44%)
Data Source: NDA Table 8.7.1.8.1				

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

PRAMA

Table 18 presents the frequency of alcohol consumption during the Treatment Phase for the PRAMA study.

For the PRAMA study, the acamprosate group demonstrated a reduced frequency of drinking compared to the placebo group. Consistently, the acamprosate group was associated with a greater percentage of abstinent patients and a lower percentage of patients drinking daily compared to the placebo group. These differences were associated with statistically significant comparisons at Days 60, 360, and the Last Visit ($p=0.025$, $p=0.047$, and $p=0.049$, respectively).

Table 18. Frequency of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study PRAMA

Study Day	Frequency of Alcohol Consumption	ACAMP (N=136)	Placebo (N=136)	P-value
Day 0	Abstinent ≤2 times/week >2 times/week Every day	NA	NA	NA
Day 30	Abstinent ≤2 times/week >2 times/week Every day	100 (83%) 10 (8%) 6 (5%) 4 (3%)	85 (74%) 14 (12%) 5 (4%) 11 (10%)	0.067
Day 60	Abstinent ≤2 times/week >2 times/week Every day	91 (82%) 11 (10%) 8 (7%) 1 (<1%)	70 (71%) 10 (10%) 6 (6%) 13 (13%)	0.025*
Day 90	Abstinent ≤2 times/week >2 times/week Every day	84 (81%) 5 (5%) 8 (8%) 7 (7%)	60 (71%) 7 (8%) 8 (10%) 9 (11%)	0.140
Day 180	Abstinent ≤2 times/week >2 times/week Every day	66 (74%) 6 (7%) 9 (10%) 8 (9%)	39 (60%) 8 (12%) 8 (12%) 10 (15%)	0.070
Day 270	Abstinent ≤2 times/week >2 times/week Every day	59 (69%) 7 (8%) 9 (11%) 10 (12%)	39 (64%) 5 (8%) 2 (3%) 15 (25%)	0.313
Day 360	Abstinent ≤2 times/week >2 times/week Every day	57 (73%) 1 (1%) 10 (13%) 10 (13%)	30 (55%) 5 (9%) 9 (16%) 11 (20%)	0.047*
Last Visit	Abstinent ≤2 times/week >2 times/week Every day	80 (67%) 8 (7%) 16 (13%) 16 (13%)	64 (55%) 10 (9%) 15 (13%) 27 (23%)	0.049*
Data Source: NDA Table 8.7.1.8.2				

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: Percentages are based on the number of patients in the ITT population with an assessment.

Note: P-values are based on a mean score chi-square test using standardized midranks.

Summary of Frequency of Alcohol Consumption

In summary, as shown in the Pelc II and PRAMA studies, the frequency of alcohol consumption was lower for acamprosate patients compared to placebo patients throughout the Treatment Phase. Patients treated with acamprosate had a consistently higher percentage of abstinence and a lower percentage of daily drinkers compared to patients treated with placebo throughout the Treatment Phase. Effects were also seen in the 1332 mg/day group in the Pelc II study, with more patients reporting abstinence and fewer patients reporting daily drinking compared to placebo-treated patients.

4.4.3.6.2 Quantity of Alcohol Consumption

Results for the analysis of quantity of alcohol consumption showed that patients treated with acamprosate had a higher percentage of abstinence compared to patients treated with placebo at each assessment day. The percentage of patients who consumed alcohol was generally lowest for patients in the acamprosate 1998/2000 mg/day group (or acamprosate group for the PRAMA study).

No statistical testing of pairwise treatment group comparisons was performed for any of the 3 studies.

Pelc II

Table 19 presents the quantity of alcohol consumption during the Treatment Phase for the Pelc II study.

At every visit in the Treatment Phase of the Pelc II study, both the acamprosate 1332 mg/day group and the acamprosate 1998/2000 mg/day group had a greater percentage of patients drinking zero standard drinks per day (abstinent) compared to the placebo group. At all visits there was also a higher percentage of patients in the placebo group drinking 5-10 standard drinks per day or >10 drinks/day compared to the acamprosate 1998/2000 mg/day group. This set of results demonstrates that patients in the acamprosate 1998/2000 mg/day group drank lower quantities of alcohol than patients in the placebo group during the Treatment Phase. Similar trends were observed for the

acamprosate 1332 mg/day group relative to placebo. No statistical testing was performed on this parameter.

Table 19. Quantity of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study Pelc II

Study Day	Quantity of Alcohol Consumption	ACAMP 1332 mg/day (N=63)	ACAMP 1998/2000 mg/day (N=63)	Placebo (N=62)
Day 0	Abstinent	63 (100%)	63 (100%)	60 (97%)
	1-<5 standard drinks per day	0	0	0
	5-10 standard drinks per day	0	0	1 (2%)
	>10 standard drinks per day	0	0	1 (2%)
Day 8	Abstinent	52 (84%)	54 (86%)	38 (61%)
	1-<5 standard drinks per day	7 (11%)	5 (8%)	11 (18%)
	5-10 standard drinks per day	3 (5%)	0	6 (10%)
	>10 standard drinks per day	0	4 (6%)	7 (11%)
Day 15	Abstinent	43 (72%)	49 (82%)	35 (65%)
	1-<5 standard drinks per day	8 (13%)	8 (13%)	12 (22%)
	5-10 standard drinks per day	6 (10%)	1 (2%)	2 (4%)
	>10 standard drinks per day	3 (5%)	2 (3%)	5 (9%)
Day 30	Abstinent	39 (68%)	46 (79%)	29 (56%)
	1-<5 standard drinks per day	9 (16%)	8 (14%)	15 (29%)
	5-10 standard drinks per day	4 (7%)	1 (2%)	3 (6%)
	>10 standard drinks per day	5 (9%)	3 (5%)	5 (10%)
Day 45	Abstinent	38 (72%)	39 (68%)	25 (53%)
	1-<5 standard drinks per day	7 (13%)	10 (18%)	12 (26%)
	5-10 standard drinks per day	3 (6%)	5 (9%)	6 (13%)
	>10 standard drinks per day	5 (9%)	3 (5%)	4 (9%)
Day 60	Abstinent	34 (68%)	36 (67%)	18 (43%)
	1-<5 standard drinks per day	8 (16%)	8 (15%)	12 (29%)
	5-10 standard drinks per day	3 (6%)	5 (9%)	6 (14%)
	>10 standard drinks per day	5 (10%)	5 (9%)	6 (14%)
Day 75	Abstinent	31 (65%)	33 (65%)	17 (45%)
	1-<5 standard drinks per day	8 (17%)	9 (18%)	6 (16%)
	5-10 standard drinks per day	2 (4%)	1 (2%)	5 (13%)
	>10 standard drinks per day	7 (15%)	8 (16%)	10 (26%)
Day 90	Abstinent	28 (61%)	32 (68%)	16 (47%)
	1-<5 standard drinks per day	8 (17%)	7 (15%)	6 (18%)
	5-10 standard drinks per day	5 (11%)	1 (2%)	2 (6%)
	>10 standard drinks per day	5 (11%)	7 (15%)	10 (29%)
Last Visit	Abstinent	33 (53%)	34 (54%)	20 (32%)
	1-<5 standard drinks per day	9 (15%)	9 (14%)	9 (15%)
	5-10 standard drinks per day	7 (11%)	3 (5%)	6 (10%)
	>10 standard drinks per day	13 (21%)	17 (27%)	27 (44%)
Data Source: NDA Table 8.7.1.9.1				

Note: ACAMP 1332 = Acamprosate 1332 mg/day; ACAMP 1998/2000 = Acamprosate 1998/2000 mg/day.

Note: Number of standard drinks per day is based on the definition of a standard drink of 12g of pure alcohol.

Note: Percentages are based on the number of patients in the ITT population with an assessment.

PRAMA

Table 20 presents the quantity of alcohol consumption during the Treatment Phase for the PRAMA study. Percentages are based on the number of patients in the ITT population (i.e., patients with missing data for quantity of consumption are included in the denominator) and may not sum to 100%.

For the PRAMA study, the analysis of the quantity of alcohol consumption did not yield consistent results. While the acamprosate group was associated with a larger percentage of patients with a zero quantity of alcohol consumed, the mean number of standard drinks per day, for patients who drank, was higher at most visits compared to the placebo group. At the Last Visit, the median number of standard drinks consumed per day by patients who were drinking was 14 (mean of 17.4) for the acamprosate group compared to 13 (mean of 16.7) for the placebo group, even though somewhat fewer acamprosate patients (18%) reported >10 drinks per day compared to placebo patients (20%). Part of this finding may be associated with the amount of missing data at each evaluation. No statistical testing was performed for this parameter.

Table 20. Quantity of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study PRAMA

Study Day	Quantity of Alcohol Consumption	ACAMP (N=136)	Placebo (N=136)
Day 0	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day	NA	NA
Day 30	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day	100 (74%) 2 (1%) 2 (1%) 12 (9%)	85 (63%) 4 (3%) 7 (5%) 15 (11%)
Day 60	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day	91 (67%) 2 (1%) 5 (4%) 12 (9%)	70 (51%) 3 (2%) 6 (4%) 17 (13%)
Day 90	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day	84 (62%) 0 3 (2%) 11 (8%)	60 (44%) 3 (2%) 3 (2%) 14 (10%)
Day 180	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day	66 (49%) 0 3 (2%) 12 (9%)	39 (29%) 1 (<1%) 6 (4%) 17 (13%)
Day 270	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day	59 (43%) 3 (2%) 4 (3%) 16 (12%)	39 (29%) 2 (1%) 4 (3%) 15 (11%)
Day 360	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day	57 (42%) 1 (<1%) 6 (4%) 13 (10%)	30 (22%) 2 (1%) 11 (8%) 9 (7%)
Last Visit	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day	83 (61%) 2 (1%) 9 (7%) 24 (18%)	68 (50%) 4 (3%) 17 (13%) 27 (20%)
Data Source: NDA Table 8.7.1.9.2			

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

Note: NA = Not available.

Note: Number of standard drinks per day is based on the definition of a standard drink of 12 g of pure alcohol.

Note: Percentages are based on the number of patients in the ITT population with an assessment.

Note: Last Visit contains the last visit that the patient reported drinking the type of alcohol summarized.

Paille

Table 21 presents the quantity of alcohol consumption during the Treatment Phase for the Paille study.

For the Paille study, more patients in the acamprosate 1998/2000 mg/day group (52%) were abstinent at the Last Visit than in the placebo group (44%). This association was repeated at each evaluation visit, even if patients with missing data are excluded (due to treatment imbalance with missing data). Generally, the acamprosate 1332 mg/day group was also associated with a higher percentage of abstinent patients at each evaluation compared to placebo. However, this trend was not observed at the Last Visit (43% in the acamprosate 1332 mg/day group vs. 44% in the placebo group).

Of the patients reporting alcoholic drink consumption, the acamprosate 1998/2000 mg/day group showed a higher mean (median) number of standard drinks (7.8^[7]) at the Last Visit compared to the placebo group (mean 6.6^[4]), while the acamprosate 1332 mg/day group (mean 6.0^[4]) had lower numbers than either the acamprosate 1998 mg/day or placebo groups.

Table 21. Quantity of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study Paille

Study Day	Quantity of Alcohol Consumption	ACAMP 1332 mg/day (N=188)	ACAMP 1998/2000 mg/day (N=173)	Placebo (N=177)
Day 0	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day Missing	NA	NA	NA
Day 30	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day Missing	114 (61%) 29 (15%) 21 (11%) 8 (4%) 16 (9%)	123 (71%) 24 (14%) 6 (3%) 7 (4%) 13 (8%)	97 (55%) 36 (20%) 23 (13%) 4 (2%) 17 (10%)
Day 60	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day Missing	93 (49%) 30 (16%) 23 (12%) 7 (4%) 35 (19%)	103 (60%) 25 (14%) 13 (8%) 3 (2%) 29 (17%)	83 (47%) 32 (18%) 18 (10%) 9 (5%) 35 (20%)
Day 90	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day Missing	91 (48%) 33 (18%) 23 (12%) 5 (3%) 36 (19%)	80 (46%) 36 (21%) 14 (8%) 8 (5%) 35 (20%)	69 (39%) 28 (16%) 25 (14%) 13 (7%) 42 (24%)
Day 120	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day Missing	88 (47%) 29 (15%) 16 (9%) 6 (3%) 49 (26%)	86 (50%) 31 (18%) 12 (7%) 0 44 (25%)	63 (36%) 25 (14%) 18 (10%) 5 (3%) 66 (37%)
Day 150	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day Missing	79 (42%) 21 (11%) 19 (10%) 3 (2%) 66 (35%)	82 (47%) 27 (16%) 6 (3%) 6 (3%) 52 (30%)	66 (37%) 17 (10%) 14 (8%) 6 (3%) 74 (42%)
Day 180	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day Missing	73 (39%) 22 (12%) 20 (11%) 6 (3%) 67 (36%)	77 (45%) 24 (14%) 18 (10%) 3 (2%) 51 (29%)	52 (29%) 19 (11%) 18 (10%) 5 (3%) 83 (47%)
Day 240	Abstinent 1-<5 standard drinks per day 5-10 standard drinks per day >10 standard drinks per day Missing	58 (31%) 27 (14%) 13 (7%) 8 (4%) 82 (44%)	64 (37%) 27 (16%) 16 (9%) 5 (3%) 61 (35%)	48 (27%) 19 (11%) 11 (6%) 6 (3%) 93 (53%)

Table 21 (cont'd). Quantity of Alcohol Consumption During Treatment Phase – Pivotal Efficacy Study Paille

Study Day	Quantity of Alcohol Consumption	ACAMP 1332 mg/day (N=188)	ACAMP 1998/2000 mg/day (N=173)	Placebo (N=177)
Day 300	Abstinent	56 (30%)	65 (38%)	38 (21%)
	1-<5 standard drinks per day	17 (9%)	20 (12%)	21 (12%)
	5-10 standard drinks per day	13 (7%)	8 (5%)	8 (5%)
	>10 standard drinks per day	6 (3%)	8 (5%)	4 (2%)
	Missing	96 (51%)	72 (42%)	106 (60%)
Day 360	Abstinent	52 (28%)	60 (35%)	33 (19%)
	1-<5 standard drinks per day	18 (10%)	18 (10%)	18 (10%)
	5-10 standard drinks per day	16 (9%)	13 (8%)	12 (7%)
	>10 standard drinks per day	3 (2%)	4 (2%)	0
	Missing	99 (53%)	78 (45%)	114 (64%)
Last Visit	Abstinent	80 (43%)	90 (52%)	78 (44%)
	1-<5 standard drinks per day	31 (16%)	33 (19%)	38 (21%)
	5-10 standard drinks per day	46 (24%)	28 (16%)	41 (23%)
	>10 standard drinks per day	19 (10%)	10 (6%)	8 (5%)
	Missing	12 (6%)	12 (7%)	12 (7%)
Data Source: NDA Table 8.7.1.9.3				

Note: ACAMP 1332 = Acamprosate 1332 mg/day; ACAMP 1998/2000 = Acamprosate 1998/2000 mg/day.

Note: NA = Not available.

Note: Number of standard drinks per day is based on the definition of a standard drink of 12g of pure alcohol.

Note: Percentages are based on the number of patients in the ITT population with an assessment.

Summary of Quantity of Alcohol Consumption

In summary, the results for the analysis of quantity of alcohol consumption showed that the percentage of patients who consumed alcohol was generally lowest for patients in the acamprosate 1998/2000 mg/day group (or acamprosate group for the PRAMA study). However, of those patients taking at least 1 drink, there were only small differences between the treatment groups.

4.4.3.6.3 Pattern of Alcohol Consumption

Of the 3 pivotal studies, only the Paille study collected data on pattern of alcohol consumption. The results from the analysis of the pattern of alcohol consumption from this study showed a higher percentage of abstinent patients in both acamprosate groups compared to the placebo group. At the end of the double-blind Treatment Phase (Day 360), 35% of the patients in the acamprosate 1998/2000 mg/day group were abstinent compared to 19% of the patients in the placebo group. At the end of the entire

study (through the follow-up period at Day 540) the benefits of acamprosate were maintained with 37% of the patients in the acamprosate 1998/2000 mg/day group remaining abstinent or controlled compared to 23% of the patients in the placebo group. The number and percentage (rounded to the nearest whole number) of patients who were abstinent, had controlled drinking (1 g-40 g), uncontrolled drinking (>40 g), or no data are presented in Table 22 on a by-visit basis for the entire study duration. Statistical testing results are based on a Mantel-Haenszel test for linear association among all treatment groups.^[31]

Table 22. Pattern of Alcohol Consumption During Entire Study Phase – Pivotal Efficacy Study Paille

Study Day	Pattern of Alcohol Consumption	ACAMP 1332 mg/day (N=188)	ACAMP 1998/2000 mg/day (N=173)	Placebo (N=177)	P-value
Day 30	Abstinent	116 (62%)	123 (71%)	100 (56%)	0.021*
	Controlled (1-40g)	27 (14%)	22 (13%)	32 (18%)	
	Uncontrolled (>40g)	31 (16%)	15 (9%)	31 (18%)	
	Drop out / No data	14 (7%)	13 (8%)	14 (8%)	
Day 60	Abstinent	94 (50%)	103 (60%)	85 (48%)	0.038*
	Controlled (1-40g)	23 (12%)	25 (14%)	23 (13%)	
	Uncontrolled (>40g)	37 (20%)	16 (9%)	36 (20%)	
	Drop out / No data	34 (18%)	29 (17%)	33 (19%)	
Day 90	Abstinent	93 (49%)	81 (47%)	70 (40%)	0.079
	Controlled (1-40g)	27 (14%)	31 (18%)	24 (14%)	
	Uncontrolled (>40g)	34 (18%)	27 (16%)	42 (24%)	
	Drop out / No data	34 (18%)	34 (20%)	41 (23%)	
Day 120	Abstinent	89 (47%)	86 (50%)	65 (37%)	0.004**
	Controlled (1-40g)	27 (14%)	24 (14%)	19 (11%)	
	Uncontrolled (>40g)	24 (13%)	19 (11%)	29 (16%)	
	Drop out / No data	48 (26%)	44 (25%)	64 (36%)	
Day 150	Abstinent	79 (42%)	84 (49%)	67 (38%)	0.009**
	Controlled (1-40g)	17 (9%)	22 (13%)	16 (9%)	
	Uncontrolled (>40g)	26 (14%)	17 (10%)	21 (12%)	
	Drop out / No data	66 (35%)	50 (29%)	73 (41%)	
Day 180	Abstinent	73 (39%)	77 (45%)	53 (30%)	<0.001**
	Controlled (1-40g)	19 (10%)	24 (14%)	16 (9%)	
	Uncontrolled (>40g)	29 (15%)	21 (12%)	26 (15%)	
	Drop out / No data	67 (36%)	51 (29%)	82 (46%)	
Day 240	Abstinent	59 (31%)	64 (37%)	48 (27%)	0.003**
	Controlled (1-40g)	24 (13%)	21 (12%)	14 (8%)	
	Uncontrolled (>40g)	24 (13%)	27 (16%)	22 (12%)	
	Drop out / No data	81 (43%)	61 (35%)	93 (53%)	
Day 300	Abstinent	56 (30%)	66 (38%)	39 (22%)	<0.001**
	Controlled (1-40g)	16 (9%)	15 (9%)	18 (10%)	
	Uncontrolled (>40g)	20 (11%)	21 (12%)	15 (8%)	
	Drop out / No data	96 (51%)	71 (41%)	105 (59%)	
Day 360	Abstinent	52 (28%)	60 (35%)	33 (19%)	<0.001**
	Controlled (1-40g)	16 (9%)	16 (9%)	13 (7%)	
	Uncontrolled (>40g)	21 (11%)	19 (11%)	17 (10%)	
	Drop out / No data	99 (53%)	78 (45%)	114 (64%)	
Day 420	Abstinent	52 (28%)	56 (32%)	35 (20%)	0.004**
	Controlled (1-40g)	12 (6%)	12 (7%)	13 (7%)	
	Uncontrolled (>40g)	13 (7%)	15 (9%)	10 (6%)	
	Drop out / No data	111 (59%)	90 (52%)	119 (67%)	

Table 22 (cont'd). Pattern of Alcohol Consumption During Entire Study Phase – Pivotal Efficacy Study Paille

Study Day	Pattern of Alcohol Consumption	ACAMP 1332 mg/day (N=188)	ACAMP 1998/2000 mg/day (N=173)	Placebo (N=177)	P-value
Day 480	Abstinent	47 (25%)	49 (28%)	29 (16%)	0.002**
	Controlled (1-40g)	14 (7%)	16 (9%)	11 (6%)	
	Uncontrolled (>40g)	11 (6%)	15 (9%)	16 (9%)	
	Drop out / No data	116 (62%)	93 (54%)	121 (68%)	
Day 540	Abstinent	41 (22%)	48 (28%)	28 (16%)	0.002**
	Controlled (1-40g)	13 (7%)	16 (9%)	12 (7%)	
	Uncontrolled (>40g)	16 (9%)	12 (7%)	12 (7%)	
	Drop out / No data	118 (63%)	97 (56%)	125 (71%)	
Data Source: NDA Table 8.7.1.9.3 and Table 7 (Paille statistical report)					

* Significant at the 0.050 level; ** significant at the 0.010 level.

Note: ACAMP 1332 = Acamprosate 1332 mg/day; ACAMP 1998/2000 = Acamprosate 1998/2000 mg/day.

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

Note: P-values are based on Mantel-Haenszel tests for linear association (Table 7, Paille statistical report).

At all visits (except Day 90) through Day 540 in the Paille study, there was a statistically significant trend in the results with the acamprosate 1998/2000 mg/day group having the most abstinent and controlled patients and the least number of non-attending (or no data) patients. The results for the acamprosate 1332 mg/day group were always between those of the acamprosate 1998/2000 mg/day group and the placebo group.

By Day 30, 84% of the patients in the acamprosate 1998/2000 mg/day group were abstinent or controlled compared to 75% of the patients in the placebo group. The difference in the percentage of abstinent and controlled patients between the acamprosate 1998/2000 mg/day group and placebo group was at a maximum at Days 180 and 360. At the end of the double-blind Treatment Phase (Day 360), 44% of the patients in the acamprosate 1998/2000 mg/day group were abstinent or controlled and 45% had no data or dropped out. The corresponding percentages in the placebo group were 26% abstinent or controlled, and 64.4% had no data or dropped out. For the 1332 mg/day group, 37% were abstinent or controlled and 53% had no data or dropped out.

During the follow-up phase of the Paille study, all patients received placebo. However, as summarized according to the Treatment Phase study drug assignments, patients in both acamprosate groups continued to have a higher percentage of abstinence during the follow-up phase compared to the placebo group. Specifically, at the end of the study

(Day 540), 37% of the patients in the acamprosate 1998/2000 mg/day group were abstinent or had controlled drinking compared to 23% of the patients in the placebo group and 29% in the acamprosate 1332 mg/day group. This suggested that the benefits of acamprosate were maintained after discontinuation of treatment.

In summary, the pattern of alcohol consumption analysis from the Paille study showed a higher percentage of abstinent or controlled patients in both the 1332 mg/day and the 1998/2000 mg/day acamprosate groups compared to the placebo group. By the end of the double-blind Treatment Phase (Day 360), 44% of the patients in the acamprosate 1998/2000 mg/day group were abstinent or controlled compared to 26% of the patients in the placebo group. Moreover, there appeared to be no loss of effectiveness in the acamprosate patients after treatment was withdrawn during the single-blind placebo follow-up phase.

4.4.3.6.4 Overall Clinical Assessment

The overall clinical assessment is evaluated using the clinical global impression (CGI) severity and CGI-improvement scores from the Pelc II and Paille studies, and the global investigator assessment of treatment from the PRAMA study. The original rating scores are presented from the individual study reports.

The analysis of the overall clinical assessment as evaluated by the investigator showed a greater improvement for both acamprosate groups (acamprosate group for PRAMA study) compared to the placebo group. Statistically significant results were observed at various assessment days within the studies. At the Last Visit, the investigator assessment indicated that there was a benefit of treatment with acamprosate. The benefits observed by the investigator support the benefits reported by the patients.

Pelc II

For the Pelc II study, the CGI of the severity of the signs and symptoms of alcoholism displayed by the patient was made by the investigator and rated on a 7-point scale. The CGI-severity scores were 1=Absent, 2=Insignificant, 3=Slight, 4=Mild, 5=Moderate, 6=Severe, and 7=Extremely severe.

Results for the CGI-severity ratings showed that severity ratings of “absent” or “insignificant” were more common among acamprosate patients (both groups) than placebo patients. At the Last Visit, 58% of acamprosate 1332 mg/day patients and 60% of acamprosate 1998/2000 mg/day patients were assessed as having “absent” or “insignificant” signs and symptoms of alcoholism, compared to 46% of placebo patients. Few of the pairwise comparisons yielded statistical significance and hence, definitive trends were not concluded.

The CGI-improvement was evaluated at each assessment day by the investigator and the change in clinical response was rated and compared to the Baseline status (Table 23). For the Pelc II study, response was rated as “marked improvement”, “moderate improvement”, “mild improvement”, “no change”, “mild deterioration”, “moderate deterioration”, or “severe deterioration”.

Table 23. Clinical Global Impression Improvement During Treatment Phase – Pivotal Efficacy Study Pelc II

Study Day	Number of Responses/ Improvement Score	ACAMP 1332 mg/day (N=63)	ACAMP 1998/2000 mg /day (N=63)	Placebo (N=62)	P-value for ACAMP 1998/2000 mg/day vs. Placebo
Day 8	N	61	59	56	0.058
	Marked improvement	10 (16%)	6 (10%)	3 (5%)	
	Moderate improvement	22 (36%)	24 (41%)	17 (30%)	
	Mild improvement	15 (25%)	19 (32%)	18 (32%)	
	No change	9 (15%)	4 (7%)	13 (23%)	
	Mild deterioration	3 (5%)	4 (7%)	1 (2%)	
	Moderate deterioration	2 (3%)	2 (3%)	4 (7%)	
	Severe deterioration	0	0	0	
	Missing	2	4	6	
Day 15	n	59	58	52	0.270
	Marked improvement	10 (17%)	8 (14%)	5 (10%)	
	Moderate improvement	23 (39%)	30 (52%)	23 (44%)	
	Mild improvement	13 (22%)	11 (19%)	16 (31%)	
	No change	7 (12%)	6 (10%)	4 (8%)	
	Mild deterioration	2 (3%)	2 (3%)	1 (2%)	
	Moderate deterioration	2 (3%)	0	3 (6%)	
	Severe deterioration	2 (3%)	1 (2%)	0	
	Missing	4	5	10	
Day 30	n	55	58	48	0.075
	Marked improvement	9 (16%)	14 (24%)	7 (15%)	
	Moderate improvement	19 (35%)	27 (47%)	18 (38%)	
	Mild improvement	9 (16%)	5 (9%)	12 (25%)	
	No change	7 (13%)	7 (12%)	4 (8%)	
	Mild deterioration	3 (5%)	4 (7%)	2 (4%)	
	Moderate deterioration	6 (11%)	0	4 (8%)	
	Severe deterioration	2 (4%)	1 (2%)	1 (2%)	
	Missing	8	5	14	
Day 45	n	50	54	46	0.012*
	Marked improvement	13 (26%)	19 (35%)	6 (13%)	
	Moderate improvement	15 (30%)	20 (37%)	16 (35%)	
	Mild improvement	8 (16%)	3 (6%)	9 (20%)	
	No change	3 (6%)	5 (9%)	8 (17%)	
	Mild deterioration	4 (8%)	2 (4%)	3 (7%)	
	Moderate deterioration	6 (12%)	3 (6%)	2 (4%)	
	Severe deterioration	1 (2%)	2 (4%)	2 (4%)	
	Missing	13	9	16	

Table 23 (cont'd). Clinical Global Impression Improvement During Treatment Phase – Pivotal Efficacy Study Pelc II

Study Day	Number of Responses/ Improvement Score	ACAMP 1332 mg/day (N=63)	ACAMP 1998/2000 mg /day (N=63)	Placebo (N=62)	P-value for ACAMP 1998/2000 mg/day vs. Placebo
Day 60	n Marked improvement Moderate improvement Mild improvement No change Mild deterioration Moderate deterioration Severe deterioration Missing	49 19 (39%) 8 (16%) 10 (20%) 3 (6%) 3 (6%) 4 (8%) 2 (4%) 14	52 16 (31%) 20 (38%) 6 (12%) 4 (8%) 2 (4%) 1 (2%) 3 (6%) 11	39 7 (18%) 12 (31%) 7 (18%) 5 (13%) 3 (8%) 4 (10%) 1 (3%) 23	0.054
Day 75	n Marked improvement Moderate improvement Mild improvement No change Mild deterioration Moderate deterioration Severe deterioration Missing	48 14 (29%) 9 (19%) 9 (19%) 8 (17%) 2 (4%) 3 (6%) 3 (6%) 15	47 18 (38%) 19 (40%) 2 (4%) 5 (11%) 1 (2%) 2 (4%) 0 16	34 8 (24%) 10 (29%) 7 (21%) 5 (15%) 0 3 (9%) 1 (3%) 28	0.039*
Day 90	n Marked improvement Moderate improvement Mild improvement No change Mild deterioration Moderate deterioration Severe deterioration Missing	46 16 (35%) 8 (17%) 7 (15%) 5 (11%) 3 (7%) 6 (13%) 1 (2%) 17	45 24 (53%) 11 (24%) 3 (7%) 2 (4%) 1 (2%) 2 (4%) 2 (4%) 18	32 7 (22%) 8 (25%) 6 (19%) 3 (9%) 0 6 (19%) 2 (6%) 30	<0.010**
Last Visit	n Marked improvement Moderate improvement Mild improvement No change Mild deterioration Moderate deterioration Severe deterioration Missing	61 19 (31%) 10 (16%) 8 (13%) 8 (13%) 6 (10%) 7 (11%) 3 (5%) 2	60 26 (43%) 17 (28%) 4 (7%) 4 (7%) 3 (5%) 3 (5%) 3 (5%) 3	56 11 (20%) 15 (27%) 9 (16%) 7 (13%) 0 10 (18%) 4 (7%) 6	<0.010**
Data Source: NDA Table 8.7.1.11.1					

* Significant at the 0.050 level; ** significant at the 0.010 level.

Note: Clinical global impression improvement score: 1=Marked improvement, 2=Moderate improvement, 3=Mild improvement, 4=No change, 5=Mild deterioration, 6=Moderate deterioration, 7=Severe deterioration.

Note: Percentages are based on non-missing results for each visit.

Note: P-values are for the pairwise comparison of ACAMP 1998/2000 mg/day vs. placebo and are based on a Kruskal-Wallis test.

The CGI-improvement for the Pelc II study showed greater percentages of acamprosate 1998/2000 mg/day patients and acamprosate 1332 mg/day patients with moderate or marked improvement compared to placebo patients. Statistical significance in favor of the acamprosate 1998/2000 mg/day group relative to the placebo group was demonstrated at Day 45 ($p=0.012$), Day 75 ($p=0.039$), Day 90 ($p<0.010$), and the Last Visit ($p<0.010$). Differences between the acamprosate 1332 mg/day group and placebo group were not statistically significant at any assessment day, although there were consistently more patients in the acamprosate 1332 mg/day group rated as having “marked improvement” at each visit compared to the placebo group.

PRAMA

In the PRAMA study, the investigator’s global assessment was based on the patient’s declaration of abstinence with family confirmation, breath alcohol (Breathalyzer) test, and GGT and/or MCV values. The patient’s drinking behavior was rated as “success” or “failure” at each assessment time. Table 24 presents the investigator’s global assessment of success/failure during the Treatment Phase for the PRAMA study.

Table 24. Investigator’s Global Assessment of Success/Failure During Treatment Phase – Pivotal Efficacy Study PRAMA

Study Day	Number of Responses/ Investigator’s Global Assessment	ACAMP (N=136)	Placebo (N=136)	P-value for ACAMP vs. Placebo
Day 30	Success Failure	98 (72%) 38 (28%)	83 (61%) 53 (39%)	0.054
Day 60	Success Failure	91 (67%) 45 (33%)	68 (50%) 68 (50%)	0.005**
Day 90	Success Failure	83 (61%) 53 (39%)	59 (44%) 76 (56%)	0.004**
Day 180	Success Failure	62 (46%) 74 (54%)	38 (28%) 97 (72%)	0.003**
Day 270	Success Failure	59 (43%) 77 (57%)	36 (27%) 99 (73%)	0.004**
Day 360	Success Failure	58 (43%) 78 (57%)	28 (21%) 107 (79%)	<0.001**
Data Source: NDA: Table 8 (PRAMA study report)				

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: Percentages are based on the number of responses at each assessment.

For the PRAMA study, with the exception of Day 30 ($p=0.054$), all other assessments through Day 360 ($p<0.001$) had a statistically significantly higher percentage of patients rated as “successes” in the acamprosate group compared to the placebo group.

Paille

For the Paille study, the CGI-severity scores were grouped into categories of “not ill”, “very mildly ill”, “slightly ill”, “moderately ill”, “markedly ill”, “severely ill”, and “extremely ill”. Table 25 presents the CGI-severity during the Treatment Phase for the Paille study. Clinical assessments are presented for Day 0, Day 90, Day 180, Day 360, and Last Visit.

Table 25. Clinical Global Impression Severity During Treatment Phase – Pivotal Efficacy Study Paille

Study Day	Number of Responses/ Severity Score	ACAMP 1332 mg/day (N=188)	ACAMP 1998/2000 mg /day (N=173)	Placebo (N=177)	P-value for ACAMP 1998/2000 mg/day vs. Placebo
Day 0	n	188	172	177	0.352
	Not ill	0	0	0	
	Very mildly ill	2 (1%)	1 (<1%)	0	
	Slightly ill	4 (2%)	2 (1%)	3 (2%)	
	Moderately ill	33 (18%)	36 (21%)	30 (17%)	
	Markedly ill	115 (61%)	106 (62%)	115 (65%)	
	Severely ill	30 (16%)	24 (14%)	29 (16%)	
	Extremely ill	4 (2%)	3 (2%)	0	
	Unevaluable	0	0	0	
Day 90	n	153	137	137	0.006**
	Not ill	59 (39%)	46 (34%)	45 (33%)	
	Very mildly ill	21 (14%)	25 (18%)	16 (12%)	
	Slightly ill	25 (16%)	23 (17%)	20 (15%)	
	Moderately ill	25 (16%)	31 (23%)	28 (20%)	
	Markedly ill	17 (11%)	8 (6%)	22 (16%)	
	Severely ill	4 (3%)	4 (3%)	5 (4%)	
	Extremely ill	0	0	1 (<1%)	
	Unevaluable	2 (1%)	0	0	
Day 180	n	123	123	96	0.277
	Not ill	54 (44%)	57 (46%)	36 (38%)	
	Very mildly ill	20 (16%)	24 (20%)	17 (18%)	
	Slightly ill	10 (8%)	13 (11%)	8 (8%)	
	Moderately ill	19 (15%)	14 (11%)	19 (20%)	
	Markedly ill	16 (13%)	7 (6%)	13 (14%)	
	Severely ill	4 (3%)	5 (4%)	0	
	Extremely ill	0	0	1 (1%)	
	Unevaluable	0	3 (2%)	2 (2%)	
Day 360	n	89	95	63	0.084
	Not ill	46 (52%)	53 (56%)	26 (41%)	
	Very mildly ill	12 (13%)	18 (19%)	12 (19%)	
	Slightly ill	12 (13%)	11 (12%)	4 (6%)	
	Moderately ill	10 (11%)	6 (6%)	10 (16%)	
	Markedly ill	8 (9%)	7 (7%)	10 (16%)	
	Severely ill	1 (1%)	0	0	
	Extremely ill	0	0	0	
	Unevaluable	0	0	1 (2%)	

Table 25 (cont'd). Clinical Global Impression Severity During Treatment Phase – Pivotal Efficacy Study Paille

Study Day	Number of Responses/Severity Score	ACAMP 1332 mg/day (N=188)	ACAMP 1998/2000 mg/day (N=173)	Placebo (N=177)	P-value for ACAMP 1998/2000 mg/day vs. Placebo
Last Visit	n	156	138	138	0.005**
	Not ill	61 (39%)	63 (46%)	44 (32%)	
	Very mildly ill	19 (12%)	28 (20%)	22 (16%)	
	Slightly ill	19 (12%)	16 (12%)	12 (9%)	
	Moderately ill	24 (15%)	15 (11%)	24 (17%)	
	Markedly ill	23 (15%)	13 (9%)	29 (21%)	
	Severely ill	8 (5%)	3 (2%)	4 (3%)	
	Extremely ill	0	0	1 (<1%)	
	Unevaluable	2 (1%)	0	2 (1%)	
Data Source: NDA Table 8.7.1.10.3					

* Significant at the 0.050 level; ** significant at the 0.010 level.

Note: Percentages are based on non-missing results for each visit.

Note: P-values for the pairwise treatment group comparisons are based on a chi-square test (with Clinical Global Impression Severity grouped into categories of Not ill/Very mildly ill/Slightly ill/Moderately ill, and Markedly ill/Severely ill/Extremely ill). Unevaluable was excluded from the treatment comparisons.

The CGI-severity for the Paille study showed few patients rated as “severely ill” or “extremely ill”, although at Day 0, approximately two-thirds of the patients were in the “markedly ill” category. Thereafter, there was global improvement in all treatment groups. At the Last Visit, 11% of acamprosate 1998/2000 mg/day and 20% of acamprosate 1332 mg/day patients were classified as markedly, severely, or extremely ill, compared to 25% of placebo patients. At Day 90 and at the Last Visit, CGI-severity was statistically significantly better in the acamprosate 1998/2000 mg/day group compared to the placebo group ($p=0.006$ and $p=0.005$, respectively). There were no statistical differences between the acamprosate 1332 mg/day group and the placebo group at any assessment day.

In the Paille study, CGI-improvement scores were categorized as “considerable improvement”, “marked improvement”, “slight improvement”, “unaltered”, “slight deterioration”, “marked deterioration”, “considerable deterioration”, and “unevaluable”. The results of the analysis for the CGI-improvement scores showed that very few patients were rated as having a deterioration at any assessment day. At the Last Visit, the

difference between the acamprosate 1998/2000 mg/day group (93% showing some improvement) and the placebo group (77% showing some improvement) with respect to CGI-improvement was statistically significant ($p=0.002$) in favor of the acamprosate 1998/2000 mg/day group. The acamprosate 1332 mg/day group (82% showing some improvement) also showed statistically significant improvement over the placebo group at the Last Visit ($p=0.035$). These trends were also evident through the follow-up period. At Day 540, 96%, 95%, and 91% of patients in the acamprosate 1332 mg/day, acamprosate 1998/2000 mg/day, and placebo groups, respectively, reported some improvement.

Summary of Overall Clinical Assessment

In summary, the analysis of the overall clinical assessment as evaluated by the investigator showed a greater improvement for both acamprosate groups (and the acamprosate group for PRAMA study) compared to the placebo group. The observed results were supportive of the findings of the primary efficacy analyses, the results of which indicated a treatment benefit realized by the patients. Specifically, at the Last Visit, the investigator assessment indicated that there was a benefit of treatment with acamprosate, in providing improvement of or reduction in the symptoms of alcoholism relative to Baseline levels.

4.4.3.6.5 Study Retention

The results from the analysis of time on study (“study retention”) showed that patients treated with acamprosate had longer study retention than patients treated with placebo. Specifically, differences between the acamprosate 1998/2000 mg/day group (or acamprosate group for the PRAMA study) and the placebo group were statistically significant in the PRAMA and Paille studies ($p=0.026$ and $p=0.014$, respectively) and approached statistical significance in the Pelc II study ($p=0.054$).

Table 26 presents the days on study during the Treatment Phase for the pivotal efficacy studies. P-values in this table compare the acamprosate 1998/2000 mg/day group versus the placebo group (Pelc II and Paille studies) or acamprosate versus the placebo group

(PRAMA study). Corresponding p-values involving the acamprosate 1332 mg/day group are presented textually as appropriate.

**Table 26. Days on Study During Treatment Phase – Pivotal Efficacy Studies
Pelc II, PRAMA, and Paille**

Study	Statistic	ACAMP 1332 mg/day	ACAMP 1998/2000 mg/day	Placebo	P-value
Pelc II	n	63	63	62	0.054
	Mean (SE)	73.1 (3.7)	77.7 (3.2)	64.7 (4.2)	
	Median	85	85	84	
	Min, Max	1, 110	6, 116	4, 110	
PRAMA	n	-	136	136	0.026*
	Mean (SE)	-	224.6 (12.1)	181.6 (12.7)	
	Median	-	281	126	
	Min, Max	-	0, 427	0, 455	
Paille	n	188	173	177	0.014*
	Mean (SE)	253.5 (9.4)	272.3 (9.6)	230.8 (9.8)	
	Median	320	355	239	
	Min, Max	0, 430	0, 528	0, 420	
Data Source: NDA Tables 8.7.1.13.1, 8.7.1.13.2, and 8.7.1.13.3					

* Significant at the 0.050 level; ** significant at the 0.010 level.

Note: For days on study, p-values are for the comparison of ACAMP 1998/2000 versus placebo (Pelc II and Paille) or ACAMP versus placebo (PRAMA) and are based on an F-test from a rank ANOVA model.

Note: Results from the ACAMP group in PRAMA are presented in the ACAMP 1998/2000 column.

Note: Days on study is calculated as the days between the first and last Treatment Phase visits, inclusive.

Pelc II

For the Pelc II study, the mean (median) number of days on study was 73.1 (85) days for the acamprosate 1332 mg/day group, 77.7 (85) days for the acamprosate 1998/2000 mg/day group, and 64.7 (84) days for the placebo group. The difference in the mean number of days on study between the acamprosate 1998/2000 mg/day group and the placebo group failed to reach statistical significance (p=0.054) despite a 13-day difference and less variation among patients in the acamprosate 1998/2000 mg/day group. The differences between the acamprosate 1332 mg/day group and the acamprosate 1998 mg/day and placebo groups were also non-significant (p=0.172 and p=0.643, respectively).

PRAMA

For the PRAMA study, the mean number of days on study was longer for the acamprosate group (224.6 days, median 281 days) compared to the placebo group

(181.6 days, median 126 days). This difference was statistically significant ($p=0.026$). The difference between treatment groups was primarily attributable to the increased number of placebo patients with ≤ 90 days on treatment (40%) compared to acamprosate 1998/2000 mg/day patients (25%).

Paille

For the Paille study, the mean (median) number of days on study was 253.5 (320) days for the acamprosate 1332 mg/day group, 272.3 (355) days for the acamprosate 1998/2000 mg/day group, and 230.8 (239) days for the placebo group. Study retention was statistically significantly longer for the acamprosate 1998/2000 mg/day group compared to the placebo group ($p=0.014$). The difference between the acamprosate 1332 mg/day and placebo groups was not significant ($p=0.163$).

Summary of Study Retention

In summary, statistically significantly longer study retention was observed in the acamprosate 1998/2000 mg/day group (acamprosate group for the PRAMA study) compared to the placebo group in the PRAMA and Paille studies ($p=0.026$ and $p=0.014$, respectively). Differences in days on study between the acamprosate 1998/2000 mg/day group and the placebo group approached statistical significance in the Pelc II study ($p=0.054$).

4.4.3.6.6 Alcohol Craving

Alcohol craving was measured in the PRAMA and Paille studies, but not in Pelc II. Similar alcohol craving between acamprosate patients and placebo patients was observed in the PRAMA study. In the Paille study, there was some evidence that less alcohol craving was associated with the acamprosate 1998/2000 mg/day group compared to the placebo group.

Alcohol craving was summarized from the visual analogue scale (VAS where 1=I feel a strong aversion to alcohol and 200=I have a very strong craving for alcohol) used in the PRAMA study and from the clinical evaluation of the patient's craving for alcohol used in the Paille study.

PRAMA

For the PRAMA study, the mean alcohol craving score remained less than 100 (indifferent to alcohol) for both treatment groups throughout the Treatment Phase. At the Last Visit, the mean (median) alcohol craving score was 72.5 (89) for the acamprosate group and 72.4 (86) for the placebo group. There were no statistically significant differences in alcohol craving between the treatment groups at any assessment day.

Paille

In the Paille study, at each full clinical evaluation, the patient's craving for alcohol was recorded as "none", "under control", or "no control". The results of the analysis of alcohol craving showed a dose-response relationship for no alcohol craving at most assessment days with the acamprosate 1998/2000 mg/day group having the highest percentage (60% at Last Visit) of patients with no craving, followed by the acamprosate 1332 mg/day group (50% at the Last Visit) and placebo group (43% at the Last Visit), respectively. At Day 90 and at the Last Visit, there were statistically significant differences between the acamprosate 1998/2000 mg/day group and placebo group ($p=0.001$ and $p=0.003$, respectively). There were no significant differences between the acamprosate 1332 mg/day group and the placebo group at any assessment day.

Summary of Effects on Alcohol Craving

In summary, alcohol craving was similar between acamprosate patients and placebo patients in the PRAMA study, while there was some evidence that less alcohol craving was associated with the acamprosate 1998/2000 mg/day group compared to the placebo group in the Paille study.

4.4.3.6.7 Patient Global Impression of Improvement

Patient global impression of improvement was only measured in the Pelc II study.

Pelc II

The results of the analysis for the patient global impression of improvement showed that the acamprosate 1998/2000 mg/day group consistently had higher percentages of patients who rated themselves as improved (“marked” or “moderate” improvement combined) compared to the placebo group at all assessment days (including the Last Visit). Specifically, patient ratings were statistically significantly better in the acamprosate 1998/2000 mg/day group than in the placebo group at Day 75 ($p=0.021$), Day 90 ($p=0.011$), and the Last Visit ($p<0.010$). At the Last Visit, 75% of patients in the acamprosate 1998/2000 mg/day group rated their improvement as “marked” or “moderate” compared to those in the placebo group (61%) (Table 27). This difference was particularly noticeable for marked improvement (50% vs. 25%, respectively). Throughout the Treatment Phase, a higher percentage of patients in the acamprosate 1998/2000 mg/day group rated themselves as improved compared to patients in the acamprosate 1332 mg/day group. These comparisons were statistically significant at Day 75, Day 90, and at the Last Visit. There were no statistically significant differences between the acamprosate 1332 mg/day group and the placebo group across assessment days.

Table 27. Patient Global Impression of Improvement at the Last Visit – Pivotal Efficacy Study Pelc II

Study Day	Number of Responses/ Improvement Score	ACAMP 1332 mg/day (N=63)	ACAMP 1998/2000 mg/ day (N=63)	Placebo (N=62)	P-value for ACAMP 1998/2000 mg/ day vs. Placebo
Last Visit	n	61	60	56	<0.010**
	Marked improvement	21 (34%)	30 (50%)	14 (25%)	
	Moderate improvement	14 (23%)	15 (25%)	20 (36%)	
	Mild improvement	6 (10%)	6 (10%)	5 (9%)	
	No change	10 (16%)	4 (7%)	8 (14%)	
	Mild deterioration	5 (8%)	1 (2%)	3 (5%)	
	Moderate deterioration	2 (3%)	2 (3%)	3 (5%)	
	Severe deterioration	3 (5%)	2 (3%)	3 (5%)	
	Missing	2	3	6	
Data Source: NDA Table 8.7.1.12.1					

* Significant at the 0.050 level; ** significant at the 0.010 level.

Note: Patient global impression scores with respect to Baseline: 1=Marked improvement, 2=Moderate improvement, 3=Mild improvement, 4=No change, 5=Mild deterioration, 6=Moderate deterioration, 7=Severe deterioration.

Note: Percentages are based on the non-missing results for each visit.

Note: The p-value for the pairwise comparison is based on a Kruskal-Wallis test.

4.4.3.7 Overall Summary of Primary and Secondary Efficacy Parameters for the Pivotal Efficacy Studies

The corrected cumulative abstinence duration (CCAD), time to first drink, and rate of complete abstinence were the primary efficacy parameters discussed for the pivotal efficacy studies.

Mean and median CCAD values were greater for patients treated with acamprosate compared to patients treated with placebo. Differences in median CCAD values between the acamprosate 1998 mg/day (or acamprosate in *PRAMA*) and placebo groups ranged from 20% (*Paille*) to 38% (*Pelc II*). Patients treated with acamprosate 1998/2000 mg/day (in the *Paille* and *Pelc II* studies) and acamprosate (in the *PRAMA* study) remained abstinent for a statistically significantly greater percentage of time while on study than patients treated with placebo. This finding was replicated in each of the 3 studies. In the 2 studies with a low dose group (1332 mg/day) mean values (and to some extent median values) for CCAD were intermediate between CCAD values for the placebo and acamprosate 1998 mg/day groups. The difference between acamprosate 1332 mg/day

and placebo was statistically significant in Pelc II ($p < 0.001$), but not in Paille. The difference between acamprosate 1332 mg/day and acamprosate 1998/2000 mg/day was not significant in either study, although it approached significance in the Paille study ($p = 0.071$).

Analyses of the time to first drink showed that patients treated with acamprosate had longer durations of continuous abstinence compared to patients treated with placebo. The results of the uncensored analyses showed highly statistically significant differences in favor of the acamprosate 1998/2000 mg/day group (in Paille and Pelc II) and the acamprosate group (in the PRAMA study) compared to the placebo group. Differences between the acamprosate 1998 mg/day (or acamprosate group in PRAMA) and placebo groups in the median time to first drink ranged from 29 days (Paille study) to 89.5 days (PRAMA study). In these studies, the median time to first drink for patients treated with acamprosate 1998 mg/day (or acamprosate) was 2.0 times (Paille study) to 3.1 times (*Pelc II*) that of placebo. Analysis findings from the censored analyses showed similar results and were supportive of the uncensored analysis results. These findings were replicated across all 3 studies. In the Pelc II study, median time to first drink for the 1332 mg/day group was identical to the value for the 1998 mg/day group, statistically significantly longer than placebo. There was also a statistically significant increase in time to first drink in the 1332 mg/day group in the Paille study, compared to placebo. In the Paille study, the median value was greater than the placebo group, but less than the 1998/2000 mg/day group

The rate of complete abstinence during the Treatment Phase was consistently higher for patients in both acamprosate groups compared to patients in the placebo group with absolute differences in the rate of complete abstinence ranging from 8% (Paille study) to 26% (Pelc II study). Ratios of the rate of complete abstinence suggested that patients treated with acamprosate 1998/2000 mg/day (or acamprosate) were 1.7 times (Paille study) to 2.7 times (Pelc II study) more likely to remain completely abstinent than patients treated with placebo. Specifically, the acamprosate 1998/2000 mg/day group (Pelc II and Paille studies) and the acamprosate group (PRAMA study) had statistically significantly larger percentages of patients remain in abstinence compared to patients in

the placebo group. In the 2 studies with low dose acamprosate groups, complete abstinence rates were greater than in the respective placebo groups and were statistically significant in the Pelc II study.

The secondary efficacy parameters for the pivotal efficacy parameters were the frequency, quantity, and pattern of alcohol consumption, overall clinical assessment, study retention, alcohol craving, and the patient global impression of improvement.

Analysis of the frequency, quantity, and pattern of alcohol consumption showed that patients in the acamprosate 1998/2000 mg/day group (or acamprosate group for the PRAMA study) generally drank less frequently and smaller amounts compared to the placebo group throughout the Treatment Phase of the studies.

The overall clinical assessments demonstrated that patients treated with acamprosate were rated as having better overall clinical assessments than patients treated with placebo.

Patients in both acamprosate groups stayed on study longer than patients treated with placebo. Specifically, differences between the acamprosate 1998/2000 mg/day group (or acamprosate group for the PRAMA study) and the placebo group were statistically significant in the PRAMA and Paille studies ($p=0.026$ and $p=0.014$, respectively) and approached statistical significance in the Pelc II study ($p=0.054$).

The observed results from the PRAMA and Paille studies for alcohol craving suggested that acamprosate patients tended to have a lesser craving for alcohol than placebo patients, although the statistical evidence was not conclusive across studies.

As shown in the Pelc II study, a higher percentage of patients rated themselves as improved (marked or moderate improvement combined) compared to the placebo group at all assessment days including the Last Visit. Towards the end of the Treatment Phase (and at the Last Visit), patient ratings in the acamprosate 1998/2000 mg/day group were statistically significantly better than the placebo group.

In conclusion, for the primary efficacy parameters of CCAD and time to first drink, analyses showed that patients treated with acamprosate 1998/2000 mg/day had

statistically significantly longer durations of abstinence compared to patients treated with placebo. Likewise, the results from the analysis of the rate of complete abstinence showed that patients treated with acamprosate 1998/2000 mg/day had statistically significantly higher abstinent rates compared to patients treated with placebo. These findings were consistently reported across each of the 3 studies. Results for these same parameters for the 1332 mg/day treatment groups were consistently better than in the respective placebo groups, tended to be less robust than results in the 1998/2000 mg/day, and were occasionally statistically significantly different from placebo, suggesting an intermediate level of effectiveness. Finally, throughout the Treatment Phase, patients treated with acamprosate experienced more favorable secondary efficacy outcomes compared to patients treated with placebo. Compared to patients treated with placebo, patients treated with acamprosate generally consumed alcohol less frequently, consumed smaller amounts of alcohol when they did drink, had longer study retention, and reported better clinical assessments. The observed results of the secondary efficacy parameters support the results of the primary efficacy analyses.

4.4.4 Controlled Clinical Studies. European Short-Term Supportive Efficacy Studies

4.4.4.1 Controlled European Short-Term Supportive Efficacy Studies

The 6 controlled European Short-Term Supportive efficacy studies include the Poldrugo, Tempesta, BENELUX, Ladewig, UKMAS, and ADISA studies, all of which had a 6-month Treatment Phase duration. The results of these 6 studies, involving 1776 randomized alcohol-dependent patients (880 randomized to acamprosate and 896 randomized to placebo) and conducted in 7 European countries, are presented as supportive evidence of the efficacy of acamprosate. Poldrugo^[32], Tempesta^[33], BENELUX^[34], UKMAS^[35], and ADISA^[36] have published study results in English.

4.4.4.2 Study Design and Summary

The same study design was used in each of the European Short-Term Supportive studies, with the exception of ADISA.

Each study was a multicenter, randomized, double-blind, parallel-group comparison of acamprosate versus placebo. An objective of each 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. In all the studies except ADISA, alcohol withdrawal preceded initiation of randomized study medication administration. Thus, theoretically, all patients began treatment from a platform of abstinence. In the ADISA study, patients began study medication simultaneously with an alcohol withdrawal program.

A second objective of each study, 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 did not have a follow-up phase, and the secondary objective of this study was to evaluate the clinical and biological tolerance of acamprosate during the double-blind Treatment Phase.

Psychosocial support was not standardized in any of the studies, but followed the general practice of the individual alcoholism treatment center.

The studies were all initiated before 1991 except for ADISA, which began in 1993.

Table 28 presents the details of the conduct of each study.

Table 28. Summary of Conduct of Study Information for the European Short-Term Supportive Studies

Study Information	Poldrugo	Tempesta	BENELUX	Ladewig	UKMAS	ADISA
Country	Italy	Italy	Belgium, Netherlands, Luxembourg	Switzerland	UK	Spain
Number of Sites	7	18	22	3	20	11
Study Duration (days)	180	180	180	180	168	180
Follow-up Duration (days)	180	90	180	180	28	NA
Years Study Conducted	1989-1992	1989-1993	1990-1992	1989-1991	1990-1993	1993-1994
Data Source: European Short-Term Supportive study reports in NDA						

NA = Not Applicable.

Each study entered male and female patients age 18 to 65 years with alcohol dependence of the chronic or episodic type as defined by the DSM-III or DSM-III-R Classification of the American Psychiatric Association.

Patients in each European Short-Term Supportive study were randomly assigned to treatment with either acamprosate or placebo. In the Poldrugo, BENELUX, and Ladewig studies, the daily dosage was related to the patient's weight. Patients with a body weight >60 kg were to receive 1998 mg/day of acamprosate or placebo to be taken as 2 tablets of 333 mg acamprosate (or placebo) in the morning, at mid-day, and in the evening. Patients with a body weight ≤60 kg were to receive 1332 mg/day of acamprosate or placebo taken as 2 tablets of 333 mg acamprosate (or placebo) in the morning and 1 tablet of 333 mg acamprosate (or placebo) at mid-day and in the evening. In the other 3 studies, depending upon the treatment randomization assignment, patients received 666 mg t.i.d. of acamprosate or placebo.

With the exception of the UKMAS study, the duration of the double-blind Treatment Phase was 180 days (UKMAS double-blind Treatment Phase was 168 days). The duration of the follow-up observation phase was 180 days for the Poldrugo, BENELUX,

and Ladewig studies, 90 days for the Tempesta study, and 28 days for the UKMAS study. The ADISA study did not have a follow-up observation phase.

On the Day of Selection, patients were initially assessed by the CAGE ^[19] and MAST ^[20] questionnaires to determine whether they conformed to the inclusion and exclusion criteria. The BENELUX study also screened patients using the MALT questionnaire.^[25] Assessment visits for each of the studies occurred on various study days during the double-blind Treatment Phase. In the Poldrugo and Ladewig studies patients were evaluated on study Days 30, 90, and 180. In the BENELUX study, patient evaluations took place on study Days 30, 60, 90, 135, and 180. In the Tempesta and ADISA studies the evaluations were on study Days 30, 60, 90, 120, 150, and 180. In the UKMAS study, patients were evaluated on study Days 7, 14, 28, 56, 84, 112, 140, and 168.

Table 29 presents a list of the primary and secondary efficacy parameters for each of the 6 European Short-Term supportive efficacy studies.

Table 29. Primary and Secondary 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
Corrected Cumulative Abstinence Duration (CCAD)	1	1	1	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			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	2
Patient's subjective improvement rating					2	2
Psychological dependence		2	2	2		2
Data Source: European Short-Term Supportive study reports in NDA.						

Note: 1= primary efficacy parameter; 2 = secondary efficacy parameter.

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.

Assessment of drinking behavior was primarily by self-report. The exception was the UKMAS study, where abstinent days and daily maximum alcohol consumption were recorded in a drinking diary.

Each of the controlled European Short-Term Supportive efficacy studies followed the same modified ITT principle. Any randomized patient who had taken at least 1 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. This approach of assessing outcome criteria was implemented to avoid bias potentially introduced by analysis of solely the on-treatment evaluations. For the purpose of analysis and presentation of the data from the Poldrugo, BENELUX, and Ladewig studies, where dosing (subsequent to randomization) was on the basis of body weight, data for both acamprosate doses are grouped as "ACAMP". The acamprosate group is presented as "ACAMP 1998/2000 mg/day" in summaries of the data from the Tempesta, UKMAS, and ADISA studies. In the textual summaries, the subjects summarized as ACAMP or ACAMP 1998/2000 are both referred to as the "acamprosate group".

4.4.4.3 Patient Disposition

Patient disposition across the 6 studies is summarized in Table 30. A total of 880 patients were randomized to receive acamprosate and 896 patients were randomized to receive placebo. All but 8 of the randomized patients were included in the ITT population.

The Tempesta, Ladewig, and ADISA studies had the highest percentage of patients complete the double-blind Treatment Phase (75%, 66%, and 63%, respectively), whereas the Poldrugo, BENELUX, and UKMAS studies had 46%, 27%, and 35% patients complete the double-blind Treatment Phase, respectively. The reasons for discontinuation were generally similar between treatment groups for each study, with the most common reasons for discontinuation due to "Lost to follow-up", "Other", and "Treatment failure".

Table 30. Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Studies Combined

Parameter	Statistic	ACAMP (N=880)	Placebo (N=896)
Number of Patients Randomized	n	880	896
Number of Patients in the ITT Population	n (%)	873 (99%)	895 (>99%)
Number of Patients Who Completed the Double Blind Treatment Phase	n (%)	442 (50%)	415 (46%)
Number of Patients Who Discontinued the Double Blind Treatment Phase	n (%)	438 (50%)	481 (54%)
Reasons for Discontinuation:			
Adverse Event	n (%)	63 (7%)	48 (5%)
Lost to Follow-up	n (%)	132 (15%)	142 (16%)
Treatment Failure	n (%)	94 (11%)	124 (14%)
Death	n (%)	2 (<1%)	2 (<1%)
Protocol Violation	n (%)	22 (3%)	28 (3%)
Other	n (%)	125 (14%)	137 (15%)
Data Source: NDA Table 8.7.2.1.1, Table 8.7.2.1.2, Table 8.7.2.1.3, Table 8.7.2.1.4, Table 8.7.2.1.5, and Table 8.7.2.1.6.			

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

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

Patient disposition for the European Short-Term Supportive studies was similar to the pivotal efficacy studies (Pelc II, PRAMA, and Paille studies). The same percentage (48%) of patients completed the Treatment Phase for both efficacy study groups, and the percentage of patients who discontinued for various reasons were similar between both efficacy study groups. Detailed results for patient disposition for the European Short-Term Supportive studies are presented below.

Poldrugo

Patient disposition (including reasons for discontinuation) during the double-blind Treatment Phase for the Poldrugo study is presented Table 31. In the Poldrugo study, 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%).

Table 31 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: NDA Table 8.7.2.1.1			

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

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

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

In the Poldrugo study, fewer patients (57 [47%]) discontinued in the acamprosate group than in the placebo group (77 [62%]) during the 180-days of treatment. Apart from “adverse event” and “treatment failure”, which were reported as the reason for discontinuation by a larger percentage of patients in the placebo group (13% and 23%, respectively) compared to the acamprosate group (8% and 16%, respectively), the reasons for discontinuation were similar between treatment groups.

Tempesta

Patient disposition during the double-blind Treatment Phase is presented in Table 32. In the Tempesta 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%]).

Table 32. 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: NDA Table 8.7.2.1.2			

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

Note: Other includes refusal or inability to continue, non-compliance, and serious aggravation.

Forty (24%) patients in the acamprosate group and 44 (27%) patients in the placebo group prematurely discontinued study participation during the Treatment Phase. The reasons for discontinuation were similar between treatment groups, with slightly more patients being discontinued in the placebo group (11%) for the reason “other” compared to the acamprosate group (7%). The category of “other” included subcategories such as “patient refusal or inability to continue”, “non-compliance”, and “serious aggravation” (of alcoholism).

BENELUX

Patient disposition during the double-blind Treatment Phase is presented in Table 33. A total of 262 patients were randomized into the BENELUX trial. A total of 128 patients (49%) were assigned to the acamprosate group and 134 patients (51%) were assigned to the placebo group. Twelve patients were not randomized because they failed to satisfy study entry criteria. A total of 70 patients completed the 180-day Treatment Phase, 38 (30%) in the acamprosate group and 32 (24%) in the placebo group.

Table 33. Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study BENELUX

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

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

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

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

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

Ladewig

Patient disposition during the double-blind Treatment Phase is presented in Table 34. In the Ladewig study, a total of 62 patients were screened but only 61 patients were randomized (29 to acamprosate and 32 to placebo) and included in the ITT population. The 1 patient who was not randomized required rehospitalization on Day 0 for a further period of detoxification. The percentage of patients that completed the study (66%) is the same for the 2 treatment groups. The reasons for discontinuation were similar for the 2 treatment groups with 2 exceptions. More placebo (22%) patients discontinued due to “treatment” failure than acamprosate patients (7%), while more acamprosate patients (17%) had “Other” discontinuation reasons than placebo patients (6%).

Table 34. Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study Ladewig

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

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

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

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

UKMAS

Patient disposition during the double-blind Treatment Phase is presented in Table 35. A total of 581 patients were randomized in the UKMAS study: 289 patients were assigned to receive acamprosate and 292 patients were assigned to receive placebo. The majority of the 83 patients who were screened but not randomized either defaulted, did not meet the selection criteria, or refused medication. A total of 203 patients completed the study, 100 patients (35%) in the acamprosate group and 103 patients (35%) in the placebo group.

Table 35. Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study UKMAS

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

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

Note: Other includes concurrent illness, condition worsened, refused medication, and non-compliance.

A similar percentage of patients discontinued from the UKMAS study (65% in each treatment group) with “lost to follow-up” reported as the most frequent reason for discontinuation (22% of acamprosate and 25% of placebo patients). More patients discontinued due to the reason of “adverse event” in the acamprosate group (38 patients, 13%) than in the placebo group (23 patients, 8%). Less than 10% of patients in each treatment group (7% in the acamprosate group and 9% in the placebo group) were discontinued prematurely for “treatment failure”.

ADISA

Patient disposition during the double-blind Treatment Phase is presented in Table 36. In the ADISA study, 296 patients were screened and randomized (148 on each treatment). One patient did not receive any medication for reasons unknown and 7 patients were excluded as no key data were available after the Day 0 visit. Therefore, there were 288 patients in the ITT population with 141 patients assigned to acamprosate and 147 patients assigned to placebo. A total of 186 patients, 96 patients in the acamprosate group (65%) and 90 patients in the placebo group (61%), completed the study. The percentage of patients who discontinued for each individual reason was similar between treatment groups. “Lost to follow-up” was the predominant reason for patients discontinuing the study.

Table 36. Patient Disposition During Treatment Phase – European Short-Term Supportive Efficacy Study ADISA

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=148)	Placebo (N=148)
Number of Patients Randomized	n	148	148
Number of Patients in the ITT Population	n (%)	141 (95%)	147 (>99%)
Number of Patients Who Completed the Double Blind Treatment Phase	n (%)	96 (65%)	90 (61%)
Number of Patients Who Discontinued the Double Blind Treatment Phase	n (%)	52 (35%)	58 (39%)
Reasons for Discontinuation:			
Adverse Event	n (%)	3 (2%)	4 (3%)
Lost to Follow-up	n (%)	24 (16%)	28 (19%)
Treatment Failure	n (%)	4 (3%)	7 (5%)
Death	n (%)	0	0
Protocol Violation	n (%)	9 (6%)	7 (5%)
Other	n (%)	12 (8%)	12 (8%)
Data Source: NDA Table 8.7.2.1.6			

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

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

4.4.4.4 Demographic and Baseline Characteristics

Demographic characteristics of gender, age, and weight are presented, along with the following parameters for history of alcohol use at Baseline, as available:

- Duration of alcohol dependence/abuse;

- Average standard drinks per day at study entry;
- Family history of alcohol problems;
- Number of prior treatments for alcoholism;
- Other measures of disease severity (e.g., CAGE, MAST);
- Employment status;
- Marital status;
- Living situation;
- Detoxification prior to randomization; and
- Abstinence at Baseline.

Statistical tests to compare treatment group differences were not performed.

The majority (79%) of patients in these studies were male (percentages ranged from 69% to 87% across the studies) and between the ages of 40 to 59 years (percentages ranged from 45% to 69% across studies). The mean age was 43.1 years. On study entry, the majority of patients (51% to 77%) within each study drank more than 10 standard drinks per day (12 g of pure alcohol per standard drink). Standard drink information was not available for the Ladewig study.

All patients in the European Short-Term Supportive efficacy studies (with the exception of 1 patient in the Poldrugo study and 93 patients in the ADISA study), had undergone detoxification therapy to withdraw from alcohol. Such therapy was generally inpatient and given prior to entering the study. Accordingly, the majority of patients (86%) were abstinent prior to the initiation of study medication at Baseline. Although patients in the UKMAS study also underwent alcohol withdrawal, after its completion there was a “stabilization period” of variable duration during which time the patients did not take any study medication. As a result, almost one-third of UKMAS patients had resumed drinking prior to study drug initiation and only 70% of patients were abstinent at Baseline.

Poldrugo

Demographic characteristics and history of alcohol use at Baseline for the Poldrugo study are presented in Table 37. At the selection assessment for the Poldrugo study, treatment groups were well-matched with regard to gender and age. 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 (12 g of pure alcohol per standard drink) 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). There was 1 patient in the acamprosate group who did not have a detoxification prior to randomization and was not abstinent at Baseline.

Table 37. 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)
Age Distribution (years)	n	122	124
16-39	n (%)	46 (38%)	44 (35%)
40-59	n (%)	65 (53%)	72 (58%)
≥60	n (%)	11 (9%)	8 (6%)
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: NDA Table 8.7.2.2.1 and 8.7.2.3.1			

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

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

Tempesta

Demographic characteristics and history of alcohol use at Baseline for the Tempesta study are presented in Table 38. Treatment groups were well-matched with regard to the demographic characteristics. 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 and 51% in the placebo group) of the patients consumed more than 10 standard drinks (12 g of pure alcohol per standard drink) per day at study entry. One-third (31% of acamprosate patients and 35% of placebo patients) of the patients had at least 1 prior treatment for alcoholism. All patients in both treatment groups received detoxification prior to randomization and were abstinent at Baseline.

Table 38. Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study Tempesta

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=164)	Placebo (N=166)
Gender	n	164	166
Male	n (%)	139 (85%)	134 (81%)
Female	n (%)	25 (15%)	32 (19%)
Age (years)	n	164	166
	Mean (SE)	45.9 (0.9)	46.0 (0.9)
Age Distribution (years)	n	164	166
16-39	n (%)	49 (30%)	45 (27%)
40-59	n (%)	92 (56%)	96 (58%)
≥60	n (%)	23 (14%)	25 (15%)
Weight (kg)	n	164	166
	Mean (SE)	71.2 (0.7)	70.6 (0.7)
	Min, Max	57, 95	51, 102
Marital Status	n	164	166
Married	n (%)	111 (68%)	114 (69%)
Not Married	n (%)	53 (32%)	52 (31%)
Detoxification Prior to Randomization	n	164	166
Yes	n (%)	164 (100%)	166 (100%)
No	n (%)	0	0
Abstinence at Baseline	n	164	166
Yes	n (%)	164 (100%)	166 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)	n	95	105
	Mean (SE)	11.5 (0.9)	11.5 (0.9)
Average Standard Drinks per Day at Study Entry	n	164	166
<5	n (%)	6 (4%)	9 (5%)
5 – 10	n (%)	68 (41%)	72 (43%)
>10	n (%)	90 (55%)	85 (51%)
Prior Treatment or Detoxes for Alcoholism	n	164	166
0	n (%)	113 (69%)	108 (65%)
1	n (%)	17 (10%)	23 (14%)
2	n (%)	13 (8%)	12 (7%)
3	n (%)	6 (4%)	5 (3%)
>3	n (%)	15 (9%)	18 (11%)
Data Source: NDA Table 8.7.2.2.2 and 8.7.2.3.2			

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

BENELUX

Demographic characteristics and history of alcohol use at Baseline for the BENELUX study are presented in Table 39. In the BENELUX study, the treatment groups were similar with regards to the demographic characteristics. Most patients were male (76% in both treatment groups) and the mean age was 41 years (40.3 years for the acamprosate group and 41.7 years for the placebo group). History of alcohol use at Baseline was also similar between treatment groups. Patients had a mean duration of alcohol dependence or abuse of 11 years (11.2 years for the acamprosate group and 10.9 years for the placebo group) and 74% (78% in the acamprosate group and 70% in the placebo group) of the patients consumed more than 10 standard drinks (12 g of pure alcohol per standard drink) per day at study entry. Sixty percent (56% in the acamprosate group and 64% in the placebo group) of the patients had at least 1 prior treatment for alcoholism. All patients received detoxification prior to randomization and were abstinent at Baseline.

Table 39. Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study BENELUX

Parameter	Statistic	ACAMP (N=128)	Placebo (N=134)
Gender	n	128	134
Male	n (%)	97 (76%)	102 (76%)
Female	n (%)	31 (24%)	32 (24%)
Age (years)	n	126	132
	Mean (SE)	40.3 (0.8)	41.7 (0.7)
Age Distribution (years)	n	126	132
16-39	n (%)	59 (47%)	52 (39%)
40-59	n (%)	63 (50%)	78 (59%)
≥60	n (%)	4 (3%)	2 (2%)
Weight (kg)	n	125	133
	Mean (SE)	71.6 (1.1)	73.3 (1.2)
	Min, Max	44, 105	43, 152
Marital Status	n	80	86
Married	n (%)	42 (53%)	42 (49%)
Not Married	n (%)	38 (48%)	44 (51%)
Detoxification Prior to Randomization	n	128	134
Yes	n (%)	128 (100%)	134 (100%)
No	n (%)	0	0
Abstinence at Baseline	n	128	134
Yes	n (%)	128 (100%)	134 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)	n	95	100
	Mean (SE)	11.2 (0.8)	10.9 (0.7)
Average Standard Drinks per Day at Study Entry	n	125	132
<5	n (%)	2 (2%)	6 (5%)
5 – 10	n (%)	26 (21%)	33 (25%)
> 10	n (%)	97 (78%)	93 (70%)
Prior Treatment or Detoxes for Alcoholism	n	124	132
0	n (%)	55 (44%)	47 (36%)
1	n (%)	21 (17%)	27 (20%)
2	n (%)	12 (10%)	22 (17%)
3	n (%)	11 (9%)	12 (9%)
>3	n (%)	25 (20%)	24 (18%)
Data Source: NDA Table 8.7.2.2.3 and 8.7.2.3.3			

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

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

Ladewig

Demographic characteristics and history of alcohol use at Baseline for the Ladewig study are presented in Table 40. Treatment groups were well-matched with regards to the demographic characteristics. Seventy-seven percent (86% in the acamprosate group and 69% in the placebo group) of the patients were male and the mean age was 47 years (47.7 years in the acamprosate group and 49.9 years in the placebo group). History of alcohol use at Baseline was also similar between treatment groups. Duration of alcohol dependence or abuse averaged 12 years (11.9 years for the acamprosate and 12.6 years for the placebo group) and 85% (90% in the acamprosate group and 81% in the placebo group) of the patients had at least 1 prior treatment for alcoholism. All of the patients received detoxification prior to randomization and were abstinent at Baseline.

Table 40. Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study Ladewig

Parameter	Statistic	ACAMP (N=29)	Placebo (N=32)
Gender	n	29	32
Male	n (%)	25 (86%)	22 (69%)
Female	n (%)	4 (14%)	10 (31%)
Age (years)	n	29	32
	Mean (SE)	47.7 (2.0)	46.9 (1.7)
Age Distribution (years)	n	29	32
16-39	n (%)	7 (24%)	7 (22%)
40-59	n (%)	17 (59%)	22 (69%)
≥60	n (%)	5 (17%)	3 (9%)
Weight (kg)	n	20	32
	Mean (SE)	68.0 (2.2)	68.9 (2.3)
	Min, Max	42, 97	48, 92
Marital Status	n	NA	NA
Married	n (%)		
Not Married	n (%)		
Detoxification Prior to Randomization	n	29	32
Yes	n (%)	29 (100%)	32 (100%)
No	n (%)	0	0
Abstinence at Baseline	n	29	32
Yes	n (%)	29 (100%)	32 (100%)
No	n (%)	0	0
Duration of Alcohol Dependence/Abuse (years)	n	29	31
	Mean (SE)	11.9 (1.9)	12.6 (1.7)
Average Standard Drinks per Day at Study Entry	n		
<5	n (%)	NA	NA
5 – 10	n (%)		
>10	n (%)		
Prior Treatment or Detoxes for Alcoholism	n	29	32
0	n (%)	3 (10%)	6 (19%)
1	n (%)	13 (45%)	9 (28%)
2	n (%)	8 (28%)	4 (13%)
3	n (%)	3 (10%)	7 (22%)
>3	n (%)	2 (7%)	6 (19%)
Data Source: NDA Table 8.7.2.2.4 and 8.7.2.3.4			

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

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

NA = Not Available.

UKMAS

Demographic characteristics and history of alcohol use at Baseline for the UKMAS study are presented in Table 41. In the UKMAS study, there were more males in the acamprosate group (87%) than in the placebo group (80%). The mean age was 43 years (42.3 years in the acamprosate group and 43.3 years in the placebo group). The history of alcohol use at Baseline was similar between treatment groups. Seventy-two percent of the patients (77% in the acamprosate group and 67% in the placebo group) had been consuming more than 10 standard drinks (12 g of pure alcohol per standard drink) per day at study entry. Of note, 30% of patients (27% in the acamprosate group and 30% in the placebo group) were not abstinent at Baseline, although all patients had completed alcohol withdrawal prior to randomization. As noted above, after alcohol withdrawal, there was a “stabilization period” of variable duration, during which time patients did not receive any study medication, and relapses occurred then, resulting in non-abstinence at Baseline.

Table 41. Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study UKMAS

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=289)	Placebo (N=292)
Gender	n	289	292
Male	n (%)	252 (87%)	233 (80%)
Female	n (%)	37 (13%)	59 (20%)
Age (years)	n	289	292
	Mean (SE)	42.3 (0.6)	43.3 (0.6)
Age Distribution (years)	n	289	292
16-39	n (%)	117 (40%)	105 (36%)
40-59	n (%)	160 (55%)	169 (58%)
≥60	n (%)	12 (4%)	18 (6%)
Weight (kg)	n	289	292
	Mean (SE)	73.5 (0.7)	73.5 (0.8)
	Min, Max	50, 119	50, 119
Marital Status	n		
Married	n (%)	NA	NA
Not Married	n (%)		
Detoxification Prior to Randomization	n	289	292
Yes	n (%)	289 (100%)	292 (100%)
No	n (%)	0	0
Abstinence at Baseline	n	280	284
Yes	n (%)	201 (70%)	195 (67%)
No	n (%)	79 (27%)	89 (30%)
Duration of Alcohol Dependence/Abuse (years)	n	NA	NA
	Mean (SE)		
Average Standard Drinks per Day at Study Entry	n	289	291
<5	n (%)	22 (8%)	29 (10%)
5 – 10	n (%)	44 (15%)	67 (23%)
>10	n (%)	223 (77%)	195 (67%)
Prior Treatment or Detoxes for Alcoholism	n		
0	n (%)		
1	n (%)		
2	n (%)		
3	n (%)		
>3	n (%)		
Data Source: NDA Table 8.7.2.2.5 and 8.7.2.3.5			

NA = Not Available.

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

ADISA

Demographic characteristics and history of alcohol use at Baseline for the ADISA study are presented in Table 42. The demographic characteristics for the 2 treatment groups were similar. Eighty percent (80% in the acamprosate group and 79% in the placebo group) of patients were male and the mean age was 41 years (41.4 years for the acamprosate group and 40.7 years for the placebo group). History of alcohol use at Baseline was similar between both treatment groups with a mean duration of alcohol dependence or abuse of 13 years (12.6 years for acamprosate and 12.9 years for placebo). Approximately two-thirds (66%) of the patients consumed more than 10 standard drinks (12 g of pure alcohol per standard drink) per day at study entry and 58% of the patients in each treatment group had at least 1 prior treatment for alcoholism.

In this study, in contrast to all the other Group I studies, treatment with study medication commenced on the first day of acute alcohol weaning therapy. Dependent on the routine of the participating study centers, alcohol weaning therapy could have theoretically been administered on either an inpatient or an outpatient basis for 8 days. In fact, all patients were detoxified on an outpatient basis and detoxification did not involve medication for 93 of them (44 in the acamprosate group and 49 in the placebo group).

Table 42. Demographic and Baseline Characteristics – European Short-Term Supportive Efficacy Study ADISA

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=141)	Placebo (N=147)
Gender	n	141	147
Male	n (%)	113 (80%)	116 (79%)
Female	n (%)	28 (20%)	31 (21%)
Age (years)	n	141	147
	Mean (SE)	41.4 (0.8)	40.7 (0.8)
Age Distribution (years)	n	141	147
16-39	n (%)	61 (43%)	75 (51%)
40-59	n (%)	75 (53%)	66 (45%)
≥60	n (%)	5 (4%)	6 (4%)
Weight (kg)	n	141	147
	Mean (SE)	67.8 (1.1)	69.2 (1.1)
	Min, Max	43, 103	43, 128
Marital Status	n	141	147
Married	n (%)	104 (74%)	91 (62%)
Not Married	n (%)	37 (26%)	56 (38%)
Detoxification During First Week of Study	n	141	147
Yes	n (%)	97 (69%)	98 (67%)
No	n (%)	44 (31%)	49 (33%)
Abstinence at Baseline	n	141	147
Yes	n (%)	123 (87%)	123 (84%)
No	n (%)	18 (13%)	24 (16%)
Duration of Alcohol Dependence/Abuse (years)	n	141	147
	Mean (SE)	12.6 (0.7)	12.9 (0.6)
Average Standard Drinks per Day at Study Entry	n	141	147
<5	n (%)	6 (4%)	5 (3%)
5 – 10	n (%)	45 (32%)	41 (28%)
>10	n (%)	90 (64%)	101 (69%)
Prior Treatment or Detoxes for Alcoholism	n	141	147
0	n (%)	59 (42%)	62 (42%)
1	n (%)	39 (28%)	51 (35%)
2	n (%)	22 (16%)	16 (11%)
3	n (%)	9 (6%)	6 (4%)
>3	n (%)	12 (9%)	12 (8%)
Data Source: NDA Table 8.7.2.2.6 and 8.7.2.3.6, Study Report Tables 6.5 and 6.6			

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

Summary of Demographic and Baseline Characteristics

In summary, the European Short-Term Supportive efficacy studies were well-balanced with regard to the demographic and Baseline characteristics. The majority of patients in the study were married, male, and between the ages of 40 to 59. On study entry, ≥51% of

the patient in each treatment group within each study drank more than 10 standard drinks (12 g of pure alcohol per standard drink) per day.

Excluding the ADISA study, all patients in the remaining European Short-Term Supportive efficacy studies (with the exception of 1 patient in the Poldrugo study) had undergone detoxification prior to entering the study and the majority of the patients were abstinent prior to the initiation of study medication (Baseline). However, in the UKMAS study, 30% of patients were not abstinent at Baseline.

4.4.4.5 Drug Exposure

The duration of study drug exposure was calculated as the difference in weeks between the last date of study medication and first date of study medication, inclusive. Exposure is summarized as a continuous parameter and by duration categories of 0 to <4 weeks, 4 to <8 weeks, 8 to <13 weeks, 13 to <26 weeks, and ≥ 26 weeks. Compliance (%) and the percentage of patients who were $\geq 75\%$ compliant are also summarized. Statistical tests to compare treatment group differences were not performed.

Drug exposure between treatment groups was similar within each study, but was somewhat different across studies. In the Poldrugo, BENELUX, and UKMAS studies, the duration of exposure was approximately 15 weeks in the acamprosate group and 13 weeks in the placebo group. However, in the Tempesta, Ladewig, and ADISA studies, the duration of exposure was approximately 21 weeks in the acamprosate group and 20 weeks in the placebo group. A high percentage of compliance to study medication was observed in each study indicating that patients took study medication as prescribed. Mean compliance ranged from 91.5% (ADISA study) to 102.4% (Poldrugo study) for the acamprosate group, and 91.4% (ADISA study) to 98.8% (Poldrugo study) for the placebo group.

Poldrugo

Drug exposure for the Poldrugo study is presented in Table 43. Patients in the acamprosate group had a mean (median) duration of exposure of 15.6 weeks (26 weeks) compared to 12.1 weeks (4 weeks) in the placebo group. The median compliance was 102.4% for the acamprosate group and 98.8% for the placebo indicating that, on average, patients took medication as directed.

Table 43. Drug Exposure – European Short-Term Supportive Efficacy Study Poldrugo

Parameter	Statistic	ACAMP (N=122)	Placebo (N=124)
Duration of Exposure (weeks)	n Mean (SE)	122 15.6 (1.0)	124 12.1 (1.0)
Exposure by Duration Category (weeks)	n	122	124
0 - <4	n (%)	24 (20%)	36 (29%)
4 - <8	n (%)	23 (19%)	29 (23%)
8 - <13	n (%)	10 (8%)	11 (9%)
13 - <26	n (%)	65 (53%)	48 (39%)
Compliance (%)	n Mean (SE)	94 102.4 (1.5)	78 98.8 (2.0)
Number of Patients Who Were ≥75% Compliant	n (%)	93 (99%)	75 (96%)
Data Source: NDA Table 8.7.2.4.1			

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

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

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

Tempesta

Drug exposure for the Tempesta study is presented in Table 44. The treatment groups were similar with regard to the duration of exposure and compliance. The average treatment duration of exposure in each treatment group was approximately 21 weeks and 77% of the patients in each treatment group completed at least 13 weeks of treatment. Mean compliance was similar between treatment groups (95.1% for the acamprosate group and 92.6% for the placebo group).

Table 44. Drug Exposure – European Short-Term Supportive Efficacy Study Tempesta

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=164)	Placebo (N=166)
Duration of Exposure (weeks)	n Mean (SE)	164 21.3 (0.6)	166 21.0 (0.7)
Exposure by Duration Category (weeks)	n	164	166
0 - <4	n (%)	5 (3%)	9 (5%)
4 - <8	n (%)	16 (10%)	15 (9%)
8 - <13	n (%)	16 (10%)	15 (9%)
13 - <26	n (%)	127 (77%)	127 (77%)
Compliance (%)	n Mean (SE)	108 95.1 (0.6)	104 92.6 (1.0)
Number of Patients Who Were ≥75% Compliant	n (%)	106 (98%)	97 (93%)
Data Source: NDA Table 8.7.2.4.2			

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

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

BENELUX

Drug exposure for the BENELUX study is presented in Table 45. In the BENELUX study, mean duration of exposure was 14.4 weeks for the acamprosate group and 12.1 weeks for the placebo group. More patients in the acamprosate group (48%) had at least 13 weeks of exposure to treatment than in the placebo group (36%). Mean compliance was similar (93.5% for the acamprosate group and 93.3% for the placebo group) between groups.

Table 45. Drug Exposure – European Short-Term Supportive Efficacy Study BENELUX

Parameter	Statistic	ACAMP (N=128)	Placebo (N=134)
Duration of Exposure (weeks)	n Mean (SE)	128 14.4 (0.9)	134 12.1 (0.9)
Exposure by Duration Category (weeks)	n	128	134
0 - <4	n (%)	21 (16%)	29 (22%)
4 - <8	n (%)	22 (17%)	24 (18%)
8 - <13	n (%)	23 (18%)	33 (25%)
13 - <26	n (%)	62 (48%)	48 (36%)
Compliance (%)	n Mean (SE)	93 93.5 (4.0)	94 93.3 (2.3)
Number of Patients Who Were ≥75% Compliant	n (%)	78 (84%)	83 (88%)
Data Source: NDA Table 8.7.2.4.3			

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

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

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

Ladewig

Drug exposure for the Ladewig study is presented in Table 46. The treatment groups were similar with regard to the duration of exposure and compliance. Slightly more patients in the acamprosate group (34%) completed 26 weeks or more of treatment compared to the placebo group (22%). Mean compliance was lower in the acamprosate group (84.8%) than in placebo group (92.2%).

**Table 46. Drug Exposure – European Short-Term Supportive Efficacy Study
Ladewig**

Parameter	Statistic	ACAMP (N=29)	Placebo (N=32)
Duration of Exposure (weeks)	n Mean (SE)	29 20.0 (1.7)	32 20.0 (1.7)
Exposure by Duration Category (weeks)	n	29	32
0 - <4	n (%)	3 (10%)	3 (9%)
4 - <8	n (%)	1 (3%)	3 (9%)
8 - <13	n (%)	1 (3%)	3 (9%)
13 - <26	n (%)	14 (48%)	16 (50%)
≥26	n (%)	10 (34%)	7 (22%)
Compliance (%)	n Mean (SE)	24 84.8 (3.3)	26 92.2 (5.5)
Number of Patients Who Were ≥75% Compliant	n (%)	18 (75%)	21 (81%)
Data Source: NDA Table 8.7.2.4.4			

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

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

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

UKMAS

Drug exposure for the UKMAS study is presented in Table 47. The duration of exposure to treatment was similar across treatment groups. Fifty percent of acamprosate patients and 54% of placebo patients had at least 13 weeks of exposure to study medication. Compliance was similar across treatment groups (93.0% in the acamprosate group and 93.4% in the placebo group) indicating that most patients took study medication as prescribed.

Table 47. Drug Exposure – European Short-Term Supportive Efficacy Study UKMAS

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=289)	Placebo (N=292)
Duration of Exposure (weeks)	n Mean (SE)	289 14.2 (0.6)	292 14.9 (0.6)
Exposure by Duration Category (weeks)	n	289	292
0 - <4	n (%)	65 (22%)	70 (24%)
4 - <8	n (%)	43 (15%)	26 (9%)
8 - <13	n (%)	36 (12%)	40 (14%)
13 - <26	n (%)	119 (41%)	119 (41%)
≥26	n (%)	26 (9%)	37 (13%)
Compliance (%)	n Mean (SE)	256 93.0 (1.1)	261 93.4 (1.3)
Number of Patients Who Were ≥75% Compliant	n (%)	227 (89%)	235 (90%)
Data Source: NDA Table 8.7.2.4.5			

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

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

ADISA

Drug exposure for the ADISA study is presented in Table 48. Exposure to treatment was similar between treatment groups. Eighty percent of patients in the acamprosate group and 75% of patients in the placebo group had at least 13 weeks of drug exposure. Compliance was similar across treatment groups (91.5% in the acamprosate group and 91.4% in the placebo group).

Table 48. Drug Exposure – European Short-Term Supportive Efficacy Study ADISA

Parameter	Statistic	ACAMP 1998/2000 mg/day (N=141)	Placebo (N=147)
Duration of Exposure (weeks)	n Mean (SE)	141 21.4 (0.7)	147 20.0 (0.8)
Exposure by Duration Category (weeks)	n	141	147
0 - <4	n (%)	8 (6%)	10 (7%)
4 - <8	n (%)	11 (8%)	17 (12%)
8 - <13	n (%)	9 (6%)	10 (7%)
13 - <26	n (%)	47 (33%)	50 (34%)
≥26	n (%)	66 (47%)	60 (41%)
Compliance (%)	n Mean (SE)	137 91.5 (0.9)	141 91.4 (1.1)
Number of Patients Who Were ≥75% Compliant	n (%)	125 (91%)	126 (89%)
Data Source: NDA Table 8.7.2.4.6			

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

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

Summary of Drug Exposure

In summary, drug exposure between treatment groups was similar within each study. However, patients in the Tempesta, Ladewig, and ADISA studies experienced, on average, a longer duration of exposure compared to patients in the Poldrugo, BENELUX, and UKMAS studies. This exposure was consistent with higher percentages of patients completing the Tempesta, Ladewig, and ADISA studies. A high level of compliance to study medication dosing was observed in each study, indicating that patients generally took study medication as prescribed.

4.4.4.6 Primary Efficacy Parameters

Results of the analyses of the following primary efficacy parameters are provided for the European Short-Term Supportive studies:

- CCAD,
- Time to first drink or relapse, and
- Rate of complete abstinence.

Efficacy results are presented for the ITT population of each study separately.

4.4.4.6.1 Corrected Cumulative Abstinence Duration

Cumulative abstinence duration (CAD) was defined as the total number of abstinent days, calculated as the sum of only those periods of complete abstinence. It is presented for all European Short-Term studies. Corrected cumulative abstinence duration (CCAD) is an expression of CAD as a percentage of the potential duration of treatment during which there was no alcohol consumption:

$$\text{CCAD} = \frac{\text{Total number of days of abstinence} \times 100}{\text{Total potential duration of exposure to treatment}}$$

Analyses of CCAD are presented for 4 of the 6 European Short-Term Supportive efficacy studies (*Poldrugo*, *Tempesta*, *BENELUX*, and *Ladewig*), all of which had a potential treatment duration of 180 days. In these studies, the estimated treatment duration for patients discontinuing for a reason not associated with study drug (e.g, concurrent illness) was considered to be from Day 0 up to the last visit attended.

Treatment group differences in mean CCAD were assessed using a Student's t-test.^[37] Statistical testing was performed on actual and transformed data. The square-root of CCAD was calculated in order to transform the data into an approximate normal distribution for purposes of statistical testing. Likewise, the inverse sine of CCAD (or arcsin of CCAD) was calculated in the *Tempesta* study.

Table 49 presents CAD and CCAD results for all of the European Short-Term Supportive Efficacy studies. Results from each of these 4 studies showed that patients in the acamprosate group had a statistically significantly greater percentage of abstinence time

during the double-blind Treatment Phase compared to patients in the placebo group. Between-group differences in mean CCAD ranged from 10.1% to 21%.

After completing the double-blind Treatment Phase, patients in each of the European Short-Term Supportive efficacy studies (except for the ADISA study) were observed during a follow-up phase where patients did not continue on treatment. Although there was a limited amount of CCAD data from the study reports for the entire study phase (Treatment Phase plus follow-up phase), there was evidence to suggest that, when compared to patients in the placebo group, the benefits of treatment with acamprosate were maintained after patients were taken off study treatment. Detailed results for the analysis of CCAD (and CAD) are presented below.

Table 49. CAD and CCAD During Treatment Phase – European Short-Term Supportive Studies

Study	Statistic	CAD (days)		CCAD (%)	
		ACAMP	Placebo	ACAMP	Placebo
Poldrugo	Mean (SD) p-value	99.1 (80.0) 0.004**	70.4 (74.1)	72 (44) 0.027**	59 (46)
Tempesta	Mean (SD) p-value	109.8 (76.5) 0.016*	89.3 (77.3)	66 (42) 0.008**	54 (44)
BENELUX	Mean (SD) p-value	61.1 (70.1) 0.025*	43.1 (58.0)	34.5 (39.0) 0.026*	24.4 (32.8)
Ladewig	Mean (SD) p-value	83.8 (78.3) 0.039*	46.9 (59.0)	47 (43) 0.033*	26 (33)
UKMAS	Mean (SD) p-value	77.2 (64.0) 0.492	80.9 (65.9)	NA NA	NA
ADISA	Mean (SD) p-value	93 (75) 0.006**	74 (75)	NA NA	NA
Data Source: Table 7 (Poldrugo study report), Table 3.1.1.c (Tempesta study report), Table 8 (BENELUX study report), Table 7 (Ladewig study report), Table 10 (UKMAS study report), Table 6.11 (ADISA study report) in the NDA.					

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

NA = Not available.

Note: P-values for CAD in the Poldrugo, Tempesta, BENELUX, and Ladewig studies were obtained from a two sample t-test. P-values for CAD in the UKMAS and ADISA studies were obtained from an analysis of variance.

Note: The UKMAS and ADISA study reports only presented CAD for the double-blind Treatment Phase.

Poldrugo

The mean (SD) CCAD for the double-blind Treatment Phase was 72% (44) for the acamprosate group and 59% (46) for the placebo group. A Student's t-test^[37] performed on transformed values showed a statistically significantly greater CCAD for the acamprosate group compared to the placebo group ($p=0.047$).

The entire study phase duration (Treatment Phase plus follow-up phase) for the Poldrugo study was 360 days. Treatment group differences in mean CCAD (actual values) across the entire study approached statistical significance ($p=0.082$) in favor of the acamprosate group (mean [SD] CCAD was 68% [42] in the acamprosate group compared to 58% [46] in the placebo group). It should be noted, that the mean (SD) CAD for the acamprosate group of 167.7 days (151.1 days) was statistically significantly longer ($p=0.014$) compared to the mean (SD) CAD of 120.5 days (146.8 days) for the placebo group. A similar result for CAD using data transformed by taking the square-root of CAD was obtained ($p=0.009$).

Tempesta

The mean (SD) CCAD for the double-blind Treatment Phase was 66% (42) for the acamprosate group and 54% (44) for the placebo group. Student's t-tests^[37] performed using actual values ($p=0.008$) and arcsin transformed values ($p=0.004$) both showed a statistically significantly greater CCAD for the acamprosate group compared to the placebo group.

For the Tempesta study, the entire study phase duration (Treatment Phase plus follow-up phase) was 270 days. Mean (SD) CCAD across the entire study phase was 64% (42) for the acamprosate group and 53% (44) for the placebo group. Student's t-tests^[37] performed using actual values ($p=0.018$), and arcsin transformed values ($p=0.016$) both showed statistically significantly greater mean abstinence duration in the acamprosate group compared to the placebo group.

BENELUX

For the BENELUX study, mean (SD) CCAD for the double-blind Treatment Phase was 34.5% (39.0) for the acamprosate group and 24.4% (32.8) for the placebo group. A Student's t-test ^[37] performed on transformed values showed a statistically significantly greater CCAD for the acamprosate group compared to the placebo group ($p=0.026$).

For the BENELUX study, CCAD was not presented for the entire study phase (360 days), although CAD was presented for the entire study phase (Treatment Phase plus follow-up phase). Mean CAD for the entire study phase was observed to be longer for the acamprosate group (221.8 days, SD=140.1 days) than for the placebo group (190.8 days, SD=127.0 days). The difference between treatment groups using actual values was not statistically significant ($p=0.338$), but the observed difference suggests that there was no apparent reversal of effect after patients discontinued study drug.

Ladewig

For the Ladewig study, mean (SD) CCAD for the double-blind Treatment Phase was 47% (43) for the acamprosate group and 26% (33) for the placebo group. A Student's t-test ^[37] performed on transformed values showed a statistically significantly greater duration of abstinence in the acamprosate treated patients ($p=0.033$).

For the Ladewig study, greater abstinence time across the entire study phase was observed for the acamprosate group compared to the placebo group. The mean (SD) CCAD was 61% (62) for the acamprosate group and 39% (47) for the placebo group. The difference between treatment groups was not statistically significant ($p=0.113$). However, patients in the acamprosate group continued to maintain a higher level of abstinence compared to patients in the placebo group.

UKMAS

Corrected cumulative abstinence duration was not available for the UKMAS study. The mean CAD for the double-blind Treatment Phase was similar between the treatment groups (acamprosate, 77.2 days; placebo, 80.9 days).

ADISA

Corrected cumulative abstinence duration was not available for the ADISA study. The mean (SD) CAD for the double-blind Treatment Phase was 93 (75) days in the acamprosate group and 74 (75) days in the placebo group. The average length of cumulative abstinence was statistically significantly ($p=0.006$) longer in the acamprosate group than in the placebo group.

Summary of CAD/CCAD

In summary, for each of the 6 month studies where CCAD was presented for the double-blind Treatment Phase (Poldrugo, Tempesta, BENELUX, and Ladewig studies), patients treated with acamprosate had a statistically significantly greater percent of abstinence time compared to patients treated with placebo. Treatment group differences in mean CCAD (mean for the acamprosate group minus the mean for the placebo group) were similar for the Poldrugo, Tempesta, and BENELUX studies (13%, 12%, and 10.1%, respectively). This difference was even larger for the Ladewig study (21%). Although the results for CCAD were not presented for the UKMAS and ADISA studies, results from the analyses of CAD in the ADISA study also showed a statistically significantly longer abstinence duration for acamprosate patients compared to patients in the placebo group ($p=0.006$).

Of these studies, only the UKMAS study showed no statistically significant difference between treatment groups in mean CAD and mean CCAD.

From the limited amount of CCAD data available from the individual study reports for the entire study phase (Treatment Phase plus follow-up phase), there was evidence to suggest that the benefits of treatment with acamprosate were maintained after the patients were taken off treatment.

4.4.4.6.2 Time to First Drink

In all of these studies except UKMAS, the time to first drink was longer for patients treated with acamprosate compared to placebo, as evidenced by a greater percentage of acamprosate patients abstinent at Day 90 and Day 180 compared to placebo. Between-group differences in the percentage of abstinent patients for the studies, excluding

UKMAS, ranged from 7% to 21% for Day 90 and from 10% to 20% for Day 180, in favor of acamprosate. In the Poldrugo and Tempesta studies, the results of the analysis for time to first drink showed that patients in the acamprosate group remained abstinent statistically significantly longer than patients in the placebo group during the double-blind Treatment Phase ($p \leq 0.001$). In the BENELUX, Ladewig, and ADISA studies, the difference between groups in the time to first drink during the Treatment Phase approached statistical significance ($p \leq 0.098$). For the entire study phase (Treatment Phase plus follow-up phase), there was evidence that abstinence continued to be longer in the acamprosate group for up to 180 days after treatment was discontinued (as suggested by the Poldrugo and Tempesta studies).

The survival analysis for time to first drink or relapse is presented for each European Short-Term Supportive study. Survival analysis assumptions for each study are presented where possible. Time to first drink is presented for the double-blind Treatment Phase. In addition, the entire study duration (Treatment Phase plus follow-up phase) is discussed for the Poldrugo and Tempesta studies. With the exception of the BENELUX study, each study report presented the time to first drink as the cumulative percentage of patients in abstinence. The BENELUX study report presented the number of patients who relapsed for the first time (i.e., had 1 or more alcoholic drinks) at each study assessment day.

A summary of the cumulative percentage of patients who were abstinent at Day 90 (Day 84 for UKMAS) and Day 180 (Day 168 for UKMAS) is presented for the European Short-Term Supportive studies in Table 50.

Table 50. Cumulative Percentage of Abstinent Patients at Day 90 (or 84) and Day 180 (or 168) During Treatment Phase – European Short-Term Supportive Efficacy Studies

European Study	Time Interval (Days)	ACAMP	Placebo	P-value
Poldrugo	Day 90	55%	34%	<0.001**
	Day 180	41%	21%	
Tempesta	Day 90	53%	43%	0.009**
	Day 180	47%	31%	
BENELUX	Day 90	28%	19%	0.098
	Day 180	20%	10%	
Ladewig	Day 90	41%	19%	0.064
	Day 180	17%	3%	
UKMAS	Day 84	19%	21%	0.826
	Day 168	12%	11%	
ADISA	Day 90	45%	38%	0.068
	Day 180	37%	27%	
Data Source: Table II (Poldrugo statistical report), Table IV (Tempesta study report), Table 9 (BENELUX study report), Table 8 (Ladewig study report), Table 9 (UKMAS study report), Table 6.10 (ADISA study report) in the NDA.				

*Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-values for Poldrugo, Tempesta, BENELUX are from the Lee-Desu test; p-value for Ladewig is from the generalized Savage Mantel-Cox test; p-value for UKMAS is from the Mann-Whitney U test (number of continuous abstinent days); and the p-value for ADISA is from the log rank test.

Poldrugo

The occurrence of the first relapse (consumption of any drink) was compared between treatment groups, ignoring the possibility of an improvement after the first relapse. The occurrence of relapse was estimated step-wise over 45-day periods. Patients were excluded for reasons not related to their alcoholism (e.g., concurrent illness, protocol violation). Only patients terminating on time without a relapse throughout the study period were considered a success. The cumulative percentage of patients in abstinence during the double-blind Treatment Phase for the Poldrugo study is presented in Table 51.

Forty-one percent of patients in the acamprosate group remained abstinent through the end of the double-blind Treatment Phase, whereas, the corresponding incidence was half as large for patients in the placebo group (21%). The median survival time was 150.5 days for the acamprosate group and 61.0 days for the placebo group. The median survival time difference between treatment groups was highly statistically significant

($p=0.0004$, Lee-Desu statistic ^[38]) indicating a longer abstinence duration for the acamprosate group compared to the placebo group. Likewise, the mean time of continuous abstinence was highly statistically significant in favor of the acamprosate group (mean \pm SD: 90.1 days \pm 52.0 days) compared to the placebo group (66.9 days \pm 52.1 days; $p=0.001$, t-test).

Table 51. Cumulative Percentage of Patients in Abstinence During Treatment Phase (\pm SE) – European Short-Term Supportive Efficacy Study Poldrugo

Time Interval (Days)	ACAMP (N=122)	Placebo (N=124)	P-value
0	100%	100%	
45	75.4% \pm 3.9%	58.9% \pm 4.4%	
90	54.9% \pm 4.5%	33.9% \pm 4.3%	
135	54.9% \pm 4.5%	33.9% \pm 4.3%	
180	40.7% \pm 5.1%	20.8% \pm 4.2%	<0.001**
Data Source: Table II (Poldrugo statistical report in NDA)			

*Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-value is from Lee-Desu statistic.

Table 52 presents the cumulative percentage of patients continuously abstinent during the entire study phase (Treatment Phase plus follow-up phase) for the Poldrugo study. Patients in the acamprosate group experienced a greater chance of remaining abstinent than patients in the placebo group. The median survival time to first drink was 162 days for the acamprosate group and 61 days for the placebo group. The difference in median survival time between treatment groups was highly statistically significant ($p=0.001$, Lee-Desu statistic ^[38]), indicating a longer continuous abstinence duration for the acamprosate group compared to the placebo group. In addition, the mean time of continuous abstinence was highly statistically significant in favor of the acamprosate group (158 days \pm 123 days) compared to the placebo group (109 days \pm 118 days; $p=0.002$, t-test).

Table 52. Cumulative Percentage of Patients Continuously Abstinent During Entire Study Phase (\pm SE) – European Short-Term Supportive Efficacy Study Poldrugo

Time Interval (Days)	ACAMP (N=122)	Placebo (N=124)	P-value
0	100%	100%	0.001**
45	75.4% ±3.9%	58.9% ±4.4%	
90	54.9% ±4.5%	33.9% ±4.3%	
135	54.9% ±4.5%	33.9% ±4.3%	
180	46.7% ±4.5%	25.8% ±3.9%	
225	46.7% ±4.5%	25.8% ±3.9%	
270	28.7% ±4.1%	21.0% ±3.7%	
315	28.7% ±4.1%	21.0% ±3.7%	
360	28.7% ±4.1%	19.4% ±3.7%	
Data Source: Table VII (Poldrugo statistical report in NDA)			

*Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-value is from Lee-Desu statistics.

Tempesta

The occurrence of the first relapse (consumption of any drink) was compared between treatment groups ignoring the possibility of an improvement after the first relapse. The occurrence of relapse was estimated step-wise over 30-day periods for the double-blind Treatment Phase and over two 45-day periods for the 90-day follow-up observation phase. Patients with confirmed relapse or missing interviews were considered as treatment failures. Patients with confirmed abstinence at the end of the treatment interval were considered a success. Table 53 presents the cumulative percentage of patients in abstinence during the double-blind Treatment Phase for the Tempesta study.

For the double-blind Treatment Phase, patients in the acamprosate group were in the study longer before the first relapse (defined as even a single drink) compared to patients in the placebo group. At any given time interval, the patients in the acamprosate group exhibited a greater chance of remaining in abstinence. The difference between the treatment groups increased slightly between 120 days and 180 days. The median time of abstinence before the first relapse was statistically significantly greater for the acamprosate group (135.0 days) compared to the placebo group (58 days; $p=0.009$, Lee-Desu statistic^[38]).

Table 53. Cumulative Percentage of Patients in Abstinence During Treatment Phase (\pm SE) – European Short-Term Supportive Efficacy Study Tempesta

Time Interval (Days)	ACAMP 1998/2000 mg/day (N=164)	Placebo (N=166)	P-value
0	100%	100%	0.009**
30	68.3% ±3.6%	56.0% ±3.9%	
60	61.0% ±3.8%	48.8% ±3.9%	
90	53.1% ±3.9%	42.8% ±3.8%	
120	50.0% ±3.9%	38.6% ±3.8%	
150	48.2% ±3.9%	36.1% ±3.7%	
180	47.0% ±4.0%	30.6% ±3.9%	
Data Source: Table IV (Tempesta study report in NDA)			

* Significant at the 0.050 level; ** significant at the 0.010 level.

Note: P-value is from Lee-Desu statistics.

Table 54 presents the cumulative percentage of patients in continuous abstinence during the entire study phase (270 days) for the Tempesta study. The survival analysis indicated a similar result to that observed during the double-blind Treatment Phase. Namely, patients in the acamprosate group showed a greater chance of remaining continuously abstinent compared to patients in the placebo group. The median duration of continuous abstinence before the first relapse was statistically significantly longer for the acamprosate group (135.0 days) compared to the placebo group (57.5 days; $p=0.015$, Lee-Desu statistic ^[38]).

Table 54. Cumulative Percentage of Patients Continuously Abstinent During Entire Study Phase (\pm SE) European Short-Term Supportive Efficacy Study Tempesta

Time Interval (Days)	ACAMP 1998/2000 mg/day (N=164)	Placebo (N=166)	P-value
0	100%	100%	0.015*
30	68.3% ±3.6%	56.0% ±3.9%	
60	61.0% ±3.8%	48.8% ±3.9%	
90	53.1% ±3.9%	42.8% ±3.8%	
120	50.0% ±3.9%	38.6% ±3.8%	
150	48.2% ±3.9%	36.1% ±3.7%	
180	47.6% ±3.9%	33.1% ±3.7%	
225	42.1% ±3.9%	30.1% ±3.6%	
270	37.5% ±4.1%	28.9% ±3.6%	
Data Source: Table X (Tempesta study report in NDA)			

* Significant at the 0.050 level; ** significant at the 0.010 level.

Note: P-value is from Lee-Desu statistics.

BENELUX

The occurrence of the first relapse (consumption of any drink) was compared between treatment groups, ignoring the possibility of an improvement after the first relapse. The occurrence of relapse was estimated step-wise over varying intervals of time. Patients were excluded for reasons not related to their alcoholism (e.g., concurrent illness, protocol violation). Only patients terminating on time without a relapse throughout the study period were considered a success.

Table 55 presents the time to first relapse during the double-blind Treatment Phase for the BENELUX study. Through Day 112.5 of the BENELUX study, more patients in the placebo group (88%) relapsed compared to patients in the acamprosate group (77%). On average, the median time to first relapse was longer in the acamprosate group (34.1 days) compared to the placebo group (27.5 days). This difference approached statistical significance (p=0.098).

Table 55. Time to First Relapse During Treatment Phase – European Short-Term Supportive Efficacy Study BENELUX

Time Interval (Days)	ACAMP (N=128)	Placebo (N=134)	P-value
15	61 (48%)	73 (54%)	
45	22 (17%)	26 (19%)	
75	9 (7%)	10 (7%)	
112.5	7 (5%)	9 (7%)	
157.5	4 (3%)	3 (2%)	
180	25 (20%)	13 (10%)	
Median	45 days	15 days	0.098
Median estimated by life-table analysis	34.1 days	27.5 days	
Data Source: Table 9 (BENELUX study report in NDA)			

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-value is from Lee-Desu statistics.

Ladewig

The occurrence of the first relapse (consumption of any drink) was compared between treatment groups, ignoring the possibility of an improvement after the first relapse. The occurrence of relapse was estimated step-wise over 30-day periods. Any consumption of alcohol or missing data was considered a failure (relapse). Early terminations were also considered to be failures, but patients were excluded for reasons not related to their alcoholism (e.g., concurrent illness, protocol violation). All other termination codes were considered as a failure. Only patients terminating on time without a relapse throughout the study period and who attended all clinic visits were considered a success. Table 56 presents the cumulative percentage of patients in abstinence during the double-blind Treatment Phase for the Ladewig study.

Table 56. Cumulative Percentage of Patients Continuously Abstinent During Treatment Phase – European Short-Term Supportive Efficacy Study Ladewig

Time Interval (Days)	ACAMP (N=32)	Placebo (N=29)	P-value
30	72%	41%	0.064
60	72%	41%	
90	41%	19%	
120	41%	19%	
150	41%	19%	
180	17%	3%	
Data Source: Table 8 (Ladewig study report in NDA)			

*Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-value is from the generalized Savage Mantel-Cox Test.

The cumulative percentage of patients remaining abstinent was consistently higher for the acamprosate group compared to the placebo group during the double-blind Treatment Phase for the Ladewig study. The cumulative survival rate study during the double-blind Treatment Phase favored the acamprosate group over the placebo group, however it did not reach statistical significance (p=0.064).

UKMAS

For the UKMAS study, the definition of continuous abstinence was based on information recorded on the patients' diary card and the absence of alcohol on a breath test. The occurrence of relapse was estimated step-wise over varying intervals of time. The cumulative percentage of patients in abstinence during the double-blind Treatment Phase was compared at each time interval (Table 57). Note that for this survival analysis it was assumed that all patients were abstinent at Day 0 (start of treatment), despite the fact that many of the patients reported a relapse in the pretreatment period. Patients who relapsed prior to Day 0 were counted as having a relapse in the Day 7 interval.

Table 57. Cumulative Percentage of Patients in Abstinence During Treatment Phase – European Short-Term Supportive Efficacy Study UKMAS

Time Interval (Days)	ACAMP 1998/2000 mg/day (N=289)	Placebo (N=292)	P-value
0	100%	100%	
7	64.7%	63.0%	0.671
14	49.8%	50.0%	0.967
28	33.9%	39.4%	0.171
56	23.9%	28.8%	0.181
84	18.7%	21.2%	0.442
112	16.3%	14.4%	0.529
140	14.2%	12.3%	0.509
168	11.8%	11.0%	0.760
Mean number of days of continuous abstinence			
N	289	292	
Mean	37.4	39.7	
SD	57.3	57.0	
Mann-Whitney U test for comparison between treatments	2 tailed p-value (corrected for ties) = 0.826		
Data Source: Table 9 (UKMAS study report in NDA)			

*Significant at the 0.050 level; ** significant at the 0.010 level.

Note: P-values for each time interval were obtained from a chi-square test.

During the double-blind Treatment Phase, there were no statistically significant differences between the treatment groups at any time interval. At 168 days, the percentages of patients in abstinence were similar (11.8% and 11.0% for the acamprosate and placebo groups, respectively). The 2 treatment groups were compared with respect to the number of continuously abstinent days to the last visit. The mean values were

37.4 days for the acamprosate group and 39.7 days for the placebo group. The difference in the number of continuous abstinent days between the treatment groups was not statistically significant ($p=0.826$, Mann-Whitney U test^[39]).

ADISA

For the ADISA study, the double-blind Treatment Phase was 180 days. The occurrence of relapse was estimated step-wise over 30-day periods. All patients lost to follow-up were considered treatment failures. The statistical survival analysis was based on abstinence for patients in the ITT population, defined as self-declaration of abstinence plus a GTT level less than the Baseline value, and less than 1.3 times the limit of normal values on Days 60, 90, 135, and 180.

Table 58 presents the cumulative percentage of patients in abstinence, as so-defined, during the double-blind Treatment Phase for the ADISA study. During the ADISA double-blind Treatment Phase, survival analysis for time to first drink showed that the highest frequency of first relapses occurred between Day 0 and Day 30, during which 95 patients relapsed. Throughout the double-blind Treatment Phase, patients in the acamprosate group remained abstinent longer than the placebo group. The difference in survival distributions approached statistical significance ($p=0.068$, log rank test). Up to Day 180, a greater percentage of patients in the acamprosate group (37%) maintained continuous abstinence compared to patients in the placebo group (27%).

Table 58. Cumulative Percentage of Patients in Abstinence During Treatment Phase – European Short-Term Supportive Efficacy Study ADISA

Time Interval (Days)	ACAMP 1998/2000 mg/day (N=141)	Placebo (N=147)	P-value
0-30	72%	63%	0.068
31-60	60%	50%	
61-90	45%	38%	
91-120	39%	31%	
121-150	37%	27%	
151-180	37%	27%	
>180	35%	26%	
Data Source: Table 6.10 (ADISA study report in NDA)			

*Significant at the 0.050 level; ** significant at the 0.010 level.

Note: P-value was obtained from the log rank test.

Summary of Time to First Drink

In summary, during the respective double-blind Treatment Phases of the European Short-Term Supportive studies, patients in the acamprosate groups remained continuously abstinent for a statistically significantly longer period of time compared to patients in the placebo groups. For the entire study phase (Treatment Phase plus follow-up phase), there was evidence from the Poldrugo and Tempesta studies that abstinence continued to be longer in the acamprosate group for up to 180 days after treatment was discontinued.

4.4.4.6.3 Rate of Complete Abstinence

The results of analysis of the rate of complete abstinence in these six 6-month studies showed that, with the exception of the UKMAS study, the rate of complete abstinence was greater in the acamprosate group compared to the placebo group in each study, with between-group differences in the rate of complete abstinence ranging from 10% (BENELUX and ADISA) to 20% (Poldrugo). In the UKMAS study, the rate of complete abstinence was slightly higher for acamprosate patients (12%) compared to placebo patients (11%). The Poldrugo and BENELUX studies had approximately twice the rate of complete abstinence in the acamprosate group compared to the placebo group, and the rate of complete abstinence was almost 5 times greater in the acamprosate group compared to the placebo group in the Ladewig study. Statistically significantly greater rates of complete abstinence in favor of the acamprosate group over the placebo group were observed in the Poldrugo ($p=0.004$), Tempesta ($p=0.029$), and Ladewig ($p=0.002$) studies.

The rate of complete abstinence was determined from the last treatment day result from the survival analysis of time to first drink. These rates were determined only from patients who terminated on time without a relapse throughout the double-blind Treatment Phase. Patients who discontinued during the double-blind Treatment Phase were considered to be treatment failures and were not censored from this analysis (similar to the uncensored analysis presented for the pivotal studies). In the Poldrugo, BENELUX, and Ladewig studies, patients discontinuing for a reason not associated with study drug (i.e., concurrent illness) had a potential treatment duration calculated from the last visit

attended. Two-sided p-values from Fisher's exact test ^[40] are presented to determine the statistical relationship between treatment group abstinence rates.

Table 59 presents the rate of complete abstinence during the double-blind Treatment Phase for the European Short-Term Supportive studies.

Table 59. Rate of Complete Abstinence During Treatment Phase – European Short-Term Supportive Efficacy Studies

European Study	Duration of Double-Blind Treatment Phase (days)	ACAMP	Placebo	Treatment Effect	P-value
Poldrugo	180	41%	21%	20%	0.004**
Tempesta	180	47%	31%	16%	0.029*
BENELUX	180	20%	10%	10%	0.073
Ladewig	180	17%	3%	14%	0.002**
UKMAS	168	12%	11%	1%	>0.999
ADISA	180	37%	27%	10%	0.172
Data Source: Table II (Poldrugo statistical report), Table IV (Tempesta study report), Table 9 (BENELUX study report), Table 8 (Ladewig study report), Table 9 (UKMAS study report), Table 6.10 (ADISA study report), all in NDA.					

*Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: Treatment Effect = Difference in abstinence rates (ACAMP minus Placebo).

Note: P-values are from Fisher's exact chi-square tests.

In summary, the rate of complete abstinence was greater in the acamprosate group compared to the placebo group in each study, with treatment effect ranging from 1-20%. Statistically significantly greater rates of complete abstinence in favor of the acamprosate group compared to the placebo group were observed in 3 of the 6 studies: Poldrugo, Tempesta, and Ladewig studies ($p \leq 0.029$). In the BENELUX study, the treatment group difference in the rate of complete abstinence approached statistical significance in favor of the acamprosate group. In the ADISA study, the rate of complete abstinence was greater in the acamprosate group compared to the placebo group (37% versus 27%, respectively). However, this difference in complete abstinence rates between treatment groups was not statistically significant ($p = 0.172$). In the UKMAS study, the rate of complete abstinence was 12% for the acamprosate group and 11% for the placebo group. The difference between rates was not statistically significant ($p = >0.999$).

4.4.4.6.4 *Summary for Primary Efficacy Parameters for the European Short-Term Supportive Efficacy Studies*

The primary efficacy parameters are the CCAD, time to first drink, and rate of complete abstinence.

In the 4 studies in which it was examined (Poldrugo, Tempesta, BENELUX, and Ladewig) the percentage of time in abstinence, as measured by the CCAD parameter, was statistically significantly greater for patients in the acamprosate group during the double-blind Treatment Phase ($p \leq 0.033$). Treatment group differences in mean CCAD ranged from 10.1% to 21% in favor of acamprosate. Although the results for CCAD were not presented for the UKMAS and ADISA studies, results from the analyses of CAD in the ADISA study also showed a statistically significantly longer abstinence duration for acamprosate patients compared to patients in the placebo group ($p = 0.006$). In the UKMAS study, the difference between treatment groups in mean CAD was not statistically significant ($p = 0.492$).

After completing the double-blind Treatment Phase, patients in each of the European Short-Term Supportive efficacy studies (except for the ADISA study) were observed during a follow-up phase during which they did not receive treatment. Although there was a limited amount of CCAD data from the study reports for the entire study phase, there was evidence to suggest that CCAD remained greater for patients treated with acamprosate compared to patients treated with placebo.

In all of these studies except UKMAS, the time to first drink was longer for patients treated with acamprosate compared to placebo, as evidenced by a greater percentage of acamprosate patients remaining abstinent at Day 90 and Day 180 compared to placebo. However, it should be recalled that only 70% of the patients in the UKMAS study were abstinent at Baseline. Between-group differences in the percentage of patients who remained abstinent at various visits for the studies (excluding UKMAS) ranged from 7% to 21% at Day 90 and from 10% to 20% at Day 180 (final Treatment Phase visit). In the Poldrugo and Tempesta studies, the results of the analysis for time to first drink showed that patients in the acamprosate group remained abstinent statistically significantly longer

than patients in the placebo group during the double-blind Treatment Phase ($p \leq 0.001$). In the BENELUX, Ladewig, and ADISA studies, the difference between groups in the time to first drink during the Treatment Phase approached statistical significance ($p \leq 0.098$). For those patients who completed the entire study phase (Treatment Phase plus follow-up phase), there was evidence that abstinence continued to be longer in the acamprosate group for up to 180 days after treatment was discontinued (as suggested by the Poldrugo and Tempesta studies).

In general, the rate of complete abstinence was greater in the acamprosate group compared to the placebo group. Across all of the European Short-Term Supportive efficacy studies (with the exception of UKMAS), the between-group differences in the rate of complete abstinence ranged from 10% (BENELUX and ADISA) to 20% (Poldrugo). In the UKMAS study, the rate of complete abstinence was slightly higher for acamprosate patients (12%) compared to placebo patients (11%). Across all of these studies except UKMAS, the rates of complete abstinence were 1.4 to 5.7 times greater in the acamprosate group than in the placebo group, even though the difference between treatment groups was shown to be statistically significant in only 3 studies.

Results of the primary efficacy parameters in the UKMAS study were not consistent with those in the other European Short-Term Supportive efficacy studies, where a benefit of treatment with acamprosate was clearly demonstrated. In the UKMAS study, all patients had undergone withdrawal from alcohol followed by a “stabilization” period of variable duration. During this “stabilization” period, a substantial proportion of patients (30%) relapsed to drinking so that when study medication was initiated (mean of 24.6 days after detoxification), these patients did not begin their medical therapy from a platform of abstinence. Results of the UKMAS study suggest that acamprosate may be more effective when therapy commences immediately after withdrawal and the establishment of abstinence from alcohol.

In conclusion, CCAD and time to first drink indicated that patients in the acamprosate group had a statistically significantly longer period of abstinence compared to patients in

the placebo group. The findings for the rate of complete abstinence were supportive of the results for CCAD and time to first drink.

4.4.4.7 Summary of Results on Secondary Efficacy Parameters

The secondary efficacy parameters for the European Short-Term Supportive studies are:

- Frequency of alcohol consumption;
- Quantity of alcohol consumption;
- Pattern of alcohol consumption;
- Overall clinical assessment (CGI);
- Study retention;
- Alcohol craving assessed by Visual Analog Scale (VAS); and
- Patient Global Impression of Improvement.

The frequency of alcohol consumption was presented for the entire Treatment Phase in the Poldrugo and Tempesta studies, and for the double-blind Treatment Phase in the BENELUX study. Frequency of alcohol consumption was not analyzed in the Ladewig, UKMAS, and ADISA studies. The results of the analysis of frequency of alcohol consumption showed that alcohol consumption was less frequent in the acamprosate group than in the placebo group during the double-blind treatment period. Statistically significant differences between treatment groups were observed only at various assessment days within the Tempesta study, however, the observed findings support the primary efficacy results previously reported.

The quantity of alcohol consumption for the entire study phase was measured in the Poldrugo, Tempesta, BENELUX, and Ladewig studies. The results of the analysis of quantity of alcohol consumption showed that the amount of alcohol consumed was generally lower in the acamprosate group compared to the placebo group. Statistically significant differences between treatment groups were detected only at various assessment days within each study, and the assessment days at which significant differences were observed were not consistent across studies. The results from the

quantity of alcohol consumption analysis support the primary efficacy results previously reported for the European Short-Term Supportive studies.

The UKMAS study was the only European Short-Term Supportive efficacy study with an analysis of the pattern of alcohol consumption. The patterns for the treatment groups were similar for all visits with the exception of Day 140 where the differences were statistically significant ($p=0.004$). In the UKMAS study report, this significant difference was attributed to an imbalance in the numbers of controlled (fewer acamprosate versus placebo) and uncontrolled (more acamprosate versus placebo) drinkers between the treatment groups.

Overall clinical assessments were evaluated through the investigator's Clinical Global Impression (CGI) of the patient's condition (*Poldrugo*, *Tempesta*, *BENELUX*, and *Ladewig*). The UKMAS study did not evaluate CGI. The investigators' CGI rated a higher percentage of patients as "better" in the acamprosate group compared to the placebo group. Statistically significant differences between treatment groups in CGI were not generally observed in the European Short-Term Supportive efficacy studies.

Study retention was reported for the BENELUX and UKMAS studies. Overall study retention was similar for the 2 treatment groups. In the BENELUX studies, patients in the acamprosate group were exposed to study medication longer than patients in the placebo group. On the other hand, more patients in the placebo group attended clinic visits in the UKMAS study compared to the acamprosate group. Neither of the differences were statistically significant.

Alcohol craving tended to decrease over time in both treatment groups, but no statistically significant differences between treatment groups were detected.

A summary of the patient global impression of improvement was not available for the European Short-Term Supportive efficacy studies.

In conclusion, patients in the acamprosate group tended to have less frequent and lower amounts of alcohol consumption, as well as lesser alcohol craving over time compared to patients in the placebo group. In addition, the CGI of the patient as rated by the

investigators confirmed the benefits of acamprosate over placebo. Statistical treatment group comparisons for the secondary efficacy analyses were not conclusive. However, the findings of these analyses were supportive of the results of the primary efficacy analyses.

4.4.5 Controlled Clinical Studies. US Short-Term Supportive Efficacy Study

4.4.5.1 Controlled US Short-Term Supportive Study

In this section of the Briefing Document, aspects of the study design, patient disposition, demographics, Baseline characteristics, treatment exposure, and efficacy analysis results are presented for ACAMP/US/96.1 (US 96.1), the placebo-controlled Short-Term supportive safety and efficacy study conducted in the United States by Lipha Pharmaceuticals, Inc., under an IND. This was the only double-blind trial conducted with the 500 mg tablet strength of acamprosate, using a twice daily dosing schedule (see below) and also the only clinical trial that explored a higher daily dose of acamprosate (3000 mg/day, given as 1500 mg b.i.d.).

4.4.5.2 Study Design and Summary

This double-blind, randomized, placebo controlled study of acamprosate was conducted between 1997 and 1999 at 21 sites throughout the US which specialize in the treatment of alcoholism. Principal investigators were all alcohol specialists and either psychiatrists, psychologists, or internists. The US study sought to provide the first experience with the clinical schedule of 1000 mg (two 500 mg tablets) b.i.d. (total daily dose, 2000 mg), in order to allow reasonable comparisons with the European study results. The study also explored the higher dose level of 1500 mg (three 500 mg tablets) b.i.d. (total daily dose, 3000 mg), since 6 tablets per day seemed to be accepted by European patients and no true dose-limiting toxicity had been identified at the conventional dose and only an increased incidence of GI side-effects had been seen in rising dose studies (*Dewland I*).

In European clinical trials of acamprosate in alcohol-dependent patients, a total acamprosate daily dose of 1998 mg (two 333 mg t.i.d.), administered for periods up to 1 year, resulted in significantly longer periods of complete abstinence from alcohol and higher rates of abstinence compared to placebo, with minimal side-effects. Prior to this study, there was virtually no prior experience with higher total doses of acamprosate given in a sustained fashion.

A 500 mg tablet, formulated identically to the 333 mg tablet of earlier studies, was developed by Lipha's Centre de Recherche (Lyon, France) and a multiple-dose, randomized, 2-period crossover pharmacokinetic study was performed in normal healthy volunteers which established that two 333 mg tablets, given t.i.d. (1998 mg, total daily dose) met criteria of bioequivalence with two 500 mg tablets, given b.i.d. (2000 mg, total daily dose) (*Theodor I*).

Based on these considerations, total daily doses of 2000 mg (two 500 mg tablets b.i.d.) and 3000 mg (three 500 mg tablets b.i.d.) were selected for this trial.

The objectives of US 96.1 were to:

- Confirm the efficacy and safety of acamprosate in U.S. alcohol-dependent patients, at the customary total daily dose of 1998/2000 mg/day, when given in a schedule of 1000 mg b.i.d. (two 500 mg tablets b.i.d.) and in association with standardized, but minimal psychosocial support, guided by a protocol-specific manual;
- Explore the efficacy and safety of acamprosate at a total daily dose of 3000 mg/day, given in a schedule of 1500 mg b.i.d. (three 500 mg tablets b.i.d.) under these same circumstances; and
- Explore the efficacy and safety of acamprosate therapy when initiated within ≥ 2 to ≤ 10 days of any hazardous drinking or completion of medicated detoxification.

Admission criteria across European trials were fairly standard. However, a key objective of US 96.1 was to evaluate the safety of acamprosate in a broad spectrum of US outpatients with alcohol dependence. These patients are believed to have more polysubstance abuse and less access to inpatient detoxification than their European counterparts. Therefore, detoxification was not a requirement for study entry and randomized subjects testing positive for illicit drugs on study were not removed as protocol violators. Additionally, unlike prior studies, there were no exclusion criteria involving an upper age limit and because acamprosate is not metabolized and its pharmacokinetics are not affected by liver disease, there was no upper threshold for liver function test values. Two strategies for assessing efficacy while controlling for the

potential “noise” introduced by the heterogeneity of the safety population were defined a priori: 1) an efficacy evaluable population was defined (see below); and 2) standardized measures of patient characteristics commonly associated with alcoholism treatment outcome (e.g., severity of dependence on alcohol and other drugs, treatment goals, etc.) were included in the case report forms for examination as potential covariates.

Inclusion criteria for the study included the following:

- Alcohol dependence according to DSM-IV criteria;
- Males and females ≥ 18 years of age;
- ≥ 2 days to ≤ 10 days since any hazardous drinking (>2 drinks per day for females; >3 drinks per day for males) or since completion of medicated detoxification at randomization;
- Expressed a desire to cut down or stop drinking;
- In acceptable overall health;
- Able to complete/understand questionnaires in English and adequate cognitive function to participate in study (Score of >22 on Mini-Mental State Exam) ^[41];
- Ability to comply with the requirements of the study;
- Signed, witnessed informed consent; and
- Availability of a collateral informant.

Patients meeting any of the following criteria were excluded from study participation:

- Moderately severe or severe alcohol withdrawal symptoms (CIWA >32 or based on clinical judgment), who required medicated detoxification. Such patients could proceed with the Screening evaluation after completion of detoxification;
- Clinically significant and symptomatic medical disorder(s), requiring active intervention and treatment. (Examples included: poorly controlled diabetes, symptomatic cardiac disease, hyperparathyroidism, ascites, encephalopathy, portal hypertension, pancreatic failure);
- Renal insufficiency or established primary renal disease (examples included polycystic kidney disease, obstructive uropathy, diabetic nephropathy with gross albuminuria and/or renal function impairment);

- Met DSM-IV criteria for dependence on substances other than alcohol, nicotine or caffeine or whose urine tested positive for illicit drugs (with the exception of cannabis) at Screening, such as cocaine, heroin, PCP, etc.;
- Sexually active female patients with childbearing potential who were pregnant, nursing or refused to use a reliable method of birth control (hormonal or barrier);
- Met DSM-IV criteria for a major AXIS I disorder, other than alcohol dependence, for which pharmacotherapy was required;
- Hepatic failure or active hepatitis;
- Major gastrointestinal surgery within the 2 months preceding study entry or underwent a liver transplant at any time;
- Treatment of alcoholism mandated by a legal authority;
- Active malignancy. Active malignancy was defined as the presence of a malignancy (other than non-melanoma skin cancer or carcinoma *in situ* of the uterine cervix) within 5 years of beginning the study. Patients who had a malignancy treated more than 5 years prior to the start of the study and had no evidence of recurrent malignancy on screening history and physical examination were to be included;
- Ingested an investigational drug within 1 month of study entry;
- Treated within the month prior to screening with medications which might have influenced drinking outcome (e.g., disulfiram, naltrexone, antidepressants or other psychotropic agents). The exception to the latter was the use of benzodiazepines or other similar agents during medicated detoxification at the time of alcohol withdrawal;
- No fixed domicile and/or no availability by telephone or beeper;
- More than 10 days of abstinence between completion of alcohol withdrawal or medicated detoxification and randomization;
- Prior treatment with acamprosate; and
- Intolerable adverse events (AEs) during Single-Blind Placebo Phase.

Patients were not required to complete inpatient or outpatient alcohol detoxification.

Patients were initially assessed (Day of Selection) to determine whether they conformed with all of the inclusion and exclusion criteria. Provided the patient met the inclusion criteria, the patient was reassessed and the Baseline parameters for measuring efficacy and safety were determined (Day 0). During this run-in period, patients were on placebo medication (single-blind). Patients who were eligible for the study were passively stratified according to whether or not they had medicated detoxification (either inpatient or outpatient) and were randomized to 1 of 3 groups: acamprosate 1998/2000 mg/day (2 tablets acamprosate 500 mg and 1 tablet of placebo in the morning and in the evening), acamprosate 3000 mg/day (3 tablets acamprosate 500 mg in the morning and in the evening), or placebo, in a 3:1:3 ratio. The planned duration of exposure was 24 weeks.

Post-randomization assessments were made on Weeks 1, 2, 4, 8, 13, 16, 20, and 24. All patients participating in the study received standardized, manual-guided psychosocial support from a qualified therapist, consisting of brief intervention and medication compliance procedures of established efficacy to support abstinence, which were specific for this study.

Upon completion of the Treatment Phase of the study, double-blind study medication was discontinued and patients entered an 8-week follow-up phase, during which time they were seen twice (1 week and 8 weeks) after completing the Treatment Phase. Although the study blind was maintained during this period, patients did not receive any medication during the follow-up phase.

The original efficacy parameters for the US study were selected on the basis of experience accrued from the European multicenter clinical efficacy and safety trials described herein. These included cumulative abstinence duration (CAD), rate of complete abstinence, time to first drink, and time to first heavy drinking day. In the European clinical trials, as already noted, detoxification, primarily inpatient, which utilized medication and supportive care, and typically lasted 1 week, was a standard component of alcoholism management prior to initiation of study medication. Accordingly, European patients were entirely abstinent for at least 5 days prior to randomization and

almost 100% of patients began their participation in the respective clinical trial from a firm commitment to abstinence.

In contrast to the European situation, a shift toward minimal outpatient management of alcohol withdrawal in the US resulted in an unexpectedly low percentage of the US study population receiving detoxification treatment (only about 10%), and this was primarily done on an outpatient basis and because of clinically evident symptoms of alcohol withdrawal as assessed by CIWA-AR. Thus, the vast majority of patients in the US study did not have the benefits of beginning the study from a platform of abstinence, reinforced by both medication and the inpatient setting, as in the European clinical trials. In fact, a large proportion of US 96.1 patients (approximately 50%) were not abstinent at randomization. Furthermore, although the intent of the protocol was to recruit patients who wanted to change their drinking habits, a substantial proportion (approximately 60%) of study participants did not have a Baseline treatment goal of abstinence.

As a consequence, planned analyses which depended on the entire population beginning from a state of abstinence (time to first drink, time to first heavy drinking day, and rate of complete abstinence) were no longer relevant to the majority of US study participants. In order to understand the therapeutic effect of acamprosate, subsets of the US 96.1 patient population were identified, which were thought to more closely resemble their European counterparts, based in part on their declared treatment goal of complete abstinence at study onset.

As described above, originally planned analyses of efficacy parameters were not considered relevant, based on the drinking status of the ITT and Efficacy Evaluable populations at Baseline. For purposes of the Briefing Document, the revised efficacy parameters from the final study report are presented for all populations.

The primary efficacy variable was corrected cumulative abstinence duration (CCAD) for the Treatment Phase.

The secondary efficacy parameters were the:

- Categorized CCAD, with proportion of good responders (CCAD $\geq 90\%$);

- Rate of complete abstinence during the interval between the last 2 Treatment Phase visits;
- Change from Baseline in the average number of drinking days per week (across the entire Treatment Phase);
- Change from Baseline in the average number of drinking days per week (across the entire Treatment Phase);
- Alcohol consumption during the Treatment Phase as a percentage of alcohol consumption at Baseline (in terms of drinks per day); and

Information on drinking behavior was obtained from patient self-report (through completion of a daily drinking diary), corroborated by a significant other, and by breath alcohol levels and laboratory assessments at each visit.

Four analysis populations were defined for the further understanding of acamprosate's therapeutic effect and evaluation of efficacy:

- Intent-to-Treat (ITT) Population – all randomized patients who took at least 1 dose of double-blind study medication, and for whom some post-Baseline efficacy data were recorded;
- Efficacy Evaluable (EFF) Population – an *a priori*-defined subgroup consisting of all randomized patients who: a) took double-blind study medication for at least 7 days; b) returned for at least 1 post-Baseline visit; c) did not have a positive urine test for a drug of abuse at any time after randomization; and d) were at least 75% compliant with the treatment regimen for the duration of participation in the Treatment Phase;
- Motivated ITT Population – all patients in the ITT population who had a treatment goal of complete abstinence; and
- Motivated EFF Population – all patients in the EFF population who had a treatment goal of complete abstinence.

4.4.5.3 Patient Disposition

In the US 96.1 study, a total of 601 patients (258, 83, and 260 in the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups, respectively) were randomized. All patients who were randomized took at least 1 dose of study medication.

Patient disposition and efficacy analysis populations are summarized separately in Tables 60 and 61, respectively.

Of the 601 patients who were randomized, 258 patients were randomized to the acamprosate 1998/2000 mg/day group, 83 patients to the acamprosate 3000 mg/day group, and 260 patients to the placebo group. Overall, a total of 292 patients (49%) completed the Treatment Phase. A lower percentage of patients completed the Treatment Phase in the acamprosate 1998/2000 mg/day group (41%) compared to the acamprosate 3000 mg/day (52%) and placebo (55%) groups. This difference seemed to be associated with a higher percentage of patients in the acamprosate 1998/2000 mg/day group terminating prematurely for “Lost to Follow-up” (18% in the acamprosate 1998/2000 mg/day group, compared to 12% in the acamprosate 3000 mg/day group and 13% in the placebo group) and “Other” (30% in the acamprosate 1998/2000 mg/day group, compared to 28% in the acamprosate 3000 mg/day group and 23% in the placebo group). “Patient decision” was the predominant reason for discontinuation within the “Other” category. The 3 groups had identical percentages of patients terminating early for the reason of “Treatment Failure” (5% of patients in each treatment group) and similar percentages for the reasons of “Adverse Event” and “Protocol Violation”.

No deaths occurred during the Treatment Phase.

Table 60. 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: NDA Table 8.7.3.1.1				

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

The ITT Population was comprised of 592 patients (99% of those randomized) and the EFF Population included 431 patients (72% of those randomized). Of the 592 patients in the ITT Population, 241 patients (40% of those randomized) had a treatment goal of total abstinence at Baseline and were part of the Motivated ITT Population. The Motivated EFF Population was comprised of 172 patients (29% of those randomized).

Table 61. Populations Studied – US Short-Term Supportive Efficacy Study

Parameter	Statistic	ACAMP 1998/2000 mg/day	ACAMP 3000 mg/day	Placebo
Number of patients Randomized (n=601)	N	258	83	260
Number of patients in the Safety Population (n=601)	n (%)	258 (100%)	83 (100%)	260 (100%)
Number of patients in the Intent-to-Treat Population (n=592)	n (%)	253 (98%)	82 (99%)	257 (99%)
Number of patients in the Efficacy Evaluable Population (n=431)	n (%)	177 (69%)	56 (67%)	198 (76%)
Number of patients in the Motivated ITT Population (n=241)	n (%)	100 (39%)	26 (31%)	115 (44%)
Number of patients in the Motivated Efficacy Evaluable Population (n=172)	n (%)	71 (28%)	15 (18%)	86 (33%)
Data Source: NDA Table 8.7.3.1.1				

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

4.4.5.4 Demographic and Baseline Characteristics

A summary of key demographic and Baseline characteristics is presented in Table 62.

Overall, among patients in the ITT population, the mean age was 44 years (mean age 43.6 to 44.9 across treatment groups), 68% were male (65% to 72% across treatment groups), the mean body weight was 80 kg (78.9 to 80.9 across treatment groups). Eighty-six percent of the patients were white. Nearly half of the patients were married and more than 66% were employed. Ten percent of patients (7% to 12% across treatment group) had undergone detoxification prior to Baseline and 50% were abstinent at Baseline. The mean (median) duration of alcohol dependence was 13 (10) years and the mean (median) number of standard drinks (12 g of pure alcohol per standard drink) consumed per day was 8 (7). Importantly, 80% of patients had a history of polysubstance use and only 41% had a treatment goal of total abstinence. In general, demographic and Baseline characteristics were similar across the groups.

The overall age range was 21 to 72 and 11% of patients were age 60 or above. For the ITT Population, the mean age was 44.9 years in the acamprosate 1998/2000 mg/day group, 43.6 years in the acamprosate 3000 mg/day group, and 44.4 years in the placebo group. The groups had a similar percentage of men and women with approximately twice as many men as women in each of the 3 groups (70% in the acamprosate 1998/2000 mg/day group, 72% in the acamprosate 3000 mg/day group, and 65% males in the placebo group.). The racial composition of the groups was reasonably reflective of the general US population, with approximately 86% of patients categorized as “white” in each group and approximately 10% categorized as “black” in the 2 acamprosate groups and 7% in the placebo group. The mean weight and height were similar among groups.

There was a statistically significant difference in employment status among the acamprosate groups and the placebo group (p-value=0.014) with a lower employment rate for the acamprosate 1998/2000 mg/day group (66%) compared to the acamprosate 3000 mg/day group (77%) and the placebo group (73%).

For the ITT Population, 46% of patients in the acamprosate 1998/2000 mg/day group and 41% of patients in the acamprosate 3000 mg/day group were married, compared to 52%

of the placebo group. In the acamprosate 1998/2000 mg/day group, 21% of the patients lived alone, compared to 18% in the acamprosate 3000 mg/day group and 17% in the placebo group.

There were no other statistically significant treatment group differences with respect to demographic characteristics.

The Baseline characteristics of the EFF, Motivated ITT, and Motivated EFF populations were similar to those of the ITT population.

Table 62. Demographic Characteristics at Baseline – US Short-Term Supportive Efficacy Study – ITT Population

Characteristic	Statistic	ACAMP 1998/2000 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: NDA Table 8.7.3.2.1, Table 8.7.3.3.1

Note: Percentages are based on the number of patients in the ITT population with an assessment.

For the ITT Population, the proportion of patients who had undergone alcohol detoxification prior to randomization and the overall proportion of patients who were abstinent prior to starting study medication was low. The percentage of patients who had detoxification prior to randomization was 12% in the acamprosate 1998/2000 mg/day group, 7% in the acamprosate 3000 mg/day group, and 10% in the placebo group. In contrast to the European studies, only about 50% of the patients in all 3 groups were abstinent at Baseline. In addition, only 40%, 32%, and 45% of patients in the acamprosate 1998/2000, acamprosate 3000 and placebo groups, respectively, had a treatment goal of total abstinence.

The median duration of alcohol dependence/abuse was slightly longer in the acamprosate 1998/2000 mg/day group (11 years versus 10 years for the acamprosate 3000 mg/day group and the placebo groups). The percentage of patients with a history of at least 1 prior treatment and/or detoxes for alcoholism was slightly higher in the acamprosate 1998/2000 mg/day group (32%) compared to the acamprosate 3000 mg/day group (28%) and the placebo group (25%). A similar percentage of patients among the 3 groups had a family history of alcohol problems (39% to 42% across treatment groups). The median average number of standard drinks (12 g of pure alcohol per standard drink) per day at study entry was slightly higher in the acamprosate 1998/2000 mg/day group (8.6 drinks/day), compared to the acamprosate 3000 mg/day group and placebo groups (8.2 drinks/day). As evidenced by mean CGI-severity values of 4.4 to 4.6 (possible range from 1 = “not dependent” to 7 = “extremely severe”), the severity of the disease was “moderate” to “severe” among patients in the ITT population. Other characteristics of the disease (e.g., Alcohol Dependence Severity, polysubstance use, and illicit drug index) were similar across treatment groups, as well. Patients in the acamprosate 2000 mg 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.

Compared to the ITT population, patients in the Motivated ITT population and Motivated EFF populations had longer durations of alcohol dependence. Median values for duration of alcohol dependence ranged from 10-11 years across groups in the ITT population, from 12-13 years in the Motivated ITT population, and from 11-14 years in the Motivated EFF population. In addition, the number of standard drinks tended to be higher in the Motivated populations compared to the ITT population. Mean (median) values for the number of standard drinks ranged from 7.6 (7) to 8.6 (8) in the ITT population, from 9.2 (8) to 9.9 (10) in the Motivated ITT population, and 8.0 (7) to 9.4 (8) in the Motivated EFF populations. These results suggest that patients with more severe disease (longer history of disease and drank more per day) had a greater motivation to abstain completely from alcohol use. By definition, all patients in the Motivated ITT and Motivated EFF populations had total abstinence as a treatment goal. Other demographic and Baseline characteristics were similar between the ITT and Motivated populations.

4.4.5.5 Medication Exposure

Among patients in the ITT population, the mean (median) treatment duration was shorter in the acamprosate 1998/2000 mg/day group than in the acamprosate 3000 mg/day and placebo groups (16^[17] weeks, 17^[23] weeks and 18^[24] weeks, respectively). Dosing compliance was generally high across the 3 groups (mean values between 89% and 93%). Treatment duration and dosing compliance were similar in the EFF, Motivated ITT, and Motivated EFF populations compared to the ITT population, although by definition, all patients in the EFF and Motivated EFF populations had compliance of at least 75%.

A summary of treatment exposure is presented in Table 63 for the ITT population. Because of the higher rate of early termination in the acamprosate 1998/2000 mg/day group, patients in this group had a shorter mean treatment duration than patients in the acamprosate 3000 mg/day and the placebo groups. The mean (median) treatment durations were 15.97 (17) weeks in the acamprosate 1998/2000 mg/day group, 17.05 (23) weeks in the acamprosate 3000 mg/day group, and 17.98 (24) weeks in the placebo group.

For the ITT Population, the mean (median) percent medication compliance was 89.0% (94%) for the acamprosate 1998/2000 mg/day group, 88.5% (96%) for the acamprosate 3000 mg group, and 92.6% (92%) for the placebo group. Medication compliance was, due to the population definition, a bit higher in the EFF Population and Motivated EFF Population versus the ITT Population. Mean and median values of medication compliance were similar across treatments for the EFF, Motivated ITT, and Motivated EFF populations.

Table 63. 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: NDA Table 8.7.3.4.1.				

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.

4.4.5.6 Primary Efficacy Parameters

In all 4 analysis populations, mean values for CCAD were slightly larger in the acamprosate 1998/2000 mg/day group compared to the placebo group. In the ITT population, mean (median) values for CCAD were 56.1% (59%), 60.7% (63%), and 54.3% (59%), for the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups, respectively. The relative treatment difference between the acamprosate 1998/2000 mg/day and placebo groups was largest in the Motivated ITT and Motivated EFF populations (effect sizes of 21.9% and 27.5%, respectively). These results indicate that the greatest treatment benefit was realized in patients who had a treatment goal of abstinence and, to a greater extent, in patients who were committed to the treatment by virtue of a treatment goal of complete abstinence and their ability to adhere to the treatment regimen. CCAD was statistically significantly greater in the acamprosate 1998/2000 mg/day group compared to the placebo groups in all 4 analysis populations after adjusting for Baseline covariates and treatment exposure.

The primary efficacy parameter CCAD (*referred to as CAD in the US Study 96.1 study report*) is summarized descriptively (means and medians) and presented in Table 64 for all 4 efficacy analysis populations. In this table, an effect size was calculated as the difference in medians between the acamprosate 1998/2000 mg/day and placebo groups relative to the median value in the placebo group. Results of statistical testing of CCAD and model-adjusted (least-squares) means are presented in Table 65.

Table 64. Corrected Cumulative Abstinence Duration (CCAD) (%) and Effect Size – US Short-Term Supportive Efficacy Study – All Efficacy Populations

Population	Statistic	ACAMP 1998/2000 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: NDA Table 8.7.3.5.1				

Note: Effect size = {[median (ACAMP 1998/2000 mg/day) – median (placebo)] / median (placebo)} * 100.

Means (and medians) for CCAD for the ITT Population were 56.1% (59%), 60.7% (63%), and 54.3% (59%), respectively, for the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups.

Means for CCAD were higher in all 3 treatment groups for the Motivated ITT Population compared to the ITT Population: means (medians) for CCAD for the Motivated ITT Population were 66.1% (78%), 75.0% (92%), and 60.7% (64%), respectively, for the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups.

Means (medians) for CCAD for the EFF Population were similar to means for the ITT Population (59.5% [65%], 61.2% [65%], and 56.4% [60%], respectively, for the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups).

The relative treatment differences between the acamprosate 1998/2000 mg/day and placebo groups were largest among patients in the Motivated ITT and Motivated EFF populations (effect sizes of 22%, and 28%, respectively), indicative of greater treatment benefit among patients who had a treatment goal of complete abstinence and were able to adhere to the treatment regimen. The largest treatment effect among all populations was observed for the Motivated EFF Population, for which means (medians) of 70.2% (88%),

79.6% (93%), and 62.7% (69%) were observed in the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups, respectively.

Table 65. Corrected Cumulative Abstinence Duration (CCAD) (%). Treatment Group Comparisons and Adjusted Means – US Short-Term Supportive Efficacy Study – All Efficacy Populations

Population	Statistic	ACAMP 1998/2000 mg/ day	Placebo	P-Value
Intent-to-Treat	n	253	256	
	LSMean (1)	58.2	52.3	0.044*
	LSMean (2)	56.8	53.4	0.296
Efficacy Evaluable	n	177	198	
	LSMean (1)	62.3	54.8	0.023*
	LSMean (2)	60.6	55.8	0.157
Motivated Intent-to-Treat	n	100	115	
	LSMean (1)	70.0	58.1	0.021*
	LSMean (2)	68.3	59.0	0.100
Motivated Efficacy Evaluable	n	71	86	
	LSMean (1)	75.5	59.4	0.008**
	LSMean (2)	73.0	61.3	0.068
Data Source: NDA Table 8.7.3.5.1, US study report Tables 5.1.1 and 5.1.3 in NDA.				

* Significant at the 0.050 level; ** significant at the 0.010 level.

Note: LSMean (1) was obtained from an ANCOVA model including effects for treatment exposure, pooled site, Baseline CGI-severity, stage of readiness to change, psychological antecedent, addiction index, and goal of abstinence. LSMean (2) was obtained from the same model with the exclusion of treatment exposure. P-values from both models were based on a rank ANCOVA with the specified effects.

For the purposes of statistical testing of CCAD, models were fit via ANCOVA^[42] to ranked data because of the nonnormal distribution of CCAD. All reported p-values are from analyses of the ranked response values. CCAD was statistically significantly greater ($p \leq 0.044$) in the acamprosate 1998/2000 mg/day group compared to the placebo groups in all 4 analysis populations after adjusting for Baseline covariates (pooled site, Baseline CGI-severity, stage of readiness to change, psychological antecedent, addiction index, and goal of abstinence) and treatment exposure (defined as study drug compliance multiplied by treatment duration divided by 100). In a second model which excluded treatment exposure, the difference between the acamprosate 1998/2000 mg/day and placebo groups approached statistical significance for the Motivated ITT and Motivated EFF populations ($p=0.100$ and $p=0.068$, respectively). Differences between the

acamprosate 1998/2000 mg/day and placebo groups for the least-squares means from both models were greater for the Motivated ITT and Motivated EFF populations compared to the ITT and EFF populations.

4.4.5.7 Secondary Efficacy Analysis

Although abstinence was the primary outcome criterion for US and European studies, the high rate of patients drinking at the time of study entry and throughout the study made evaluation of the effects of acamprosate on key aspects of alcohol consumption relevant as secondary outcome variables for the US study population. Despite a powerful psychosocial treatment effect on drinking behavior in all 3 double-blind groups, differences in favor of acamprosate were obtained for the Motivated analysis populations across all drinking parameters, after adjusting for Baseline covariates and treatment exposure. These findings support an overall favorable effect of acamprosate on alcohol consumption in patients who have a drinking lapse but who are motivated to have abstinence as their treatment objective.

Categorized CCAD

CCAD values were categorized as $\leq 10\%$ (poor response), $>10\%$ and $<90\%$ (partial response), and $\geq 90\%$ (good response). “Good response” (defined as abstinence for at least 90% of the study participation period) is an appropriately modified version of complete abstinence in that it requires that patients be completely abstinent or close to completely abstinent for the entire Treatment Phase and takes into account the fact that half of the patients were not abstinent when the study started.

A summary of the number and percentage of patients with “Good Response” is presented in Table 66. In the table, an effect size has been calculated as the difference between the acamprosate 1998/2000 mg/day and placebo groups in the percentage of “Good response” relative to the placebo group.

Table 66. CCAD (%) Categorized as Good Response and Effect Size – US Short-Term Supportive Efficacy Study – All Efficacy Populations

Population	Statistic	ACAMP 1998/2000 mg/day	Placebo	Effect Size (%)	P-value
Intent-to-Treat Good Response (≥ 90)	N n (%) P-value (1) P-value (2)	253 53 (21%)	257 54 (21%)	0.0%	0.221 0.531
Efficacy Evaluable Good Response (≥ 90)	N n (%) P-value (1) P-value (2)	177 46 (26%)	198 45 (23%)	13.0%	0.032* 0.149
Motivated Intent-to-Treat Good Response (≥ 90)	N n (%) P-value (1) P-value (2)	100 35 (35%)	115 39 (34%)	2.9%	0.190 0.397
Motivated Efficacy Evaluable Good Response (≥ 90)	N n (%) P-value (1) P-value (2)	71 34 (48%)	86 31 (36%)	33.3%	0.003** 0.019*
Data Source: NDA Table 8.7.3.6.1					

* Significant at the 0.050 level; ** significant at the 0.010 level.

Note: Effect size = {[percentage of patients with good response (ACAMP 1998/2000 mg/day) – percentage of patients with good response (placebo)] / percentage of patients with good response (placebo)} * 100.

Note: P-value (1) was obtained from a logistic regression model adjusting for treatment exposure, pooled site, Baseline CGI-severity, stage of readiness to changes, psychological antecedent, addiction index, and goal of abstinence. P-value (2) was obtained from the same model with the exclusion of treatment exposure.

In the ITT and Motivated ITT populations, the percentage of good responders was similar between the acamprosate 1998/2000 mg/day and placebo groups. However, among patients in the EFF and Motivated EFF populations, the relative treatment difference (effect size) was more pronounced. In the EFF population, the percentage of good response was 26% and 23% in the acamprosate 1998/2000 mg/day and placebo groups, representing a relative increase in good response of 13%. This difference was even more pronounced in the Motivated EFF population, where the percentage of patients with a good response was 48% and 36% for the acamprosate 1998/2000 mg/day and placebo groups, respectively. This difference represents a 33% relative increase in favorable response for patients in the acamprosate 1998/2000 mg/day group.

Treatment group comparisons of this parameter (good response vs. other) were based on 2 logistic regression models^[43]: the first with effects for Baseline covariates (pooled site, Baseline CGI-severity, stage of readiness to change, psychological antecedent, addiction index, and goal of abstinence) and treatment exposure and the second including only the Baseline covariates.

The treatment group differences between the acamprosate 1998/2000 mg/day and placebo groups from both models were statistically significant in favor of acamprosate for the Motivated EFF Population.

Rate of Complete Abstinence During the Last Treatment Phase Visit Interval

Percentages of patients who were abstinent in the last Treatment Phase visit interval are presented in Table 67. The last Treatment Phase visit interval is defined as the interval between the last 2 attended visits in the Treatment Phase. In the table, an effect size was calculated as the difference between the acamprosate 1998/2000 mg/day and placebo groups in the percentage of patients who were abstinent during the last visit interval relative to the placebo group.

Table 67. Rate of Complete Abstinence During the Last Visit Interval and Effect Size – US Short-Term Supportive Efficacy Study – All Efficacy Populations

Population	Statistic	ACAMP 1998/2000 mg/ day	Placebo	Effect Size (%)
Intent-to-Treat Abstinent	n n (%)	253 51 (20%)	257 47 (18%)	11.1%
Efficacy Evaluable Abstinent	n n (%)	177 44 (25%)	198 41 (21%)	19.0%
Motivated Intent-to-Treat Abstinent	n n (%)	100 33 (33%)	115 31 (27%)	22.2%
Motivated Efficacy Evaluable Abstinent	n n (%)	71 31 (44%)	86 27 (31%)	41.9%
Data Source: NDA Table 8.7.3.7.1				

Note: Effect size = {[percentage of patients abstinent (ACAMP 1998/2000 mg/day) – percentage of patients abstinent (placebo)] / percentage of patients abstinent (placebo)} * 100.

In the ITT Population, the acamprosate groups had slightly higher percentages of patients who were abstinent in the last Treatment Phase visit interval (20% for 1998/2000 mg/day and 21% for 3000 mg/day) compared to placebo (18%). Results for the EFF Population were comparable to the results in the ITT population. In the Motivated ITT Population, a greater response rate was seen in the acamprosate 1998/2000 mg/day group, with 33% of patients abstinent compared to 27% for the placebo group. An even higher response was observed in the Motivated EFF Population with 44% of acamprosate 1998/2000 mg/day patients abstinent compared to 31% of placebo patients. This Motivated ITT population treatment difference represents approximately a 42% increase in complete abstinence during the last visit interval among patients who had a treatment goal of complete abstinence and were able to comply with the treatment regimen.

Treatment group comparisons on the rate of complete abstinence in the last Treatment Phase visit interval were made using 2 logistic regression models ^[43]. The first model (Model 1) included adjustments for Baseline covariates (pooled site, Baseline CGI-severity, stage of readiness to change, psychological antecedent, addiction index, and goal of abstinence), as well as treatment exposure. The second model (Model 2) included only Baseline covariates. The treatment group differences between the acamprosate 1998/2000 mg/day and placebo groups were not statistically significant using either model (Model 1 or Model 2) for the ITT, EFF, and Motivated ITT populations. Analyses within the Motivated EFF population demonstrated a statistically significant treatment group difference in favor of acamprosate 1998/2000 mg/day relative to placebo using Model 1, but not with Model 2.

Number of Drinks Per Week – Change from Baseline Across the Entire Treatment Phase

A substantial reduction in the number of drinks per week from Baseline consumption levels was observed for all treatment groups in all 4 populations, and most likely reflects the strong effects of the standardized psychosocial intervention as well as self-monitoring from the daily record-keeping of alcohol consumption. On average, the mean reduction in number of standard drinks per week ranged from 40 in the ITT and EFF populations to approximately 50 in the Motivated ITT and Motivated EFF populations. As with the rate of complete abstinence in the last visit interval above, statistically significant treatment

differences (in favor of acamprosate 1998/2000 mg/day over placebo) were observed in only 1 population, the Motivated ITT population.

In the ITT population, unadjusted means for change from Baseline in the number of standard drinks per week indicate a similar reduction in the mean number of standard drinks consumed per week for all 3 treatment groups: -40.5, -39.4, and -39.8 for the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups, respectively. Change from Baseline for the Motivated ITT Population in number of standard drinks per week indicated an even further reduction in drinking across all 3 groups: these unadjusted means were -49.8, -58.7, and -48.3 for the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups, respectively. In the EFF population, the unadjusted mean values for change from Baseline in the number of drinks per week were similar to those for the ITT Population. The largest decreases in the number of standard drinks per week for the acamprosate 1998/2000 mg/day and placebo groups were observed in the Motivated EFF Population, with mean decreases of 52.9 and 49.2 drinks per week, respectively. Overall, the Motivated ITT and Motivated EFF Populations showed the greatest reductions in number of standard drinks consumed per week, with the acamprosate 1998/2000 mg/day group indicating a more favorable response compared to placebo.

The same pattern was observed for the unadjusted means for change from Baseline in the number of drinks per week for all 4 populations.

As discussed above, the observed reduction in the number of drinks per week across the entire Treatment Phase for patients in all 4 populations was relatively similar across the 3 treatment groups. Treatment group differences in the change from Baseline in the number of drinks per week were tested using 2 models. The first included Baseline factors (pooled site, Baseline CGI-severity, stage of readiness to change, psychological antecedent, addiction index, and goal of abstinence) and treatment exposure. The second included only Baseline factors.

After adjusting for these Baseline covariates and treatment exposure, there was a statistically significant difference in favor of acamprosate between the acamprosate

1998/2000 mg/day and placebo groups for the Motivated ITT Population. Results of the tests for treatment differences for the model excluding treatment exposure were not as pronounced as those from the first model that included an effect for treatment exposure. However, the results were consistent with the previous primary model in that greater treatment effects were seen for the motivated and compliant patients.

Number of Drinking Days Per Week – Change from Baseline Across Entire Treatment Phase

Means for change from Baseline in the number of drinking days per week for the ITT Population indicate virtually the same reduction for all 3 groups: -2.8 drinking days per week for the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups. Change from Baseline for the Motivated ITT Population in number of drinking days per week showed an even larger reduction across all 3 groups; these means were -3.4, -4.2 and -3.2 drinking days per week for the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups, respectively. The change from Baseline means in the number of drinking days per week for the EFF Population were quite similar to those for the ITT Population. The largest decrease across all populations was observed in the Motivated EFF Population for which means of -3.8, -4.2, and -3.4, drinking days were seen in the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups, respectively.

Treatment group differences in change from Baseline in the number of drinking days per week were assessed using 2 rank ANCOVA models ^[42]: 1 with Baseline factors (as described above) and treatment exposure; and the second with only Baseline factors. There were statistically significant differences between the acamprosate 1998/2000 mg/day and placebo groups in the Motivated ITT and Motivated EFF Populations after adjusting for Baseline covariates and treatment exposure. Treatment differences adjusted only for Baseline covariates for change from Baseline across the entire Treatment Phase in number of drinking days per week were very similar to those from the primary model that included an effect for treatment exposure. These results were consistent with the primary model in that greater treatment effects of acamprosate were seen in the Motivated Populations.

Alcohol Consumption (Drinks Per Week) Relative to Baseline (%) – Average Across Entire Treatment Phase

A summary of alcohol consumption (drinks per week), averaged across the entire Treatment Phase, relative to Baseline alcohol consumption, is shown in Table 68. In this table, an effect size was calculated as the difference in medians between the acamprosate 1998/2000 mg/day and placebo groups relative to the median value in the placebo group.

Median values of the percentage of drinks consumed per week relative to Baseline were similar across treatment groups for the ITT population (26%, 24%, and 25% for the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day and placebo groups, respectively). Comparable results were seen for the EFF Population. In the Motivated ITT Population, an increased response (effect size of -22%) was observed in the acamprosate groups with median values of 14%, 9%, and 18% for the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups, respectively. An even greater response (relative difference of 50%) was observed for the Motivated EFF Population with patients in both acamprosate groups drinking only 8% (median value) of what they drank at Baseline compared to 16% for the placebo group.

Table 68. Percent of Alcoholic Drinks Consumed per Week Relative to Baseline – US Short-Term Supportive Efficacy Study –All Efficacy Populations

Population	Statistic	ACAMP 1998/2000 mg/ day	Placebo	Effect Size (%)
Intent-to-Treat	N	251	255	
Percent of Drinks Consumed per Week Relative to Baseline	Mean (SE)	35.9 (2.2)	38.0 (2.9)	
	Median	26	25	4.0%
Efficacy Evaluable	N	177	198	
Percent of Drinks Consumed per Week Relative to Baseline	Mean (SE)	32.5 (2.5)	36.0 (3.3)	
	Median	24	24	0%
Motivated Intent-to-Treat	N	98	114	
Percent of Drinks Consumed per Week Relative to Baseline	Mean (SE)	24.6 (3.2)	35.0 (5.4)	
	Median	14	18	-22.2%
Motivated Efficacy Evaluable	N	71	86	
Percent of Drinks Consumed per Week Relative to Baseline	Mean (SE)	19.5 (3.5)	31.3 (6.1)	
	Median	8	16	-50.0%
Data Source: NDA Table 8.7.3.10.1				

Note: Effect size = {[median (ACAMP 1998/2000 mg/day) – median (placebo)] / median (placebo)} * 100.

As discussed above, the reduction in the average number of drinks consumed per week across the entire Treatment Phase relative to Baseline for the Motivated Populations was greater than that observed for the ITT and EFF Populations. As with other secondary efficacy parameters, treatment group differences in the alcohol consumption relative to Baseline were assessed using 2 rank ANCOVA models ^[42]: the first with Baseline factors (as listed above) and treatment exposure; and the second including only Baseline factors. After adjusting for Baseline covariates and treatment exposure, statistically significant differences were observed in the Motivated ITT and Motivated EFF populations, associated with a more favorable response in the acamprosate 1998/2000 mg/day group compared to placebo. Treatment differences for the model including only Baseline covariates were not as pronounced as those from the previous model. Statistically significant treatment effects using this model were only observed in the Motivated EFF population.

4.4.5.8 Summary of Original Analyses

A brief summary of the originally planned analysis for US 96.1 is presented in Table 69. As shown in this table, the majority of patients in both the 2 acamprosate treatment groups as well as the placebo group relapsed to drinking (half in the first 4 days of treatment), over 75% relapsed to heavy drinking, and on average, patients were abstinent 78 days (mean abstinence from 72.3 to 83.3 days across treatment groups). There were no statistically significant treatment group differences with respect to these parameters in the ITT population.

Table 69. Summary of Originally Planned Efficacy Analyses – ITT Population – US Short-Term Supportive Efficacy Study

Parameter	Statistic	ACAMP 2000 mg/day	ACAMP 3000 mg/day	Placebo
Number of Patients Randomized	N	255	82	258
Number of Patients Who Relapsed to Drinking	n (%)	233 (92%)	74 (90%)	227 (89%)
Time to First Drink (days)	Median	4	4	4
Time to Heavy Drinking (days)	Median	14	17	12
Cumulative Abstinence Duration (CAD) (days)	N	253	82	256
	Mean (SE)	72.3 (3.7)	81.5 (7.1)	83.3 (3.9)
	Median	56	75	78
CCAD (%)	N	253	82	256
	Mean (SE)	45.5 (2.2)	49.9 (4.1)	51.2 (2.2)
	Median	38	47	53
Data Source: ACAMP/US/96.1 Final Study Report, Appendix I.10.8, Tables 5.1.1, 5.2.1, 5.3.1, 5.4.1., in NDA.				

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

In the US study, patients in the ITT population treated with acamprosate 2000 mg had slightly lower median CCAD values compared to patients treated with acamprosate 1998 mg in the 3 pivotal efficacy studies (59% vs. 67%-86%). The placebo response in median CCAD was more pronounced in the US study (59%) than in 2 of the pivotal efficacy studies (29% in Pelc II and 38% in PRAMA) and less pronounced than in the Paille study (66%).

4.4.5.9 Summary of Primary and Secondary Efficacy Parameters for the US Short-Term Supportive Efficacy Study

As discussed above, because of important differences between the US 96.1 and the 3 pivotal efficacy study populations at Baseline, meaningful direct comparisons of endpoints among all treated patients cannot be made. In the European studies, an entrance criterion was agreement to and successful completion of alcohol withdrawal, generally as inpatients and with medication, and, thus, essentially all patients had made a commitment to abstinent and, in fact, were abstinent at Baseline. In contrast, in US 96.1, only about 10% of patients had detoxification prior to randomization and that was because of physiological manifestations of alcohol withdrawal. Furthermore, only half of the US 96.1 patients were abstinent at Baseline and even fewer (about 40%) had a treatment goal of complete abstinence.

To explore the potential benefit of treatment with acamprosate 1998/2000 mg/day in the US study, that was observed in the 3 pivotal efficacy studies and most of the European Supportive efficacy studies, subsets of US 96.1 patients were examined, with the goal of identifying patients who demonstrated a commitment and motivation to a program of medical therapy and psychosocial support that could be thought of as similar to the commitment required for inpatient detoxification.

One such subset of patients was the Motivated ITT population, i.e., those patients who received at least 1 dose of study medication and had declared total abstinence as their treatment goal. Another subset of patients examined was the Motivated EFF population, i.e., those patients who had declared abstinence as a treatment goal, took study medication for at least 7 days, were at least 75% compliant with the treatment regimen, had post-Baseline efficacy data, and did not have a positive urine drug screen during the study. As described in the previous sections, a greater benefit of treatment with acamprosate 1998/2000 mg/day relative to placebo was observed in these populations compared to the ITT population. In general, the greatest treatment benefit was observed in the Motivated EFF population, i.e., among those patients whose commitment to treatment was expressed in their declared goal of abstinence and their ability to adhere to the dosing regimen.

Patients in these motivated populations who were treated with acamprosate 2000 mg had on average, relative to placebo:

- An increase in CCAD of 22% to 28%;
- An increase in the rate of good response on CCAD ($\geq 90\%$ abstinence while on study) up to 33%;
- An increase in the rate of complete abstinence during the last visit interval prior to leaving study of 22% to 42%; and
- A decrease in the percentage of standard drinks per week relative to Baseline of 22% to 50%.

These data confirm that similar benefits of treatment with acamprosate 1998 mg per day observed in the 3 pivotal efficacy studies were also observed in US patients who were

motivated to abstain from alcohol and adhere to the prescribed treatment regimen of acamprosate 2000 mg per day. There was also evidence of a dose-effect for some parameters, despite the fact that the 3000 mg per day group was “exploratory” and only one-third the size of the other comparator groups.

4.4.6 Controlled Clinical Studies. European Long-Term Supportive Efficacy Studies

4.4.6.1 Controlled European Long-Term Supportive Efficacy Studies

The controlled European Long-Term Supportive efficacy studies include the Lesch, Barrias, and Besson studies. These studies were conducted in 3 different European countries (Austria, Portugal, and Switzerland) and involved 868 randomized alcohol-dependent patients (435 to acamprosate, 433 to placebo). The results of these 3 studies with Treatment Phases of 1 year are presented as supportive evidence of the efficacy of acamprosate. Results from all 3 studies have been published in English (Lesch^[44], Barrias^[45], and Besson^[46] studies).

4.4.6.2 Study Design and Summary

Each of the 3 controlled European Long-Term supportive efficacy studies had a multicenter, randomized, double-blind, parallel-group, placebo-controlled study design. All 3 were conducted under the supervision of specialists in alcoholism and at centers specializing in such treatment and all 3 were initiated prior to 1991. Table 70 presents the details of the conduct of each study. 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 off treatment, observation period following the 12-month double-blind treatment period.

Table 70 Summary of Conduct of Study Information for the European Long-Term Supportive Studies

Study	Lesch	Barrias	Besson
Country	Austria	Portugal	Switzerland
Number of Sites	5	9	3
Study Duration (days)	360	360	360
Follow-up Duration (days)	360	180	360
Years Study Conducted	1990–1992	1990-1992	1989-1992
Data Source: European Long-Term Supportive study reports in NDA			

All studies enrolled patients that met the following criteria: age 18 to 65 years, diagnosed with chronic or episodic alcohol dependence as defined by the DSM-III Classification of the American Psychiatric Association, provided written informed consent, consented to alcohol weaning therapy, were abstinent for at least 5 days before entering the study, and had at least a 12-month history of alcohol dependence. Each study also required that the patient have a gamma GT value at least twice the upper limit of normal. The Lesch and Besson studies also had an additional criterion for selection based on MCV value (Lesch: ≥ 93 fl; Besson: ≥ 95 fl).

Patients were to be excluded from study participation if they had any of the following conditions: pregnancy, premenopausal women not practicing contraception, psychiatric disorders which might necessitate specific drug treatment, systemic disease (Lesch and Besson) or any condition incompatible with the study (Barrias), epilepsy unrelated to alcoholism, renal insufficiency, hypercalcemia of any etiology, patients with no fixed address or not living with a non-alcoholic spouse or friend, obvious lack of cooperation during withdrawal treatment (Barrias), or residence in post-treatment center (Barrias and Besson).

Eligible patients were randomized to receive either acamprosate or placebo, with the daily dosage adjusted thereafter according to the patient's weight. Patients with a body weight >60 kg were to receive 1998 mg/day of acamprosate or placebo to be taken as 2 tablets of 333 mg acamprosate (or placebo) in the morning, at mid-day, and in the evening. Patients with a body weight ≤ 60 kg were to receive 1332 mg/day of acamprosate or placebo taken as 2 tablets of 333 mg acamprosate (or placebo) in the morning and 1 tablet of 333 mg acamprosate (or placebo) at mid-day and in the evening. Study medication was to be taken during meal times. The duration of treatment in each study was 360 days. Each study had a designated observation period following the 12-month double-blind treatment period. The follow-up period was 360 days for patients in the Lesch and Besson studies and 180 days for patients in the Barrias study.

Psychosocial support was not standardized and consisted of whatever the particular center generally provided to patients with alcohol dependence.

Patients were initially assessed (Day of Selection) to determine whether they conformed with all of the inclusion and exclusion criteria including the CAGE and the MAST questionnaires^[19,20]. Provided the patient met the inclusion criteria, the patient underwent alcohol withdrawal treatment and was then reassessed, with determination of Baseline parameters for measuring efficacy and safety (Day 0). Subsequent assessments for efficacy and safety were made on Days 30, 90, 180, 270, and 360. Patients relapsing during treatment could continue or be admitted to the hospital to be weaned off alcohol while continuing their blinded study medication. Subsequently patients who had relapsed were returned to their outpatient status if their detoxification period was less than 14 days.

Table 71 presents a complete list of the primary and secondary efficacy parameters for each of the studies. The primary efficacy parameters defined in the 3 European Long-Term Supportive efficacy studies were CAD (and CCAD) and rate of complete abstinence (denoted in the study reports as relapse rate at each visit). Time to first drink is discussed in this Briefing Document as a primary efficacy parameter but was considered a secondary efficacy parameter (denoted as time to first relapse) in the study reports. Secondary efficacy parameters that will be summarized include frequency of alcohol consumption, quantity of alcohol consumption, overall clinical assessment (e.g., CGI), and alcohol craving (VAS).

Table 71 Primary and Secondary Efficacy Parameters for the European Long-Term Supportive Efficacy Studies

Parameter	Lesch	Barrias	Besson
Cumulative Abstinence Duration (CAD)	1	1	1
Corrected Cumulative Abstinence Duration (CCAD)	1	1	1
Relapse rate at each visit	1	1	1
Time to first relapse	2	2	2
Gamma GT relapse criterion	2	2	2
Compound gamma GT/relapse criterion	2	2	2
Frequency of alcohol consumed	2	2	2
Quantity of alcohol consumed	2	2	2
Physician's clinical global impression	2	2	2
Physician's treatment success rate	2	2	2
Biological Markers (Gamma GT and MCV)	3	3	3
Craving for Alcohol by Visual Analog Scale	3	3	3
Tremor Index	3	3	3
Psychological and Physical dependence	3	3	3
Psychosocial adaptation	3	3	3
Hamilton scale for depression	3	3	3
Hamilton scale for anxiety			3
Concomitant psychotherapy			
Attendance at Alcoholic Anonymous			
Data Source: European Long-Term Supportive Efficacy study reports in NDA.			

Note: 1= primary efficacy parameter; 2 = secondary efficacy parameter; 3 = other efficacy parameter.

Each of the controlled European Long-Term Supportive efficacy studies followed the same ITT principle. Any randomized patient who had taken at least 1 dose of study medication was eligible for analysis. All patients who terminated study participation prior to the end of the Treatment Phase were assumed to be treatment failures. This approach of assessing outcome criteria was implemented to avoid bias potentially introduced by analysis of solely the on-treatment population. For the purpose of analyses and presentation of the data, the patients randomized to receive acamprosate are referred to collectively as the "acamprosate group".

4.4.6.3 Patient Disposition

A summary of patient disposition across the 3 controlled European Long-Term Supportive efficacy studies is presented in Table 72.

Across the 3 European Long-Term Supportive studies, a total of 435 patients were randomized to receive acamprosate (either 1332 mg/day or 1998 mg/day) and 433 were

randomized to receive placebo. All but 8 of the randomized patients were included in the ITT population. The percentage of patients completing the Treatment Phase was similar for patients treated with acamprosate (46%) or placebo (43%). The percentage of patients discontinuing for each reason was similar for patients in acamprosate and placebo groups. The most common reasons for discontinuation during the double-blind Treatment Phase in order of frequency were "Other", "Treatment failure", and "Lost to follow-up".

Table 72. Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Studies Combined

	Statistic	ACAMP (N=435)	Placebo (N=433)
Number of Patients Randomized	n (%)	435 (100%)	433 (100%)
Number of Patients in the ITT Population	n (%)	429 (99%)	431 (>99%)
Number of Patients Who Completed Treatment Phase	n (%)	199 (46%)	187 (43%)
Number of Patients Who Discontinued Treatment Phase	n (%)	236 (54%)	246 (57%)
Reasons for Discontinuation:	n	236	246
Adverse Event	n (%)	24 (6%)	21 (5%)
Lost to Follow-up	n (%)	55 (13%)	58 (13%)
Treatment Failure	n (%)	69 (16%)	72 (17%)
Death	n (%)	4 (1%)	3 (1%)
Protocol Violation	n (%)	7 (2%)	5 (1%)
Other	n (%)	77 (18%)	87 (20%)
Data Source: NDA Table 8.7.4.1.1, Table 8.7.4.1.2, and Table 8.7.4.1.3			

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

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

Lesch

Patient disposition during the double-blind Treatment Phase is presented in Table 73. A total of 448 patients were randomized into the Lesch study; 224 patients each were randomized to the acamprosate and placebo groups. All randomized patients were included in the ITT population. Slightly more patients in the acamprosate group (94 patients, 42%) completed the double-blind Treatment Phase than in the placebo group (85 patients, 38%). The reasons for discontinuation were similar between the 2 treatment groups.

Table 73. Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Study Lesch

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

Data Source: NDA Table 8.7.4.1.1

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

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

Of the 179 patients that completed the double-blind Treatment Phase and entered the follow-up observation phase, 148 (33%) patients completed the entire study (data from study report). The main reasons for withdrawal across the entire study were “Treatment failure”, “Lost to follow-up”, and "Other", which included “refusal to continue” and “non-compliance”.

Barrias

Patient disposition during the double-blind Treatment Phase is presented in Table 74. A total of 302 patients were randomized into the study and included in the ITT Population. The number of patients who completed the double-blind Treatment Phase was similar between treatment groups (acamprosate, 86 [57%]; placebo, 83 patients [55%]). The reasons for discontinuation were similar between treatment groups except for discontinuation due to “Adverse event” and discontinuation due to a reason of “Other” (e.g., “refusal to continue” and “non-compliance”). A higher percentage of patients withdrew due to “Adverse event” in the acamprosate group (6%) than in the placebo group (3%). More patients in the placebo group withdrew for a reason of “Other” (31%) than patients in the acamprosate group (25%). Most of the discontinuations (>67%) from the study occurred during the first 180 days of treatment.

Table 74. Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Study Barrias

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

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

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

One hundred and sixty-nine patients completed the double-blind Treatment Phase and entered the 180-day follow-up observation period. Of these patients, 142 (84%) completed the observation phase. Over the entire study, the most common reasons for withdrawal were “Treatment failure”, “Lost to follow-up”, and “Other”.

Besson

Patient disposition during the double-blind Treatment Phase is presented in Table 75. A total of 118 patients were randomized into the Besson study. Eight patients were excluded from the ITT Population; 4 patients did not take the study medication and 4 patients did not meet the abstinence entry criteria. The ITT population was comprised of 55 patients randomized to each of the acamprosate and placebo groups. Nineteen patients in each group completed the double-blind Treatment Phase (31% for acamprosate, 33% for placebo group). The reasons for discontinuation were similar between the groups except for the discontinuations due to “Treatment failure” and “Other”. A lower percentage of patients in the acamprosate group (28%) reported the reason for discontinuation as “Treatment failure” than acamprosate patients (35%). Conversely, more patients in the acamprosate group (15%) reported reason for discontinuation due to “Other” than patients in the placebo group (9%). Most of the patients (>50%) who discontinued from the study withdrew in the first 90 days of treatment.

Table 75. Patient Disposition During Treatment Phase – European Long-Term Supportive Efficacy Study Besson

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

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

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

At the conclusion of the double-blind Treatment Phase, 38 patients entered the 360-day follow-up observation period. Of these 38 patients, 18 patients (10 in the acamprosate group [18%]; 8 in the placebo group [15%]) completed the entire study.

Summary of Patient Disposition

In summary, a total of 435 patients were treated with acamprosate and 433 were treated with placebo across the 3 European Long-Term Supportive studies. Within each study, the comparisons of the acamprosate and placebo groups were very similar. The ITT population was comprised of 99% of the patients randomized across all treatment groups. A higher percentage of patients completed the Barrias study (56%) than the Lesch (40%) and Besson (35%) studies. Similar to the 3 pivotal efficacy studies, the most common reasons for discontinuation among the 3 European Long-Term Supportive efficacy studies were “Other”, lost to follow-up, and treatment failure.

4.4.6.4 Demographic and Baseline Characteristics

Demographic characteristics of gender, age, weight, and key Baseline characteristics of alcohol history are presented in Tables 76-78.

Within each study, the demographic characteristics and alcohol history at Baseline were similar between the 2 treatment groups. Overall, 84% of patients were male and the mean age was 42 years. On study entry, 64% of patients in the Lesch and Barrias studies drank more than 10 standard drinks per day (12 g of pure alcohol per standard drink). Standard drink information was not available for the Besson study. All patients in the European Long-Term Supportive efficacy studies were abstinent prior to the initiation of study medication (Baseline) and had undergone detoxification prior to entering the study.

Lesch

Table 76 summarizes key demographic and Baseline characteristics for the Lesch study. Most patients in the Lesch study were male and between 40 and 59 years of age. There was a higher percentage of female patients in the acamprosate group (25%) compared to the placebo group (17%). The percentage of married patients was higher in the placebo group (56%) than in the acamprosate group (48%). Otherwise, the demographic characteristics were similar between the treatment groups. No differences were observed between the acamprosate and placebo groups with regard to history of alcohol use at Baseline. Most patients (63% in each treatment group) consumed >10 standard drinks

per day at study entry. All patients had detoxification prior to randomization and were abstinent prior to the initiation of study medication.

Table 76. Demographic and Baseline Characteristics – European Long-Term Supportive Efficacy Study Lesch

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

NA = Not Available

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

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

Barrias

Table 77 summarizes key demographic and Baseline characteristics for the Barrias study. The treatment groups were well-matched with respect to all demographic characteristics. The vast majority of patients in this study were male (92%). The mean age of patients in this study was 39.6 years for the acamprosate group and 41.0 years for the placebo group, which was slightly lower than the mean age of the patients in the other 2 studies. The mean weight for both treatment groups (67.2 kg for the acamprosate group and 66.6 kg for the placebo group) for the Barrias study was also lower than the mean weight for the Lesch and Besson studies.

The treatment groups were similar in the Baseline history of alcohol use. At study entry, 65% of patients consumed an average of >10 standard drinks per day. All randomized patients had detoxification prior to randomization and were abstinent at Baseline.

Table 77. Demographic and Baseline Characteristics – European Long-Term Supportive Efficacy Study Barrias

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

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

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

Besson

Table 78 summarizes key demographic and Baseline characteristics for the Besson study. The majority of patients in this study were male (80%). The mean age of patients in this study was 42 years. At study entry, the mean duration of alcohol dependence/abuse for patients in the acamprosate group was 13.5 years compared to 12.0 years for patients in the placebo group.

Some patients in the Besson study also elected to receive concomitant disulfiram treatment. Patients who received concomitant disulfiram had a higher mean score for the MAST rating of alcoholism severity (34.09 vs. 29.79), exhibited greater psychological dependence (28% vs. 14% with severe dependence), had a greater craving for alcohol

(VAS means of 48.35 vs. 33.35), and had a documented longer history of chronic alcoholism (means of 16.62 years vs. 13.79 years) compared to patients who did not receive the concomitant disulfiram treatment. Over the course of the study, 24 patients in the acamprosate group and 22 patients in the placebo group received concomitant disulfiram. Since a similar proportion of patients in each treatment group received the concomitant treatments, it is unlikely that the inclusion of the disulfiram patients had an effect on the results of the study.

Table 78. Demographic and Baseline Characteristics – European Long-Term Supportive Efficacy Study Besson

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

NA = Not Available

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

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

Summary of Demographic Features

Over all studies, there were no major imbalances between the treatment groups for demographic and history of alcohol use at Baseline. The majority of patients in the ITT population were male. The mean age across the studies ranged from 39.6 to 42.7 years for the acamprosate group and 41.0 to 42.5 years for the placebo group. The Barrias study had a higher percentage of patients in the 16-39 years category compared to the other studies and had the fewest female patients (<10%). All patients in the European Long-Term Supportive efficacy studies were abstinent prior to the initiation of study medication (Baseline) and had undergone detoxification prior to entering the study.

4.4.6.5 Drug Exposure

Drug exposure and study medication compliance for the European Long-Term Supportive efficacy studies is presented separately for each study in Tables 79-81. The duration of exposure is calculated as the difference between the last date of study medication and first date of study medication. Exposure is summarized as a continuous parameter and by duration categories of 0 to <4 weeks, 4 to <8 weeks, 8 to <13 weeks, 13 to <26 weeks, 26 to <39 weeks, 39 to <52 weeks, and ≥ 52 weeks. Study medication compliance and the percentage of patients who were $\geq 75\%$ compliant are also summarized. Statistical tests to compare treatment group differences were not performed.

In the Lesch and Barrias studies, the mean duration of exposure was slightly longer for the acamprosate group (28.0 weeks and 38.8 weeks, respectively) than in the placebo group (26.2 weeks and 37.5 weeks, respectively). In the Besson study, the average duration of exposure was the same (27.7 weeks) for the 2 treatment groups.

Lesch

As presented in Table 79, the mean duration of exposure for the Lesch study was 28.0 weeks for the acamprosate group and 26.2 weeks for the placebo group. Ninety-four patients (42%) in the acamprosate group and 85 patients (38%) in the placebo group were exposed to study medication for a period of 39 weeks to <52 weeks. The mean compliance was 92% for both treatment groups.

Table 79. Exposure and Compliance to Study Medication – European Long-Term Supportive Efficacy Study Lesch

Parameter	Statistic	ACAMP (N=224)	Placebo (N=224)
Duration of Exposure	n Mean (SE) Median Min., Max.	224 28.0 (1.4) 26 0, 51	224 26.2 (1.5) 24 0, 51
Exposure by Duration Category (weeks)	n	224	224
0 - <4	n (%)	29 (13%)	37 (17%)
4 - <8	n (%)	38 (17%)	41 (18%)
8 - <13	n (%)	38 (17%)	31 (14%)
13 - <26	n (%)	14 (6%)	15 (7%)
26 - <39	n (%)	11 (5%)	15 (7%)
39 - <52	n (%)	94 (42%)	85 (38%)
Compliance (%)	n Mean (SE) Median Min., Max.	164 92.0 (1.9) 98 0, 150	153 92.2 (1.8) 98 0, 150
Number of Patients Who Were ≥75% Compliant	n (%)	145 (88%)	132 (86%)
Data Source: NDA Table 8.7.4.4.1			

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

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

Barrias

Exposure and compliance to study medication for the Barrias study is summarized in Table 80. The mean duration of exposure for the acamprosate group (38.8 weeks) was slightly longer than the mean duration of exposure for the placebo group (37.5 weeks). However, 50% of the patients in each treatment group had duration of exposure of at least 51 weeks (medians=51). The mean compliance was 94.4% for the acamprosate group and 92.8% for the placebo group.

Table 80. Exposure and Compliance to Study Medication – European Long-Term Supportive Efficacy Study Barrias

Parameter	Statistic	ACAMP (N=150)	Placebo (N=152)
Duration of Exposure	n Mean (SE) Median Min., Max.	150 38.8 (1.4) 51 0, 51	152 37.5 (1.4) 51 0, 51
Exposure by Duration Category (weeks)	n n (%) n (%) n (%) n (%) n (%) n (%)	150 3 (2%) 6 (4%) 16 (11%) 21 (14%) 9 (6%) 95 (63%)	152 2 (1%) 14 (9%) 13 (9%) 21 (14%) 13 (9%) 89 (59%)
Compliance (%)	n Mean (SE) Median Min., Max.	147 94.4 (1.5) 95 47, 150	143 92.8 (1.8) 94 4, 145
Number of Patients Who Were ≥75% Compliant	n (%)	129 (88%)	124 (87%)
Data Source: NDA Table 8.7.4.4.2			

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

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

Besson

Table 81 presents exposure and compliance to study medication for the Besson study. The mean duration of exposure was 27.7 weeks for both the acamprosate and placebo groups, with 50% of patients receiving at least 24 and 27 weeks of treatment, respectively. Mean compliance was 86.8% and 90.2% for the acamprosate and placebo groups, respectively.

Table 81. Exposure and Compliance to Study Medication – European Long-Term Supportive Efficacy Study Besson

Parameter	Statistic	ACAMP (N=55)	Placebo (N=55)
Duration of Exposure	n	55	55
	Mean (SE)	27.7 (2.8)	27.7 (2.9)
	Median	24	27
	Min., Max.	0, 57	0, 68
Exposure by Duration Category (weeks)	n	55	55
0 - <4	n (%)	5 (9%)	7 (13%)
4 - <8	n (%)	10 (18%)	11 (20%)
8 - <13	n (%)	1 (2%)	3 (5%)
13 - <26	n (%)	13 (24%)	4 (7%)
26 - <39	n (%)	4 (7%)	8 (15%)
39 - <52	n (%)	10 (18%)	9 (16%)
≥52	n (%)	12 (22%)	13 (24%)
Compliance (%)	n	33	31
	Mean (SE)	86.8 (3.5)	90.2 (4.1)
	Median	92	94
	Min., Max.	31, 123	40, 179
Number of Patients Who Were ≥75% Compliant	n (%)	27 (82%)	25 (81%)
Data Source: NDA Table 8.7.4.4.3			

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

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

4.4.6.6 Primary Efficacy Parameters

Results of the analyses of the primary efficacy parameters CCAD, time to first drink or relapse, and rate of complete abstinence for the European Long-Term Supportive studies are presented for the ITT population of each study separately. Available results are summarized for both the double-blind Treatment Phase and the entire study phase (as appropriate) A summary of the results for all 3 studies is presented in Table 82.

4.4.6.6.1 *Corrected Cumulative Abstinence Duration*

Cumulative abstinence duration was defined as the total number of abstinent days, calculated as the sum of only those periods of complete abstinence. To be conservative, if any relapse was recorded at a specific visit, the total period from the previous visit was considered as relapse. Corrected cumulative abstinence duration was an expression of CAD as a fraction of the potential duration of treatment:

$$\text{CCAD} = \frac{\text{Total number of days of abstinence} \times 100}{\text{Total potential duration of exposure to treatment}}$$

Treatment group differences in mean CCAD were assessed using a Student's t-test.^[37] The square-root of CCAD was applied to transform the data into an approximate normal distribution for purposes of statistical testing for the Lesch study due to heterogeneity of variances. No transformations were applied to the CCAD data in the Barrias and Besson studies.

Results of the CCAD analyses for each of the 3 European Long-Term Supportive efficacy studies showed that treatment with acamprosate led to statistically significant longer periods of abstinence than treatment with placebo. Patients treated with acamprosate remained abstinent 39% to 49% (across studies) of the time compared to 21% to 36% of the time for patients treated with placebo. Table 82 presents CAD and CCAD results from the double-blind Treatment Phase for the 3 studies.

Table 82. CAD and CCAD – During the Double-Blind Treatment Phase – European Long-Term Supportive Efficacy Studies Lesch, Barrias, and Besson

Study	Statistic	CAD (days)		CCAD (%)	
		ACAMP (N = 435)	Placebo (N = 433)	ACAMP (N = 435)	Placebo (N = 433)
Lesch	Mean (SD) p-value	138.79 (137.53) 0.012*	103.79 (118.95)	39 (38) 0.021*	30 (34)
Barrias	Mean (SD) p-value	175.30 (150.81) 0.005**	128.50 (136.19)	49 (42) 0.005**	36 (38)
Besson	Mean (SD) p-value	136.91 (147.51) 0.013*	74.73 (107.99)	40 (41) 0.008**	21 (30)
Data Source: Lesch Study Report, Table 8; Barrias Study Report, Table 6; and Besson Study Report, Table 7 in NDA.					

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-values for CAD and CCAD were based on a t-test on transformed values.

Lesch

Mean CCAD values indicated that patients in the acamprosate group had a statistically significant ($p=0.021$) longer duration of abstinence (39% of the time) compared to patients taking placebo (30% of the time) during the double-blind Treatment Phase. The mean CAD value for the acamprosate group was 138.8 days and 103.8 days for the placebo group ($p=0.012$).

Mean (SD) CAD values for the entire study period (1 year Treatment Phase plus 1 year follow-up phase) were 230.76 (259.10) days for the acamprosate group and 182.95 (235.24) days for the placebo group. This difference was statistically significant ($p=0.039$). Mean CCAD values across the entire study were higher for patients treated with acamprosate compared to patients treated with placebo (33% vs. 27%). However, the difference was not statistically significant.

Barrias

The mean CCAD value for the acamprosate value during the treatment period was 49% compared to 36% for the placebo group. The results of the t-test showed a statistically significantly longer period of abstinence for the acamprosate group versus the placebo

group ($p=0.005$). The mean CAD value was 175.30 days for patients treated with acamprosate and 128.50 days for patients treated with placebo ($p=0.005$).

The CAD and CCAD over the entire study period (including the 6-month follow-up) were statistically significantly longer ($p=0.020$) in favor of the acamprosate group compared to the placebo group. Patients taking acamprosate over the entire study phase remained abstinent 43% of the time compared to 32% of the time for the placebo group. CAD in the acamprosate group was significantly longer ($p=0.025$) for the acamprosate group (225.10 days) compared to the placebo group (172.71 days).

Besson

Patients treated with acamprosate had statistically higher mean CCAD values ($p=0.008$) compared to patients treated with placebo. Patients in the acamprosate group were abstinent 40% of the time and patients in the placebo group were abstinent 21% of the time. Mean CAD values were 136.91 for the acamprosate group and 74.73 days for the placebo group ($p=0.013$).

Results for CCAD and CAD during the 1-year follow-up observation period further supported the trends seen during the double-blind Treatment Phase. Patients treated with acamprosate remained abstinent 33% of the time, while placebo patients remained abstinent 27% of the time ($p=0.088$). The CAD values were statistically significant ($p=0.039$) in favor of the acamprosate group, indicating a longer period of abstinence associated with active treatment.

4.4.6.6.2 Time to First Drink

Results for the time to first drink analyses in these studies showed that acamprosate treatment was associated with a significantly ($p\leq 0.048$) longer time to first drink compared to patients receiving placebo. Time to first drink was consistently longer for the acamprosate group than the placebo group in each of the 3 studies, as evidenced by differences in the cumulative percentage of patients in abstinence ranging from 8% to 26% at Day 180 and from 11% to 20% at Day 360. Although the drop-out rate in both groups was high, patients treated with acamprosate who did complete the study were

more likely not to drink during the 360-day Treatment Phase compared to the placebo group.

The survival analysis for time to first drink or relapse is presented separately, based on the individual study reports for each European Long-Term Supportive efficacy study. Survival analysis assumptions for each study are presented where possible. Time to first drink is presented for the double-blind Treatment Phase and the entire Treatment Phase for the 3 studies. For all studies, results from each study report presented the time to first drink as the cumulative proportion of patients in continuous abstinence. Time to first drink was estimated step-wise over 30-day periods for the Lesch and Besson studies, and over 90-day periods for the Barrias study. Only patients who completed the study without relapse throughout the double-blind treatment period were considered as abstinent for the analysis. A summary of the time to first drink analyses for the 3 European Long-Term Supportive studies is provided in Table 83.

Table 83. Cumulative Percentage of Patients in Continuous Abstinence at Day 180 and Day 360 During Treatment Phase – European Long-Term Supportive Efficacy Studies Lesch, Barrias, and Besson

Study	Time Interval (Days)	ACAMP	Placebo	P-value
Lesch	Day 180	28%	20%	<0.007**
	Day 360	18%	7%	
Barrias	Day 180	44%	30%	<0.001**
	Day 360	35%	20%	
Besson	Day 180	31%	5%	0.048*
	Day 360	25%	5%	
Data Source: Table 9 (Lesch study report), Table 9 (Barrias), Table 8 (Besson study report) in NDA.				

*Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-values were obtained from a generalized Savage Mantel-Cox test.

Lesch

The median time to first drink was 55.38 days for the acamprosate group and 42.99 days for the placebo group. More patients treated with acamprosate (18.3%) were totally abstinent at Day 360 compared to patients treated with placebo (7.1%). The difference between treatment groups was statistically significant in favor of acamprosate (Mantel-Cox test ^[47] p=0.007; Tarone-Ware test ^[48] p=0.002; Breslow test ^[49] p=0.006). Table 84 presents the cumulative survival rate for both treatment groups across time intervals.

Table 84. Cumulative Proportion of Patients Continually Abstinent During Treatment Phase – European Long-Term Supportive Efficacy Study Lesch

Time Interval (Days)	ACAMP (N=224)	Placebo (N=224)	P-value
0-29	100.0%	100.0%	
30-59	69.6%	63.0%	
60-89	46.4%	33.0%	
90-119	46.4%	33.0%	
120-149	28.1%	20.1%	
150-179	28.1%	20.1%	
180-209	27.7%	20.1%	
210-239	21.0%	10.3%	
240-269	21.0%	10.3%	
270-299	21.0%	10.3%	
300-329	18.3%	7.1%	
330-360	18.3%	7.1%	0.007**
Data Source: Table 9 (Lesch study report) in NDA			

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-value is based on a generalized Savage Mantel-Cox test.

Barrias

The median survival time to first drink was 111.0 days for the acamprosate group and 54.6 days for the placebo group for the Barrias study. More patients treated with acamprosate (35%) were totally abstinent at Day 360 compared to patients treated with placebo (20%). The difference between treatment groups was statistically significant in favor of acamprosate (Mantel-Cox test ^[47] $p < 0.001$; Tarone-Ware test ^[48] $p < 0.001$; Breslow test ^[49] $p < 0.001$). Table 85 presents the cumulative survival rate for both treatment groups.

Table 85. Cumulative Proportion of Patients Continually Abstinent During Treatment Phase – European Long-Term Supportive Efficacy Study Barrias

Time Interval (Days)	ACAMP (N=150)	Placebo (N=152)	P-value
0	100%	100%	
30	81%	68%	
90	64%	46%	
180	44%	30%	
270	37%	22%	
360	35%	20%	<0.001**
Data Source: Table 9 (Barrias study report) in NDA			

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-value is based on a generalized Savage Mantel-Cox test.

Besson

The cumulative proportion of patients in the acamprosate group was statistically significantly higher (Savage Mantel-Cox test ^[47] p=0.048) than for the placebo group. The difference between the acamprosate and placebo groups in the cumulative proportion of patients in abstinence ranged between 20% to 28% at every timepoint in favor of acamprosate. More patients treated with acamprosate (25%) were totally abstinent at Day 360 compared to patients treated with placebo (5%). Table 86 presents the cumulative survival rate for both treatment groups.

Table 86. Cumulative Proportion of Patients Continually Abstinent During Treatment Phase – European Long-Term Supportive Efficacy Study Besson

Time Interval (Days)	ACAMP (N=61)	Placebo (N=57)	P-value
1-30	49%	24%	
31-60	49%	24%	
61-90	35%	7%	
91-120	35%	7%	
121-150	35%	7%	
151-180	31%	5%	
181-210	31%	5%	
211-240	31%	5%	
241-270	25%	5%	
271-300	25%	5%	
301-330	25%	5%	
331-360	25%	5%	0.048*
Data Source: Table 8 (Besson study report) in NDA			

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-value is based on a generalized Savage Mantel-Cox test.

During the follow-up observation period in each of the 3 studies, the proportion of patients who remained abstinent in the acamprosate group gradually diminished compared to the placebo group. There was no statistically significant difference in abstinence between the 2 treatment groups.

4.4.6.6.3 *Rate of Complete Abstinence*

The rate of complete abstinence was consistently higher in acamprosate-treated patients than in placebo-treated patients in all 3 studies. Across the 3 studies, the proportion of patients who remained abstinent during the 360-day treatment period ranged from 25% to 39% for the acamprosate groups and from 15% to 26% for the placebo groups, with between group differences of 9% to 13%. Statistically significant differences in rate of complete abstinence were seen in the Lesch and Barrias studies.

In the double-blind Treatment Phase of each of the 3 European Long-Term Supportive efficacy studies, patients were assessed at Days 30, 90, 180, 270, and 360. At each assessment the investigator placed each patient into 1 of 3 categories: “abstinent”, “relapsed”, or “non-attendant”. Only patients who consumed no alcohol were rated as abstinent. The rate of complete abstinence was obtained from the last treatment day (Day 360) result from these assessments. Patients were included in this analysis if they completed the study without a relapse throughout the double-blind Treatment Phase. Patients who discontinued during the double-blind Treatment Phase were considered treatment failures (relapses). The rate of complete abstinence was additionally computed with the number of patients with a non-attendant status combined with the patients considered treatment failures. Treatment group differences were tested using a chi-square test.

Table 87. Rate of Complete Abstinence During Treatment Phase – European Long-Term Supportive Efficacy Studies Lesch, Barrias, and Besson

Study	Statistic	ACAMP	Placebo	P-value (1)	P-value (2)
Lesch	%	30%	21%	0.043*	0.021*
Barrias	%	39%	26%	0.029*	0.011*
Besson	%	25%	15%	0.141	0.149
Data Source: Tables 6-7 (Lesch study report); Tables 7-8 (Barrias study report) and Tables 5-6 (Besson study report).					

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-values are from chi-square test. P-value (1) is based on 3 categories: abstinent, relapsed, and non-attendant. P-value (2) is based on 2 categories of abstinent and combined relapsed and non-attendant.

As shown in Table 87, the rate of complete abstinence was higher in the acamprosate groups than in the placebo groups in each of the European Long-Term supportive efficacy studies.

Lesch

The rate of complete abstinence in the Lesch study was 30% for the acamprosate group and 21% for the placebo group. This higher percentage of abstinent patients in the acamprosate group at Day 360 was statistically significant ($p=0.043$) compared to the placebo group. The chi-square test with the relapsed and non-attendant categories combined also was statistically significant ($p=0.021$) in favor of the acamprosate group compared to the placebo group.

During the 1-year follow-up observation phase, the difference between the acamprosate and placebo groups in duration of abstinence gradually diminished over time (29% for acamprosate vs. 23% for placebo at Day 450; 21% for acamprosate vs. 20% for placebo at Day 720). There were no statistically significant differences in the rate of abstinence between the 2 groups.

Barrias

For the Barrias study, the rate of complete abstinence was higher in the patients treated with acamprosate (39%) than for the patients treated with placebo (26%). A statistically significantly higher percentage ($p=0.029$) of acamprosate-treated patients had complete abstinence at Day 360 than placebo-treated patients. When the non-attendant patients were combined with the relapsed patients, the results for rate of complete abstinence were very similar to the first analysis, with a statistically significant treatment group effect ($p=0.011$).

During the 6-month follow-up observation phase, the difference between the acamprosate and placebo groups in rate of complete abstinence gradually diminished over time (27% for acamprosate vs. 24% for placebo at Day 450; 28% for acamprosate vs. 26% for placebo at Day 540). There were no statistically significant differences in the rate of complete abstinence between the 2 groups.

Besson

At Day 360 in the Besson study, 25% patients in the acamprosate group and 15% patients in the placebo group were rated completely abstinent. Although the percentage of abstinent patients was higher in the acamprosate group, a significant treatment effect was not detected ($p=0.141$). However, a significant treatment group difference was detected at all earlier assessments in the double-blind Treatment Phase. The treatment group difference using the combined categories was not statistically significant ($p=0.149$).

During the 1-year follow-up observation phase, the rate of complete abstinence in both the acamprosate and placebo groups gradually diminished over time (15% for acamprosate vs. 13% for placebo at Days 540 and 630; 13% for acamprosate vs. 11% for placebo at Day 720). There were no statistically significant differences in the rate of complete abstinence between the 2 groups.

4.4.6.7 Secondary Efficacy Parameters

The secondary efficacy parameters discussed in the Briefing Document for the European Long-Term Supportive efficacy studies are:

- Frequency and quantity of alcohol consumption;
- Overall clinical assessment;
- Alcohol craving (VAS);

Results of the analyses of the secondary efficacy parameters showed that patients treated with acamprosate had a statistically significant decrease in the frequency and quantity of alcohol consumed during the double-blind Treatment Phase compared to patients treated with placebo. Patients treated with acamprosate also experienced a reduction in the intensity of craving for alcohol as measured on a VAS. Overall clinical assessments by the investigators confirmed the apparent reduction in the use of alcohol reported by the patients.

For the Lesch study, analyses of frequency and quantity of alcohol consumption and alcohol craving were conducted on an “on-treatment” population which only used data

for patients who did not deviate from the protocol criteria. All other results are presented for the ITT population where applicable.

4.4.6.7.1 Frequency of Alcohol Consumption

Treatment with acamprosate was associated with a statistically significant decrease in the frequency and quantity of alcohol consumption compared to treatment with placebo.

Frequency of alcohol consumption was measured on a categorical scale. The 4 categories were: abstinence, drinking 2 times per week, not every day, and every day. These assessments were collected at Day 30, 90, 180, 270, and 360 during the European Long-Term Supportive efficacy studies. Table 88 and 89 summarize the frequency of alcohol consumption during the double-blind Treatment Phase for the Lesch and Barrias studies, respectively. Treatment group differences were assessed using a Kendall-Tau test ^[50].

In the Lesch study (Table 88), a greater proportion of patients taking acamprosate reported abstinence as measured by the frequency of alcohol consumption categories than patients taking placebo at each assessment during the double-blind Treatment Phase. By Day 360, 72.7% of the patients treated with acamprosate reported abstinence compared to 55.8% of patients treated with placebo. Treatment group differences, in favor of acamprosate, were statistically significant at all timepoints after Day 30 ($p \leq 0.026$).

Table 88 Frequency of Alcohol Consumption During Treatment Phase – European Long-Term Supportive Efficacy Study Lesch

Day/Alcohol Frequency	Statistic	ACAMP (N= 223)	Placebo (N = 224)	P-value
Day 0	n	223	224	-
Abstinence	n (%)	223 (100.0%)	224 (100.0%)	
2 Days/Week	n (%)	0	0	
Not Every Day	n (%)	0	0	
Every Day	n (%)	0	0	
Day 30	n	186	170	0.093
Abstinence	n (%)	150 (80.7%)	128 (75.3%)	
2 Days/Week	n (%)	24 (12.9%)	23 (13.5%)	
Not Every Day	n (%)	6 (3.2%)	12 (7.1%)	
Every Day	n (%)	6 (3.2%)	7 (4.1%)	
Day 90	n	150	124	0.017*
Abstinence	n (%)	109 (72.7%)	77 (62.1%)	
2 Days/Week	n (%)	24 (16.0%)	20 (16.1%)	
Not Every Day	n (%)	12 (8.0%)	19 (15.3%)	
Every Day	n (%)	5 (3.3%)	8 (6.5%)	
Day 180	n	112	100	0.003**
Abstinence	n (%)	79 (70.5%)	53 (53.0%)	
2 Days/Week	n (%)	20 (17.9%)	26 (26.0%)	
Not Every Day	n (%)	9 (8.0%)	11 (11.0%)	
Every Day	n (%)	4 (3.6%)	10 (10.0%)	
Day 270	n	100	89	0.026*
Abstinence	n (%)	68 (68.0%)	46 (51.7%)	
2 Days/Week	n (%)	12 (12.0%)	18 (20.2%)	
Not Every Day	n (%)	10 (10.0%)	18 (20.2%)	
Every Day	n (%)	10 (10.0%)	7 (7.9%)	
Day 360	n	88	77	0.008*
Abstinence	n (%)	64 (72.7%)	43 (55.8%)	
2 Days/Week	n (%)	12 (13.6%)	11 (14.3%)	
Not Every Day	n (%)	5 (5.7%)	14 (18.2%)	
Every Day	n (%)	7 (8.0%)	9 (11.7%)	
Data Source: Tables 245 - 250 (Lesch statistical report in NDA)				

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-values are based on a chi-square test.

During the follow-up phase, significant treatment group differences were also observed at Day 450 (p=0.021) and Day 540 (p=0.030). After Day 540, the number of patients who reported a frequency of “abstinence” in the acamprosate group gradually diminished compared to the placebo group.

In the Barrias study, the number of patients reported as abstinent was consistently higher in the acamprosate group compared to the placebo group. At the end of the double-blind Treatment Phase, 64% of the acamprosate group and 45% of the placebo group reported the frequency of alcohol consumption as “abstinent”. As shown in Table 89, statistically significant differences between treatment groups, in favor of acamprosate, were detected at each assessment after Day 30 for frequency of alcohol consumption. At every visit, there were consistently lower percentages of patients reporting daily drinking in the acamprosate group compared to the placebo group.

No treatment group differences in the frequency of alcohol consumption were observed during the follow-up phase.

Table 89 Frequency of Alcohol Consumption During Treatment Phase – European Long-Term Supportive Efficacy Study Barrias

Day/Alcohol Frequency	Statistic	ACAMP (N = 136)	Placebo (N = 146)	P-value
Day 0	n	136	146	-
Abstinence	n (%)	136 (100.0%)	146 (100.0%)	
2 Days/Week	n (%)	0	0	
Not Every Day	n (%)	0	0	
Every Day	n (%)	0	0	
Day 30	n	135	144	0.005**
Abstinence	n (%)	114 (84.4%)	102 (70.8%)	
2 Days/Week	n (%)	4 (3.0%)	15 (10.4%)	
Not Every Day	n (%)	10 (7.4%)	16 (11.1%)	
Every Day	n (%)	7 (5.2%)	11 (7.6%)	
Day 90	n	122	131	<0.001**
Abstinence	n (%)	92 (75.4%)	71 (54.2%)	
2 Days/Week	n (%)	9 (7.4%)	13 (9.9%)	
Not Every Day	n (%)	10 (8.2%)	22 (16.8%)	
Every Day	n (%)	11 (9.0%)	25 (19.1%)	
Day 180	n	102	111	0.029*
Abstinence	n (%)	63 (61.8%)	54 (48.7%)	
2 Days/Week	n (%)	12 (11.8%)	16 (14.4%)	
Not Every Day	n (%)	9 (8.8%)	14 (12.6%)	
Every Day	n (%)	18 (17.7%)	27 (24.3%)	
Day 270	n	88	88	0.009**
Abstinence	n (%)	57 (64.8%)	40 (45.5%)	
2 Days/Week	n (%)	9 (10.2%)	14 (15.9%)	
Not Every Day	n (%)	7 (8.0%)	13 (14.8%)	
Every Day	n (%)	15 (17.1%)	21 (23.9%)	
Day 360	n	88	84	0.007**
Abstinence	n (%)	56 (63.6%)	38 (45.2%)	
2 Days/Week	n (%)	10 (11.4%)	11 (13.1%)	
Not Every Day	n (%)	8 (9.1%)	13 (15.5%)	
Every Day	n (%)	14 (15.9%)	22 (26.2%)	
Data Source: Tables 219 - 224 (Barrias statistical report in NDA)				

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-values are based on a chi-square test.

4.4.6.7.2 Quantity of alcohol consumption

Patients in the acamprosate groups drank less alcohol, on average, compared to the patients in the placebo group during the double-blind Treatment Phase. Statistically significant differences in the quantity of alcohol consumed were detected between the acamprosate and placebo groups at each assessment after Day 30.

In the European Long-Term Supportive efficacy studies, the quantity of alcohol consumption was also measured on a categorical scale at Day 30, 90, 180, 270, and 360. The categories for quantity of alcohol consumption were defined as: abstinence, <5 drinks per day, 5-10 drinks per day, and >10 drinks per day. Quantity of alcohol consumed was not collected for the Besson study. Tables 82 and 83 present a summary of the quantity of alcohol consumed by patients during the double-blind Treatment Phase for the Lesch and Barrias studies, respectively. Treatment group differences were assessed using a Kendall-Tau test ^[50].

In the Lesch study (Table 90), patients treated with acamprosate reported lower quantities of alcohol consumption than the placebo group at each assessment. Treatment group differences were significant in favor of acamprosate at all assessments after Day 30 ($p < 0.026$). In addition, of those patients who were not abstinent at each assessment day, a greater percentage of patients in the placebo group had at least 5 drinks per day compared to the acamprosate group.

The effect of acamprosate with regard to lower alcohol consumption levels was also observed during the follow-up phase. Acamprosate-treated patients reported statistically significantly lower levels of alcohol consumption at Day 450 ($p = 0.027$) and Day 540 ($p = 0.036$) compared to placebo-treated patients.

Table 90. Quantity of Alcohol Consumption During Treatment Phase – European Long-Term Supportive Efficacy Study Lesch

Day/Alcohol Quantity (Drinks/Day)	Statistic	ACAMP (N = 223)	Placebo (N = 224)	P-value
Day 0	n	223	224	-
Abstinence	n (%)	223 (100%)	224 (100%)	
<5	n (%)	0	0	
5 – 10	n (%)	0	0	
>10	n (%)	0	0	
Day 30	n	186	170	0.101
Abstinence	n (%)	150 (80.7%)	128 (75.3%)	
<5	n (%)	22 (11.8%)	22 (12.9%)	
5 – 10	n (%)	7 (3.8%)	13 (7.7%)	
>10	n (%)	7 (3.8%)	7 (4.1%)	
Day 90	n	150	124	0.026*
Abstinence	n (%)	109 (72.7%)	77 (62.1%)	
<5	n (%)	26 (17.3%)	25 (20.2%)	
5 – 10	n (%)	6 (4.0%)	14 (11.3%)	
>10	n (%)	9 (6.0%)	8 (6.5%)	
Day 180	n	112	100	0.001**
Abstinence	n (%)	79 (70.5%)	53 (53.0%)	
<5	n (%)	19 (17.0%)	16 (16.0%)	
5 – 10	n (%)	8 (7.1%)	18 (18.0%)	
>10	n (%)	6 (5.4%)	13 (13.0%)	
Day 270	n	99	89	0.008**
Abstinence	n (%)	68 (68.7%)	46 (51.7%)	
<5	n (%)	16 (16.2%)	18 (20.2%)	
5 – 10	n (%)	9 (9.1%)	19 (21.4%)	
>10	n (%)	6 (6.1%)	6 (6.7%)	
Day 360	n	88	77	0.017*
Abstinence	n (%)	64 (72.7%)	43 (55.8%)	
<5	n (%)	12 (13.6%)	17 (22.1%)	
5 – 10	n (%)	4 (4.6%)	10 (13.0%)	
>10	n (%)	8 (9.1%)	7 (9.1%)	
Data Source: Tables 234-239 (Lesch statistical report in NDA)				

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-values are based on a chi-square test.

Table 91 summarizes the quantity of alcohol consumed during the double-blind Treatment Phase in the Barrias study. Patients treated with acamprosate consumed statistically significantly lower quantities of alcohol compared to patients treated with placebo at all assessments ($p < 0.007$) except at Day 180 ($p = 0.051$). Of patients who consumed alcohol, the acamprosate group had fewer patients who consumed at least 5 drinks compared to the placebo group.

No treatment group differences in the quantity of alcohol consumption were observed during the 6 month follow-up observation period.

Table 91. Quantity of Alcohol Consumption During Treatment Phase – European Long-Term Supportive Efficacy Study Barrias

Day/Alcohol Quantity (Drinks/Day)	Statistic	ACAMP (N = 136)	Placebo (N = 146)	P-value
Day 0	n	136	146	-
Abstinence	n (%)	136 (100%)	146 (100%)	
<5	n (%)	0	0	
5 – 10	n (%)	0	0	
>10	n (%)	0	0	
Day 30	n	135	144	0.005**
Abstinence	n (%)	114 (84.4%)	102 (70.8%)	
<5	n (%)	11 (8.2%)	26 (18.1%)	
5 – 10	n (%)	7 (5.2%)	14 (9.7%)	
>10	n (%)	3 (2.2%)	2 (1.4%)	
Day 90	n	122	131	<0.001**
Abstinence	n (%)	92 (75.4%)	71 (54.2%)	
<5	n (%)	16 (13.1%)	32 (24.4%)	
5 – 10	n (%)	8 (6.6%)	23 (17.6%)	
>10	n (%)	6 (4.9%)	5 (3.8%)	
Day 180	n	102	111	0.051
Abstinence	n (%)	63 (61.8%)	54 (48.7%)	
<5	n (%)	21 (20.6%)	34 (30.6%)	
5 – 10	n (%)	15 (14.7%)	21 (18.9%)	
>10	n (%)	3 (2.9%)	2 (1.8%)	
Day 270	n	88	88	0.002**
Abstinence	n (%)	57 (64.8%)	40 (45.5%)	
<5	n (%)	18 (20.5%)	21 (23.9%)	
5 – 10	n (%)	10 (11.4%)	19 (21.6%)	
>10	n (%)	3 (3.4%)	8 (9.1%)	
Day 360	n	88	84	0.007**
Abstinence	n (%)	56 (63.6%)	38 (45.2%)	
<5	n (%)	17 (19.3%)	21 (25.0%)	
5 – 10	n (%)	10 (11.4%)	18 (21.4%)	
>10	n (%)	5 (5.7%)	7 (8.3%)	
Data Source: Tables 210 – 215 (Barrias statistical report in NDA)				

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-values are based on a chi-square test.

4.4.6.7.3 Overall Clinical Assessment

Two overall clinical assessments were made in the European Long-Term Supportive efficacy studies: the investigator's CGI of the patient's response and the investigator's

opinion of the success or failure of the study treatment. These investigator assessments affirm the results that treatment with acamprosate leads to longer periods of abstinence and less drinking during the study as reported by the patient.

The CGI of the patient's response was rated by the investigator on each assessment day using a 5-point rating scale. For analysis purposes, the 5-level response was reduced to 3 categories:

Worse = Worse, much worse, and missing values;
Stable = Unchanged; and
Better = Better, much better.

Also on the final assessment day, the investigator rated the patient's treatment as "success" or "failure". The success category included patients who were abstinent as well as patients who had reduced their alcohol intake. The evaluation of success versus failure was made by the investigator at each assessment in the Barrias study. Treatment group differences were assessed using a chi-square test.

In the Besson study, the investigator made an additional assessment of the final CGI of response to treatment based on 4 categories: "unchanged", "variable", "satisfactory", and "very satisfactory". A chi-square test was used to test for a treatment group difference.

In the Lesch study, the majority of patients in both groups were rated as "Stable" or "Better" at each assessment. More patients in the acamprosate group (51%, 26%, and 14%) were rated by the investigator as "Better" compared to patients in the placebo group (44%, 22%, and 12%) at the Day 30, 90, and 360 assessments, respectively. At Day 90, the difference between the groups was statistically significant ($p=0.044$). No statistically significant differences were observed at the other timepoints. The percentage of patients rated as "worse" was lower in the acamprosate group than in the placebo group at all assessments.

At Day 360, the investigator rated 113 (50%) and 99 (44%) of the patients in the acamprosate group and placebo groups, respectively, as a success. This included patients

who were abstinent along with patients who had reduced their alcohol intake. This difference was not statistically significant.

In the Barrias study, the patients' responses to treatment were rated more often by the investigators as "Stable" or "Better" for patients in the acamprosate group (44% to 86%) than for patients in the placebo group (14% to 56%). Fewer patients in the acamprosate group (11% to 51%) received an assessment of "Worse" than patients in the placebo group (14% to 56%) at each assessment. No statistically significant differences were found between the 2 treatment groups.

In this study, investigators rated the patient's treatment as a success or failure throughout the study period. The percentage of patients who were rated as a success was higher in the acamprosate group (45% to 87%) than in the placebo group (35% to 83%) across all timepoints. At the end of the double-blind Treatment Phase, 45% of patients treated with acamprosate and 35% of patients treated with placebo were rated as successes. There were no statistically significant differences detected with these analyses.

In the Besson study, no statistically significant differences were observed between the treatment groups in the analysis of the investigator's overall CGI of the patient's response to treatment. Patients treated with acamprosate were rated higher than placebo patients at all assessments except Day 360. At the end of the study, 49% of the acamprosate-treated patients and 42% of the placebo-treated patients were considered a success. This difference was not statistically significant ($p=0.221$).

Table 92. Final Clinical Global Impression of Response to Treatment – European Long-Term Supportive Efficacy Study Besson

Final Assessment	Statistic	ACAMP (N=55)	Placebo (N=55)	P-value
Unchanged	n (%)	8 (15%)	19 (35%)	0.021*
Variable	n (%)	18 (33%)	15 (27%)	
Satisfactory	n (%)	15 (28%)	12 (22%)	
Very Satisfactory	n (%)	13 (24%)	9 (16%)	
Data Source: Table 13 (Besson study report in NDA)				

* Significant at the 0.050 level; ** significant at the 0.010 level.

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

Note: P-value is from chi-square test.

As shown in Table 92, in the Besson study patients in the acamprosate group were rated as having a more favorable response at the final CGI assessment compared to patients in the placebo group. Fifty-two percent of the acamprosate group were rated as having a satisfactory or very satisfactory response compared to 38% of the patients in the placebo group. This difference was statistically significant ($p=0.021$).

4.4.6.7.4 Alcohol Craving (Visual Analog Scale or VAS)

The intensity of the patient's craving for alcohol was measured on a 100 mm VAS ranging from no desire (0) to an uncontrollable desire for alcohol (100). Treatment group differences were assessed using a two-sample t-test.

Treatment with acamprosate reduced the intensity of craving for alcohol compared to placebo treatment. Across the 3 studies, both groups showed an improvement in mean alcohol craving scores, and these improvements were maintained during the course of treatment. In the Lesch and Besson studies, mean scores were consistently lower for patients in the acamprosate group compared to patients in the placebo group. At the end of the study, mean VAS scores were 14.89 and 19.05 for the acamprosate and placebo groups, respectively in the Besson study. In the Lesch study, mean VAS scores at the end of the study were 22.16 and 26.96 for the acamprosate and placebo groups, respectively). No statistically significant differences were detected between the groups for alcohol craving on the VAS scale.

4.4.6.7.5 *Summary of Primary and Secondary Efficacy Parameters for European Long-Term Supportive Efficacy Studies*

The results of the European Long-Term Supportive efficacy studies supported the conclusions reached in the pivotal efficacy studies.

Patients treated with acamprosate were more likely to be abstinent and to remain abstinent than patients treated with placebo. Results from the CCAD analyses showed that acamprosate-treated patients remained abstinent 39% to 49% of the time, while placebo-treated patients remained abstinent for 21% to 36% of the time.

Longer cumulative abstinence durations were statistically significant in favor of the acamprosate groups compared to the placebo groups in each of the 3 Long-Term supportive studies.

Time to first drink was significantly longer for the acamprosate group than the placebo group in each of the 3 studies, as evidenced by differences in the cumulative percentage of patients in abstinence ranging from 8% to 26% at Day 180 and from 11% to 20% at Day 360.

The rate of complete abstinence was also higher in the acamprosate groups (range from 25% to 39%) compared to the placebo groups (range from 15% to 26%). Statistically significant differences in rate of complete abstinence were seen in the Lesch and Barrias studies.

Further evidence of the efficacy of acamprosate was demonstrated by the results of the analyses of the secondary efficacy parameters. Treatment with acamprosate was associated with a statistically significant decrease in the frequency and quantity of alcohol consumed during the Treatment Phase compared to treatment with placebo. Overall clinical assessments by the investigators confirmed the improvement that was reported by the patients. Patients treated with acamprosate also experienced a reduction in the intensity of the craving of alcohol as measured on the VAS.

4.4.7 Overall Summary of All Supportive Studies

The results of the 10 supportive efficacy studies performed in 9 additional European countries and in the United States generally confirmed the conclusions found in the 3 pivotal European efficacy studies. The analyses of CCAD and time to first drink showed that patients treated with acamprosate generally had statistically significantly longer durations of abstinence compared to patients treated with placebo. Acamprosate-treated patients also often had statistically significantly higher complete abstinence rates compared to placebo-treated patients. Results from the secondary efficacy parameters which included quantitative assessments of drinking behavior and global evaluations of status also confirmed the benefit of treatment with acamprosate over placebo. Overall clinical assessments by the investigators supported the benefit of acamprosate treatment reported by patients in these studies.

Overall, in 7 of these 10 studies, patients began the study with a commitment to abstinence and had completed alcohol withdrawal treatment and were 100% abstinent at study start. The 3 exceptions were the UKMAS, ADISA, and US 96.1 studies. In UKMAS, despite withdrawal treatment, 30% of patients had resumed drinking prior to starting study medication and, thus, did not begin the study in an abstinent state as did patients in the other studies. In the ADISA study, alcohol withdrawal was to begin simultaneously with the initiation of study medication. Overall, 68% of patients in the ADISA study underwent detoxification and 85% of the patients were abstinent at Baseline. In the U.S. study, withdrawal from alcohol was not required and only about 10% of the study population underwent detoxification (almost entirely outpatient) because of physiologic evidence of withdrawal. In US 96.1, 50% of the patients were not abstinent at study start and only about 40% identified total abstinence as their treatment goal (“motivated” subpopulation).

Results from the CCAD analyses during the double-blind Treatment Phase of the six 6-month European Short-Term Supportive efficacy studies showed that the percentage of abstinent time on study in the acamprosate group ranged from 35% to 72%, while in the placebo group the percentage abstinent time ranged from 24% to 59%. Differences between the acamprosate and placebo groups with respect to CCAD were statistically

significant in all 4 of the 6 European Short-Term Supportive studies in which CCAD was analyzed. Although CCAD was not analyzed in the ADISA study, treatment group differences in CAD were also statistically significant. Only the UKMAS study failed to show a significant difference in CAD between acamprosate and placebo groups. Among the 3 European Long-Term Supportive studies, results from the CCAD analyses showed that acamprosate-treated patients remained abstinent 39% to 49% of the study participation time, while placebo-treated patients remained abstinent for 21% to 36% of that time. All differences were statistically significant in these 1 year studies. In US 96.1, in the motivated population subsets, representing about 40% of the total study population of 601, there was a relative increase in median CCAD of 22% to 28%, compared to placebo.

Collectively, in the supportive studies, the improvement in CCAD seen in the acamprosate group was consistent with findings in the pivotal studies wherein all 3 studies had statistically significant increases in CCAD in the acamprosate group, with differences in mean percentages between acamprosate and placebo ranging from 24% in the 3 month Pelc II study and between 10.7 and 17.1% in the 1 year PRAMA and Paille studies.

Among the European Short-Term Supportive studies, the results of the analysis for time to first drink in the Poldrugo and Tempesta studies showed that patients in the acamprosate group remained continuously abstinent statistically significantly longer than patients in the placebo group during the double-blind Treatment Phase ($p \leq 0.001$). In the BENELUX, Ladewig, and ADISA studies, the difference between groups in the time to first drink during the Treatment Phase approached statistical significance ($p \leq 0.098$). The European Long-Term Supportive studies had similar findings, with time to first drink significantly longer for the acamprosate group than the placebo group in each of the 3 studies, as evidenced by differences in the cumulative percentage of patients continuously abstinent ranging from 8% to 26% at Day 180 and from 11% to 20% at Day 360. Time to first drink could not be accurately assessed in US 96.1 because of non-abstinence of half the population at Baseline.

The rate of complete abstinence in the European Short-Term Supportive studies ranged from 12% to 47% for patients in the acamprosate group and from 3% to 21% for patients in the placebo group. Excluding UKMAS, differences in complete abstinence rates between the acamprosate and placebo groups were between 10 and 20%, in favor of acamprosate. In 3 of the 6 Supportive studies, the difference was statistically significant; it approached statistical significance ($p=0.073$) in a fourth; and was not significant in ADISA ($p=0.172$) or UKMAS ($p>0.999$).

Findings were similar in the European Long-Term Supportive studies, where the rate of complete abstinence ranged from 25% to 39% for the acamprosate groups and ranged from 15% to 26% across the placebo groups. These differences were statistically significant for 2 of the 3 Long-Term studies.

Although complete abstinence rates could not be assessed in US 96.1, for the endpoint of “good response” (i.e., abstinence for 90% or more of time on study), the “motivated” populations on acamprosate had a relative increase of 33% in this variable compared to placebo.

Collectively, these results were consistent with the results of the pivotal efficacy studies, where complete abstinence for acamprosate-treated patients was 41% in the 3-month Pelc II study and 29% (*PRAMA*) and 19% (*Paille*) in the 1-year studies, compared to respective rates in the placebo group of 15%, 12%, and 11%.

Results of the secondary efficacy analyses for the European Short-Term Supportive studies showed that patients in the acamprosate group generally had less frequent and lower amounts of alcohol consumption, and a reduction in the intensity of craving for alcohol over time. The overall assessment of the patient response to treatment as rated by the investigators (Clinical Global Impression or CGI) affirmed the benefit of acamprosate over placebo in these studies.

In US 96.1, motivated subpopulations on acamprosate had a relative decrease in drinks per week as a function of Baseline drinking of 22% to 50%, compared to placebo.

In the European Long-Term Supportive studies, treatment with acamprosate led to a statistically significant decrease in the frequency and quantity of alcohol consumed during the Treatment Phase compared to treatment with placebo. Overall clinical assessments by the investigators confirmed the improvement that was reported by the patients. Patients treated with acamprosate also experienced a reduction in the intensity of craving for alcohol over time.

For all these studies, the results of the secondary efficacy parameters were consistent with findings in the pivotal efficacy studies.

4.4.8 Summary of Meta-Analyses

Two meta-analyses were performed in response to the FDA's interest in: 1) how acamprosate efficacy may extend across study populations and methodologies; 2) identifying a population of alcohol dependent patients who may derive the greatest benefit from acamprosate; and 3) confirming the generalizability of these findings for US and non-US populations.

- The first meta-analysis examined the overall relative benefit of acamprosate on abstinence from alcohol across 16 randomized, double-blind, placebo-controlled clinical trials, most of which had a duration of 6 to 12 months. The data-set included the 13 trials discussed above and 3 additional placebo-controlled trials (2 early clinical experience studies and 1 clinical pharmacology study) for which similar parameters were available, involving, overall nearly 4500 alcohol-dependent outpatients, where acamprosate was most commonly administered at a daily dose of 1998 mg, given in 3 divided doses. The purpose of the meta-analysis was to reconcile differences in study populations and methods. No statistical modeling was used in the outcome analyses of any of the studies included in this meta-analysis. The main outcome parameter was the continuous abstinence rate at 6 months. Secondary endpoints included continuous abstinence rates at 3 and 12 months, point prevalence of abstinence at 6 and 12 months, and the percentage of abstinent time on study (corrected Cumulative Abstinence Duration or CCAD) at 3, 6 and 12 months. The conclusions were:

- The relative benefit of acamprosate compared with placebo in increasing the continuous abstinence rate compared with placebo was seen at 6 months (145% relative benefit), as well as at 3 months (131%) and 12 months (195%).
 - Acamprosate also significantly increased the prevalence of abstinence at months 6 and 12 (point prevalence of abstinence) compared with placebo, with a relative benefit at 6 months of 137% and at 12 months of 162%.
 - The percentage of abstinent time on study (CCAD) was significantly increased by acamprosate compared with placebo. At 3, 6, and 12 months the increases in the acamprosate group were approximately 10%, 10%, and 13%, respectively.
 - The results of this meta-analysis support a sustained long-term benefit of acamprosate across populations.
- The second meta-analysis sought to assess similar patient characteristics across these same studies, through utilization of individual data from the 4457 study participants, and the relationship of these characteristics with treatment outcome. The objective was to create a statistical model predictive of response to treatment, irrespective of a patient's national origin.

Box plots and bar charts for 7 variables (age, gender, Body Mass Index, alcohol dependence severity at Baseline, whether or not the patient lived with a partner and children, medication compliance during the first week on study, and drinking behavior during the first 2 days on study) showed that patient samples were generally comparable and overlapping across studies.

Correlation coefficients of these variables with a more precise definition of CCAD, termed “CAD-meta”, tended also to be of similar magnitude and directionality across studies, as well as between European and US populations. Furthermore, examination of CAD-meta in the European and US populations as a function of various subgroups of each variable, showed similar influences of the main predictors on outcome across these 2 populations, with similar directionality. These results attested to the comparability of the populations, irrespective of national origin.

A model utilizing these key variables was developed and tested on the entire dataset, using CAD-meta, and was shown to fit all studies. This universal model is consistent with factors thought to be clinically relevant in terms of their influence on alcoholism treatment outcome and includes 5 predictors: drinking behavior (abstinent/non-abstinent) at the onset of treatment; initial medication compliance during the first week of treatment; baseline alcohol dependence severity; the existence of family support (i.e., living with a partner and child); and the treatment itself. The conclusions were:

- Acamprosate was less effective in patients who were non-abstinent at the onset of treatment.
- An adjusted relative benefit of acamprosate on CAD-meta of 7.56% was estimated compared with placebo using the universal model. When treatment exposure was included in the model, this estimated benefit increased to 11.71%, lending further support to the positive effects of acamprosate when taken as prescribed over the entire study period.
- There was no significant interaction between treatment and whether the study was US or European, thus supporting the generalizability of the model for predicting treatment outcome across populations and national boundaries.
- The model also has clinical relevance and may be useful in the general management of alcohol-dependent patients and in optimizing the therapeutic response to acamprosate.

4.5 SUMMARY OF SAFETY INFORMATION

The summary of safety information in this Briefing Document focuses on US 96.1 and on conclusions drawn from the overall experience in the double-blind, placebo-controlled Group I studies. Additional safety data from all other studies (clinical pharmacology studies, early clinical experience studies, open-label Phase IV studies) is summarized, when relevant.

Of the double-blind, placebo-controlled Short-Term and Long-Term (Group I) studies, the US 96.1 study used acamprosate doses of 2000 mg/day (1000 mg b.i.d.) and 3000 mg/day (1500 mg b.i.d.), while the European studies used doses of 1332 mg/day (666 mg in the morning, 333 mg at mid-day and in the evening) and 1998 mg/day (666 mg TID). In the integrated safety database, the 1998 mg/day and 2000 mg/day dose groups were pooled and an additional group, identified as the “pooled acamprosate group”, presents data based on patients treated with acamprosate of any dosage.

4.5.1 Safety Summary from US 96.1

(See Section 4.4.5.2 for Study Design and Section 4.4.5.3 for Patient Disposition)

Deaths

There were no deaths during this 6-month study which involved 601 randomized alcohol-dependent patients (258, 83, and 260 in the acamprosate 1998/2000 mg/day, acamprosate 3000 mg/day, and placebo groups, respectively).

Adverse Events Leading to or Contributing to Early Study Termination

Among the 601 randomized patients, the overall incidence of patients experiencing adverse events which led to premature study termination (primary reason) or contributed to such termination (secondary reason) was similar among the 3 treatment groups: acamprosate 2000 mg, 21 patients (8%); acamprosate 3000 mg, 4 patients (5%); and placebo, 15 patients (6%). All of these discontinuations were in the 6-month Treatment Phase of the study.

In the acamprosate 2000 mg group, 6 of the 21 patients (29% of those discontinuing) had primary or secondary adverse events that were drinking-related, compared to 3 of the 15 patients (20% of those discontinuing) in the placebo group and none in the acamprosate 3000 mg group. When drinking-related events were excluded, the overall incidence of adverse events leading to premature study withdrawal (primary or secondary) was similar among the acamprosate 2000 mg (15 patients; 6%), acamprosate 3000 mg (4 patients; 5%), and placebo (12 patients; 5%) treatment groups. Furthermore, no apparent patterns emerged suggestive of a preponderance of events in the acamprosate treatment groups.

An adverse event was the primary reason for premature study discontinuation in 6 patients (2%) in the acamprosate 2000 mg treatment group, 2 patients (2%) in the acamprosate 3000 mg treatment group, and 6 patients (2%) in the placebo group. For all these patients (except one patient in the acamprosate 2000 mg group), these events were not drinking related. Table 93 provides a by-patient listing for patients who terminated prematurely where an adverse event was the primary reason. The listing is by treatment group and includes investigator-assessed severity and causality.

Table 93. By-Patient* Listing of Premature Study Terminations Due to an Adverse Event as Primary Reason – US Short-Term Supportive Efficacy Study

Treatment Group	Case “Number”*	Adverse Event (COSTART) Term	Assessment of Severity/Relatedness
Placebo	Case A	Rash	Severe/Possible
	Case B	Diarrhea Rectal disorder Nausea Vomiting Peripheral vascular disorder Ulcerative colitis	Moderate/Probable Mild/Unrelated Moderate/Unrelated Moderate/Unrelated Mild/Unrelated Severe/Unrelated
	Case C	Diarrhea	Severe/Probable
	Case D	Face edema	Moderate/Possible
	Case E	Flatulence	Mild/Possible
	Case F	Arthralgia	Moderate/Possible
Acamprosate 2000 mg	Case G	Pruritus Rash	Severe/Possible Severe/Possible
	Case H	Depression	Severe/Unrelated
	Case I	Diarrhea Headache	Moderate/Possible Moderate/Possible
	Case J**	Depression Drug dependence	Severe/Unrelated Severe/Unlikely
	Case K	Headache	Severe/Possible
	Case L	Abdominal pain Kidney pain	Mild/Unrelated Mild/Unrelated
Acamprosate 3000 mg	Case M	Diarrhea	Moderate/Probable
	Case N	Dysphagia Fever Gastritis Headache Vomiting	Mild/Possible Moderate/Unlikely Severe/Possible Mild/Unlikely Severe/Possible

Data Source: US 96.1 Study Report, Table 8.10 in NDA

* For purposes of the Briefing Document, actual Patient ID numbers have not been used.

** This patient terminated prematurely for both a drinking related and non-drinking related adverse event.

Digestive System events led to or contributed to premature study withdrawal (primary or secondary reason) in equal percentages of patients in the acamprosate 2000 mg (6 patients; 2%) and placebo groups (5 patients; 2%), and a higher percentage of patients in the acamprosate 3000 mg group (4 patients; 5%). When only Digestive System events as a primary reason for termination were considered, these percentages decreased to 1% of patients for both the acamprosate 2000 mg and placebo groups and 2% for the acamprosate 3000 mg group.

Diarrhea as a primary or secondary reason for premature study termination was reported by more patients in the acamprosate treatment groups compared to the placebo group, although the percentage was still low: acamprosate 2000 mg, 4 patients (2%); acamprosate 3000 mg, 2 patients (2%); and placebo, 2 patients (<1%). As a primary reason for early discontinuation, diarrhea was contributory in only one patient (<1%) in the acamprosate 2000 mg group, one patient (1%) in the acamprosate 3000 mg group, and 2 patients (<1%) in the placebo group.

Two patients in the placebo group (<1%) discontinued because of nausea (1 primary reason, 1 secondary reason), compared to a single patient in the acamprosate 2000 mg group (<1%) (secondary reason) and none in the acamprosate 3000 mg group.

Depression resulting in premature study withdrawal was reported by 3 patients (1%) in the placebo treatment group (all secondary reasons), 6 patients (2%) in the acamprosate 2000 mg treatment group (2 primary reasons, 4 secondary reasons), and no patients in the acamprosate 3000 mg treatment group.

A dermatologic event was the primary reason for early discontinuation in 1 patient (<1% of patients) in the acamprosate 2000 mg group (pruritus and rash) and in 1 patient (<1% of patients) in the placebo group (rash). No patients in the acamprosate 3000 mg group discontinued for a dermatologic event.

Overall Incidence of Adverse Events

Adverse events were coded from the investigator-provided terms into standardized terminology, using the COSTART dictionary.^[51]

As seen in Table 94, the overall percentage of patients with adverse events was similar among the 3 treatment groups: acamprosate 2000 mg, 86% (221 patients); acamprosate 3000 mg, 88% (73 patients); and placebo, 85% (220 patients).

The only COSTART body system with a significant difference in the incidence of adverse events was the Digestive System, with significantly (p-value<0.001) more adverse events in the acamprosate treatment groups than placebo: acamprosate 2000 mg,

53% (136 patients); acamprosate 3000 mg, 59% (49 patients); and placebo, 37% (96 patients).

The Digestive System event which was most frequent in the acamprosate treatment groups relative to placebo was diarrhea: acamprosate 2000 mg, 33% (86 patients); acamprosate 3000 mg, 40% (33 patients); and placebo, 18% (48 patients) (p-value<0.001).

The only other events which occurred in a statistically significantly greater percentage of patients in the acamprosate 2000 mg and acamprosate 3000 mg groups compared to the placebo group were: flatulence (9%, 5%, and 3%, respectively), dyspepsia (4%, 8%, and 2%, respectively), vomiting (4%, 5%, and <1%, respectively), and impotence (<1%, 2%, and 0%, respectively).

The overall incidence of adverse events was higher among all 3 treatment groups in the earlier part of the study (initial 12 weeks) than later (\geq Week 12 of Treatment Phase).

The majority of adverse events were mild or moderate in severity and were assessed by investigators as having an unlikely or no relationship to study medication. Diarrhea rated as “severe” was reported by 3% of acamprosate 2000 mg patients, 1% of acamprosate 3000 mg patients, and <1% of placebo patients. Diarrhea was considered as having a possible or probable relationship to study drug in approximately 90% of patients with diarrhea in the acamprosate treatment groups compared to approximately 70% of those with diarrhea in the placebo group.

Table 94. Incidence of Most Frequent ($\geq 5\%$ of Patients in a Treatment Group) Treatment Emergent Adverse Events (Safety Population) in US 96.1

	Statistic	Placebo (n=260)	Acamprosate 2000 mg/day (n=258)	Acamprosate 3000 mg/day (n=83)	P-value ¹
Number of Patients with an Adverse Event	n (%)	220 (85%)	221 (86%)	73 (88%)	0.751
Body System Preferred Term					
Body as a Whole	n (%)	133 (51%)	119 (46%)	45 (54%)	0.333
Headache	n (%)	58 (22%)	48 (19%)	20 (24%)	0.440
Accidental injury	n (%)	33 (13%)	19 (7%)	11 (13%)	0.095
Pain	n (%)	23 (9%)	16 (6%)	3 (4%)	0.214
Flu syndrome	n (%)	15 (6%)	17 (7%)	8 (10%)	0.468
Asthenia	n (%)	13 (5%)	11 (4%)	6 (7%)	0.559
Abdominal pain	n (%)	11 (4%)	16 (6%)	3 (4%)	0.485
Back pain	n (%)	9 (3%)	12 (5%)	2 (2%)	0.599
Digestive System	n (%)	96 (37%)	136 (53%)	49 (59%)	<0.001**
Diarrhea	n (%)	48 (18%)	86 (33%)	33 (40%)	<0.001**
SGOT increased	n (%)	15 (6%)	12 (5%)	4 (5%)	0.838
Nausea	n (%)	14 (5%)	12 (5%)	7 (8%)	0.419
SGPT increased	n (%)	14 (5%)	12 (5%)	3 (4%)	0.795
Liver function tests abnormal	n (%)	10 (4%)	13 (5%)	4 (5%)	0.797
Flatulence	n (%)	8 (3%)	22 (9%)	4 (5%)	0.026*
Dyspepsia	n (%)	6 (2%)	10 (4%)	7 (8%)	0.040*
Vomiting	n (%)	2 (<1%)	10 (4%)	4 (5%)	0.038*
Nervous System	n (%)	96 (37%)	86 (33%)	30 (36%)	0.683
Insomnia	n (%)	20 (8%)	14 (5%)	9 (11%)	0.226
Drug dependence	n (%)	17 (7%)	19 (7%)	4 (5%)	0.717
Depression	n (%)	16 (6%)	13 (5%)	5 (6%)	0.850
Anxiety	n (%)	8 (3%)	7 (3%)	5 (6%)	0.328
Libido decreased	n (%)	8 (3%)	7 (3%)	4 (5%)	0.631
Hypertension	n (%)	5 (2%)	12 (5%)	2 (2%)	0.190
Respiratory System	n (%)	74 (28%)	52 (20%)	17 (20%)	0.064
Pharyngitis	n (%)	43 (17%)	32 (12%)	11 (13%)	0.388
Rhinitis	n (%)	17 (7%)	16 (6%)	2 (2%)	0.355
Cough increased	n (%)	16 (6%)	8 (3%)	1 (1%)	0.077
Skin and Appendages	n (%)	48 (18%)	42 (16%)	11 (13%)	0.519
Rash	n (%)	16 (6%)	14 (5%)	3 (4%)	0.675
Pruritus	n (%)	12 (5%)	14 (5%)	2 (2%)	0.525
Data Source: US 96.1 Study Report, Table 8.1 in NDA					

* Significant at the 0.050 level; ** significant at the 0.010 level.

¹ P-values for the overall treatment group comparison for body systems and events occurring in at least 5% of patients or for events of special interest are from a chi-square test, or a Fisher's exact test if the sample size is not sufficient.

Table 94 (cont'd). Incidence of Most Frequent ($\geq 5\%$ of Patients in a Treatment Group) Treatment Emergent Adverse Events (Safety Population) in US 96.1

	Statistic	Placebo (n=260)	Acamprosate 2000 mg/day (n=258)	Acamprosate 3000 mg/day (n=83)	P-value ¹
Metabolic and Nutritional Disorders	n (%)	37 (14%)	35 (14%)	13 (16%)	0.891
Hyperglycemia	n (%)	12 (5%)	10 (4%)	8 (10%)	0.104
Hemic and Lymphatic System	n (%)	24 (9%)	27 (10%)	6 (7%)	0.670
Erythrocytes abnormal	n (%)	8 (3%)	8 (3%)	4 (5%)	0.717
Data Source: US 96.1 Study Report, Table 8.1 in NDA					

* Significant at the 0.050 level; ** significant at the 0.010 level.

¹ P-values for the overall treatment group comparison for body systems and events occurring in at least 5% of patients or for events of special interest are from a chi-square test, or a Fisher's exact test if the sample size is not sufficient.

Serious Adverse Events

For more than half of the patients experiencing serious adverse events, the event was hospitalization for treatment of alcohol relapse. Excluding such cases, there were no clinically meaningful differences among treatment groups in the percentage of patients who experienced individual serious adverse events.

Adverse Events in Patients Testing Positive for Illicit Drugs

During the Treatment Phase of the study, 40 (16%) of the 258 patients in the acamprosate 2000 mg treatment group, 14 (17%) of the 83 patients in the acamprosate 3000 mg treatment group, and 32 (12%) of the 260 patients in the placebo treatment group had at least one urine test which was positive in a screen for illicit drugs.

Table 95 summarizes the incidence of the most frequent ($\geq 5\%$ of patients in a treatment group) treatment emergent adverse events for such patients for each of the 3 treatment groups, utilizing COSTART body systems and preferred terms.

The overall incidence of adverse events in patients with positive drug screens was similar in the acamprosate 2000 mg (39 patients; 98%) and placebo (30 patients; 94%) treatment groups and slightly lower in the acamprosate 3000 mg treatment group (10 patients; 71%).

The most frequent adverse events for patients with positive drug screens were terms coded to “drug dependence” and diarrhea. Diarrhea occurred in 30% of this subpopulation receiving acamprosate 2000 mg (compared to 33% for the treatment group overall), in 36% of this subpopulation receiving acamprosate 3000 mg (compared to 40% for the treatment group overall), and in 25% of this subpopulation receiving placebo (compared to 18% for the treatment group overall).

Table 95. Incidence of Most Frequent (≥5% of Patients in a Treatment Group) Treatment Emergent Adverse Events in Patients with Positive Drug Screens During the Treatment Phase

		Placebo (n=260)	Acamprosate 2000 mg/day (n=258)	Acamprosate 3000 mg/day (n=83)
Number of patients (%) with positive drug screen during Treatment Phase		32 (12%)	40 (16%)	14 (17%)
Number of patients (%) with an adverse event among those with a positive drug screen	n (%)	30 (94%)	39 (98%)	10 (71%)
Body System Preferred Term	Statistic			
Nervous System	n (%)	23 (72%)	19 (48%)	6 (43%)
Drug dependence	n (%)	9 (28%)	13 (33%)	3 (21%)
Dizziness	n (%)	6 (19%)	0	1 (7%)
Insomnia	n (%)	5 (16%)	2 (5%)	0
Depression	n (%)	3 (9%)	2 (5%)	1 (7%)
Hypertension	n (%)	2 (6%)	2 (5%)	0
Withdrawal syndrome	n (%)	2 (6%)	1 (3%)	1 (7%)
Libido decreased	n (%)	1 (3%)	0	1 (7%)
Neuropathy	n (%)	0	0	1 (7%)
Body as a Whole	n (%)	18 (56%)	22 (55%)	7 (50%)
Headache	n (%)	6 (19%)	7 (18%)	3 (21%)
Accidental injury	n (%)	4 (13%)	4 (10%)	2 (14%)
Flu syndrome	n (%)	3 (9%)	4 (10%)	2 (14%)
Pain	n (%)	3 (9%)	3 (8%)	0
Abdominal pain	n (%)	3 (9%)	0	1 (7%)
Infection	n (%)	2 (6%)	1 (3%)	0
Asthenia	n (%)	1 (3%)	4 (10%)	0
Back pain	n (%)	1 (3%)	4 (10%)	0
Malaise	n (%)	1 (3%)	0	1 (7%)
Laboratory test abnormal	n (%)	0	2 (5%)	0
Data Source: US 96.1 Study Report, Table 8.5 in NDA				

Table 95 (cont'd). Incidence of Most Frequent (≥5% of Patients in a Treatment Group) Treatment Emergent Adverse Events in Patients with Positive Drug Screens During the Treatment Phase

		Placebo (n=260)	Acamprosate 2000 mg/day (n=258)	Acamprosate 3000 mg/day (n=83)
Digestive System	n (%)	14 (44%)	23 (58%)	6 (43%)
Diarrhea	n (%)	8 (25%)	12 (30%)	5 (36%)
Nausea	n (%)	4 (13%)	1 (3%)	0
SGOT increased	n (%)	3 (9%)	3 (8%)	1 (7%)
Constipation	n (%)	3 (9%)	1 (3%)	0
Liver function tests abnormal	n (%)	2 (6%)	8 (20%)	1 (7%)
Anorexia	n (%)	2 (6%)	1 (3%)	0
Flatulence	n (%)	2 (6%)	1 (3%)	0
SGPT increased	n (%)	1 (3%)	3 (8%)	1 (7%)
Tooth disorder	n (%)	1 (3%)	2 (5%)	0
Vomiting	n (%)	1 (3%)	2 (5%)	0
Dyspepsia	n (%)	0	2 (5%)	1 (7%)
Gastrointestinal disorder	n (%)	0	2 (5%)	0
Respiratory System	n (%)	11 (34%)	10 (25%)	1 (7%)
Pharyngitis	n (%)	6 (19%)	7 (18%)	0
Cough increased		3 (9%)	1 (3%)	0
Rhinitis		3 (9%)	1 (3%)	0
Asthma	n (%)	1 (3%)	3 (8%)	0
Skin and Appendages	n (%)	9 (28%)	6 (15%)	0
Rash	n (%)	4 (13%)	3 (8%)	0
Pruritus	n (%)	3 (9%)	1 (3%)	0
Hemic and Lymphatic System	n (%)	8 (25%)	4 (10%)	0
Anemia	n (%)	3 (9%)	0	0
Erythrocytes abnormal	n (%)	3 (9%)	0	0
Hypochromic anemia	n (%)	2 (6%)	0	0
Leukopenia	n (%)	2 (6%)	0	0
Eosinophilia	n (%)	0	2 (5%)	0
Metabolic and Nutritional Disorders	n (%)	4 (13%)	6 (15%)	2 (14%)
Hyperglycemia	n (%)	3 (9%)	3 (8%)	1 (7%)
Alcohol intolerance	n (%)	1 (3%)	2 (5%)	1 (7%)
Hyperuricemia	n (%)	0	1 (3%)	1 (7%)
Urogenital	n (%)	4 (13%)	3 (8%)	0
Urinary tract infection	n (%)	2 (6%)	1 (3%)	0
Data Source: US 96.1 Study Report, Table 8.5 in NDA				

Within the positive urine drug screen subpopulation, COSTART Nervous System events were more frequent in the placebo group compared to the acamprosate treatment groups: placebo, 72%; acamprosate 2000 mg group, 48%; and acamprosate 3000 mg group, 43%. Specific Nervous System adverse events which seemed to occur more frequently in the placebo group in this subpopulation were dizziness (placebo 19%; acamprosate 2000 mg, no patients; and acamprosate 3000 mg, 7%) and insomnia (placebo, 16%; acamprosate 2000 mg, 5%; and acamprosate 3000 mg, no patients).

Clinical Laboratory Evaluations

There were no clinically meaningful differences between treatment groups for any hematologic parameter tested (complete hemogram).

Among the liver function evaluations, mean Baseline values for GGT were above the upper limit of normal (ULN) in all 3 treatment groups, probably reflecting the significant and recent alcohol intake of this largely non-abstinent patient population. With reduction in alcohol consumption, the mean values decreased substantially in all groups. Decreases in mean AST and ALT from Baseline values (which were above or at the ULN) also occurred in all treatment groups. Larger decreases from Baseline were seen in the acamprosate treatment groups compared to the placebo treatment group for all liver function tests, with the magnitude of change suggesting a dose-effect at Treatment Phase Endpoint. The direction of change in all instances supported an improvement in liver function during the course of the study.

Table 96 summarizes results of additional serum chemistry tests (creatinine, blood urea nitrogen, uric acid, electrolytes, calcium, inorganic phosphorous, glucose, total protein, and albumin) at Baseline and their mean change from Baseline at Treatment Phase Endpoint by treatment group. There were no clinically significant changes in any of these chemistry parameters, including serum calcium, nor clinically meaningful differences among treatment groups in any of these tests. Similar results were seen for patients with positive drug screens.

Table 96. Additional Serum Chemistry Tests (Safety Population) in US 96.1

Laboratory Test (Reference Range) Treatment Group	Baseline		Change from Baseline to Treatment Phase Endpoint	
	N	Mean	N	Mean
Creatinine (F. 0.4-1.2; M. 0.5-1.3 mg/dL) ¹				
Placebo	259	0.88	226	0.01
Acamprosate 2000 mg/day	258	0.89	226	0.02
Acamprosate 3000 mg/day	83	0.90	72	0.00
Blood urea nitrogen (4-24 mg/dL)				
Placebo	259	12.8	226	0.5
Acamprosate 2000 mg/day	258	13.1	226	0.2
Acamprosate 3000 mg/day	83	12.4	72	0.5
Uric acid (F. 2.1-6.9; M. 2.4-8.7 mg/dL)				
Placebo	259	5.52	226	0.09
Acamprosate 2000 mg/day	258	5.64	226	0.17
Acamprosate 3000 mg/day	83	5.63	72	-0.00
Sodium (132-147 mEq/L)				
Placebo	259	137.9	226	0.2
Acamprosate 2000 mg/day	258	138.2	226	0.2
Acamprosate 3000 mg/day	83	137.7	72	0.6
Potassium (3.3-5.5 mEq/L)				
Placebo	259	4.29	226	-0.06
Acamprosate 2000 mg/day	258	4.27	226	0.00
Acamprosate 3000 mg/day	83	4.28	72	0.04
Chloride (94-111 mEq/L)				
Placebo	259	102.2	226	0.3
Acamprosate 2000 mg/day	258	102.8	226	-0.0
Acamprosate 3000 mg/day	83	102.2	72	0.6
Calcium (8.4-10.3 mg/dL)				
Placebo	259	9.24	226	-0.09
Acamprosate 2000 mg/day	258	9.15	226	-0.03
Acamprosate 3000 mg/day	83	9.23	72	-0.06
Data Source: NDA Table 9.1.4				

¹F=Females; M=Males.

Table 96. (cont'd) Additional Serum Chemistry Tests (Safety Population) in US 96.1

Laboratory Test (Reference Range) Treatment Group	Baseline		Change from Baseline to Treatment Phase Endpoint	
	n	Mean	N	Mean
Inorganic phosphorous (2.3-5.1 mg/dL)				
Placebo	259	3.52	226	0.08
Acamprosate 2000 mg/day	258	3.48	226	0.08
Acamprosate 3000 mg/day	83	3.52	72	0.07
Glucose (68–118 mg/dL)				
Placebo	258	99.9	226	-0.8
Acamprosate 2000 mg/day	258	99.9	226	-1.0
Acamprosate 3000 mg/day	83	96.2	72	2.5
Bicarbonate (21–33 mEq/L)				
Placebo	259	28.4	226	-2.0
Acamprosate 2000 mg/day	258	28.2	226	-1.2
Acamprosate 3000 mg/day	83	28.4	72	-1.4
Total Protein (6.0-8.4 g/dL)				
Placebo	259	7.50	226	-0.22
Acamprosate 2000 mg/day	258	7.41	226	-0.13
Acamprosate 3000 mg/day	83	7.55	72	-0.17
Albumin (3.2-5.0 g/dL)				
Placebo	259	4.61	226	-0.07
Acamprosate 2000 mg/day	258	4.57	226	-0.02
Acamprosate 3000 mg/day	83	4.58	72	-0.00
Data Source: NDA Table 9.1.4				

[†]F=Females; M=Males.

Vital Signs, Clinical Exams, and ECGs

The 3 treatment groups in US 96.1 were similar at Baseline and at each study visit with respect to systolic and diastolic blood pressure, pulse rate, and body weight. The percentage of patients with clinically significant changes in systolic and diastolic blood pressure, pulse rate, and body weight (increase or decrease) was similar among treatment groups.

The percentage of patients with normal to abnormal shifts from Baseline to Treatment Phase Endpoint in physical examination findings was similar among treatment groups for each body system. Overall, the most frequent normal to abnormal shift from Baseline to Treatment Phase Endpoint occurred in the neurological system. A normal to abnormal shift in the neurological system was reported by a lower percentage of patients in the

acamprosate groups compared to the placebo group: acamprosate 3000 mg, 2 patients (4%); acamprosate 2000 mg, 7 patients (5%); and placebo, 19 patients (11%).

The percentage of patients with abnormal, but acceptable ECGs at Baseline was similar among the 3 treatment groups: acamprosate 2000 mg, 76 patients (30%); acamprosate 3000 mg, 29 patients (35%); and placebo, 83 patients (32%). The percentage of patients with treatment emergent ECG abnormalities was also similar among the 3 groups: acamprosate 2000 mg, 10 patients (6%); acamprosate 3000 mg, 5 patients (9%); and placebo, 10 patients (6%). Overall, the changes noted were of a non-specific variety.

There were no statistically significant changes in QTc interval from Baseline to Final Visit ECG evaluation.

In conclusion, in US 96.1, acamprosate was well tolerated during the study, both at 2000 mg/day and 3000 mg/day, and there was no evidence of a rebound or withdrawal effect within 1 week of study drug discontinuation. No deaths occurred. The most frequent adverse events were diarrhea and headache, but only diarrhea had a higher incidence in the acamprosate groups. The overall incidence of adverse events, serious adverse events and premature withdrawals due to adverse events was similar among treatment groups. There were no clinically significant effects of acamprosate on standard clinical laboratory parameters and no apparent effects on vital signs, physical examination findings, or ECG results.

4.5.2 Safety Summary from Group I Studies

A total of 4243 alcohol-dependent patients were randomized in the double-blind, placebo-controlled studies Group I studies: 2565 patients in the Short-Term studies (601 patients in the US 96.1 study and 1964 patients in the European Short-Term studies) and 1678 patients in the Long-Term studies.

Most patients randomized to acamprosate were to receive either 1998 mg/day (666 mg TID, European studies) or 2000 mg/day (1000 mg BID, US 96.1 study) acamprosate. Of the 4243 patients randomized, only 9 patients were excluded from the Safety Population.

Approximately half of the randomized patients completed the Treatment Phase, 49% in the Short-Term studies and 45% in the Long-Term studies. The 3 most common reasons for withdrawal overall were “Other” (mostly subcategories of “Patient decision/Refusal” and “Non-compliance”), “Lost to follow-up”, and “Treatment failure” in both the Short-Term and Long-Term controlled studies. There were no important treatment group differences noted regarding the reasons for withdrawal.

The age of the patients ranged from 16 years to 72 years, and the mean age varied from 41.8 years to 43.6 years among the treatment groups in the controlled Short-Term and Long-Term studies, respectively. The racial composition of the treatment groups was available only for the US 96.1 study.

In some of the European studies, patients randomized to acamprosate were assigned to the 1332 mg/day or 1998 mg/day dose based on their body weight. Consequently, the acamprosate 1332 mg/day group had a higher percentage of females, lower mean body weight, and height compared to the other groups. There were no other relevant differences noted among the groups in the controlled studies regarding demographic variables.

A few differences were noted between the US and the European patient population in the controlled studies regarding Baseline characteristics related to alcohol use. An overall trend toward a slightly longer history of alcoholism, less amount of alcohol consumed on a regular basis, and less prior treatments or detoxifications in the past was observed in the US 96.1 study compared to the European patient populations. Clinically significant liver function test (LFT) abnormalities at Baseline were also less common in the US 96.1 study compared to the European patient populations. Consequently, a few differences were noted among the dose groups in the pooled (US + European) Short-Term studies due to the different composition of the dose groups, i.e., all patients in the acamprosate 3000 mg/day group were enrolled in the US 96.1 study while all patients in the acamprosate 1332 mg/day group were from the European studies. There were no other relevant treatment group differences noted regarding the history of alcohol use in the controlled studies.

The planned duration of treatment was either 24 weeks or 26 weeks in the Short-Term studies (except for *Pelc II*, which was 13 weeks) and 48 weeks to 52 weeks in the European Long-Term studies. The mean duration of exposure to study medication and the proportion of patients who completed at least 13 weeks of treatment in the Short-Term studies was equal between the pooled acamprosate and placebo groups (16.2 weeks and 58%, respectively). Of note, the mean duration of exposure was lower in the acamprosate 1332 mg/day group compared to the other dose groups, due in part to the fact that almost half of the patients in the acamprosate 1332 mg/day group were enrolled in the *Pelc II* study, with only 13 weeks of planned treatment. In the controlled Long-Term studies, the mean duration of exposure to study medication was longer in the acamprosate groups (34.7 weeks in the 1332 mg/day and 33.1 weeks in the 1998 mg/day dose groups) compared to the placebo group (29.9 weeks). Correspondingly, the proportion of patients who completed at least 39 weeks of treatment was higher in the acamprosate groups (54% and 51%) than in the placebo group (44%). Most patients in the controlled studies were at least 75% compliant with the study medication (81% to 94% in the Short-Term studies and 79% to 82% in the Long-Term studies).

Deaths

During the Treatment Phase (or within 10 days of double-blind treatment discontinuation) of the Group I studies, there were 20 deaths among the 4243 randomized patients. These are shown in Table 97, according to treatment group. As can be seen, the majority of deaths were due to accidents, suicides, or cardiac arrest and failure.

Table 97. Deaths that Occurred During Treatment Phase in the Controlled Double-Blind Group I Studies*

Treatment	Study	Gender	Age	Cause of Death
Acamprosate 1332 mg/day	PRAMA	Female	35	Severe craniocerebral trauma
Acamprosate 1332 mg/day	Paille	Male	41	Car crash
Acamprosate 1332 mg/day	Paille	Male	46	Hematemesis
Acamprosate 1998/2000 mg/day	Poldrugo	Male	64	Atrial fibrillation
Acamprosate 1998/2000 mg/day	Lesch	Male	56	Suicide by ingestion of massive doses of meclonamides. Body found by police 12 days after last study visit (reason for withdrawal from study was reported as death). ¹
Acamprosate 1998/2000 mg/day	Lesch	Male	47	Death by natural cause (circa 1 month after he started the study). The study medication box was found indicating that the patient did not take any study medication.
Acamprosate 1998/2000 mg/day	PRAMA	Male	33	Suicide (strangulation)
Acamprosate 1998/2000 mg/day	Paille	Male	55	Mesenteric infarction
Acamprosate 1998/2000 mg/day	UKMAS	Male	61	Acute subdural hemorrhage
Acamprosate 1998/2000 mg/day	Paille	Male	57	Accidental fall
Acamprosate 1998/2000 mg/day	Besson	Male	53	Suicide
Acamprosate 1998/2000 mg/day	Barrias	Male	34	Cardiac failure
Placebo	Paille	Male	42	Motorbike crash
Placebo	Ladewig	Male	44	Suicide 2 days after withdrawing from the study.
Placebo	PRAMA	Female	42	Suicide
Placebo	UKMAS	Male	34	Accidental fall, fatal intracranial hemorrhage, and fractured skull
Placebo	Paille	Male	40	Accidental fall
Placebo	Lesch	Male	50	Cardiac failure
Placebo	Besson	Male	51	Cardiac arrest
Placebo	Barrias	Male	45	Left ventricular hypertrophy due to an alcohol induced cardiomyopathy

* Patient ID numbers have been deleted from this table.

ND: No data are available.

¹ This patient was included despite the death being reported 12 days after last study visit because the exact day of death is unknown.

An additional 13 patients died during the off-treatment Follow-up Phases of these studies (1 had been in the acamprosate 1332 mg/day group, 6 had been in the acamprosate 1998/2000 mg/day group, and 6 had been in the placebo group). The most common cause of death was suicide. No relevant treatment group differences were identified regarding the reported causes of death.

Treatment-Emergent Serious Adverse Events

Overall, a similar percentage of patients experienced a treatment-emergent serious adverse event (SAE) in the acamprosate 1998/2000 mg/day (ranging from 3% to 6%, depending on study groupings) and the placebo group (ranging from 2% to 4%, depending on study grouping). The most frequent SAEs were accidental injury, depression, and overdose (paracetamol, 2 patients; paracetamol and diazepam, 1 patient; panadol, herbal drugs, and placebo, 1 patient; panadol alone, 1 patient; acamprosate 1 patient; and unknown, 1 patient). There were no clinically relevant differences among treatment groups in the percentage of patients who experienced treatment-emergent SAEs in any of the study groupings.

During follow-up in the US 96.1 and Paille studies, a total of 5 SAEs were reported among the 550 enrolled patients. The 5 patients were receiving placebo at the time of the event(s).

Adverse Events Leading to Study Withdrawal

For patients in the Short-Term and Long-Term Group I studies pooled, a similar percentage of patients experienced an adverse event (AE) leading to premature study termination in the acamprosate 1998/2000 mg/day group (140 patients, 8%) and the placebo group (125 patients, 6%).

The most frequently reported AE leading to study withdrawal was diarrhea, experienced by 1% to 3% of patients in the acamprosate 1998/2000 mg/day group depending on study grouping, and <1% in the placebo group. There were no clinically relevant differences among treatment groups in the percentage of patients who experienced each individual AE leading to early termination in any of the study groupings. However, a higher

number of patients withdrew due to diarrhea in the acamprosate pooled group compared to the placebo group in all study groupings. Most events leading to premature termination were experienced by a small number of patients in a particular treatment group.

Treatment-Emergent Adverse Events

The overall incidence of spontaneously reported treatment-emergent adverse events (TEAEs) for the controlled studies was highest in the US 96.1 study (85%, 512/601), followed by the pooled European Short-Term studies UKMAS and ADISA (64%, 560/876) and the pooled European Long-Term studies PRAMA and Paille (55%, 447/810). There were no important treatment group differences observed regarding the overall incidence of spontaneously reported TEAEs in any study grouping.

The most common ($\geq 10\%$ of patients overall) TEAEs in the pooled Short-Term studies were diarrhea (21%) and headache (18%). Further events with an incidence of $\geq 5\%$ of patients overall in the Short-Term studies included pain, abdominal pain, accidental injury, depression, insomnia, diarrhea, nausea, pharyngitis, and rhinitis. The most common ($\geq 5\%$ of patients overall) TEAEs in the Long-Term studies were diarrhea (9%), accidental injury (6%), and depression (5%).

In each study grouping, the incidence of diarrhea and flatulence was significantly higher in either the acamprosate 1998/2000 mg/day group and/or the pooled acamprosate group compared to placebo, reflecting an association of these events with acamprosate treatment. Other events with a significantly higher incidence in acamprosate-treated patients compared to placebo included vomiting in the US 96.1 study, malaise in the Short-Term European studies, and flu syndrome in the Long-Term European studies.

Some of the European studies used a 43-item symptom checklist to supplement spontaneous adverse event reporting. Analyses of these checklist events were supportive of the conclusions made from the incidence of spontaneously reported TEAEs regarding diarrhea.

Based on analysis of the incidence of TEAEs for the pooled controlled Short-Term and Long-Term Group I studies, events with a significantly higher incidence in the acamprosate 1998/2000 mg/day group and the pooled acamprosate group compared to the placebo group included diarrhea and flatulence for spontaneously reported TEAEs, and diarrhea for TEAEs associated with the checklist (reported either spontaneously or by the checklist).

Clinical Laboratory Results

Analysis of laboratory data for the controlled studies showed that Baseline mean values for liver enzymes (GGT, AST, ALT) and MCV were typically above the normal range which is consistent with the high prevalence of alcoholic liver disease and folic acid deficiency expected in this patient population. A substantial improvement was observed in all these parameters during the study period, with a slightly more favorable response seen for GGT in the acamprosate groups compared to the placebo group.

There were no meaningful treatment group differences detected for any other laboratory test. Patients in the European studies showed more severe signs of alcohol dependence/abuse as reflected by higher liver enzyme and MCV values at Baseline, and more apparent improvement was seen in these parameters in the European patient population compared to the US 96.1 study. Laboratory data did not raise any safety concerns related to the use of acamprosate.

Vital Signs and ECGs

Vital signs data collected in the Group I studies, and ECG data from the US 96.1 and UKMAS revealed no treatment group differences.

Influence of Demographic Features and Concomitant Medications

The incidence of treatment-emergent adverse events and the means and mean changes from Baseline in liver function tests (AST, ALT, GGT, and total bilirubin) were analyzed by demographic variables of age (16-39 years, 40-59 years, ≥ 60 years), gender (male, female), race (White, Black, other), and duration of alcohol dependence/abuse (< 10 years, ≥ 10 years) for the pooled studies in the integrated safety database. No

important safety concerns were raised by drug/demographic interactions that would necessitate dose adjustments for acamprosate in any of the demographic categories examined.

The incidence of treatment-emergent adverse events were analyzed by concomitant medication categories, consisting of antidepressants (SSRIs, tricyclics, MAOIs), anxiolytics (e.g., benzodiazepines), hypnotics and sedatives (including the barbiturate phenobarbital), H₂ antagonists (e.g., ranitidine), and analgesics (excluding opioids and anti-migraine preparations). Based on the lack of any meaningful differences, no dose adjustments for acamprosate are considered necessary during concomitant use of any of these drugs.

The incidence of treatment-emergent adverse events was analyzed in patients with or without clinically significant abnormal liver function tests at Baseline for the pooled studies in the integrated database. No significant differences were noted.

Safety Conclusions

In summary, the review of the available safety data for acamprosate from placebo-controlled studies lasting up to 1 year and involving 4243 alcohol-dependent patients has raised no unexpected safety concerns. There were no relevant treatment group differences regarding the incidence and types of serious adverse events or causes of death. A higher number of patients withdrew due to diarrhea in the pooled acamprosate group compared to the placebo group in all study groupings. The most common adverse events associated with the use of acamprosate (based on statistically significantly higher incidences in the acamprosate groups compared to the placebo group) were diarrhea and flatulence (26% vs 15% for diarrhea and 7% vs 3% for flatulence in the acamprosate 1998/2000 mg/day group vs placebo in the Short-Term studies, and 12% vs 6% and 2% vs 0% in the Long-Term studies). Laboratory data for the controlled studies showed a substantial improvement in liver enzymes (GGT, AST, ALT) and MCV in both the acamprosate- and the placebo-treated patients and did not raise any safety concerns related to the use of acamprosate. There were no notable changes in vital signs or ECG results. Because acamprosate is eliminated entirely by the renal route, acamprosate

should not be used in patients with severe renal insufficiency. These findings support the safety of acamprosate at a dose of 1998/2000 mg/day (666 mg t.i.d. or 1000 mg b.i.d.) for a duration of up to one year in the maintenance therapy of abstinence in alcohol-dependent patients.

4.5.3 Additional Safety Information from Clinical Trials

Additional safety information (not included in the integrated safety database) was presented in the integrated safety summary of the acamprosate New Drug Application based on 797 subjects/patients treated in the clinical pharmacology studies (494 subjects received acamprosate), 923 patients in the early clinical experience studies (482 patients received acamprosate), and 3665 patients treated with acamprosate in the European open-label Phase IV post-marketing studies.

Most of the subjects/patients enrolled in the completed clinical pharmacology studies were healthy volunteers and most of these studies enrolled only male subjects/patients, therefore, this population is different from the patient population of the controlled studies regarding demographic characteristics. The patient population enrolled in the early clinical experience studies and the European Phase IV studies was similar in general to the population in the controlled studies regarding demographic characteristics and alcohol dependence history.

In the clinical pharmacology studies, subjects/patients were treated with various doses and formulations of acamprosate for approximately 10 days. The majority of acamprosate-treated patients in the early clinical experience studies received the 1332 mg/day dose for ≥ 90 days. The Phase IV studies, most of which were 6 months in duration, all used total daily doses of 1998 mg/day or the weight-adjusted doses (1332 mg/day for patients ≤ 60 kg and 1998 mg/day for patients > 60 kg).

A total of 16 patients died during the early clinical experience studies (7 patients) and Phase IV studies (9 patients) (4588 patients: 923 in the early clinical experience studies and 3665 in the Phase IV studies). Two of the patients were on placebo (1 cerebrovascular accident, 1 accident). Of the remaining patients, there was 1 death

from homicide, 2 deaths due to accidents or trauma, and 3 patients committed suicide. Five patients died as a result of complications related to chronic alcoholism (variceal bleeding, cirrhosis, pancreatitis, massive alcohol intoxication), there was 1 sudden death; 1 death from surgical complications, and 1 death from circulatory failure in association with asthmatic attack.

In the clinical pharmacology studies, adverse events (AEs) with a higher incidence in acamprosate-treated subjects compared to placebo-treated subjects included headache, diarrhea, nausea, abdominal pain, and flatulence. Acamprosate-treated patients in the early clinical experience studies had a slightly higher incidence of abdominal pain and nausea compared to placebo-treated patients. The most frequently ($\geq 5\%$) reported AEs in the Phase IV studies included diarrhea (21%), headache, insomnia, pruritus, and depression.

In addition, safety results (e.g., incidence of AEs, vital signs, physical examination, laboratory measurements, and ECG recordings) and pharmacokinetic results were analyzed when there was concomitant administration/use of ethyl alcohol, disulfiram, diazepam, imipramine, naltrexone, Atrium, Equanil, and Seresta for patients in the clinical pharmacology studies. Based on these results, no dose adjustments for acamprosate are considered necessary during concomitant use of any of these drugs.

Safety results (e.g., incidence of AEs, vital signs, physical examination, laboratory measurements, and ECG recordings) were analyzed for patients with hepatic or renal impairment in the clinical pharmacology studies. In addition, for patients with hepatic or renal impairment, pharmacokinetic results were analyzed. Based on the safety and pharmacokinetic results, no dose adjustments for acamprosate are considered necessary for patients with hepatic impairment. The pharmacokinetic and renal clearance values for patients with renal impairment strongly suggest that prolonged dosing with acamprosate would lead to accumulation of the drug in these patients. Thus, acamprosate should not be used in patients with severe renal insufficiency.

4.6 SUMMARY OF EVIDENCE OF EFFICACY AND SAFETY FROM GROUP I CONTROLLED CLINICAL TRIALS

4.6.1 Summary of Efficacy

- Across 3 pivotal efficacy studies in alcohol-dependent outpatients, conducted in Belgium, Germany, and France, a total of 623 patients on acamprosate and 375 patients on placebo were evaluated with regard to the effectiveness of acamprosate in maintaining abstinence following withdrawal from alcohol. All patients had completed alcohol-withdrawal treatment and were abstinent prior to beginning study medication. Two dose levels of acamprosate were examined in 2 of the studies (1332 mg/day and 1998 mg/day, both with t.i.d. divided dosing) and in the 3rd study, acamprosate was dosed on the basis of body weight, but most patients received 1998 mg/day. Treatment periods were 1 year in 2 of the studies and 3 months in the remaining study. Analyses of primary efficacy parameters reflective of abstinence in these studies demonstrated that patients treated with acamprosate realized improvements in their disease that were statistically significant and clinically meaningful. Patients treated with acamprosate in these studies abstained from their first drink 2 to 3 times longer, had a complete abstinence rate 2 to 3 times greater, and were abstinent 20% to 38% more days while on study than patients treated with placebo. For these primary efficacy parameters, there was also evidence of dose-relatedness of response in the 2 studies which generated these data, with patients in the 1998 mg/day group showing a stronger treatment effect than the 1332 mg/day group.
- Additional analyses of secondary parameters in these 3 studies, predominantly related to quantitative assessment of drinking behavior and global outcome, were consistent with these findings. These benefits were consistent across subgroups of patients defined by demographic characteristics, aspects of the history of alcohol use, and categories of concomitant medications frequently used in alcohol-dependent patients.
- In the two pivotal 1-year studies (PRAMA and Paille), both of which had follow-up periods, it was apparent that the benefits of treatment with acamprosate were

maintained while patients continued to be followed, off treatment (but still under double-blind conditions relative to the completed treatment phase), for an additional year (PRAMA) or while on placebo-only for a 6-month follow-up period (Paille). During the follow-up period, abstinence rates in groups previously assigned to acamprosate and placebo gradually decreased, but the difference was still apparent.

- The effectiveness of acamprosate demonstrated in the 3 pivotal efficacy studies was also evaluated relative to the findings in 9 European supportive efficacy studies of similar design conducted in Austria, Belgium, Italy, Luxemburg, the Netherlands, Portugal, Spain, Switzerland, and the United Kingdom. These studies involved 2628 alcohol-dependent patients, 1302 on acamprosate and 1326 on placebo. In 8 of the 9 studies, patients underwent alcohol withdrawal therapy and were to be abstinent for at least 5 days prior to starting study medication. In the remaining trial, study medication was to be started concurrently with withdrawal therapy (ADISA).

In 5 of the 6 short-term (6-month) and all 3 long-term (1-year) supportive studies, acamprosate was also associated with more days of abstinence (and a higher percentage of abstinent time while on study), a longer period of time to the first drink, and a higher rate of complete abstinence. The single study (UKMAS) which failed to show a significant difference between the acamprosate and placebo groups was noteworthy for its high rate of relapse to drinking (30%) prior to initiation of study medication and the long latent period between the end of withdrawal therapy and initiation of study medication.

- In the US study (US 96.1), which did not require alcohol withdrawal or medicated detoxification prior to study entry and which had a high rate of non-abstinence at baseline (50%), the planned primary analysis also showed no significant difference between acamprosate and placebo in the ITT population.

However, since the patients in the US study had not begun their study treatment in an abstinent condition or with necessarily a significant level of commitment to treatment (as had patients in the European studies), effectiveness of acamprosate was examined more closely in a subset of patients in the US study who were clearly more motivated

to become or maintain abstinence, in that they had identified total abstinence as their treatment goal. This group constituted about 40% of the total US 96.1 study population. Results of efficacy analyses among these patients in the US study who had a treatment goal of abstinence (Motivated ITT population) showed that treatment with acamprosate had a beneficial effect on cumulative abstinence duration and drinking behavior. Even more promising results were seen in the subset of these motivated patients who had a greater commitment to their own treatment as demonstrated by their adherence with the study requirements and treatment regimen (Motivated EFF population). Among patients in the Motivated ITT and Motivated EFF populations treated with acamprosate, the relative percentage of abstinent days while on study was 22% and 28% higher, respectively, than that for patients treated with placebo. In the Motivated EFF population, the rate of “good” response on CCAD (abstinent at least 90% of time on study) was 33% higher for patients treated with acamprosate compared to those on placebo. Results in the subset of Motivated patients from the US study thus support the overall findings of effectiveness in the European studies.

4.6.2 Summary of Safety Information

A total of 4243 alcohol-dependent patients were randomized in the Group I double-blind, placebo-controlled studies: 2565 patients in the short-term studies (601 patients in the US 96.1 study and 1964 patients in the European short-term studies) and 1678 patients in the long-term studies. Collectively, there were 2272 patients in this group who were randomized to acamprosate. Additional safety information based on 797 subjects/patients treated in the Group II clinical pharmacology studies (494 subjects received acamprosate), 923 patients in the Group III early clinical experience studies (482 patients received acamprosate), and 3665 patients treated with acamprosate in the Group IV post-marketing studies has been reviewed. In total, almost 7000 patients (6913) have been exposed to acamprosate in clinical trials.

- A total of 49 deaths were reported in all these study groupings combined. The most frequently reported causes of death were suicide and accidents, which is not

unexpected for a study population of alcohol-dependent patients. No relevant differences were seen between treatment groups regarding the reported causes of death.

- Overall,^p a similar percentage of patients experienced a treatment-emergent serious adverse event (SAE) in the acamprosate group (range 3% to 6%^q), compared to the placebo group (range 2% to 4%). The most frequent SAEs were accidental injury, depression, and overdose (only 1 of the 7 overdoses was with acamprosate). There were no clinically relevant differences among treatment groups in the percentage of patients who experienced treatment-emergent SAEs in any of the study groupings.
- Withdrawals from clinical trials due to an adverse event (AE) were slightly higher in the acamprosate group (range 8% to 12%), than in the placebo group (range 7% to 9%). The most frequently reported AE leading to withdrawal was diarrhea, responsible for withdrawal by from 1% to 3% of patients in the acamprosate group, and <1% in the placebo group. There were no clinically relevant differences among treatment groups in the percentage of patients who experienced any other individual AE leading to withdrawal in any of the study groupings. Most events leading to withdrawal were experienced by a small number of patients in a particular treatment group.
- There were no important treatment group differences observed regarding the overall incidence of spontaneously reported treatment-emergent adverse events (TEAEs) in any study grouping.
- In each study grouping the only body system with a statistically significantly higher incidence of adverse events in the acamprosate group was the Digestive System, because of an increase in the incidence of diarrhea. The difference in the incidence of diarrhea between the acamprosate groups and the placebo group, ranged from an

^p In the discussion of adverse event incidence, only information from the Group I studies is presented, with the primary comparison being the acamprosate group at the recommended daily dose (1998/2000 mg/day) and placebo groups, unless otherwise specified.

^q Wherever ranges are given, they are derived from results of the various study groupings used in the ISS analysis .

excess of 6% (*Paille, PRAMA*) to 17% (*US 96.1*) in the acamprosate-treated patients. The difference between the acamprosate and placebo groups for most of the European studies was an excess of 8% of cases in the acamprosate group. The other Digestive System symptom which occurred significantly more often in the acamprosate groups was flatulence, with an excess incidence in the acamprosate groups of 3% to 5%, compared to the placebo group.

- Based on information from the early clinical experience studies it was considered that, in addition to diarrhea, acamprosate was associated with an increased incidence of pruritus and other dermatologic conditions, as well as changes in libido. However, based on the current review and integrated analyses of Group I controlled-trial data, only diarrhea and flatulence occur with a significantly greater incidence in acamprosate-treated patients, across the study groupings.

5. OVERALL CONCLUSIONS

As noted above, alcohol dependence is more than a physical disease. It is an addictive behavior with complex biological, psychological, and social aspects. In order to break the cycle of alcohol dependence, a high degree of involvement and commitment on the part of the patient is required. Prior to beginning a multi-faceted approach to maintaining abstinence, the patient must withdraw from alcohol.

The availability in the United States of acamprosate enteric-coated tablets, a unique centrally-acting drug, specifically developed for maintaining long-term abstinence in the alcohol-dependent patient who has discontinued alcohol intake, will add a new dimension to the therapeutic possibilities of this disease. Its effectiveness on mean values for relevant parameters related to abstinence (improvement in abstinence rate, more abstinent days, longer time to first drink, decreased alcohol consumption), although modest, are consistently seen over diverse populations, which included alcohol-dependent patients of varying severity. Those who will benefit most from acamprosate are patients with:

- moderately severe alcohol dependence,
- a commitment to remaining abstinent,
- medication compliance, both initial and continued, and
- a supportive family structure.

However, this should not preclude the relevance of acamprosate treatment for other alcohol-dependent patients. Motivation enhancement strategies can be used for patients with the milder symptoms and more intensive, comprehensive treatment programs can be developed for those with more severe dependence.

A variety of psychosocial therapies can be used with acamprosate, and should not affect therapeutic response. Acamprosate can be safely used with a variety of other therapeutic agents commonly employed as part of supportive care for the alcohol-dependent patient who has discontinued or is discontinuing alcohol use.

It is recommended that acamprosate treatment be given for one year.

Acamprosate is not metabolized and is not protein bound. It is eliminated by renal excretion. It can be used in patients with mild or moderate hepatic impairment. It should not be used in patients with renal insufficiency, unless dosage can be adjusted. Acamprosate has a high safety margin, and even single doses as great as 56 grams have been ingested without significant symptomatology. Acamprosate does not appear to have abuse or dependence potential.

6. REFERENCES

1. Mc Lellan A.T., Lewis D.C., O'Brien, C.P., Kleber, H.D. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation *JAMA* 2000, 284:1689-1695.
2. Cooper S.J. Benzodiazepine mechanisms and drinking in water deprived rats. *Neuropharmacology*, 1982, 21:775-780.
3. Goldstein D.B. Alcohol withdrawal reactions in mice: Effects of drugs that modify neurotransmission. *Pharmac. Exp. Ther.*, 1973, 186:1-9.
4. Volicer L. GABA levels and receptor binding after acute and chronic ethanol administration. GABA Neurotransmission. *Brain Research Bulletin*, 1980,5(2): 809-813.
5. Tran G. Acetyl homotaurinate de calcium : Pharmacologie et orientation therapeutique calcium acetylhomotaurinate: Pharmacology and therapeutic orientation. Diplome D'etude et de Recherche en Biologie Humaine, 1984, 13 June: 1-92.
6. Zeise M.L., Kasparov W.S., Capogna M., Zieglgansberger W. Calciumdiacetylhomotaurinate (Ca-AOTA) decreases the action of excitatory amino acids in the rat neocortex in vitro. *Prog. Clin. Biol. Res.*, 1990, 351:237-242.
7. Zeise M.L., Kasparov S., Capogna M., Zieglgansberger W. Acamprosate (calciumacetylhomotaurinate) decreases postsynaptic potentials in the rat neocortex: possible involvement of excitatory amino acid receptors. *Eur. J. Pharmacol.*, 1993, 231.1:47-52.
8. Naassila M., Hammoum I .S., Legrand E., Durbin P., Daoust M. Mechanism of action of acamprosate. Part 1: Characterization of Spermidine-sensitive Acamprosate binding site in rat brain. *Alcohol. Clin. Exp. Res.*, 1998, 22.4:802-809.
9. Al Qatari M., Bouchenafa O., Littleton J.M. Mechanism of action of Acamprosate. Part 2 :Ethanol dependence modifies effects of acamprosate on NMDA receptor binding in membranes from rat cerebral cortex. *Alcohol. Clin. Exp. Res.*, 1998, 22.4:810-814.
10. Boismare F., Daoust M., Moore N.D., Saligaut C., Lhuintre J.P., Chretien P., Durlach J. A homotaurine derivative reduces the voluntary intake of ethanol by rats : are cerebral GABA receptors involved ? *Pharmacol. Biochem. Behav.*, 1984, 21.5:787-789.
11. Boismare F., Daoust M., Moore N.D., Chretien P., Saligaut C. Les récepteurs gabaergiques sont-ils concernés dans la prise volontaire d'éthanol (PVE) par le rat? Are the gabaergic receptors involved in the voluntary intake of ethanol (VIE) by the rat? *J. Pharmacol.*, 1984, 15.4:457-458.

12. Spanagel R., Holte R.S.M., Allingham K., Landgraf R., Zieglgansberger W. Acamprosate and alcohol: I. Effects on alcohol intake following alcohol deprivation in the rat. *Eur. J. Pharmacol.*, 1996, 305:1-3:39-44.
13. Heyser C.J., Schulteis G., Durbin P., Koob G.F. Chronic acamprosate eliminates the alcohol deprivation effect while having limited effects on baseline responding for ethanol in rats. *Neuropsychopharmacology*, 1998, 18.2:125-133.
14. Spanagel R., Zieglgansberger W., Hund T.W. Acamprosate and alcohol : III Effects on alcohol discrimination in the rat. *Eur. J. Pharmacol.*, 1996, 305:51-56.
15. Littleton J. Acamprosate: expert report 1997. Univ. of Kentucky, Tobacco and Health Research Institute, 1997.
16. Lhuintre J.P., Moore N.D., Saligaut C., Boismare F., Daoust M., Chretien P., Tran G., Hillemand B. Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. *Lancet*, 1985, 1.8436:1014-1016.
17. Lhuintre J.P., Moore N.D., Tran G., Steru L., Langrenon S., Daoust M., Parot P., Ladure P., Libert C., Boismare F., Hilleman D.B. Acamprosate appears to decrease alcohol intake in weaned alcoholics. *Alcohol Alcohol.*, 1990, 25.6:613-622.
18. Pelc I., Verbanck P., Le Bon O., Gavrilovic M., Lion K., Leheret P. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients. *Br. J. Psychiatry*, 1997, 171:73-77.
19. Ewing J.A. Detecting alcoholism: the CAGE questionnaire. *JAMA*. 1984;252:1905-1907.
20. Selzer M.L. The Michigan Alcoholism Screening Test: The quest for a new diagnostic instrument. *Am J Psychiatry* 127:1653-1658, 1971.
21. Sass H., Soyka M., Mann K., Zieglgansberger W. Relapse prevention by Acamprosate. Results from a placebo-controlled study on alcohol dependence. *Arch. Gen. Psy.*, 1996, 53.8:673-680.
22. Sass H., Mann K., Soyka M. Medikamentöse Unterstützung der Rückfallprophylaxe bei alkoholkranken Patienten mit Acamprosat - Ergebnisse einer doppelblinden, randomisierten, placebokontrollierten Studie. Medication support with acamprosate for relapse prevention in alcoholic patients – Results of a double-blind, randomized, placebo-controlled study. *Sucht*, 1996, 42.5:316-322.
23. Schadlich P.K., Brecht J.G. The cost effectiveness of Acamprosate in the treatment of alcoholism in Germany. Economic evaluation of the prevention of relapse with acamprosate in the management of alcoholism (PRAMA-Study). *Pharmacoeconomics*, 1998, 13.6:719-730.
24. International Statistical Classification of Diseases and Related Health Problems (Ninth Revision). World Health Organization, 1975.

25. Feuerlein W., Ringer C., Kofner H., and Antons K. Diagnosis of alcoholism. The Munich Alcoholism Test (MALT). (Author's transl) *Mtlnchn Med Wschr* 119:1275-1282, 1977.
26. Die "Göttinger Abhängigkeitsskala (GABS)"; Ein Verfahren zur differentiellen Erfassung der Schwere der Alkoholabhän-gigkeit. *Suchtgefahren* 33, 23-26 (1987).
27. Paille F., Guelfi J.D., Perkins A., Royer R.J., Steru L., Parot P. Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. *Alcohol Alcohol.*, 1995, 30.2:239-247.
28. Paille F., Guelfi J.D., Perkins A., Royer R.J., Steru L., Parot P. Etude multicentrique en double aveugle de l'acamprosate dans le maintien du sevrage alcoolique. Double blind multicenter study of acamprosate in the maintenance of withdrawal from alcohol. *Alcoolologie*, 1996, 18.1:15-22.
29. Paille F., Parot P., Gillet C. Contribution of acamprosate in maintaining abstinence in weaned alcohol dependent patients : Additional results of the second French multicentre study. 1st Campral Symposium, 1996, Ed. Soyka M. Springer Verlag:143-154, (Proceedings of the 1st Campral Symposium, Stuttgart, Germany, 6-9 Sept., 1995).
30. Kaplan E.L., Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*, 1958;53:457-81.
31. Cochran W G. "Some methods of strengthening the common χ^2 tests," *Biometrics*, 10 (1954), 417-451.
32. Poldrugo F. Acamprosate treatment in a long-term community-based alcohol rehabilitation. *Addiction*, 1997, 92.11:1537-1546.
33. Tempesta E., Janiri L., Bignamini A.A., Chabac S., Potgieter A.S. Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. *Alcohol Alcohol.*, 2000, 35.2:202-209.
34. Geerlings P., Ansoms C., Van Den Brink W. Acamprosate and prevention of relapse in alcoholics. Results from a randomized, placebo-controlled double-blind study in out-patient alcoholics in the Netherlands, Belgium and Luxembourg. *Eur. Addict. Res.*, 1997, 3:129-137.
35. Chick J., Howlett H., Morgan M.Y., Ritson B. United Kingdom Multicentre Acamprosate Study (UKMAS): A 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. *Alcohol Alcohol.* 2000, 35.2:176-187.

36. Gual A and Leher P. Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. *Alcohol & Alcoholism* 2001, 36:5:413-18
37. Armitage P, Berry G. Statistical methods in medical research (2nd ed). Blackwell Scientific Publications, Oxford, 1987:107-12.
38. Lee E., Desu, M.. "A computer program for comparing k-samples with right-censored data", Computer Programs in Biomedicine, 1972; 2:315.
39. Mann, H.B., and D. R. Whitney, "On a Test of Whether One of Two Random Variables Is Stochastically Larger than the Other," *Ann. Math. Statist.*, 18 (1947), 50-60.
40. Armitage P., Berry G. Statistical methods in medical research (2nd ed). Blackwell Scientific Publications, Oxford, 1987:129-32.
41. Spencer M.P., and Folstein M.F. The Mini-Mental State Examination. In: P.A. Keller and L.G. Ritt (Eds). *Innovations in Clinical Practice: A Source Book*. Vol 4. Sarasota, FL: Professional Resource Exchange, Inc., 307-308, 1985.
42. Neter J., Wasserman W., Kutner M. Applied linear statistical models. Richard D. Irwin, Inc, Homewood, Illinois, 1990:861-906.
43. Hosmer D., Lemeshow S. Applied Logistic Regression. John Wiley and Sons, Inc., New York, 1989.
44. Whitworth A.B., Fischer F., Lesch O.M., Nimmerichter A., Oberbauer H., Platz T., Potgieter A.S., Walter H., Fleischhacker W.W. Comparison of acamprosate and placebo in long-term treatment of alcohol dependence *Lancet* 1996 347.9013:1438-1442.
45. Barrias J.A., Chabac S., Ferreira L., Fonte A., Potgieter A.S., Teixeira D.E., Sousa E. Acamprosate : Estudo português, multicêntrico de avaliação da eficácia e tolerância Acamprosate: Portuguese multicenter study evaluating efficacy and tolerance. *Psiquiatr. Clin.* 1997, 18.2:149-160.
46. Besson J., Aebly F., Kasas A., Leher P., Potgieter A.S. Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism : a controlled study. *Alcohol. Clin. Exp. Res.* 1998, 22.3:573-579.
47. Savage I.R. *Ann. Math. Statist.*, 1956; 27:590-616.
48. Tarone R.E., Ware J. On distribution-free tests for equality of survival distributions. *Biometrika*, 1977; 64:156-60.
49. Breslow N.E., Day N.E. Statistical Methods in Cancer Research, Volume 1: The Analysis of Case-Control Studies, Lyon, International Agency for Research on Cancer, 1980.
50. Kendall M.G. *Biometrika*, 1938; 30: 81-93.

51. Dept. of Health and Human Services. "COSTART": Coding Symbols for Thesaurus of Adverse Reaction Terms. 5th Edition, U.S. Government Printing Office, Washington, 1995.