

**Clinical Background Materials for
Psychopharmacologic Drugs
Advisory Committee Meeting**

May 10, 2002

**NDA 21-431
Acamprosate for Maintenance of
Abstinence in Alcoholics after
Detoxification**

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EXECUTIVE SUMMARY

1 Questions

The committee is asked to consider the evidence of efficacy of acamprosate in the treatment of alcoholism and to provide advice on the following questions:

- Given the conflicting results between the older, European studies and the more recently conducted American study, is there sufficient evidence of the efficacy of acamprosate in the treatment of alcoholism to warrant approval?
- How can the discrepant results be reconciled? Do the data support any conclusions regarding subgroups of patients more likely to benefit from acamprosate?

Should additional clinical studies be undertaken to evaluate the responsiveness of the US alcoholic population to acamprosate at higher doses?

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

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. Acamprosate was authorized for marketing in France, for the indication of maintaining abstinence from alcohol post-withdrawal, in 1987 and has been commercially available (as Aotal) there since 1989, in the 333 mg tablet strength. Lipha also markets the acamprosate 333 mg tablets (as Campral) in 38 additional countries. On 6/25/96, Lipha met with the FDA in a Pre-IND meeting to discuss plans to seek marketing authorization in the United States. The initial program proposed consisted of a single multi-center efficacy trial using a new (but compositionally proportional) 500 mg tablet, intended to offer a simpler (b.i.d.) regimen with a total daily dose very similar to the labeled dose for the 333 mg tablet (2000 mg as 500 mg, ii p.o. b.i.d. vs 1998 mg as 333 mg ii p.o. t.i.d.). The single U.S. trial was to support the application as a pivotal safety and efficacy trial; two completed European trials using the 333 mg tablet were to be submitted as confirmatory evidence of efficacy. When the U.S. trial failed to demonstrate superiority of acamprosate over placebo, further discussions were held and Lipha elected to submit an application for the 333 mg tablet using the European data as pivotal.

The clinical program reviewed for this briefing includes the three pivotal European studies, the U.S. study, and 10 additional European studies submitted without primary data.

2.2 Efficacy

Four studies were available for complete review of primary data. Ten additional studies were available for review of final study reports.

Of the four studies reviewed as primary datasets, three were European studies conducted in late 1980's-early 1990's which provided evidence of efficacy of acamprosate in maintaining abstinence in recently-detoxified alcoholics. The sponsor's primary endpoint, the mean percent of study days subjects spent in an abstinent state, was rejected by the reviewer as representing a false precision, given the method of data collection. However, other analyses relying less on imputation of data supported the efficacy of acamprosate. The single recent, carefully-conducted American study which featured recording of drinking behavior on a day-to-day basis, was unable to demonstrate an effect of acamprosate on any measure. Attempts to identify a subset which did benefit (based on similarity to the European study populations on various parameters) were not successful.

The ten additional studies also used the percent days abstinent/cumulative abstinence duration outcome, which was judged by the reviewer to be overly reliant on imputed data. Of these, only one study (conducted in the U.K.) featured daily recording of drinking behavior to facilitate analysis of drinking data on a day to day basis, and only this one failed to demonstrate an effect of acamprosate. The other studies did, however, tend to show effects of acamprosate on more conservative measures relying less on imputed data.

2.3 Safety

Acamprosate is poorly absorbed and not metabolized. In general, it presents a fairly benign safety profile notable only GI effects.

2.4 Dosing

The proposed to-be-marketed dose of acamprosate is 1998 mg/day (two 333 mg tablets t.i.d.). Early studies on acamprosate described by the sponsor suggested this dose to be more effective than lower doses, while higher doses were not studied as a regimen requiring more than six tablets per day was deemed impractical. Some data has been generated using a 500 mg tablet at a 3000 mg/day dose, but it is insufficient to assess the risk/benefit ratio of this dose.

REVIEW AND EVALUATION OF EFFICACY DATA

1 INTRODUCTION AND BACKGROUND

1.1 General Information

- Drug Established Name: Acamprosate Tablets (USAN ballot pending)
- Chemical Name: calcium acetylamino propane sulfonate
- Proposed Trade Name: TBA
- Drug Class:
- Sponsor's Proposed Indication(s): for the maintenance of abstinence from alcohol in patients with alcohol dependence who have been withdrawn from alcohol and want to maintain their abstinence [to be used as] part of a comprehensive management program that includes psychosocial support.
- Dose: 333 mg tablets
- Regimens: 666 mg (two tablets) p.o. t.i.d.
- Age Groups: Adults

Studies in adolescents deferred to Phase IV
Studies in children waived

1.2 State of Armamentarium for Indication

Alcoholism is commonly treated with non-pharmacologic psychosocial therapy and/or mutual self-help groups (Alcoholics Anonymous, e.g.). When pharmacologic treatment is used, the usual practice in this country is to combine medication with psychosocial treatment. However, it should be noted that the paucity of pharmacologic options has tended to drive the treatment of alcoholism into the "behavioral health" arena. The availability of effective pharmacologic treatment may be expected to shift the treatment of alcoholism into the primary care venue.

There are two drugs approved for the treatment of alcoholism, disulfiram and naltrexone.

Disulfiram (Antabuse), a DESI drug approved prior to the requirement of evidence of efficacy, works through a mechanism unlikely to be approved by today's standards. Disulfiram interferes with the hepatic oxidation of acetaldehyde resulting in a 5-10 fold increase serum acetaldehyde concentrations and associated dramatically aversive physical symptoms. Disulfiram's efficacy is limited by poor compliance, and it is generally used only in highly motivated individuals or in compulsory treatment settings. In addition, the label notes that "hepatic toxicity including hepatic failure resulting in transplantation or death have been reported. Severe and sometimes fatal hepatitis associated with disulfiram therapy may develop even after many months of therapy. Hepatic toxicity has occurred in patients with or without prior history of abnormal liver function."

Naltrexone, approved initially for the blockade of exogenously administered opioids,

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received supplemental approval for the treatment of alcoholism in 1995. Its efficacy is also limited by problems with compliance, and its post-approval acceptance has been limited. Naltrexone's label also carries a warning concerning hepatic toxicity.

1.3 Important Milestones in Product Development

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. Acamprosate was authorized for marketing in France, for the indication of maintaining abstinence from alcohol post-withdrawal, in 1987 and has been commercially available (as Aotal) there since 1989, in the 333 mg tablet strength. Lipha also markets the acamprosate 333 mg tablets (as Campral) in 38 additional countries. On 6/25/96, Lipha met with the agency in a Pre-IND meeting to discuss plans to seek marketing authorization in the United States. The initial program proposed consisted of a single multi-center efficacy trial using a new (but compositionally proportional) 500 mg tablet, intended to offer a simpler (b.i.d.) regimen with a total daily dose very similar to the labeled dose for the 333 mg tablet (2000 mg as 500 mg, ii p.o. b.i.d. vs 1998 mg as 333 mg ii p.o. t.i.d.). The single U.S. trial was to support the application as a pivotal safety and efficacy trial; two completed European trials using the 333 mg tablet were to be submitted as confirmatory evidence of efficacy. When the U.S. trial failed to demonstrate superiority of acamprosate over placebo, further discussions were held and Lipha elected to submit an application for the 333 mg tablet using the European data as pivotal.

Several milestones in the development program are noted in the table below.

| | | |
|----------|-------------------|---|
| 6/25/96 | Pre-IND meeting | Proposal to study 500 mg tablet (ii p.o. b.i.d) in a single U.S. study, and to submit this plus two completed European studies of 333 mg tablet (ii p.o. t.i.d.) as pivotal. Agreement in principle by Agency. |
| 10/29/96 | IND 51,809 opened | |
| 10/27/98 | "update" meeting | Need for safety data in polysubstance abusers discussed; sponsor also encouraged to consider geriatric and pediatric issues. |
| 1/27/00 | Pre-NDA meeting | US Trial failed to meet primary efficacy endpoint; post-hoc analysis proposed but not accepted by Agency. Plan for NDA revised to current approach of seeking marketing authorization for 333 mg tablet using completed European trials as support. |
| 6/7/00 | | Letter from NIAAA indicating that there were no concerns about the applicability of European data to the American alcoholic population. |
| 12/27/01 | NDA submission | |

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| 5/10/02 | PDAC Meeting | Discussion of conflicting results of American vs. European studies |
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1.4 Other Relevant Information

1.4.1 Foreign Marketing Status

Acamprosate is marketed in 39 countries. It was first made available in France in 1989, and Lipha estimates that over 1 million patients with alcohol dependence have been treated with acamprosate since that time. The table below (sponsor's in-text table 3.3.1) illustrates acamprosate's global regulatory status as of 11/01.

Table 1.4.1 Foreign Marketing Status of Acamprosate

| Country | Registration Procedure | Submission Date (day/month/yr) | Approval Date (day/month/yr) | AMM Holder | Trade Name | Registration Number | Presentation Registered (# of tablets/box) | Launch Date (day/month/yr) |
|---------------------------|----------------------------|--------------------------------|------------------------------|-------------------------|---------------------|---------------------|--|----------------------------|
| ACAMPROSATE 333 MG | | | | | | | | |
| ARGENTINA | National | 19.09.1996 | 13.05.1997 | MERCK QUIMICA ARGENTINA | Camprol | 46200 | 60, 84, 180, 200 | 01.04.2000 |
| AUSTRALIA | National | 30.10.1997 | 08.1999 | LIPHA SA | Camprol | - | - | 10.1999 |
| AUSTRIA | National | 20.09.1994 | 25.04.1996 | MERCK GmbH WIEN | Camprol | 1 - 21427 | 84* | 01.07.1996 |
| | National (2nd application) | 09.06.1997 | 22.01.1998 | LIPHA S.A. LYON | Acamprosate "LIPHA" | 1-22348 | 84, 168 | |
| BELGIUM | EU multi-state | 18.11.1994 | 29.08.1996 | MERCK BELGOLABO | Camprol | 177 IS 14 F 3 | 24; 84* | 21.04.1997 |
| BOLIVIA | National | 14.08.1995 | 23.03.1999 | INTI BOLIVIA | Camprol | II-19424.99 | 84 | - |
| BRAZIL | National | 25.03.1998 | 06.10.1998 | MERCK BRAZIL | Camprol | 790 | 48, 84 | 01.01.2000 |
| CHILE | National | 02.09.1996 | 30.09.1997 | MERCK QUIMICA CHILENA | Camprol | F-0024197 | 10, 12, 30, 34, 30, 36, 48, 5060, 72, 84* | 15.06.1998 |
| COLOMBIA | National | 08.11.1996 | 03.11.1997 | MERCK COLOMBIA S.A. | Camprol | SA-007278 | 84 | - |
| COSTA RICA | National | 04.1998 | 16.01.1999 | MERCK CENTROAMERICANA | Camprol | - | 84 | - |
| CZECH REPUBLIC | National | 01.08.1996 | 23.11.1998 | LIPHA S.A LYON | Camprol | 87.529.98-C | 60, 84, 200 | 01.01.2000 |
| DENMARK | National | 12.05.1995 | 09.11.1999 | LIPHA S.A LYON | Camprol | 17543 | - | 03.2000 |
| DOMINICAN REPUBLIC | National | 04.2000 | 21.06.2001 | MERCK CENTROAMERICANA | Sobrol | 2001-1047 | 84 | |
| ECUADOR | National | 10.11.97 | 01.12.1998 | MERCK ECUADOR | Camprol | 22470-11-98 | 84 | - |

1.5 Important Issues with Pharmacologically Related Agents

There are no pharmacologically related agents.

2 CLINICALLY RELEVANT CHEMISTRY, ANIMAL PHARMACOLOGY AND

TOXICOLOGY, AND BIOPHARMACEUTICS ISSUES

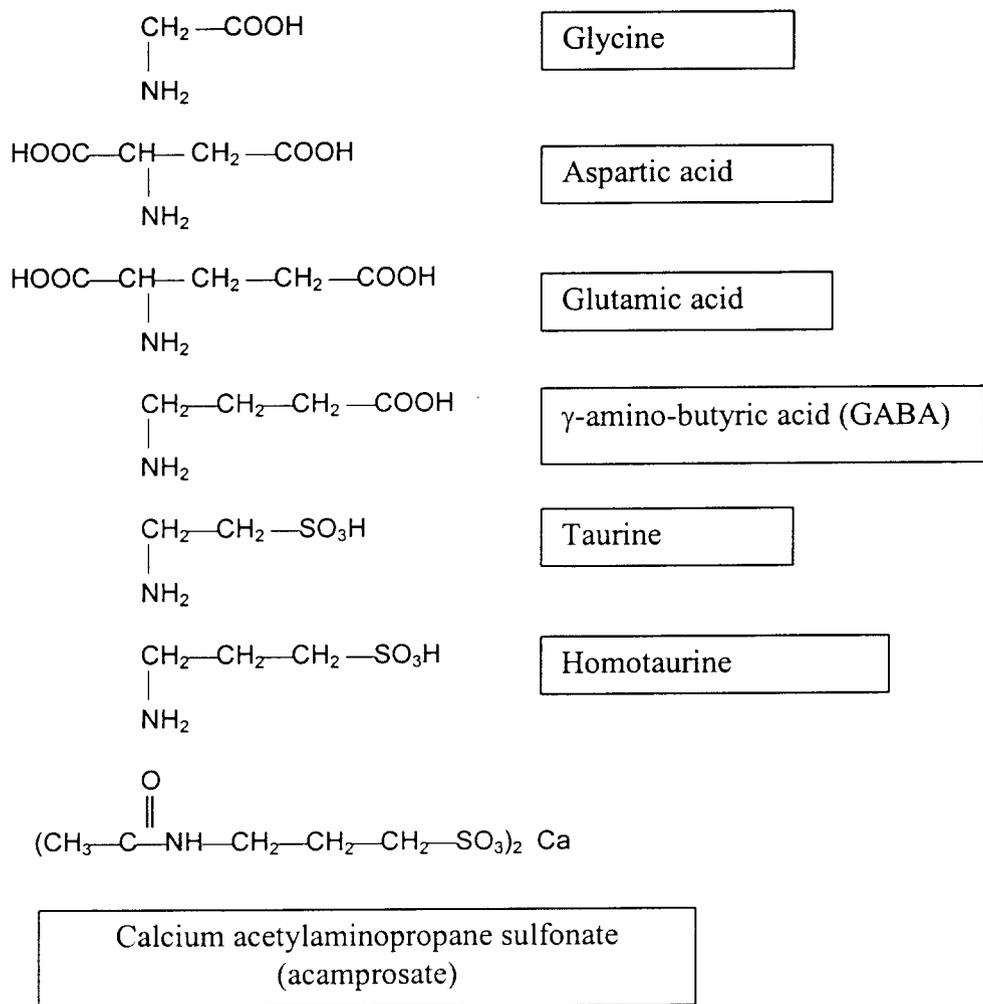
Much of the material below is taken from the sponsor's NDA summary.

2.1 Pre-clinical Efficacy

Acamprosate, a homotaurine derivative with modified polarity, was synthesized in order to improve the cerebral transfer of homotaurine.

Homotaurine (3-amino-propanesulfonic acid) is a higher homologue of the naturally occurring amino acid, taurine, with structural similarities to the neurotransmitter, γ -amino butyric acid (GABA) (see figure below). 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. Cerebellar GABA concentrations have also been shown to decrease after chronic alcoholization. Homotaurine, a GABA agonist which is not naturally occurring, does not cross the blood-brain barrier; acamprosate has been synthesized to overcome this limitation. 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.

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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. 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

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when levels of endogenous activators are high (as in alcohol withdrawal). 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.

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. Acamprosate appears to restore this balance, with a major mechanism being the normalization of function of glutamate receptors of the NMDA receptor subtype.

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. 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, 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. Animal studies have also shown that acamprosate is devoid of hypnotic, anxiolytic or myorelaxant properties, thereby distinguishing it from barbiturates and benzodiazepines. It has also been largely inactive in studies to detect antidepressant activity. Finally, there is no animal evidence that acamprosate has abuse potential.

3 HUMAN PHARMACOKINETICS

Initial clinical studies for the European multinational marketing authorization dossier (and other national registration dossiers), carried out by Lipha s.a., and presented in this NDA used a formulation of acamprosate 333 mg enteric-coated tablets that was thereafter modified by Lipha s.a. to meet current international industrial requirements. Since the change in formula, the reformulated tablets have been used in subsequent (Phase IV) studies. This formulation is the enteric-coated tablet which is currently marketed worldwide is proposed for marketing in the U.S.

Bioequivalence could be established for $AUC_{0-\infty}$, but not for C_{max} after single dose administration of 666 mg tablets using the clinical development formulation (reference) and the currently marketed formulation (test). A period effect in that study precluded, 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. After administration of 666 mg t.i.d. of the same formulations under steady-state conditions, the formulations were bioequivalent (confidence intervals of the ratios within 0.8 to 1.25) with respect to $AUC_{0-\infty}$, AUC_{0-last} and AUC_{0-n} and C_{max} .

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The acamprosate 500 mg enteric-coated tablet was also manufactured with the “current formula” and differs from the 333 mg tablet only in proportion of ingredients. The 500 mg tablet strength was, and continues to be, utilized in clinical trials in the United States under IND 51,809.

3.1 Pharmacokinetic Parameters

Much of the text below is taken from the sponsor’s summary of pharmacokinetics.

The oral absolute bioavailability of acamprosate tablets after single-dose administration has been shown to be approximately 11%. After administration of two 333 mg tablets, the C_{max} of approximately 94 ng/ml is reached at T_{max} of 4.5 hours. After multiple-dose administration of 666 mg t.i.d., the C_{max} is approximately 353 ng/ml and steady state is reached within 5 days.

Acamprosate is not protein bound. It does not appear to be metabolized, and is excreted unchanged in urine. Renal clearance is high following either oral or intravenous administration, suggesting a role of tubular secretion.

The $T_{1/2}$ after oral administration of acamprosate tablets is approximately 21 hours. This is attributed to rate-limiting absorption, as the terminal half-life is much shorter after i.v. administration (6 hours) and somewhat shorter after administration of oral solution (14-18 hours).

Food effect studies showed that the C_{max} of single-dose acamprosate was decreased by 45% and the AUC was decreased by 23% in the presence of food. However, the effect of food in the multiple-dose, steady-state context has not been evaluated and most clinical trials specifically instructed subjects to take acamprosate with meals.

No gender differences in pharmacokinetics have been identified. Age differences have not been studied.

In alcohol-dependent patients, following alcohol withdrawal, treated with acamprosate tablets at a dose of 666 mg t.i.d for 29 days, acamprosate PK did not differ from historical controls in the same analytical laboratory.

Studies in subjects with chronic to acute hepatic impairment were performed after single and repeated doses of acamprosate on a t.i.d schedule. There was no modification of acamprosate pharmacokinetics in mild to moderate hepatic-impaired subjects compared to healthy subjects.

Single-dose studies in renal impairment showed that clearance decreased with decreasing

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creatinine clearance, while C_{max} was increased and T_{max} and plasma elimination half-life were prolonged in patients with renal impairment. Statistically significant increases were seen in patients with severe renal impairment compared to normal controls. Due to the risk of accumulation, the sponsor recommends acamprosate not be used in renally impaired patients.

Acamprosate had no inducing potential on the cytochrome CYP1A2 and 3A4 systems, and in vitro enzyme inhibition studies suggest that acamprosate does not inhibit in vivo metabolism mediated by cytochrome CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4.

Various interaction studies have been performed with acamprosate, relevant to the treatment of alcohol-dependent patients. There was no significant effect of multiple doses of acamprosate on the pharmacokinetics of a standardized dose of ethanol. In a complementary study, there was no evidence of an effect of ethanol on the pharmacokinetic parameters of a single dose of acamprosate tablets (1332 mg). There was no significant effect of disulfiram on the pharmacokinetic parameters of acamprosate, following multiple daily doses in tablet form of both drugs. There was no significant effect of acamprosate on the kinetics of diazepam (or its major metabolite, nordiazepam), following multiple doses of tablets of both drugs. Likewise, there was no significant effect of diazepam on acamprosate AUC under these conditions. There was no significant effect of acamprosate on the kinetics of imipramine (or its major metabolite, desipramine), when a single dose of imipramine was given after multiple doses of acamprosate tablets. There was no significant effect of acamprosate on the kinetics of naltrexone (or its major metabolite, 6- β -naltrexol), when multiple daily doses of acamprosate and naltrexone tablets were co-administered. Conversely, under these conditions, naltrexone increased the rate and extent of absorption of acamprosate, resulting in a significant increase in acamprosate C_{max} (33%) and AUC (about 25%).

4 DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Overall Data

All of the data in the application are from the development programs of Laboratories Meram and Lipha Pharmaceuticals. The sponsor has grouped the clinical data as follows:

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

Group I:

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

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

4.2 Tables Listing the Clinical Trials

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

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| TABULAR SUMMARY OF GROUP I STUDIES: PLACEBO-CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS ¹ | | | | | | | | | | | | | | |
|--|--|--|------------------|------------------------------------|---|---|---------------------------------|---|---|-------------------------|------------------------------|------------------------------|----------------------------|----|
| Study #, (Common Name) Principal Investigator, Country | Status (Start - End Dates) ² | Location (Item #/Vol. #/Starting page #) | | | Study Design (Drug Treatment Duration) | Treatment Groups | | | Demographics | | | | | |
| | | Full Report | Data Listings | CRF Tabs. (CRF) ³ | | Drug, Dosage Form, Strength (Formulation & Batch #) | Total Daily Dose in mg | Regimen | #, Type of Patients Entered per Group (# completed) | Age Range (mean) | Sex: M/F (%) | Race: W/B/H/O (%) | | |
| AOTA 411.198 (PRAMA) H. Sass, Germany | C (Oct 16, 1990 to Dec. 3, 1992) | | | | (90 days) | | | Grp. C: 1998 | midday, 1 acamp tab + 1 P tab in evening | Grp. C: 2 tabs tid | Grp. C: 63 ADS (43) | Grp. C: 26-59 (40.5) | Grp. C: 54/9 (86/14) | ND |
| | | | | | Pro, MC (12), R, DB, PC, PG (2: acamp vs P, with pre- randomization stratification according to body weight) S/E study in ADS, after withdrawal from alcohol (48 weeks) | Acamp, tabs, 333 mg (#3251) | 1998* ⁴ (1332) | 2 tabs tid | 2 tabs tid | 136 ADS (79) | 21-58 (41.9) | 102/34 (75/25) | ND | |
| | | | | | | Placebo, tabs (#3248) | 6 tabs (4 tabs) | 2 tabs tid | 2 tabs tid | 136 ADS (55) | 21-65 (40.5) | 109/27 (80.1/ 19.9) | ND | |
| 544 (Paille) F. Paille, France | C (April, 1989 to Nov., 1992) | | | | Pro, MC (31), R, DB, PC, PG (3: Treatment 1 = P, vs Treatment 2 = acamp, 1332 mg; vs Treatment 3 = acamp, 1998 mg) S/E study in ADS, committed to abstinence, after | Placebo, tabs (#41320) | 6 tabs | Trt. 1: 2 tabs tid | Trt. 1: 2 tabs tid | Trt. 1: 177 ADS (62) | Trt. 1: ND (42.5) | Trt. 1: 147/30 (83/17) | Trt. 1: ND | |
| | | | | | | Acamp, tabs, 333 mg (#41319, 41328, 41368) | Trt. 2: 1332 + 2 P tabs | Trt. 2: 2 acamp morning; 1 acamp + 1 P | Trt. 2: 188 ADS (85) | Trt. 2: ND (43.7) | Trt. 2: 146/42 (78/22) | Trt. 2: ND | | |

⁴ For studies where acamprostate dose is marked with an asterisk, daily dosage was on the basis of body weight. For patients with a bodyweight greater than 60 kg (or for PRAMA, ≥60 kg), 2 tabs of acamprostate (666 mg) or placebo in the morning, 2 tabs of acamprostate (666 mg) or placebo at midday, and 2 tabs of acamprostate (666 mg) or placebo in the evening (total daily dose of 1998 mg). For patients with a bodyweight less than or equal to 60 kg (or for PRAMA, <60 kg), 2 tabs of acamprostate (666 mg) or placebo in the morning, 1 tab of acamprostate (333 mg) or placebo at midday, and 1 tab of acamprostate (333 mg) or placebo in the evening (total daily dose of 1332 mg). In these same studies, number of patients entered per treatment group and number of patients completing per treatment group are provided for the entire group, irrespective of weight considerations.

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| TABULAR SUMMARY OF GROUP I STUDIES: PLACEBO-CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS¹ | | | | | | | | | | | | |
|--|--|--|------------------|-----------------------------------|---|---|---------------------------------|------------------------------|---|---------------------|---------------------------|-------------------------|
| Study #, (Common Name) Principal Investigator, Country | Status (Start - End Dates) ² | Location (Item #/Vol. #/Starting page #) | | | Study Design (Drug Treatment Duration) | Treatment Groups | | | Demographics | | | |
| | | Full Report | Data Listings | CRF Tabs (CRF) ³ | | Drug, Dosage Form, Strength (Formulation & Batch #) | Total Daily Dose in mg | Regimen | #, Type of Patients Entered per Group (# completed) | Age Range (mean) | Sex: M/F (%) | Race: W/B/H/O (%) |
| AOTA/NL/91.1 AOTA/B/90.2 (BENEFLUX) P. Geerlings and C. Ansoms, Belgium, The Netherlands | C (May, 1990 to Oct., 1992) | | | | treatment period of ≥ 7 days was to occur between end of alcohol withdrawal and randomization. (24 weeks) | Placebo, tabs (#1623) | 6 tabs | 2 tabs tid | 292 ADS (103) | ND (43.8) | 233/59 (79.8/ 20.2) | ND |
| | | | | | Pro, MC (22), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days) | Acamp, tabs, 333 mg (#1519, 3306, 1580 and 3250) | 1998* (1332) | 2 tabs tid 2-1-1 tabs tid | 128 ADS (38) | 19-65 (40.3) | 97/31 (76/24) | ND |
| | | | | | Pro, MC (11), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS from onset of alcohol withdrawal. (180 days) | Placebo, tabs (#1518, 3305, 1579 and 3247) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 134 ADS (32) | 21-63 (41.7) | 102/32 (76/24) | ND |
| AOTA/E/91.1 (ADISA) A. Gual, Spain | C (May, 1993 to Oct., 1994) | | | | Pro, MC (3), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. | Acamp, tabs, 333 mg (#3306) | 1998 | 2 tabs tid | 148 ADS (96) | 21-61 (41.4) | 119/29 (80/20) | ND |
| AD 04 089 (Ladewig) D. Ladewig, Switzerland | C (Aug., 1989 to Jan., 1991) | | | | Pro, MC (3), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. | Placebo, tabs (#3305) | 6 tabs | 2 tabs tid | 148 ADS (90) | 22-64 (40.6) | 117/31 (79/21) | ND |
| | | | | | Pro, MC (3), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. | Acamp, tabs, 333 mg (#1580) | 1998* (1332) | 2 tabs tid 2-1-1 tabs tid | 29 ADS (19) | 28-68 (47.7) | 25/4 (86/14) | ND |
| | | | | | Pro, MC (3), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. | Placebo, tabs (#1579) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 32 ADS (21) | 31-70 (46.9) | 22/10 (69/31) | ND |

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TABULAR SUMMARY OF GROUP I STUDIES: PLACEBO-CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS⁵

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

⁵ Randomization was in a ratio of 3:3:1 for the treatment groups placebo, acamp 2 g/day and acamp 3g/day, respectively.

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| TABULAR SUMMARY OF GROUP I STUDIES: PLACEBO-CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS ¹ | | | | | | | | | | | | |
|--|--|--|---------------|------------------------------|--|--|--|--|---|----------------------------------|--|-------------------|
| Study #, (Common Name) Principal Investigator, Country | Status (Start - End Dates) ² | Location (Item #/Vol. #/Starting page #) | | | Study Design (Drug Treatment Duration) | Treatment Groups | | | Demographics | | | |
| | | Full Report | Data Listings | CRF Tabs. (CRF) ³ | | Drug, Dosage Form, Strength (Formulation & Batch #) | Total Daily Dose in mg | Regimen | #, Type of Patients Entered per Group (# completed) | Age Range (mean) | Sex: M/F (%) | Race: W/B/H/O (%) |
| (Barriss) J.C. Barriss, Portugal | (Nov., 1989 to Oct., 1992) | | | | PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days) | 333 mg (#1580) Placebo, tabs (#1579) | (1332) 6 tabs (4 tabs) | 2-1-1 tabs tid 2 tabs tid 2-1-1 tabs tid | (86) 152 ADS (83) | (39.7) 23-63 (41.0) | (92.7/7.3) 139/13 (91.4/8.6) | ND |
| AA 11 088 (Besson) J. Besson, Switzerland | C (Jan., 1989 to Jan., 1993) | | | | Pro, MC (3), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight and open-label use (yes/no) of Antabuse (disulfiram) as associated therapy, S/E study in ADS, after withdrawal from alcohol. (360 days) | Acamp, tabs, 333 mg (#1243 and 3249) Placebo, tabs (#1242 and 3247) | 1998* (1332) 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid 2 tabs tid 2-1-1 tabs tid | 61 ADS (19) ⁶ 57 ADS (19) | 25-62 (42.6) 26-62 (42.6) | 50/11 (82.0/18) 43/14 (75.4/24.6) | ND ND |
| EUROPEAN/US ONGOING/INCOMPLETE CONTROLLED SHORT-TERM STUDIES | | | | | | | | | | | | |
| CAMP/D/99.01 (A.P.D.T.) Dr. Nickel, Germany | O (May 1, 2000 to ---) | | | | Pro, MC, R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS, with study drug treatment started prior to and during detox- | Acamp, tabs, 333 mg (#ND) Placebo, tabs | 1998 | 2 tabs tid | 200 ADS planned for | ND | ND | ND |

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

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| TABULAR SUMMARY OF GROUP 1 STUDIES: PLACEBO-CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS ⁷ | | | | | | | | | | | | | | | |
|--|---|--|------------------|------------------------------------|--|---|---------------------------------|--------------------------|---|---------------------|--------------------|-------------------------|----|--|--|
| Study #, (Common Name) Principal Investigator, Country | Status (Start- End Dates) ² | Location (Item #/Vol. #/Starting page #) | | | Study Design (Drug Treatment Duration) | Treatment Groups | | | Demographics | | | | | | |
| | | Full Report | Data Listings | CRF Tabs. (CRF) ³ | | Drug, Dosage Form, Strength (Formulation & Batch #) | Total Daily Dose in mg | Regimen | #, Type of Patients Entered per Group (# completed) | Age Range (mean) | Sex: M/F (%) | Race: W/B/H/O (%) | | | |
| COMBINE Pilot # 3 (Pilot 3) --- United States | O (Sept., 1999 to ---) | | | | ification from alcohol. (approx. 14 weeks) Pro, MC (11), R, DB (double dummy), PG (9 treatment combination cells of nal and/or acamp with various psychosocial interventions) S/E study in ADS, abstinent at randomization. (4 months) | (#ND) | 6 tabs | 2 tabs tid | | | | | | | |
| | | | | | | Acamp, tabs, 500 mg | 3000 | 2 tabs tid | 108 ADS planned for | ND | ND | ND | ND | | |
| | | | | | | Placebo for acamp, tabs, | 6 tabs | 2 tabs tid | | | | | | | |
| | | | | | | Naltrexone, tabs, 50 mg | 100 ⁷ | 2 tabs in the morning | | | | | | | |
| | | | | | | Placebo for naltrexone, tabs | | 2 tabs in the morning | | | | | | | |

Sponsor's In-Text Table 3.8.4.1

The following abbreviations are used throughout the table above:

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

⁷ Dosage of naltrexone is to be titrated as follows: 25 mg/day for Days 1-4; 50 mg/day for Days 5-7; 100 mg/day thereafter. All doses are single doses given in the morning.

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

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

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

4.3 Postmarketing Experience

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

4.4 Clinical Efficacy Review Methods

4.4.1 Description of Review Conduct

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

The safety review was conducted by Dr. Michael Sevka, whose methods are described in his review (not included in this briefing package).

4.4.2 Overview of Materials Consulted in Review

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

4.4.3 Overview of Methods Used to Evaluate Data Quality and Integrity

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

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

4.4.4 Adherence to Accepted Ethical Standards in Trial Conduct

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

5 INTEGRATED REVIEW OF EFFICACY

5.1 Brief Statement of Conclusions

In three European pivotal efficacy studies, subjects randomized to acamprosate were more likely than subjects randomized to placebo to be assessed by the clinician as abstinent, using either continuous abstinence or intermittent periods of abstinence as the success measure. These measures of efficacy differ from the sponsor's labeling claim, which reports the "cumulative abstinence duration." The method of ascertainment of the number of drinking days in the European studies was insufficiently systematic to allow for precise counting of number of days drinking or not drinking. Therefore, although the data support the claim that acamprosate is effective in maintaining abstinence in recently-detoxified alcoholics, it is not possible to quantify the effect in terms of specific duration of abstinence. The single U.S. study failed to support the efficacy of acamprosate, and its findings must be reconciled with the European data.

5.2 General Approach to Review of the Efficacy of the Drug

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

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

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

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Table 5.2.1 Studies Included in Detail in Efficacy Review

| Study Name/ Protocol #/ PI/Location/Dates | Design | Duration | Dosage Form, Regimen, Total Daily Dose | Type of Patients, # Entered per Group (# completed), Age range/mean, Gender |
|---|--|----------|--|--|
| <i>Pelc II</i> (AOTAB/90.3) I. Pelc, Belgium, France June, 1990 to April, 1992 | Prospective, Multi-Center (11), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate 1332 mg/day vs Acamprosate 1998 mg/day) | 90 days | <i>A (placebo):</i> 2 Placebo tabs tid <i>B (1332 mg/day):</i> 333 mg acamprosate tabs, 2 in morning, 1 acamprosate tab + 1 placebo tab at midday, 1 acamp rosate tab + 1 placebo tab in evening (total 1332 mg) <i>C (1998 mg/day):</i> 333 mg acamprosate tabs, 2 tabs tid (total 1998 mg) | Alcohol-dependent subjects after detoxification <i>A:</i> 62 entered (32 completed) Age 26-59 (40.9) 89% M/11%F <i>B:</i> 63 entered (44 completed) Age 21-71 (43.3) 81% M/19%F <i>C:</i> 63 entered (43 completed) Age 26-59 (40.5) 86%M/14%F |
| <i>Paille (S44)</i> F. Paille, France April, 1989 to Nov., 1992 | Prospective, Multi-Center (31), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate 1332 mg/day vs Acamprosate 1998 mg/day) | 360 days | <i>Placebo:</i> 2 placebo tabs tid <i>Trt 2 (Acamprosate 1332 mg/day):</i> 333 mg acamprosate tabs, 2 in morning, 1 acamprosate tab + 1 placebo tab at midday, 1 acamp rosate tab + 1 placebo tab in evening (total 1332 mg) <i>Trt 3 (Acamprosate 1998 mg/day)</i> 333 mg acamprosate tabs, 2 tabs tid (total 1998 mg) | Alcohol-dependent subjects after detoxification <i>Placebo:</i> 177 entered (62 completed) Mean age 42.5 83% M/17%F Acamprosate 1332 mg/day: 188 entered (85 completed)Mean age: 43.7 78%M/22%F Acamprosate 1998 mg/day: 173 entered (90 completed) Mean age: 43.3 79%M/21%F |

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| | | | | |
|--|---|-----------------|---|--|
| <p>PRAMA (AOTA 411.198) H. Sass, Germany Oct. 16, 1990 to Dec. 3, 1992</p> | <p>Prospective, Multi-Center (12), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate with pre-randomization stratification according to body weight)</p> | <p>48 weeks</p> | <p>Acamprosate: ≥60 kg: 333 mg acamprosate tabs, 2 tabs tid (total 1998 mg) <60 kg: 333 mg acamprosate tabs, 2 in morning, 1 at midday, 1 in evening (total 1332 mg) Placebo: ≥60 kg: 2 placebo tabs tid <60 kg: 2 placebo tabs, 2 in morning, 1 at midday, 1 in evening</p> | <p>Alcohol-dependent subjects after detoxification Acamprosate: 136 entered (79 completed) Age: 21-58 (41.9) 75%M/25%F Placebo: 136 entered (55 completed) Age: 21-65 (40.5) 80% M/20%F</p> |
| <p>US 96.1 (ACAMP/US/96.1) B. Mason USA</p> | <p>Prospective, Multi-Center (21), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate 2g vs Acamprosate 3 g, 3:3:1), with pre-randomization stratification according to alcohol detoxification (yes/no)</p> | <p>6 months</p> | <p>Acamprosate 2 g: 500 mg acamprosate tabs, 2 tabs + 1 placebo tab, b.i.d Acamprosate 3 g: 500 mg acamprosate tabs, 3 tabs b.i.d Placebo: Placebo tabs, 3 tabs b.i.d.</p> | <p>Alcohol-dependent subjects Acamprosate 2 g: 258 entered (106 completed) Age 23-72 (44.9) 70%M/30%F Acamprosate 3 g 83 entered (43 completed) Age 21-66 (43.6) 72%M/28%F Placebo: 260 entered (143 completed) Age 22-69 (44.4) 65%M/35%F</p> |

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

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

5.3.1 Protocol

5.3.1.1 Objective/Rationale

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

5.3.1.2 Overall Design

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

5.3.1.3 Population and Procedures

5.3.1.3.1 Inclusion/Exclusion Criteria

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

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

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

Subjects were excluded for:

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

- “Obvious lack of collaboration with the general weaning treatment”
- Prior treatment with acamprosate

Disallowed concomitant medications included:

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

5.3.1.3.2 Procedures

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

Group I: Acamprosate 1332 mg (333 mg tablets, 2 qam, 1 at midday, and 1 in the evening, with meals)

Group II: Acamprosate 1998 mg (333 mg tablets, 2 with breakfast, lunch, and dinner)

Group III: Placebo (2 tablets with breakfast, lunch, and dinner)

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

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

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

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

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

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

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

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

A “monitoring booklet” was to be distributed to patients, allowing for the “daily recording and quantification by the patient of nervousness, sleeping disorders, shaking of the hands, and desire

for alcohol.” The protocol called for the booklet to be returned at each study visit and indicated that it “will be used to monitor the patient.” The CRF indicates that subjects were to be instructed to mail back the first week’s booklet at the mid-point between the biweekly visits. The CRF does not contain fields for the data collected in the booklets.

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

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

5.3.1.4 Evaluations/Endpoints

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

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

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

5.3.1.5 Statistical Plan

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

5.3.2 Results

5.3.2.1 Study Conduct/Outcome

5.3.2.1.1 Subject Characteristics

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

5.3.2.1.1.1 Enrollment by Center

Of the total of 189 patients who were selected to participated, 188 patients were randomized: 125 in the 10 Belgian centers (range 3-37) and 63 in the French center (1 Belgian patient withdrew consent). Sixty-three patients were randomized to acamprosate 1998 mg/day, 63 to acamprosate

1332 mg/day, and 62 to placebo. All patients took at least 1 dose of study medication and are included in the ITT population.

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

Table 5.3.2.1.1.1 Enrollment by Center, Pelc-II

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

5.3.2.1.1.2 Subject Disposition

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

Table 5.3.2.1.1.2 Patient Disposition-Pelc-II

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

5.3.2.1.2 Demographics

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

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

Table 5.3.2.1.5 Demographic and Baseline Characteristics - Pelc II

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

Data Source: Sponsor's Table 8.7.1.2.1 and Table 8.7.1.3.1

Sponsor's In-Text Table 8.4.3.1.2

¹Ratio of GGT to ULN in specific laboratory used

5.3.2.1.3 Dosing Information

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

Table 5.3.2.1.3 Drug Exposure –Pelc II

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

Sponsor's In-Text Table 8.7.2.6:1

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

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

5.3.3 Efficacy Results

5.3.3.1 Sponsor's Analysis

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

For the sponsor's analysis, the following procedure was used to transform the CRF data into

daily drinking data across the inter-visit interval was as follows:

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

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

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

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

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

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

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

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

5.3.3.2 Reviewer’s Analysis

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

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

5.3.3.2.1 Non-Continuous Abstinence

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

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

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

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

There is a statistically significant difference (t-test) between either dose of acamprosate vs. placebo.

5.3.3.2.2 Responder Analysis: Complete/Continuous Abstinence

The rates of complete abstinence across the various treatment groups are shown in the table below.

Table 5.3.3.2.2 Continuous Abstinence in Study Pelc-II

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

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

5.3.3.2.2.1 Analysis by Gender

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

5.3.3.2.2.2 Analysis by Center

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

Table 5.3.3.2.2.2 Continuous Abstinence by Center--PelcII

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

5.3.3.3 Conclusions Regarding Efficacy Data in Study

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

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

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

Conducted April 1989 to November 1992

5.4.1 Protocol

5.4.1.1 Objective/Rationale

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

5.4.1.2 Overall Design

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

5.4.1.3 Population and Procedures

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

5.4.1.3.1 Inclusion/Exclusion Criteria

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

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

Subjects were excluded for:

- Assessment at “unlikely to comply with treatment over the 18 month period”
- More than 3 courses of detox in previous 2 years
- Previous treatment with acamprosate

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

Concomitant medications permitted included:

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

Disallowed concomitant medications included:

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

5.4.1.3.2 Procedures

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

Group I: Acamprosate 1332 mg (333 mg tablets, 2 qam, 1 at middday (+ 1 placebo), and 1 in the evening (+ 1 placebo), with meals)

Group II: Acamprosate 1998 mg (333 mg tablets, 2 with breakfast, lunch, and dinner)

Group III: Placebo (2 tablets with breakfast, lunch, and dinner)

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

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

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

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

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Table 5.4.1.3.2 Time-and-Events Schedule--Paille

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

¹Day -30 to Day -7, prior to detox

5.4.1.4 Evaluations/Endpoints

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

The clinical evaluation is described in the protocol as follows:

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

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

5.4.1.4.1 Statistical Plan

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

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

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

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

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

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

5.4.2 Results

5.4.2.1 Study Conduct/Outcome

5.4.2.1.1 Subject Characteristics

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

5.4.2.1.1.1 Enrollment by Center

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

Table 5.4.2.1.1.1 Enrollment by Center--Paille

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

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| Center No. | No. of Patients | Investigator | Address |
|------------|-----------------|---|--|
| 10 | 9 | Prof. Jacques DUBRUJEAUD | Hôpital André Mignot 177, rue de Versailles 78157 Le Chesnay Cedex FRANCE |
| 11 | 36 | Prof. Jean-Dominique FAVRE | Service de Psychiatrie Hopital Percy 92140 Clamart FRANCE |
| 12 | 12 | Prof. Michel AMOURETTI | Hôpital du Haut Lévêque Service U.S.N Avenue Magellan 33604 Pessac FRANCE |
| 13 | 18 | Dr Gilles-Loïc GUIDON | Ancien Hôpital des Armées Service de sevrage alcoolique et tabagique 56110 Lorient FRANCE |
| 14 | 9 | Dr Jean-Paul LATRIVE | Centre Hospitalier de Compiègne 8, rue Adenot 60208 Compiègne FRANCE |
| 15 | 22 | Dr Claude LE DEVÉHAT/ Dr Alain LEMOINE | Centre hospitalier Centre de Diabétologie Pavillon Jules Renard 1, avenue Colbert 58000 Nevers FRANCE |
| 16 | 15 | Prof. Gabriel LE MENN | Hôpital La Cavale Blanche 29200 Brest FRANCE |
| 17 | 36 | Dr Daniel VOIRIN | Hôpital d'instruction des Armées Clermont Tonnerre rue du Colonel Fonferrier 29200 Brest FRANCE |
| 18 | 18 | Dr Meri LIENHART | Centre Hospitalier de Saint-Cloud 3, Place Sully 92211 Saint Cloud FRANCE |
| 20 | 22 | Prof. Dominique BARRUCAND | Centre Hospitalier Emile Roux 48, rue Henri Barbuse 94450 Limeil Brevannes FRANCE |
| 21 | 16 | Dr Pierre MECHINAUD | 62, rue du Chêne Creux 44410 Réze FRANCE |
| 22 | 5 | Dr Gérald BERTHON | Hôpital St André Service de Médecine Interne et Thérapeutique 1 rue Jean Burguet 33075 Bordeaux Cedex FRANCE |
| 23 | 17 | Prof. François PAILLE | Hôpital Fournier Service de Médecine Interne/ Alcoologie 34 Quai de la Bataille 54037 Nancy FRANCE |

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| Center No. | No. of Patients | Investigator | Address |
|------------|-----------------|--------------------------------------|---|
| 24 | 18 | Dr Roger PLANCHE | C.H.R.U. Service de Psychiatrie 63000 Clermont Ferrand FRANCE |
| 25 | 36 | Prof. Yves POINSO | Hôpital Ste Marguerite Pavillon Ouest 270 Bd Ste Marguerite 13214 Marseille FRANCE |
| 26 | 25 | Prof. Bernard RUEFF | Hôpital Beaujon 100, boulevard du Général Leclerc 92110 Clichy FRANCE |
| 27 | 12 | Dr Michel SALFATI/ Dr Anne VALLI/ | Centre Hospitalier Jean Rostand 141 Grande Rue 92311 Sèvres FRANCE |
| 28 | 13 | Dr Chantal VENON | Service CCAA Centre Verlainé 14 Place Pierre Sémard 94190 Villeneuve-Saint-Georges FRANCE |
| 29 | 7 | Prof. Michel MARIE-CARDINE | Service Prof. Terra Centre Hospitalier le Vinatier 95 Bvd Pinel 69500 Bron FRANCE |
| 30 | 26 | Prof. François BLANC | CHU Gui de Chauviac (Hôpital Ste Eloi) Médecine Interne E 4 Avenue Bertin-Sans 34000 Montpellier FRANCE |
| 31 | 18 | Dr Bernard JOZELSON | Centre Hospitalier Centre d'alcoologie 73200 Albertville FRANCE |
| 32 | 15 | Dr Yves RAOUL | H.I.A. Ste Anne 3 Bld Ste Anne 83000 Toulon FRANCE |

5.4.2.1.1.2 Subject Disposition

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

Table 5.4.2.1.1.2 Patient Disposition During Treatment Phase –Paille

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

Sponsor's In-Text Table 8.4.2.3:1

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

5.4.2.1.2 Demographics

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

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

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

Table 5.4.2.1.2 Demographic and Baseline Characteristics – Paille

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

Data Source: Table 8.7.1.2.3 and Table 8.7.1.3.3

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

5.4.2.1.3 Dosing Information

The table below illustrates exposure duration and compliance with medication across treatment groups. Mean compliance was slightly higher (88%) in the acamprosate 1998 mg/day group than in the other two groups (82-83%). 73%-81% of subjects were >75% compliant. Duration of exposure to study medication was shorter in the placebo group (mean 32 weeks) than in the acamprosate groups (mean 35-38 weeks). Less than half of patients in the placebo group (44%) completed at least 26 weeks of treatment, whereas 59% of the patients in the acamprosate group completed at least 26 weeks of treatment.

Table 5.4.2.1.3 Drug Exposure –Paille

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

Sponsor's In-Text Table 8.7.2.6:3

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

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

5.4.3 Efficacy Results

5.4.3.1 Sponsor's Analysis

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

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

"The number of abstinent days was calculated from Day 0 to either Day 360, the date that Day 360 occurred, or the date treatment stopped, whichever gave the shorter time interval; the treatment duration was defined based on the same interval. The number of abstinent days between each pair of subsequent visits was calculated by subtracting the number of non-abstinent days from the total days between visits. The total number of abstinent days was then calculated by summing the abstinent days over all relevant visits. If a patient did not attend a particular visit, then the patient was assumed to be non-abstinent since the preceding visit." [Section 10.7]

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

Table 5.4.3.1 Cumulative Abstinence Duration--Paille

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

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

5.4.3.2 Reviewer's Analysis

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

Again, it should be noted that the methods of data collection (the apparent lack of separation between data collection personnel and treatment personnel) may have introduced demand characteristics which would discourage subjects from reporting drinking. Subjects described as being "abstinent" may be more accurately characterized as being those subjects who managed to convey the impression of abstinence to the evaluating clinician. Given tendency of therapists to

look for improvement, it is likely that this number over-estimates the actual abstinence rate. If the treatment was somehow unmasked (perhaps by the occurrence of adverse events), there would be obvious bias in the data. However, given the relatively benign safety profile one can hope that the bias towards underreporting drinking and the bias towards seeing improvement would be randomly distributed across treatment groups.

5.4.3.2.1 Non-Continuous Abstinence

This analysis compares the patterns of the number of visits at which each subject was assessed as abstinent by the evaluating clinician. This approach acknowledges that subjects whose abstinence is not continuous may also be regarded as successful. Rather than transforming this binary assessment into an arbitrary number of days, I simply counted the “abstinent visits” and analyzed the distribution across treatment groups.

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

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

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

Table prepared by reviewer using datasets PI_EFFVS + PI_POP

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

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

5.4.3.2.2 Responder Analysis: Continuous Abstinence

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

Table 5.4.3.2.2 Continuous Abstinence Throughout Treatment--Paille

| | | | |
|---|-----------------------------|-----------------------------|--------------------|
| Number (%) with continuous abstinence of ≥360 days from day 0 | Acamprosate 1332 N = 188 | Acamprosate 1998 N = 173 | Placebo N = 177 |
| | 33(18%) | 33 (19%) | 20 (11%)* |
| *p <.04 vs acamprosate 1998 mg Chi-Square | | | |

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

5.4.3.2.2.1 Analysis by Gender

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

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

5.4.3.2.2.2 Analysis by Center

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

Table 5.4.3.2.2.2 Continuous Abstinence by Center--Paille

| Center # | Total | | Acamprosate 1332 mg/day | | Acamprosate 1998 mg/day | | Placebo | |
|----------|----------------|----------------|----------------------------|----------------|----------------------------|----------------|----------------|----------------|
| | N Abstinent | % Abstinent | N Abstinent | % Abstinent | N Abstinent | % Abstinent | N Abstinent | % Abstinent |
| 1 | 1 | 8% | 0 | 0% | 1 | 33% | 0 | 0% |
| 2 | 10 | 28% | 3 | 25% | 6 | 50% | 1 | 8% |
| 3 | 3 | 14% | 1 | 11% | 2 | 29% | 0 | 0% |
| 4 | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| 5 | 2 | 20% | 2 | 50% | 0 | 0% | 0 | 0% |
| 6 | 1 | 6% | 0 | 0% | 0 | 0% | 1 | 17% |
| 7 | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| 8 | 1 | 11% | 0 | 0% | 1 | 33% | 0 | 0% |
| 9 | 3 | 30% | 1 | 33% | 2 | 67% | 0 | 0% |
| 10 | 3 | 33% | 1 | 33% | 2 | 67% | 0 | 0% |
| 11 | 5 | 14% | 1 | 8% | 2 | 17% | 2 | 17% |
| 12 | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| 13 | 3 | 17% | 2 | 33% | 0 | 0% | 1 | 17% |
| 14 | 1 | 11% | 1 | 33% | 0 | 0% | 0 | 0% |
| 15 | 3 | 14% | 2 | 25% | 1 | 14% | 0 | 0% |
| 16 | 3 | 20% | 1 | 20% | 2 | 40% | 0 | 0% |
| 17 | 6 | 17% | 1 | 8% | 4 | 33% | 1 | 8% |
| 18 | 2 | 11% | 0 | 0% | 0 | 0% | 2 | 33% |
| 20 | 3 | 14% | 2 | 25% | 0 | 0% | 1 | 13% |
| 21 | 1 | 6% | 1 | 20% | 0 | 0% | 0 | 0% |
| 22 | 1 | 20% | 0 | 0% | 0 | 0% | 1 | 50% |
| 23 | 2 | 12% | 0 | 0% | 2 | 40% | 0 | 0% |
| 24 | 6 | 33% | 3 | 50% | 2 | 33% | 1 | 17% |
| 25 | 11 | 31% | 4 | 33% | 2 | 17% | 5 | 42% |
| 26 | 1 | 4% | 1 | 11% | 0 | 0% | 0 | 0% |
| 27 | 1 | 8% | 0 | 0% | 1 | 20% | 0 | 0% |
| 28 | 1 | 8% | 1 | 20% | 0 | 0% | 0 | 0% |
| 29 | 3 | 38% | 1 | 33% | 1 | 50% | 1 | 33% |
| 30 | 1 | 4% | 0 | 0% | 1 | 11% | 0 | 0% |
| 31 | 7 | 39% | 3 | 50% | 1 | 17% | 3 | 50% |
| 32 | 1 | 7% | 1 | 20% | 0 | 0% | 0 | 0% |

5.4.3.3 Conclusions Regarding Efficacy Data in Study

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

Although the sponsor's analysis of CAD and CCAD are questionable, because the reconstruction of days drinking vs. abstinent relies on more detail than was collected, the overall conclusion is supported. Both an analysis of continuous abstinence and an analysis of the pattern of visits at which the investigator assessed the subject to be abstinent support the sponsor's conclusions.

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Concerns about the validity of the data include the likelihood that both subject and investigator (who apparently also served as therapist) would be biased in reporting and assessment. This would be expected to occur evenly across treatment assignment, however, unless unmasking occurred. The safety results (per Dr. Sevka's review) show that few adverse events occurred at a higher rate in the treatment groups than in placebo groups. However, diarrhea (a recognized acamprosate-related event) occurred in 14% of the acamprosate 1998 mg group, 9% of the acamprosate 1332 mg group, and only 4% of the placebo group. This difference may have been sufficient that the occurrence of diarrhea in a subject would lead the investigator to deduce (usually correctly) treatment assignment.

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

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

5.5.1 Protocol

5.5.1.1 Objective/Rationale

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

5.5.1.2 Overall Design

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

5.5.1.3 Population and Procedures

The planned sample size was 200-300 subjects.

5.5.1.3.1 Inclusion/Exclusion Criteria

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

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

Subjects were excluded for:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5.5.1.4 Evaluations/Endpoints (how measured/appropriateness)

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

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

5.5.1.5 Statistical Plan

The statistical evaluation methods included in the protocol specified that:

- The evaluation of the study would be according to the intent-to-treat principle; wherever possible, all patients were to be fully documented during the entire planned therapy and follow-up observation phase.
- The primary variable for the evaluation was to be the point in time when a relapse occurred; to be evaluated in the form of an event analysis using a log-rank test, whereby a patient enters the statistics as an event at the time of his first relapse.
- Patients who were lost to observation and for whom no further information could be obtained were to be evaluated up to the point of the last available information.
- The total incidence of relapses in both groups was to be evaluated as a secondary variable using a comparison of incidence.
- Interim evaluation was called for when the last patient recruited to the study had completed

the 24 week evaluation.

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

5.5.2 Results

5.5.2.1 Study Conduct/Outcome

5.5.2.1.1 Subject Characteristics

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

5.5.2.1.1.1 Enrollment by Center

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

Table 5.5.2.1.1.1 Enrollment by Center--PRAMA

| Site No. | No. of Patients Randomized | Investigator(s) | Study Center Location |
|----------|----------------------------|---|--|
| -- | -- | Overall Principal Investigator: Prof. Dr. med. Henning SASS, MD | Psychiatrische Fachabteilung der RWTH Aachen Pauwelsstrasse 30 52074 Aachen GERMANY |
| 1 | 19 | Prof. Dr. med. HIPPIUS, MD (<i>principal investigator</i>) Dr.. Doris Dieterle, PhD PD Dr. med. Michael Soyka, MD | Klinikum der Universität München Klinik und Poliklinik für Psychiatrie und Psychotherapie Nußbaumstrasse 7 80336 München (Munich) GERMANY |
| 2 | 18 | Prof. Dr. med. H. DILLING, MD (<i>principal investigator</i>) Dr. med. U. John, MD Dr. med. Kanitz, MD Dr. phil. Clemens Veltrup, PhD (<i>psychologist</i>) Prof. Dr. med. T. Wetterling, MD (Univ. Frankfurt, Psychiatrie) | Medizinische Universität Lübeck Klinik für Psychiatrie Ratzeburger Allee 160 23562 Lübeck GERMANY |
| 3 | 9 | Prof. Dr. med. Karl F. MANN, MD (Zentralinst. f. Seelische Gesundheit) (<i>principal investigator</i>) Dr. Bernhard Overberg (psychologist) Frau Dipl.-Psych. Büscher | Psychiatrische Universitäts-Klinik der Eberhard- Karls-Universität Tübingen Osianderstrasse 22 72076 Tübingen GERMANY |

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| Site No. | No. of Patients Randomized | Investigator(s) | Study Center Location |
|----------|----------------------------|--|--|
| 4 | 39 | Dr. med. K. D. SEGERATH, MD (<i>principal investigator</i>) Dr. med. Johannes Haseke, MD Dr. med. Harald Landefeld | Katholisches Krankenhaus Philippsstift Fachabteilung für Suchkrankheiten Hülsmannstrasse 17 45355 Essen-Borbeck GERMANY |
| 5 | 10 | Prof. Dr. J. GROSS, MD (<i>principal investigator</i>) Prof. Dr. med. Michael Krausz, MD Dr. med. U. Niedermeyer, MD (Klinikum Frankfurt/Oder) | Universitätsklinik Eppendorf Psychiatrische Klinik Martinistraße 52 20246 Hamburg GERMANY |
| 6 | 64 | Dr. med. Hugo VON KEYSERLINGK, MD (Klinik Schweriner See) | Bezirksnervenklinik Schwerin Abteilung 1b Wismarsche Strasse 393 - 395 19055 Schwerin GERMANY |
| 7 | 7 | Dr. med. Heinz Georg BIALONSKI, MD (<i>principal investigator</i>) Med. Dir. Dr. med. S. Haas, MD | Zentrum für soziale Psychiatrie Rheinblick Kloster-Eberbach-Strasse 4 65346 Eltville GERMANY |
| 8 | 13 | PD Dr. Hubert KUHS (<i>principal investigator</i>) Dr. med. Özkent, MD Dr. med. Thomas Poehlke, MD | Klinik für Psychiatrie des Klinikums der Westfälischen Wilhelms-Universität Albert-Schweitzer-Strasse 11 48149 Münster GERMANY |
| 9 | -- | | |
| 10 | 14 | Frau Prof. Dr. med. D. ZIEGLER, MD (<i>principal investigator</i>) Dr. med. W. Trabert, MD | Universitäts-Kliniken des Saarlandes Nervenklinik und Poliklinik Psychiatrie, Gebäude 90 66421 Homburg/Saar GERMANY |
| 11 | 30 | Dr. med. Roland WEISE, MD (<i>principal investigator</i>) Dr. Tatjana Kroh | Klinik für forensische Psychiatrie Chemnitzer Strasse 50 04289 Leipzig GERMANY |
| 12 | 25 | Dr. med. Volker KIELSTEIN (<i>principal investigator</i>) Dr. Günter Groebel (psychologist) | Tagesklinik an der Sternbrücke Dr. Kielstein GmbH Planckstraße 4 - 5 39104 Magdeburg GERMANY |
| 13 | 24 | Prof. Dr. med. Jobst BÖNING (<i>principal investigator</i>) Dr. Wolfgang Sperling <i>succeeded by</i> Johannes Thome | Psychiatrische Universitäts-Klinik und-Poliklinik Füchsleinstrasse 15 97080 Würzburg GERMANY |

5.5.2.1.1.2 Subject Disposition

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

Table 5.5.2.1.1.2 Patient Disposition During Treatment Phase – PRAMA

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

Sponsor's In-Text Table 8.4.2.2:1

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

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

5.5.2.1.2 Demographics

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

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

Table 5.5.2.1.2 Demographic and Baseline Characteristics –Study PRAMA

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

Sponsor's In-Text Table 8.4.2.2:2

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

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

5.5.2.1.3 Dosing Information

The table below illustrates exposure duration and compliance with medication across treatment groups. Mean compliance was over 80% in each group, and 68-70% of subjects were >75% compliant. Groups were similar with respect to compliance. Duration of exposure to study medication was shorter in the placebo group (mean 26 weeks) than in the acamprosate group (mean 32 weeks). Less than half of patients in the placebo group (44%) completed at least 26 weeks of treatment, whereas 59% of the patients in the acamprosate group completed at least 26 weeks of treatment.

Table 5.5.2.1.3 Drug Exposure – PRAMA

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

Sponsor's In-Text Table 8.7.2.6:2

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

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

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

5.5.3 Efficacy Results

5.5.3.1 Sponsor's Analysis

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

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

“The total number of abstinent days was created assuming that visits occurred according to the visit schedule. [Reviewer's note: a difference of ± 3 days was permitted by protocol; no table of protocol violations indicating the extent to which this was adhered to is presented.] The physician's global assessment helped determine how much of that time would be abstinent. If using these two items and summing across all visits resulted in fewer abstinent days than indicated by the time to first relapse, then the number of abstinent days was set to the number of days to relapse, otherwise it was set to the number of abstinent days as summed across all visits.

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

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

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

Table 5.5.3.1:1 CAD and CCAD - PRAMA

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

¹CAD divided by 360
From In-text Table 8.7.2.7.1.1 and datasets PR_EFFPT + PR_POP

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

Table 5.5.3.1:2 Kaplan-Meier Estimates of Time to First Drink (in Days) During Treatment Phase (Discontinuations Treated as Failures)

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

From Sponsor's In-Text Table 8.7.2.7.2:1

5.5.3.2 Reviewer's Analysis

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

5.5.3.2.1 Non-Continuous Abstinence

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

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

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

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

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

Table prepared by reviewer from datasets PR_EFFVS+PR_POP

A t-test of this data shows that they are different at a level of $p < .0003$.

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

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

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

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

Table prepared by reviewer from datasets PR_EFFVS+PR_POP

A t-test shows these to be different at a p value of <0.001.

5.5.3.2.2 Responder analysis: Continuous abstinence

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

Table 5.5.3.2.2 Continuous Abstinence Throughout Treatment--PRAMA

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

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

5.5.3.2.2.1 Analysis by Gender

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

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

5.5.3.2.2.2 Analysis by Center

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

Table 5.5.3.2.2.2 Continuous Abstinence by Center -- PRAMA

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

5.5.3.3 Conclusions Regarding Efficacy Data in Study

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

Although the sponsor's analysis of CAD and CCAD are questionable, because the reconstruction of days drinking vs. abstinent relies on more detail than was collected, the overall conclusion is supported. Both an analysis of continuous abstinence and an analysis of the pattern of visits at which the investigator assessed the subject to be abstinent support the sponsor's conclusions. Concerns about the validity of the data include the likelihood that both subject and investigator (who apparently also served as therapist) would be biased in reporting and assessment. This would be expected to occur evenly across treatment assignment, however, unless unmasking occurred. The safety results (per Dr. Sevka's review) show virtually identical rates for individual adverse event terms, including diarrhea (occurring in only 9% of either treatment group). This argues against unmasking due to adverse events. However, as noted by Dr. Wang in her statistical review, the differential rate of dropout in this study does cast doubt on analyses relying on the imputation of "worst case" outcome for treatment dropouts. This method would be expected to produce results in favor of acamprosate based on missing data alone.

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

Conducted 5/97-1/99

5.6.1 Protocol

5.6.1.1 Objective/Rationale

The objectives of the study were to:

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

5.6.1.2 Overall Design

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

5.6.1.3 Population and Procedures

5.6.1.3.1 Inclusion/Exclusion Criteria

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

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

Subjects were to be excluded for:

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

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

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

5.6.1.3.2 Procedures

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

168 placebo

168 acamprosate 2000 mg/day

64 acamprosate 3000 mg/day (“exploratory” dose)

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

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

Treatment began at the screening visit with a single-blind placebo run-in. Subjects were to

return for the baseline visit at least 48 hours after the screening visit, but no more than 5 days from the last alcohol intake or from completion of medicated detox. After completion of the Screening Visit, the study consisted of 11 visits: a Baseline visit (Visit 0), 8 visits (Visits 1-8) during the Treatment Phase (at Weeks 1, 2, 4, 8, 12, 16, and 20) and 2 visits during the Follow-up Phase (at Weeks 25 and 32). Visits were to include “standardized medication management and minimal supportive therapy, with an abstinence orientation and a psychoeducational approach.” The protocol called for weekly telephone calls by study personnel to supplement scheduled visits. Telephone calls were to obtain drinking data, reinforce medication compliance, and to provide support.

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

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

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

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

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

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

• PATIENT STUDY VISIT FLOW CHART •

| ASSESSMENTS | Week | Screening and Single Blind Placebo Phase | | Randomization Baseline | | Acamprosate/Placebo Treatment Phase | | | | | | | | End of Treatment Evaluation | | Follow-up Phase | |
|---|------|--|------|------------------------|---|-------------------------------------|---|---|----|----|----|----|----|-----------------------------|---|-----------------|---|
| | | Visit | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | | | |
| | | | -0.5 | 0 | 1 | 2 | 4 | 8 | 12 | 18 | 20 | 24 | 25 | 32 | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | |
| Medical, Psych., Alcohol, & Family History | X | | | | | | | | | | | | | | | | |
| Complete Physical Exam (C) or PRN Physical Checkup (✓), ECG (E) | ✓, E | C | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | C, E | ✓ | | |
| Employ. & Treatment Service Utilization | X | | | | | | | X | | | | | | X | | X | |
| Alcohol Dependence Scale, CWA-AD, Mini-Mental State Examination | X | | | | | | | | | | | | | | | | |
| DSM-IV for Alcohol Dependence | X | | | | | | | | | | | | | X | | | X |
| Struct. Interview Guide for HAM-A & D, Global Assessment of Functioning | X | | | | | | | X | | | | | | X | | | X |
| Treatment Goals Rating | | X | | | | | | | | | | | | | | | |
| Timeline Follow Back, Craving Scale | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Psychosocial Therapy | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Clinical Global Impression | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Fagerström Test of Nicotine Dependence | | | | | | | | X | | | | | | X | | | X |
| OTHER | | | | | | | | | | | | | | | | | |
| Readiness to Change | | | | | | | | | | | | | | | | | |
| DrinC-2R, SF-12 Health Survey | | | | | | | | X | | | | | | X | | | X |
| LABORATORY | | | | | | | | | | | | | | | | | |
| Urinalysis; Serum Folic Acid/Vit B ₁₂ | X | | | | | | | | | | | | | | | | |
| Breath Alcohol Concentration (BAC) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood Chemistries ¹ , CBC (with diff) & Urine Drug Screen | X | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Acamprosate Plasma Levels ² | | | X | | | | | | | | | | | X | | | |
| Pregnancy Test ³ | X | | | | | | | | | | | | | | | | |
| OTHER | | | | | | | | | | | | | | | | | |
| Tolerance/Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medication Review | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense/Collect Drinking Diary | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense Placebo (Single Blind) | X | | | | | | | | | | | | | | | | |
| Dispense Acamprosate/Placebo | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tablet Count/Compliance Review | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Provide Manual-Guided Therapy | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

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

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

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

5.6.1.4 Evaluations/Endpoints

The protocol-specified primary efficacy parameters were:

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

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

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

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

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

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

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

5.6.1.5 Statistical Plan

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

5.6.2 Results

5.6.2.1 Study Conduct/Outcome

5.6.2.1.1 Subject Characteristics

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

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

5.6.2.1.1.1 Enrollment by Center

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

| Site Number | Principal Investigator(s) | Screened Patients | Randomized Patients |
|-------------|--|-------------------|---------------------|
| 01 | Alan J. Budney, Ph.D. Clinical Director of Substance Abuse Services Dayone-Fletcher Allen Health Care U.V.M. Department of Psychiatry South Burlington, VT | 40 | 33 |
| 02 | Raymond F. Anton, M.D. (Co-PI) Professor Medical University of South Carolina Institute of Psychiatry Charleston, SC Darlene H. Moak, M.D. (Co-PI) Assistant Professor (same location as above) | 43 | 40 |
| 03 | Donald R. Wesson, M.D. Medical and Scientific Director Friends Research Associates Berkeley, CA | 43 | 39 |
| 04 | Michael Thase, M.D. Professor of Psychiatry University of Pittsburgh Western Psychiatric Institute & Clinic Pittsburgh, PA | 39 | 33 |

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| Site Number | Principal Investigator(s) | Screened Patients | Randomized Patients |
|-------------|--|-------------------|---------------------|
| 05 | <p>Adolf Pfefferbaum, M.D. (Co-PI) Director Neuropsychiatry Program Center for Health Sciences SRI International Menlo Park, CA</p> <p>Barry Rosen, M.D. (Co-PI) Medical Director Sequoia Alcohol & Drug Recovery Center Redwood City, CA</p> | 25 | 24 |
| 06 | <p>John Grabowski, Ph.D. Professor, Department of Psychiatry & Behavioral Sciences Director SARC Substance Abuse Research Center University of Texas-Houston Houston, TX</p> | 52 | 35 |
| 07 | <p>Patrick J. McGrath, M.D. Associate Professor of Clinical Psychiatry New York State Psychiatric Institute Depression Evaluation Service New York, NY</p> | 13 | 12 |
| 08 | <p>Domenic A. Ciraulo, M.D. Professor & Chairman Division of Psychiatry Boston University Medical School Boston, MA</p> | 43 | 31 |
| 09 | <p>Robert Anthenelli, M.D. Director of Substance Abuse Programs Cincinnati VA Medical Center Cincinnati, OH</p> | 38 | 30 |
| 10 | <p>H. George Nurnberg, M.D. (Co-PI) University of New Mexico School of Medicine Mental Health Center Albuquerque, NM</p> <p>Michael P. Bogenschutz, M.D. (Co-PI) Clinical Director, Dual Diagnosis Program Assistant Professor of Psychiatry University of New Mexico School of Medicine Albuquerque, NM</p> | 27 | 20 |
| 11 | <p>Milton L. Bullock, M.D. Division Chief of Addiction & Alternative Medicine Hennepin Faculty Associates Addiction Medicine Program Minneapolis, MN</p> | 43 | 35 |
| 12 | <p>Henry Kranzler, M.D. Associate Professor University of Connecticut Health Center School of Medicine, Dept. of Psychiatry Division of Addictive Disorders Farmington, CT</p> | 43 | 34 |

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| Site Number | Principal Investigator(s) | Screened Patients | Randomized Patients |
|-------------|--|-------------------|---------------------|
| 13 | Steven Shoptaw, Ph.D. Research Director Los Angeles Addiction Treatment Research Center Los Angeles, CA | 55 | 40 |
| 14 | Allen Zweben, DSW (Co-PI) Associate Professor University of Wisconsin-Milwaukee School of Social Welfare Milwaukee, WI Lance Longo, M.D. (Co-PI) Sinai Samaritan Medical Center Outpatient Behavioral Health Milwaukee, WI | 30 | 29 |
| 15 | Mary E. McCaul, Ph.D. The Johns Hopkins University Clinical Research Unit 10753 Falls Rd. Pavilion 2, Suite 325 Lutherville, MD 21093 | 54 | 42 |
| 16 | Stephanie O'Malley, Ph.D. Associate Professor of Psychiatry Yale University School of Medicine Substance Abuse Treatment Unit New Haven, CT | 28 | 25 |
| 17 | Barbara J. Mason, Ph.D. Associate Professor Director of Alcohol Disorders Research Unit University of Miami, School Of Medicine Dept. of Psychiatry Miami, FL | 51 | 42 |
| 18 | Margaret Kotz, D.O. The Cleveland Clinic Foundation Department of Psychiatry Cleveland, OH | 15 | 10 |
| 19 | Gerard Connors, Ph.D. Director of Research, Clinical Research Center Research Institute on Addictions Buffalo, NY | 19 | 11 |
| 20 | Timothy I. Mueller, M.D. Director, Residency In Psychiatry Butler Hospital Providence, RI | 16 | 15 |
| 21 | Joseph R., Volpicelli, M.D., Ph.D. (Co-PI) University of Pennsylvania Treatment Research Center Philadelphia, PA Helen Pettinati, Ph.D. (Co-PI) (Same location as above) | 24 | 21 |

5.6.2.1.1.2 Subject Disposition

The table below illustrates patient disposition and reasons for premature discontinuation. Overall, a total of 292 patients (49%) completed the Treatment Phase. Completion rate during

the Treatment Phase was lower in the acamprosate 2000 mg treatment group (41%) compared to the placebo (55%) and acamprosate 3000 mg treatment groups (52%). Subjects in the acamprosate 2000 mg treatment group were more likely to terminate due to Patient Decision (28%) and Loss to Follow-up (18%), compared to the other 2 groups. Otherwise, the reasons for discontinuation of treatment were similarly distributed among the groups, notably including discontinuation for treatment failure and for adverse events.

Table 5.6.2.1.1.2 Patient Disposition – US 96.1

| | Statistic | ACAMP 1998/2000 mg/day | ACAMP 3000 mg/day | Placebo |
|---|-----------|------------------------------|-------------------------|-----------|
| Number of Patients Randomized | N | 258 | 83 | 260 |
| Number of Patients Who Completed Treatment Phase | n (%) | 106 (41%) | 43 (52%) | 143 (55%) |
| Number of Patients Who Discontinued Treatment Phase | n (%) | 152 (59%) | 40 (48%) | 117 (45%) |
| Reasons for Discontinuation: | | | | |
| Adverse event | n (%) | 10 (4%) | 3 (4%) | 7 (3%) |
| Lost-to-follow-up | n (%) | 47 (18%) | 10 (12%) | 33 (13%) |
| Treatment failure | n (%) | 13 (5%) | 4 (5%) | 13 (5%) |
| Death | n (%) | 0 | 0 | 0 |
| Protocol Violation | n (%) | 4 (2%) | 0 | 3 (1%) |
| Other | n (%) | 78 (30%) | 23 (28%) | 61 (23%) |
| Data Source: Table 8.7.3.1.1 | | | | |

Sponsor's In-Text Table 8.4.4.1.1:

Percentages are based on the number of patients randomized.

5.6.2.1.1.3 Demographics

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

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

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

Approximately half of the subjects were abstinent at baseline (52% in acamprosate 2000 mg group and 49% in each other group).

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

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

Data Source: Table 8.7.3.2.1, Table 8.7.3.3.1

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

Not noted in the table above, about 75% of the sample had a history of illicit substance abuse. The most commonly reported drug use was marijuana. Patients in the acamprosate 2000 mg group, 3000 mg group, and placebo group, reported a mean number of years of marijuana use, respectively, of 8.6, 10.1, and 7.7 years and of cocaine use, respectively, of 4.5, 4.9, and 4.7

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

5.6.2.1.1.3.1 Treatment Goals

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

Table 5.6.2.1.1.3.2 Treatment Goals at Baseline

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

5.6.2.1.2 Dosing Information

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

Table 5.6.2.1.2 Duration of Exposure and Medication Compliance – US 96.1 – ITT Population

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

Sponsor's In-Text Table 8.7.4.6:1

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

5.6.3 Efficacy Results

5.6.3.1 Sponsor's Analysis

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

- Abstinence was not explicitly required for admission to the study, but because patients were required to reduce their drinking to non-hazardous levels for study admission and because it was the focus of the protocol-directed behavioral therapy, it was anticipated that most patients would be abstinent at the time of randomization.
- At Baseline, patients also had to indicate their treatment goal, which could range from no

- goal at all to a goal of total abstinence.
- Broad admission criteria were used in ACAMP/U.S./96.1 relative to the European studies (e.g., no upper age limit, allowance for non-dependent cannabis use at enrollment, and other illicit drug use during the study).
 - Standardized, manual-guided psychosocial support, consisting of brief intervention and medication compliance procedures of established efficacy to support abstinence, specific for the protocol, was given to all participants. In contrast, the majority of the Phase III European studies followed a more “naturalistic” approach, with variable non-structured psychosocial therapy, reflective of the individual practice techniques of the participating site.
 - Other design features of the U.S. study which were not typical of the European studies included:
 - daily drinking diaries, maintained by the patients and reviewed with the therapist at each visit in conjunction with returned study medication;
 - specially designed “reminder” blister packaging of study medication;
 - advertising to recruit study participants from outside the existent clinical practice of the participating site;
 - weekly telephone contacts with study participants to supplement the monthly visits to the site;
 - contacts with a close friend or relative specified by the patient to evaluate the patient’s progress; and
 - mandatory follow-up algorithms for missed visits or missed telephone contacts, which included frequent attempts to contact the patient or collateral informant via phone and certified mail.

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

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

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

5.6.3.1.1 [Corrected] Cumulative Abstinence Duration

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

According to Section 10.7.12 of the application,

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

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

data was multiplied by the percent of the previous 7 days that were non-abstinent.

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

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

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

Table 5.6.3.1.1 Sponsor’s Analysis: Corrected Cumulative Abstinence Duration (CCAD) (%) – US/96.1

| Population | Statistic | ACAMP 2000 mg/day | Placebo |
|------------------------------|-----------|-------------------------|------------|
| Intent-to-Treat | N | 255 | 256 |
| | Mean (SE) | 56.1 (2.1) | 54.3 (2.2) |
| | Median | 59 | 59 |
| Efficacy Evaluable | n | 177 | 198 |
| | Mean (SE) | 59.5 (2.5) | 56.4 (2.4) |
| | Median | 65 | 60 |
| Motivated Intent-to-Treat | n | 100 | 115 |
| | Mean (SE) | 66.1 (3.4) | 60.7 (3.3) |
| | Median | 78 | 64 |
| Motivated Efficacy Evaluable | n | 71 | 86 |
| | Mean (SE) | 70.2 (4.1) | 62.7 (3.8) |
| | Median | 88 | 69 |

Sponsor’s In-Text Table 8.4.4.1:3

5.6.3.2 Reviewer’s Analysis

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

comparison between placebo and the 2000 mg/day dose, as well as a pairwise comparison between placebo and the pooled acamprosate groups.

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

A series of exploratory analyses using differently-defined populations were undertaken, and on this basis, the sponsor claims that acamprosate can be shown to be superior to placebo. However, it should be noted that any number of populations could be defined. In the analysis below, I have defined various populations in an attempt to explore the ways that the US population differed from the European population. I have used the sponsor's defined CCAD on treatment as the outcome, although a more conservative analysis might have been to choose the number of days abstinent, either untransformed, or divided by 180 to yield a CCAD (rather than using the censored treatment durations as calculated by the sponsor). As noted below, no population I defined demonstrated superiority of acamprosate over placebo, even for the somewhat less conservative sponsor-calculated CCAD; therefore no "worst case" analysis was needed.

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

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

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

5.6.3.2.1 Reviewer-defined populations

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

5.6.3.2.1.1 Baseline Abstinent

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

5.6.3.2.1.2 Motivated

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

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

Several options were available for defining this population. Subjects were coded as to whether the investigator felt they met criteria for a DSM-IV diagnosis of substance dependence on marijuana, psychedelics, opiates, stimulants, sedatives, cocaine, or heroin. Not surprisingly, as such a diagnosis was an exclusionary criterion, no subjects in the ITT study population were flagged as meeting criteria.

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

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

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

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

The populations so identified were distributed as follows:

Table 5.6.3.2.1.3.1 Reviewer-Defined Sub-populations

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

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

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

5.6.3.2.2 Non-Continuous Abstinence

This analysis uses the reported corrected cumulative abstinence duration as a measure of non-continuous abstinence, defined as described in Section 5.6.3.1.1 above. From dataset US_CAD,

CCAD during treatment (CCADTX, defined above in section on sponsor's analysis) was analyzed by treatment group. Treatment assignment was obtained through merging with dataset US_POP.

5.6.3.2.2.1 Mean Percent Days Abstinent (CCAD)

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

Table 5.6.3.2.2.1 Corrected Cumulative Abstinence Duration in Reviewer-Defined Populations—US/96.1

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

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

None of these comparisons yield statistically significant differences.

5.6.3.2.2.2 Categorical Analysis of >90% Days Abstinent

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

Table 5.6.3.2.2.2 Subjects with “good response” (CCADTX \geq 90%)—US/96.1

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

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

† reviewer’s analysis

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

5.6.3.2.3 Continuous Response

5.6.3.2.3.1 Complete Abstinence

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

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

5.6.3.2.3.2 Abstinence from sustained heavy drinking

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

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

Table 5.6.3.2.3.2 Abstinence From Sustained Heavy Drinking in Reviewer-Defined Populations—US/96.1

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

Table prepared by reviewer from datasets US_RELAP, US_POP

Demographically, although the duration of alcohol dependence was similar across studies (12.5 years in the US study, 7.5-10.4 across treatment arms in the European studies), the American population contained many fewer very heavy drinkers (>10 drinks/drinking day), with only approximately 30% in this category in baseline demographic tabulations. In contrast, in the European studies, from a low of 64% to a high of 87% of the various treatment groups were very heavy drinkers. The studies were fairly similar to one another in this regard, with PRAMA enrolling 77-80% very heavy drinkers, Paille, 64-76%, and Pelc-II, 71-87%. An analysis using sponsor-calculated CCAD on the subset of patients reporting at least 10 drinks/drinking day at baseline again failed to show an effect of acamprosate in the US study. The CCAD was $43\% \pm 4$ (SE) for the pooled acamprosate groups vs. $52\% \pm 4$ for the placebo group. In the small subset of very heavy drinkers who were abstinent at randomization (39 acamprosate and 24 placebo), the $CCAD \pm SE$ was $52\% \pm 6$ for the pooled acamprosate groups and $69\% \pm 7$ for the placebo group. In the subset of very heavy drinkers identifying goal of abstinence (66 acamprosate and 56 placebo), $CCAD \pm SE$ was $50\% \pm 4$ for acamprosate and $47\% \pm 5$ for placebo. In the 116 heavy drinkers who did not use illicit drugs other than marijuana in the past year (60 acamprosate, 56 placebo), $CCAD \pm SE$ was $47\% \pm 5$ for acamprosate and $55\% \pm 5$ for placebo. In the tiny (44 subject) group which was very heavy drinking, motivated, abstinent at randomization, and had no illicit drugs other than marijuana, $CCAD \pm SE$ was $57\% \pm 7$ for acamprosate (24 subjects) and $69\% \pm 8$ for placebo (20 subjects).

Furthermore, the studies varied in the extent to which subjects had undergone previous treatment. In PRAMA, about half had only 0-1 previous treatments or detoxes and 35% had undergone 3 or more. In Pelc-II, about two thirds had only 0-1 previous treatments and about 20-25% had 3 or more. In Paille, about 80% had only 0-1 previous treatments or detoxes, and very few (4-7%) had undergone 3 or more. The US study population was most similar to the Paille population in this respect, with about 85% having 0-1 previous treatments and 6-12% having 3 or more. However, it should be noted that due to geographic differences and secular trends in access to treatment, the number of previous treatments for alcoholism may not be a valid surrogate for illness severity.

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

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

5.6.3.3 Conclusions Regarding Efficacy Data in Study

Leaving aside entirely the issue of the sponsor replacing the protocol-specified outcome variable, this study nevertheless offers no evidence to support the effectiveness of acamprosate in the

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

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

5.7 Other Efficacy Studies

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

Table 5.7 Other Controlled Clinical Studies Related to Claims of Effectiveness

| Study #, (Common Name) Principal Investigator, Country | Study Design (Drug Treatment Duration) | Treatment Groups | | | | Demographics | | |
|---|---|---|------------------------|------------------------------|---|------------------|--------------------|-------------------|
| | | Drug, Dosage Form, Strength (Formulation & Batch #) | Total Daily Dose in mg | Regimen | #, Type of Patients Entered per Group (# completed) | Age Range (mean) | Sex: M/F (%) | Race: W/B/H/O (%) |
| Supportive Studies | | | | | | | | |
| AOTA/1/89.4 (Poldrugo) F. Poldrugo, Italy (Oct., 1989 to July, 1992) | Pro, MC (7), R, DB, PC, PG (2: acamp vs placebo) with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days) | Acamp, tabs, 333 mg (#1580) | 1998* (1332) | 2 tabs tid | 122 ADS (65) | ND (42.9) | 84/38 (69/31) | ND |
| | | Placebo, tabs (#1579) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 124 ADS (47) | ND (44.9) | 95/29 (77/23S) | ND |
| AOTA/1/90.1 (Tempesta) E. Tempesta, Italy (Oct., 1989 to April, 1993) | Pro, MC (18), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS, after withdrawal from alcohol. (180 days) | Acamp, tabs, 333 mg (#3250) | 1998 | 2 tabs tid | 164 ADS (124) | ND (45.9) | 139/25 (84.8/15.2) | ND |
| | | Placebo, tabs (#3247) | 6 tabs | 2 tabs tid | 166 ADS (122) | ND (46.0) | 134/32 (80.7/19.3) | ND |

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| Study #, (Common Name) Principal Investigator, Country | Study Design (Drug Treatment Duration) | Treatment Groups | | | | Demographics | | |
|---|---|---|---------------------------------|----------------------------------|---|---------------------|---------------------------|-------------------------|
| | | Drug, Dosage Form, Strength (Formulation & Batch #) | Total Daily Dose in mg | Regimen | #, Type of Patients Entered per Group (# completed) | Age Range (mean) | Sex: M/F (%) | Race: W/B/H/O (%) |
| AOTA/NL/91.1 AOTA/B/90.2 (BENELUX) P. Geerlings and C. Ansoms, Belgium, The Netherlands (May, 1990 to Oct., 1992) | Pro, MC (22), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days) | Acamp, tabs, 333 mg (#1519, 3306, 1580 and 3250) | 1998* (1332) | 2 tabs tid 2-1-1 tabs tid | 128 ADS (38) | 19-65 (40.3) | 97/31 (76/24) | ND |
| | | Placebo, tabs (#1518, 3305, 1579 and 3247) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 134 ADS (32) | 21-63 (41.7) | 102/32 (76/24) | ND |
| AD 04 089 (Ladewig) D. Ladewig, Switzerland (Aug., 1989 to Jan., 1991) | Pro, MC (3), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days) | Acamp, tabs, 333 mg (#1580) | 1998* (1332) | 2 tabs tid 2-1-1 tabs tid | 29 ADS (19) | 28-68 (47.7) | 25/4 (86/14) | ND |
| | | Placebo, tabs (#1579) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 32 ADS (21) | 31-70 (46.9) | 22/10 (69/31) | ND |
| AD 10 089, (Lesch) O. Lesch, Austria (Dec., 1989 to March, 1993) | Pro, MC (5), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days) | Acamp, tabs, 333 mg (#1624) | 1998* (1332) | 2 tabs tid 2-1-1 tabs tid | 224 ADS (94) | 22-64 (41.9) | 168/56 (75/25) | ND |
| | | Placebo, tabs (#1623) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 224 ADS (85) | 15-70 (42.0) | 185/39 (82.6/ 17.4) | ND |
| AOTA/P/89.1 (Barrias) J.C. Barrias, Portugal (Nov., 1989 to Oct., 1992) | Pro, MC (9), R, DB, PC, PG (2: acamp vs P), with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days) | Acamp, tabs, 333 mg (#1580) | 1998* (1332) | 2 tabs tid 2-1-1 tabs tid | 150 ADS (86) | 21-64 (39.7) | 139/11 (92.7/ 7.3) | ND |
| | | Placebo, tabs (#1579) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 152 ADS (83) | 23-63 (41.0) | 139/13 (91.4/ 8.6) | ND |

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| Study #, (Common Name) Principal Investigator, Country | Study Design (Drug Treatment Duration) | Treatment Groups | | | | Demographics | | |
|--|--|---|------------------------|----------------------------------|---|------------------|--------------------|-------------------|
| | | Drug, Dosage Form, Strength (Formulation & Batch #) | Total Daily Dose in mg | Regimen | #, Type of Patients Entered per Group (# completed) | Age Range (mean) | Sex: M/F (%) | Race: W/B/H/O (%) |
| AA 11 088 (Besson) J. Besson, Switzerland (Jan., 1989 to Jan., 1993) | Pro, MC (3), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight and open-label use (yes/no) of Antabuse (disulfiram) as associated therapy, S/E study in ADS, after withdrawal from alcohol. (360 days) | Acamp, tabs, 333 mg (#1243 and 3249) | 1998* (1332) | 2 tabs tid 2-1-1 tabs tid | 61 ADS (19) ⁸ | 25-62 (42.6) | 50/11 (82.0/18) | ND |
| | | Placebo, tabs (#1242 and 3247) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 57 ADS (19) | 26-62 (42.6) | 43/14 (75.4/24.6) | ND |
| AOTA/E/91.1 (ADISA) A. Gual, Spain (May, 1993 to Oct., 1994) | Pro, MC (11), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS from onset of alcohol withdrawal. (180 days) | Acamp, tabs, 333 mg (#3306) | 1998 | 2 tabs tid | 148 ADS (96) | 21-61 (41.4) | 119/29 (80/20) | ND |
| | | Placebo, tabs (#3305) | 6 tabs | 2 tabs tid | 148 ADS (90) | 22-64 (40.6) | 117/31 (79/21) | ND |
| Long-term Studies | | | | | | | | |
| AD 10 089, (Lesch) O. Lesch, Austria (Dec., 1989 to March, 1993) | Pro, MC (5), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days) | Acamp, tabs, 333 mg (#1624) | 1998* (1332) | 2 tabs tid 2-1-1 tabs tid | 224 ADS (94) | 22-64 (41.9) | 168/56 (75/25) | ND |
| | | Placebo, tabs (#1623) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 224 ADS (85) | 15-70 (42.0) | 185/39 (82.6/17.4) | ND |
| AOTA/P/89.1 (Barrias) J.C. Barrias, Portugal (Nov., 1989 to Oct., 1992) | Pro, MC (9), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days) | Acamp, tabs, 333 mg (#1580) | 1998* (1332) | 2 tabs tid 2-1-1 tabs tid | 150 ADS (86) | 21-64 (39.7) | 139/11 (92.7/7.3) | ND |
| | | Placebo, tabs (#1579) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 152 ADS (83) | 23-63 (41.0) | 139/13 (91.4/8.6) | ND |

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

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| Study #, (Common Name) Principal Investigator, Country | Study Design (Drug Treatment Duration) | Treatment Groups | | | | Demographics | | |
|---|---|---|---------------------------------|----------------------------------|---|---------------------|---------------------------|-------------------------|
| | | Drug, Dosage Form, Strength (Formulation & Batch #) | Total Daily Dose in mg | Regimen | #, Type of Patients Entered per Group (# completed) | Age Range (mean) | Sex: M/F (%) | Race: W/B/H/O (%) |
| AA 11 088 (Besson) J. Besson, Switzerland (Jan., 1989 to Jan., 1993) | Pro, MC (3), R, DB, PC, PG (2: acamp vs P), with pre- randomization stratification according to body weight and open-label use (yes/no) of Antabuse (disulfir- am) as associated therapy, S/E study in ADS, after withdrawal from alcohol. (360 days) | Acamp, tabs, 333 mg (#1243 and 3249) | 1998* (1332) | 2 tabs tid 2-1-1 tabs tid | 61 ADS (19) ⁹ | 25-62 (42.6) | 50/11 (82.0/ 18) | ND |
| | | Placebo, tabs (#1242 and 3247) | 6 tabs (4 tabs) | 2 tabs tid 2-1-1 tabs tid | 57 ADS (19) | 26-62 (42.6) | 43/14 (75.4/ 24.6) | ND |
| Non-Supportive Study | | | | | | | | |
| AOTA/LP90/ N001 (UKMAS) J. Chick, United King. (June, 1990 to July, 1993) | Pro, MC (20), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS, after withdrawal from alcohol. A no- treatment period of ≥7 days was to occur between end of alcohol withdrawal and randomization. (24 weeks) | Acamp, tabs, 333 mg (#1624) | 1998 | 2 tabs tid | 289 ADS (100) | ND (42.8) | 252/37 (87.2/ 12.8) | ND |
| | | Placebo, tabs (#1623) | 6 tabs | 2 tabs tid | 292 ADS (103) | ND (43.8) | 233/59 (79.8/ 20.2) | ND |

From Sponsor's Table 8.4.1

The following abbreviations are used throughout:

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

5.7.1 Short-term studies: features

The same basic study design was used in each of the European Short-Term Supportive studies: namely, each study was a multicenter, randomized, double blind parallel group comparison of acamprosate versus placebo. An objective of each study, except the ADISA study, was to evaluate the efficacy and safety (tolerance) of acamprosate versus placebo as therapy to maintain abstinence in the weaned alcoholic over a pre-specified double blind treatment phase. A second

⁹ In this study, 24 patients (20 male, 4 female) in the acamprosate treatment group and 24 patients (17 male, 7 female) in the placebo group also received Antabuse®.

objective of each study, again with the exception of the ADISA study, was to determine whether efficacy was maintained over an observation period following the double blind treatment phase. The ADISA study started study medication concurrent with onset of alcohol withdrawal therapy and did not have a follow-up phase.

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

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

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

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

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

Each of the controlled European short-term supportive efficacy studies followed the same ITT principle. Any randomized patient who had taken at least one dose of study medication was

eligible for analysis. All patients who terminated treatment prior to the end of treatment were assumed to be treatment failures.

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

5.7.2 Long-term studies: features

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

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

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

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

5.7.3 European Non-Pivotal Studies: Results

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

Continuous abstinence rates were higher for acamprosate than for placebo in all studies except

UKMAS. However, the comparison was statistically significant (by the method used in the final report of the particular study) only for the studies indicated with an asterisk in the table below

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Table 5.7.3 Summary of Results of Non-Pivotal European Studies

| Study Name Duration N | CCAD (% days abstinent during treatment period) | | Continuous Abstinence (% of subjects reaching end of treatment period without drinking) | | Other | Comments |
|---------------------------------|---|---------|--|---------|--|---|
| | Acamprosate | Placebo | Acamprosate | Placebo | | |
| Poldrugo 180 days N = 246 | 72% | 59%* | 47% | 26%* | | Only three on-treatment visits |
| Tempesta 180 days N = 330 | 66% | 54%* | 47% | 31%* | | |
| Benelux 180 days N = 262 | 35% | 24%* | 13% | 10% | Inconsistent results in abstinence-by-visit | Low completion rate; ?unblinding due to AE's; two different protocols combined for analysis |
| ADISA 180 days N = 288 | 52% | 41%* | 35% | 26% | | Treatment initiated during outpatient detox; GI symptoms may have unblinded |
| Ladewig 180 days N = 61 | 47% | 26%* | 17% | 3% | N.S. results in abstinence by visit | Very small study; Only 3 on-treatment visits; GI symptoms may have unblinded |
| UKMAS 168 days N = 581 | 46% | 48% | 12% | 11% | | Low completion rate; Used a daily drinking diary card that was collected ; each visit; Visits occurred q 3 weeks |
| Lesch 1 year N = 448 | 39% | 30%* | 18% | 7%* | | Disulfiram permitted but little-used; Only 5 on-treatment visits over 1 year; GI symptoms in 20% acamprosate vs 12% placebo |
| Barrias 1 year N = 302 | 49% | 36%* | 35% | 20%* | Inconsistent results in abstinence by visit | |
| Besson 1 year N = 110 | 40% | 21%* | 25% | 5%* | Inconsistent results in abstinence by visit | Small study; Low completion rate; ~40% used concomitant disulfiram |

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

*Significant by analysis reported in Final Study Report

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

5.8 Efficacy Conclusions

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

However, the negative findings in the American study require reconciliation.

5.8.1 Overall Efficacy Findings

The non-systematic approach to the collection of alcohol use data should be recalled.¹⁰ Because of this non-systematic approach to the collection of the drinking behavior data, reconstruction of day-by-day abstinence goes beyond the level of sensitivity of the measure. Calculation of “cumulative abstinence time” overstates the precision of the data. Indeed, it is not known how many days the subjects were drinking and how many they were abstinent. Thus it seems inappropriate to generate conclusions based on such calculations.

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

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

¹⁰ In Pelc-II, the investigator was asked to record “average frequency of alcohol consumption” as well as an estimate of intensity (drinks per drinking day). However, for the purposes of analysis, this data was transformed to a binary outcome (abstinent/non-abstinent) and that value was imputed for all days in the two week interval.

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

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

Table 5.8.1 Continuous Abstinence in European Pivotal Trials

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

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

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

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

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

5.8.2 Discussion

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

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

The only problematic issue in this dataset is the negative finding in the American study, which, unlike the European study, used a systematic approach to reconstructing drinking behavior day by day, and is amenable to analysis to determine number or percent of days abstinent. As shown in the table below, the resulting value for the acamprosate-treated group (46% days abstinent) is lower than the strikingly consistent result in the sponsor-calculated CCADs for the European studies (~62%), but this is possibly attributed to the greater precision of the data collection

method, allowing capture of more non-abstinent days. Arguing against this, the value for the placebo-treated group, however, is somewhat higher than in the European studies (51% vs 38-48%).

The most plausible explanation offered for the failure of the US study to demonstrate efficacy of acamprosate is that the ancillary treatment offered in the study (both the psychosocial component and any therapeutic benefit of the data collection process) produced a favorable response in the subjects that left little room for a contribution of medication to the effect. Indeed, using the sponsor's own calculations of percent days abstinent, the placebo response was highest in the US study. It cannot be overlooked, however, that it was higher than the percent days abstinent in the acamprosate treated group. Unfortunately, this makes it difficult to dismiss Study US96.1 as simply a trial that "failed to show a difference." Despite the presence of the three European trials that were made available for careful reanalysis, alongside a myriad of other European trials presented in summary form and offering support for acamprosate's efficacy, some effort must be made to reconcile the findings with the American trial.

Table 5.8.2 CCAD (% days abstinent) in Pivotal Studies

| | Acamprosate 1332 mg/day | Acamprosate 1998/2000 mg/day | Placebo |
|--|----------------------------|------------------------------------|---------|
| Pelc-II (1 year treatment) Mean % days abstinent (CCAD—sponsor's calculation) | 59%±5 | 63%±5 | 38%±5 |
| Paille (1 year treatment) Mean % DAYS abstinent (calculated by reviewer from sponsor's reported cumulative abstinence duration) | 55% | 62% | 48% |
| PRAMA (1 year treatment) (Dosed according to weight, but nearly all patients took 1998 mg/day) Mean % DAYS abstinent (CCAD—sponsor's calculation) | | 62%±3 | 45%±3 |
| US 96.1 (6 months treatment) Mean % days abstinent (CCAD—sponsor's calculation) | | 46% | 51% |

6 Appendix

6.1 Individual More Detailed Study Reviews

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

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

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

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

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

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

A total of 256 patients were selected, of which 246 patients were randomized to receive 180 days of treatment with acamprosate (122 patients) or placebo (124 patients) and included in the ITT population. More patients in the acamprosate group (53%) completed the double-blind treatment phase than in the placebo group (38%). More placebo patients discontinued due to treatment

failure (23% vs. 16% in acamprosate group) and for adverse events (13% vs 8% in acamprosate group). The reasons for discontinuation are listed in the table below.

Patient Disposition During Treatment Phase – Poldrugo

| Parameter | Statistic | ACAMP (N=122) | Placebo (N=124) |
|--|------------------|--------------------------|----------------------------|
| Number of Patients Randomized | n | 122 | 124 |
| Number of Patients in the ITT Population | n (%) | 122 (100%) | 124 (100%) |
| Number of Patients Who Completed the Double Blind Treatment Phase | n (%) | 65 (53%) | 47 (38%) |
| Number of Patients Who Discontinued the Double Blind Treatment Phase | n (%) | 57 (47%) | 77 (62%) |
| Reasons for Discontinuation: | | | |
| Adverse Event | n (%) | 10 (8%) | 16 (13%) |
| Lost to Follow-up | n (%) | 4 (3%) | 5 (4%) |
| Treatment Failure | n (%) | 20 (16%) | 29 (23%) |
| Death | n (%) | 1 (<1%) | 0 |
| Protocol Violation | n (%) | 1 (<1%) | 4 (3%) |
| Other | n (%) | 21 (17%) | 23 (19%) |
| Data Source: Table 8.7.2.1.1 | | | |

Sponsor's In-Text Table 8.4.3.1:1

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

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

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

Demographic and Baseline Characteristics – Poldrugo

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

Data Source: Table 8.7.2.2.1 and 8.7.2.3.1

Sponsor's In-Text Table 8.4.3.1:2

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

Compliance was almost 100% for both groups.

The primary variables for evaluating efficacy were the cumulative abstinence duration (CAD) and the relapse rate. The CAD was defined as the total number of days of abstinence and was calculated as the sum of only those periods of complete abstinence. If any relapse was recorded at a specific visit, the total period from the previous visit was considered as relapse, although, this method was conservative and may over-estimate the length of the relapse period. In

determining the period between visits, the scheduled day of assessment was taken into consideration rather than the actual day of the visit. The fraction of abstinent time during the study (corrected CAD or CCAD) was also calculated. The potential treatment duration was 180 days for all patients except those with concurrent illness who were censored. The table below shows the results for CAD and CCAD.

Cumulative Abstinence Duration (CAD) and Corrected CAD - Poldrugo

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

Sponsor's In-Text Table 8.4.3.1:3

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

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

Number (%) of Patients Assessed as Abstinent, Relapsed, or Non-Attendant – Poldrugo

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

Sponsor's In-text Table 8.4.3.1:4 (1) Mantel-Haenszel Chi²
(2) Kendall-Tau-c (T value)

Statistically significant differences were reached in this 3-category variable on day 90 and day 180, but not on day 30. If patients in the relapsed and non-attendant categories are combined and considered as treatment failures, the proportion of patients abstinent compared with treatment

failures show a statistically significantly higher proportion of patients on all assessment days in the acamprosate treatment group compared with the placebo treatment group.

In the survival analysis the time to the occurrence of the first relapse was estimated in each treatment group. The median survival time was 150.51 days for acamprosate and 60.97 days for placebo ($p=0.0004$). In the acamprosate group, 47% were abstinent throughout the treatment period, vs. 26% in the placebo group.

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

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

The CAD over the entire study period (treatment phase plus follow-up phase) remained significantly longer in the acamprosate group compared to the placebo group. The CAD for acamprosate was 157.7 ± 151.1 days and 120.5 ± 146.8 days for placebo treated patients ($p = 0.014$); however, the CCAD for the entire period failed to reach statistical significance in favor of acamprosate ($p = 0.082$).

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

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

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

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

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

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

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

Patient Disposition During Treatment Phase – Tempesta

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

Sponsor's In-Text Table 8.4.3.2:1

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

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

Demographic characteristics and history of alcohol use at Baseline were similar across groups. Eighty-three percent of patients were male and the mean age was 46 years. History of alcohol use at Baseline was also similar for both treatment groups. Duration of alcohol dependence or abuse averaged 11.5 years in both treatment groups and over half (55% in the acamprosate group and 51% in the placebo group) of the patients consumed more than 10 standard drinks per day at study entry. Most subjects (65-69%) had not had previous treatment for alcoholism. Approximately 10% had undergone more than three prior treatments. All patients in both treatment groups received detoxification prior to randomization and were abstinent at Baseline.

Demographic and Baseline Characteristics – 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 | Mean | 45.9 (0.9) | 46.0 (0.9) |
| (SE) | (SE) | | |
| Weight (kg) | N | 164 | 166 |
| Mean | Mean | 71.2 (0.7) | 70.6 (0.7) |
| (SE) | (SE) | | |
| Min, Max | 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 | Mean | 11.5 (0.9) | 11.5 (0.9) |
| (SE) | (SE) | | |
| Average Standard Drinks per Day at Study Entry | N | 164 | 166 |
| <5 | n (%) | 6 (4%) | 9 (5%) |
| 5 – 10 | n (%) | 68 (41%) | 72 (43%) |
| >10 | n (%) | 90 (55%) | 85 (51%) |
| Prior Treatment or Detoxes for Alcoholism | N | 164 | 166 |
| 0 | n (%) | 113 (69%) | 108 (65%) |
| 1 | n (%) | 17 (10%) | 23 (14%) |
| 2 | n (%) | 13 (8%) | 12 (7%) |
| 3 | n (%) | 6 (4%) | 5 (3%) |
| >3 | n (%) | 15 (9%) | 18 (11%) |
| Data Source: Table 8.7.2.2.2 and 8.7.2.3.2 | | | |

Sponsor's In-Text Table 8.4.3.2:2
the assessment.

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

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

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

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

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

Cumulative Abstinence Duration (CAD) and Corrected CAD (CCAD) –Tempesta

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

Sponsor's In-Text Table 8.4.3.2:4

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

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

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

Sponsor's In-Text Table 8.4.3.2:3

In the analysis of the time to first relapse, the median period of abstinence before the first relapse was significantly longer with acamprosate (135 days) than with placebo (58 days). In this analysis, 47% of acamprosate subjects and 31% of placebo subjects maintained abstinence

through 180 days. ($p=0.0091$, Lee-Desu statistics).

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

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

6.1.3 AOTA/NL/91.1, AOTA/B/90.2 (BENELUX): Double-Blind Controlled Study Versus Placebo to Assess the Effectiveness and Tolerance of Acamprosate (Calcium Acetyl Homotaurinate) in Helping to Maintain Abstinence in the Weaned Alcoholic

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

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

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

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

Protocol AOTA/B/90.2 excluded subjects for pregnancy, inadequate contraception, psychiatric or medical disorders, or lack of cooperation with weaning treatment. In Protocol AOTA/NL/91.1 patients who remained for 2 or more weeks in a residential setting during the study period were excluded.

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

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

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

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

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

Patient Disposition During Treatment Phase – 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: Table 8.7.2.1.3 | | | |

Sponsor's In-Text Table 8.4.3.4:1

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

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

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

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

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

Sponsor's In-Text Table 8.4.3.4.2

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

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

The primary variables for assessing efficacy were cumulative abstinence duration (CAD) and relapse rate at each visit. CAD was defined as the total number of days of abstinence and was calculated as the sum of only those periods of complete abstinence. If any relapse was recorded at a specific visit, the total period from the previous visit was considered as relapse. In determining the period between visits, the scheduled day of assessment was taken into consideration rather than the actual day of the visit. To assess CAD as a fraction of the potential duration of treatment, the corrected cumulative abstinence duration (CCAD) was calculated. The potential treatment duration was 180 days for all patients excluding those with concurrent illness who were censored during the course of the study.

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

Cumulative Abstinence Duration (CAD) and Corrected CAD (CCAD) - BENELUX

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

Sponsor's In-Text Table 8.4.3.4:3

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

Abstinence or Non-Abstinence/Non-Attendance at Each Visit – BENELUX

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

Data Source: BENELUX Study Report

Sponsor's In-Text Table 8.4.3.4:4

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

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

Follow-up Period: At Day 180, study medication was withdrawn and the 70 patients who completed the double-blind treatment entered the 180-day observation period. Fifty three (76%) of these patients completed the observation period. Among the 38 patients receiving acamprosate, six patients were lost to follow-up and two patients refused to continue treatment. Of the 32 patients receiving placebo, three patients relapsed and six patients were lost to follow-up. During the observation period the larger proportion of patients maintaining abstinence in the acamprosate group in relation to the placebo group progressively diminished. There were no statistically significant differences between the treatment groups at any follow-up assessment. Fourteen (37%) acamprosate treated patients remained abstinent throughout the entire 360 days (treatment and follow-up phase) compared with seven (22%) patients in the placebo group (Chi² test p=0.173). Over the entire study period the cumulative abstinence duration for the acamprosate group was 221.8 days ± 140.1 days and 190.8 days ± 127.0 days in the placebo group. The difference between treatment groups was not statistically significant.

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

AD 04 089 (Ladewig) was a prospective, randomized, multicenter (3 centers), double-blind, placebo-controlled, parallel group (2) comparison of the efficacy and safety of acamprosate versus placebo in maintaining abstinence in weaned alcohol-dependent outpatients, over a 6 month treatment period. The clinical portion of the study was conducted from August 1989 to January 1991 at 3 centers in Switzerland, with Prof. D. Ladewig, M.D. (Head, Department of

Psychiatry, Psychiatric University Clinic, Basel, Switzerland) as overall Principal Investigator. The investigators at the 2 other centers were both consulting psychiatrists and the centers were regional psychiatric clinics.

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

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

Primary efficacy criteria were CAD and relapse rate. Safety evaluations were performed at Baseline and Visits 1-3, and consisted of recording of spontaneously reported treatment-emergent adverse events, clinical laboratory determinations (hematology and clinical chemistry), and a questionnaire that listed 44 symptomatic complaints, which included possible withdrawal symptoms as well as adverse events.

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

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

Patient Disposition During Treatment Phase - Ladewig

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

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

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

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

Demographic characteristics and history of alcohol use at Baseline are summarized in the table below. A greater proportion of the acamprosate group was male (86% in the acamprosate group vs 69% in the placebo group). The mean ages of the groups were similar (47.7 years in the acamprosate group and 49.9 years in the placebo group). Duration of alcohol dependence or abuse averaged 12 years (11.9 years for the acamprosate and 12.6 years for the placebo group). More subjects in the acamprosate group had at least 1 prior treatment for alcoholism (90% vs 81% in the placebo group). The placebo group had more subjects with no previous treatment (19% vs. 10% in the acamprosate group) and more subjects with >3 previous treatments (19% vs. 7% in the acamprosate group). Baseline level of daily drinking was not reported. All of the patients received detoxification prior to randomization and were abstinent at Baseline.

Demographic and Baseline Characteristics –Ladewig

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

Sponsor's In-Text Table 8.4.3.6:2

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

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

NA = Not Available.

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

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

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

Cumulative Abstinence Duration (CAD) and Corrected CAD (CCAD) –Ladewig

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

Sponsor's In-Text Table 8.4.3.6:4

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

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

Number (%) of Patients Who Were Abstinent or Treatment Failures At Days 30, 90, and 180 – Ladewig

| Assessment Day | Treatment | Abstinent | Treatment Failure | Chi ² Test |
|----------------|-------------|-----------|-------------------|-----------------------|
| Day 30 | Placebo | 13 (41) | 19 (59) | 0.01 |
| | Acamprosate | 21 (72) | 8 (28) | |
| Day 90 | Placebo | 8 (25) | 24 (75) | 0.17 |
| | Acamprosate | 12 (41) | 17 (59) | |
| Day 180 | Placebo | 7 (22) | 25 (78) | 0.10 |
| | Acamprosate | 12 (41) | 17 (59) | |

Data Source: Ladewig Study Report, Table 6

Sponsor's In-Text Table 8.4.3.6:3

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

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

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

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

The objective of this study was to evaluate the efficacy and safety of acamprosate versus placebo

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

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

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

Eligible patients were randomized in a ratio of 1:1 to either 1998 mg of acamprosate or placebo per day, taken as 2 tablets of 333 mg acamprosate (or matching placebo) t.i.d. with meals. Study medication began on day 1 of an 8 day alcohol detox, which could be inpatient or outpatient, according to the routine of the participating study center. The study consisted of 8 visits: Screening Visit, Randomization Visit, and Visits 1-6 (at Day 8, 30, 60, 90, 135, 180) during the Treatment Phase.

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

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

Patient Disposition During Treatment Phase – ADISA

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

Sponsor's In-Text Table 8.4.3.5:1 Note: Percentages are based on the number of patients randomized.

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

Demographic characteristics and history of alcohol use at Baseline were similar. Eighty percent (80% in the acamprosate group and 79% in the placebo group) of patients were male and the mean age was 41 years (41.4 years for the acamprosate group and 40.7 years for the placebo group). The mean duration of alcohol dependence or abuse was 12.6 years for acamprosate and 12.9 years for placebo. Approximately two-thirds (66%) of the patients consumed more than 10 standard drinks per day at study entry and 58% of the patients in each treatment group had at least 1 prior treatment for alcoholism. Although, theoretically, alcohol withdrawal and medicated detoxification could have been administered on either an inpatient or an outpatient basis in this study, in fact, all patients were withdrawn from alcohol on an outpatient basis 34% in each group underwent non-medicated detox. During the 8-day withdrawal period, 6 patients in the acamprosate group and 1 patient in the placebo group dropped out of the study. At the end of the 8-day period, of the remaining patients, 13% in the acamprosate group and 16% in the placebo group were not abstinent.

Demographic and Baseline Characteristics – ADISA

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

Data Source: Table 8.7.2.2.6 and 8.7.2.3.6

Sponsor's In-Text Table 8.4.3.5:2

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

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

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

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

CAD and CCAD - ADISA

| | CAD | CCAD |
|-------------|------------|------|
| Placebo | 74 ± 75 | 41% |
| Acamprosate | 93 ± 75 | 52% |

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

Cumulative Continuous Abstinence Rate – ADISA

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

Data Source: ADISA Study report, Table 6.10

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

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

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

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

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

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

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

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

A total of 664 patients were screened and 581 (289 acamprosate, 292 placebo) were randomized.

The majority of the 83 screen failures dropped out, did not meet the selection criteria, or refused medication. A total of 203 patients completed the study, 100 patients (35%) in the acamprosate group and 103 patients (35%) in the placebo group. The reasons for premature discontinuation are shown in the table below, which was prepared by Lipha after examination of case report forms. Discontinuation for adverse event was more common in the acamprosate group (13%) than the placebo group (8%). Otherwise, reasons for discontinuation were similar. Most commonly, discontinuations were due to loss to follow up (22% acamprosate and 25% placebo) and “other” (including concurrent illness, condition worsened, refused medication, and non-compliance), in 19% of each group.

Patient Disposition During Treatment Phase - UKMAS

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

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

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

Demographic and Baseline Characteristics - UKMAS

| Parameter | Statistic | ACAMP 1998/2000 mg/day (N=289) | Placebo (N=292) |
|---|-----------|--------------------------------------|--------------------|
| Gender | N | 289 | 292 |
| Male | n (%) | 252 (87%) | 233 (80%) |
| Female | n (%) | 37 (13%) | 59 (20%) |
| Age (years) | N | 289 | 292 |
| | Mean (SE) | 42.3 (0.6) | 43.3 (0.6) |
| Weight (kg) | N | 289 | 292 |
| | Mean (SE) | 73.5 (0.7) | 73.5 (0.8) |
| | Min, Max | 50, 119 | 50, 119 |
| Marital Status | N | | |
| Married | n (%) | NA | NA |
| Not Married | n (%) | | |
| Detoxification Prior to Randomization | n | 289 | 292 |
| Yes | n (%) | 289 (100%) | 292 (100%) |
| No | n (%) | 0 | 0 |
| Abstinence at Baseline | n | 280 | 284 |
| Yes | n (%) | 201 (70%) | 195 (67%) |
| No | n (%) | 79 (27%) | 89 (30%) |
| Duration of Alcohol Dependence/Abuse (years) | n | 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 (%) | NA | NA |
| 2 | n (%) | | |
| 3 | n (%) | | |
| >3 | n (%) | | |

Data Source: Table 8.7.2.2.5 and 8.7.2.3.5

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

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

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

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

There were no statistically significant differences in attendance rates between the treatment groups at any time-point during the study. The attendance rates, up to and including Visit 7 (84 days), were 50.9% for acamprosate and 54.5% for placebo. The attendance rates up to and including Visit 10 (168 days) were 35.3% for acamprosate and 37.0% for placebo.

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

**Number (%) of Patients Abstinent at Each Visit and Mean Days of Continuous Abstinence
– UKMAS**

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

Sponsor's In-Text Table 8.4.3.3:3

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

The secondary efficacy parameters included CAD which was calculated for each patient by totaling the number of abstinent days recorded on all diary cards between Visit 3 and Visit 10. The mean value for each treatment group was compared using a one-way analysis of variance. The mean CAD for the acamprosate group was 77.2 days and for placebo 80.9 days. The difference was not statistically significant (p=0.492). For comparison to other studies, it is possible to calculate a CCAD (% days abstinent) by dividing CAD by the planned duration of treatment (168 days). As noted above, this imputes drinking to all days after dropout, even for

subjects whose dropout may have been unrelated to drinking. However, given the high proportion who dropped out due to “loss to follow-up,” this is a reasonable estimate. The CAD and CCAD so calculated are shown below.

CAD and CCAD - UKMAS

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

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

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

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

UKMAS Study Report Table 23, Vol 88 p40.

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

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

specialized alcoholism clinics.

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

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

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

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

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

Patient Disposition During Treatment Phase - 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: Table 8.7.4.1.1 | | | |

Sponsor's In-Text Table 8.4.5.1:1

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

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

Demographic characteristics and history of alcohol use at Baseline are were largely similar across groups. Most patients were male and between 40 and 59 years of age. There was a higher percentage of female patients in the acamprosate group (25%) compared to the placebo group (17%). The percentage of married patients was higher in the placebo group (56%) than in the acamprosate group (48%). Neither years of alcohol dependence nor history of prior treatments for alcoholism were reported. The groups were similar with respect to drinking level at Baseline. Most patients (63% in each treatment group) consumed >10 standard drinks per day at study entry. All patients had detoxification prior to randomization and were abstinent prior to the initiation of study medication.

Demographic and Baseline Characteristics –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 | | 224 | 224 |
| Married | n (%) | 107 (48%) | 125 (56%) |
| Not Married | n (%) | 117 (52%) | 99 (44%) |
| Detoxification Prior to Randomization | N | 224 | 224 |
| Yes | n (%) | 224 (100%) | 224 (100%) |
| No | n (%) | 0 | 0 |
| Abstinent at Baseline | N | 224 | 224 |
| Yes | n (%) | 224 (100%) | 224 (100%) |
| No | n (%) | 0 | 0 |
| Duration of Alcohol Dependence/Abuse (years) | | NA | NA |
| Average Standard Drinks Per Day at Study Entry | N | 224 | 224 |
| <5 | n (%) | 14 (6%) | 13 (6%) |
| 5 – 10 | n (%) | 69 (31%) | 71 (32%) |
| >10 | n (%) | 141 (63%) | 140 (63%) |
| Family History of Alcohol Problems | | NA | NA |
| Prior Treatments or Detoxes for Alcoholism | | NA | NA |
| Data Source: Tables 8.7.4.2.1 and 8.7.4.3.1 | | | |

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

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

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

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

The primary variables for evaluating efficacy were the cumulative abstinence duration (CAD)

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

Cumulative Abstinence Duration (CAD) and Corrected CAD – Lesch

| Treatment period 0-360 days | CAD | | CCAD | |
|--------------------------------|---------|---------|---------|-----|
| | Days | SD | % | SD |
| Placebo | 103.79 | ±118.95 | 30 | ±34 |
| Acamprosate | 138.75 | ±137.53 | 39 | ±38 |
| T-test (SQRT) | p=0.012 | | p=0.021 | |

Data Source: Lesch Study Report, Table 8

Sponsor's In-Text Table 8.4.5.1:3

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

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

Number (%) of Patients Who Were Abstinent, Relapsed, or Non-Attendant at Study Visits – Lesch

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

Data Source: Lesch Study Report, Table 6

Sponsor's In-Text Table 8.4.5.1:4

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

In an analysis of complete abstinence over the entire 360 days of the treatment phase, 18% of patients in the acamprosate group were totally abstinent compared to 7% of patients in the placebo group. The difference between treatment groups was statistically significant (Mantel-Cox Test, $p=0.0007$).

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

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

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

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

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

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

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

Subjects underwent detox prior to participation and were required to be abstinent at least 5 days at entry. Eligible patients were randomly assigned to receive acamprosate (1998 mg/day at meal

times for >60 kg and 1332 mg/day for lighter subjects) or placebo in a ratio of 1:1. The scheduled duration of treatment was 360 days. The study consisted of 9 visits: Visit -1 (Screening), Visit 0 (Baseline), Visits 1-5 (at Day 30, 90, 180, 270, and 360) during the Treatment Phase and Visit 6-7 (at Day 450 and Day 540, respectively) during the Follow-up Phase. Throughout the study, patients could have psychotherapy or other psychosocial support as deemed necessary.

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

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

Patient Disposition During Treatment Phase – Barrias

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

Sponsor's In-Text Table 8.4.5.2:1

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

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

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

Demographic and Baseline Characteristics – 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 |
| Detoxification Prior to Randomization | N | 150 | 152 |
| Yes | n (%) | 150 (100%) | 152 (100%) |
| No | n (%) | 0 | 0 |
| Duration of Alcohol Dependence/Abuse (years) | | NA | NA |
| Average Standard Drinks Per Day at Study Entry | N | 150 | 152 |
| <5 | n (%) | 6 (4%) | 6 (4%) |
| 5 – 10 | n (%) | 49 (33%) | 45 (30%) |
| >10 | n (%) | 95 (63%) | 101 (66%) |
| Prior Treatments or Detoxes for Alcoholism | | NA | NA |
| Data Source: Tables 8.7.4.2.2 and 8.7.4.3.2 | | | |

Sponsor's In-Text Table 8.4.5.2:2

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

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

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

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

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

Cumulative Abstinence Duration (CAD) and Corrected CAD –Barrias

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

Data Source: Barrias Study Report, Table 6

Sponsor's In-Text Table 8.4.5.2:3

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

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

Number (%) of Patients Who Were Abstinent, Relapsed, or Non-Attendant at Study Visits – Barrias

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

Data Source: Barrias Study Report, Table 7

Sponsor's In-Text Table 8.4.5.2:4

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

The median time to first relapse, according to survival analysis, was 54.55 days for placebo and

111.00 days for acamprosate. At Day 360, 34.7% of the acamprosate treated patients had remained abstinent compared to 20.2% of the placebo group (Mantel-Cox Test $p=0.0009$).

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

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

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

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

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

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

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

could have psychotherapy or other psychosocial support as deemed necessary. Concomitant therapy with disulfiram was permitted during the study and patients were stratified prior to randomization for use or non-use of disulfiram.

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

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

Patient Disposition During Treatment Phase – Besson

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

Sponsor's In-Text Table 8.4.5.3:1

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

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

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

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

Demographic and Baseline Characteristics - Besson

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

Sponsor's In-Text Table 8.4.5.3:2

NA = Not Available

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

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

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

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

Cumulative Abstinence Duration (CAD) and Corrected CAD: Besson

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

Sponsor's In-Text Table 8.4.5.3:4

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

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

Number (%) of Patients Who Were Abstinent, Relapsed, or Non-Attendant at Study Visits - Besson

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

Data Source: Besson Study report, Table 5

Sponsor's In-Text Table 8.4.5.3:3

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

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

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

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