

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE

NDA 21-431: ACAMPROSATE 333 MG TABLETS

LIPHA PHARMACEUTICALS, INC.

Friday, May 10, 2002

8:00 a.m.

Holiday Inn Bethesda
Versailles I
8120 Wisconsin Avenue
Bethesda, Maryland

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Dan Oren, M.D., Acting Chairperson
Sandra Titus, Ph.D., Executive Secretary

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Richard Fuller, M.D.

GUESTS (Non-Voting)

John R. Hughes, M.D.
Charles O'Brien, M.D., Ph.D.
Linda Porrino, Ph.D.
Alan Schatzberg, M.D.

INDUSTRY GUEST (Non-Voting)

Dilip J. Mehta, M.D., Ph.D.

FDA

Sandra L. Kweder, M.D.
Cynthia McCormick, M.D.
Celia Winchell, M.D.
Sue Jane Wang, Ph.D.

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1 P R O C E E D I N G S

2 Call to Order, Introductions

3 DR. OREN: Good morning. My name is Dan
4 Oren. I would like to call to order this meeting
5 of the Psychopharmacological Drugs Advisory
6 Committee regarding NDA 21-431 for acamprosate 333
7 milligram tablets.

8 This committee is purely an advisory
9 committee so I have the distinct pleasure of being
10 an acting chair of a committee with no power. But
11 we have an important mission and that mission is to
12 make recommendations to answer questions to give
13 some guidance to the FDA to do with what they wish.

14 I would like the members of the panel to
15 each introduce themselves. We will go around. I
16 will start with the FDA representatives who are
17 from the Review Division and ask--Sandy Kweder is
18 not here yet but we will start with Dr. Cynthia
19 McCormick.

20 DR. MCCORMICK: How do you do. I am Dr.
21 Cynthia McCormick. I am the Director of the
22 Division of Anesthetic, Critical Care and Addiction
23 Drug Products at the FDA. Welcome.

24 DR. WINCHELL: I am Celia Winchell. I am
25 the Medical Team Leader for Addiction Drug Products

1 and I did the primary clinical review for this NDA

2 DR. WANG: Good morning, everyone. My
3 name is Sue Jane Wang. I am the Statistic Leader
4 in the Alcoholism Treatment Clinical Trials. I am
5 the statistical reviewer for this project.

6 DR. OREN: As we go around to the formal
7 members of our panel, I would introduce Dr. Leon is
8 who is a new member. I want to ask everyone, in
9 addition to telling us a little bit about what you
10 do, tell us where you are from.

11 DR. LEON: I am Andrew C. Leon, Cornell
12 University Medical College. I work primarily in
13 affective disorders and anxiety disorders.

14 DR. KECK: My name is Paul Keck. I am
15 Vice Chair for Research in the Department of
16 Psychiatry at the University of Cincinnati College
17 of Medicine.

18 DR. HAMER: I am Bob Hamer. I am
19 Professor of Psychiatry and Biostatistics at the
20 University of North Carolina.

21 DR. WINOKUR: Andy Winokur from the
22 Department of Psychiatry, University of Connecticut
23 Health Center. I am Director of Psychopharmacology
24 there.

25 DR. MALONE: I am Richard Malone from the

1 Department of Psychiatry at the Medical College of
2 Pennsylvania in Philadelphia. I am involved mainly
3 in child psychiatry research.

4 DR. RUDORFER: I am Matthew Rudorfer from
5 the National Institute of Mental Health. I am the
6 Associate Director for Treatment Research in the
7 Division of Services and Interventions Research.

8 DR. TITUS: I am Sandy Titus. I am with
9 the FDA. I am the Executive Secretary for PDAC.

10 DR. OREN: I am still Dan Oren. I am an
11 Associate Professor of Psychiatry at Yale
12 University.

13 DR. ORTIZ: I am Irene Ortiz. I am from
14 the Department of Psychiatry at the University of
15 New Mexico and the Albuquerque V.A. I am in
16 geriatric psychiatry and addiction psychiatry.

17 DR. FULLER: I am Richard Fuller. I am
18 Director of the Division of Clinical and Prevention
19 Research at the National Institute on Alcohol Abuse
20 and Alcoholism.

21 DR. PORRINO: I am Linda Porrino, a
22 Professor in the Department of Physiology and
23 Pharmacology at Wake Forest University School of
24 Medicine

25 DR. HUGHES: I am John Hughes. I am a

1 Professor in Psychiatry at the University of
2 Vermont.

3 DR. MEHTA: I am Dilip Mehta. I am the
4 industry representative on this committee.

5 DR. OREN: Drs. Porrino, Hughes and Mehta
6 are guests with the committee and we are delighted
7 to have you here.

8 The three questions that we have before us
9 for today are we are asked to consider the evidence
10 of efficacy of acamprosate in the treatment of
11 alcoholism and to provide advice on three key
12 questions.

13 One, how can the discrepant results
14 between the older European studies and the more
15 recently conducted American study be reconciled?
16 Two, do the data support any conclusions regarding
17 subgroups of patients more likely to benefit from
18 acamprosate? Three, given the conflicting results,
19 is there sufficient evidence of the efficacy of
20 acamprosate in the treatment of alcoholism to
21 warrant approval?

22 I will turn the podium over to Dr. Titus.

23 Conflict of Interest Statement

24 DR. TITUS: I am going to read the
25 conflict of interest statement dealing with

1 acamprostate for this meeting. The following
2 announcement addresses the issue of conflict of
3 interest issues associated with this meeting and is
4 made a part of the record to preclude even the
5 appearance of such at this meeting.

6 Based on the submitted agenda for the
7 meeting and all relevant financial interests
8 reported by the committee participants, it has been
9 determined that all interest in firms regulated by
10 the Center for Drug Evaluation and Research present
11 no potential for an appearance of a conflict of
12 interest with the following exceptions.

13 Robert Hamer has been granted waivers
14 under 18 USC 208(b)(3) and 21 USC 355(n)(4) for his
15 and his spouse's stock in the parent company of a
16 competitor. The stock is valued between \$25,000 to
17 \$50,000.

18 Richard Fuller has been granted a waiver
19 under 21 USC 355(n)(4) for his stock in the parent
20 company of a competitor. The stock is valued from
21 \$5,001 to \$25,000. Because 5 CFR 2640.202(a) de
22 minimis exemption applies, a waiver under 18 USC
23 208(b)(3) is not required.

24 Paul Keck has been granted a waiver under
25 21 USC 355(n)(4) for his stock in the parent

1 company of a competitor. The stock is valued at
2 less than \$5,001. Because 5 CFR 2640.202(a) de
3 minimis exemption applies, a waiver under 18 USC
4 208(b)(3) is not required.

5 A copy of the waiver statements may be
6 obtained by submitting a written request to the
7 Agency's Freedom of Information Office, Room 12A30
8 of the Parklawn Building. With respect to FDA's
9 invited guests, there are reported interests that
10 we believe should be made public to allow the
11 participants to objectively evaluate their
12 comments. Dr. Anthony Schatzberg consulted with
13 Bristol-Myers Squibb within the past year on a drug
14 which is unrelated to acamprosate or its competing
15 products.

16 Dr. Charles O'Brien is Chief of Psychiatry
17 at the Philadelphia Veterans Affairs Medical
18 Center. Dr. O'Brien was previously invited by
19 Forest Laboratories to a meeting concerning
20 acamprosate. However, he was unable to attend due
21 to other commitments. Dr. O'Brien was the first to
22 initiate a study of naltrexone, a competing product
23 in alcoholism and his center participated in the
24 U.S. acamprosate trial. But he had no direct
25 involvement. His center is also participating in

1 the NIH-sponsored study of naltrexone and
2 acamprosate but he is not directly involved. Dr.
3 O'Brien previously received consultant and speaker
4 fees from Dupont Pharmaceuticals. Lastly, he has
5 been invited to be a member of Forest Laboratories
6 Advisory Board but he had not yet accepted.

7 In addition, we would like to disclose
8 that Dr. Dilip Mehta is participating in this
9 meeting as an industry guest acting on behalf of
10 regulated industry. Dr. Mehta reported that he
11 owns stock in Bristol-Myers Squibb.

12 In the event the discussions involve any
13 other products or firms not already on the agenda
14 for which an FDA participant has a financial
15 interest, the participants are aware of the need to
16 exclude themselves from such involvement and their
17 exclusion will be noted for the record.

18 With respect to all other participants, we
19 ask, in the interest of fairness, that they
20 address any current or previous financial
21 involvements with any firm whose products they may
22 wish to comment upon.

23 Thank you.

24 DR. OREN: I will now call upon Dr.
25 Cynthia McCormick, Director of the Anesthetic

1 Critical Care and Addiction Drug Products at the
2 FDA.

3 Welcome

4 DR. McCORMICK: Thank you. Dr. Chairman,
5 Advisory Committee Members, Invited Guests, members
6 of FDA and members of public, welcome to this
7 meeting of the Psychopharmacologic Drugs Advisory
8 Committee convened to discuss the efficacy of
9 acamprosate.

10 Chronic alcoholism continues to be a
11 widespread and debilitating disorder which places a
12 tremendous burden on society in healthcare costs,
13 lost wages and personal suffering. The need for
14 effective pharmacologic agents for this disorder
15 cannot be overstated. It has been estimated that
16 100,000 lives and \$184.6 billion annually are the
17 cost of chronic alcoholism in the United States.

18 Currently, there are only two
19 pharmacologic agents available for alcoholism in
20 the U.S. Antabuse was approved in 1951 and
21 marketed at times intermittently. Revia,
22 containing the opioid antagonist naltrexone, was
23 approved for this indication in 1994.

24 Despite the crying need for new and better
25 pharmacotherapies, it is very important that drugs

1 approved for this condition must meet the FDA
2 standards for safety and effectiveness. To approve
3 a drug with marginal effectiveness or no
4 effectiveness at all would have no more
5 public-health benefit than to approve no drug.

6 In December, 2001, the FDA received for
7 review a new drug application for the product
8 acamprosate. Acamprosate has been available in
9 Europe for the treatment of chronic alcoholism for
10 nearly fifteen years. The application, when filed,
11 was given a priority review status by the FDA
12 because this was hoped to have the potential to
13 affect the course of a disease with tremendous
14 morbidity and mortality.

15 The FDA team has completed the review of
16 the efficacy of this product and has struggled with
17 the contradictory efficacy results between the
18 European and United States study. The efficacy
19 data on which this application rests includes a
20 number of European clinical trials performed over
21 the last fifteen years, three of which are
22 considered pivotal studies, and a recently
23 completed U.S. multicenter trial.

24 The results of these studies on their face
25 paint a conflicting picture. The FDA team has

1 attempted to explore the apparent contradictions by
2 evaluating the differences between these studies
3 through a variety of analyses. The discussion of
4 these factors and how they contribute to our
5 understanding of the drug's efficacy will be the
6 primary focus of this meeting.

7 The three pivotal European trials, Pelc
8 II, Paille and PRAMA were of similar design,
9 methodology and outcomes. The trials have been
10 considered successful by the company and the review
11 team concurs with this assessment but with caveats
12 which the FDA team will be reviewing this morning.

13 The U.S. study, on the other hand, was not
14 successful in demonstrating superiority over
15 placebo on the primary outcome and most secondary
16 measures. Indeed, on some measures, the drug
17 appeared to perform less well than placebo.

18 Some differences between the European and
19 U.S. studies can be clearly delineated. The
20 European population was primarily one of pure
21 alcoholics. The U.S. population was largely
22 polysubstance abusers. The European patients had
23 either recently undergone detoxification and were
24 abstinent prior to randomization. The U.S.
25 patients were generally not abstinent prior to

1 randomization.

2 The ascertainment of drinking data in the
3 European studies was essentially retrospective,
4 infrequent and the values were heavily imputed. It
5 was very methodical and rigorous in the U.S. study
6 using accepted methods for reconstructing drinking
7 data and information was obtained at frequent
8 intervals. There were also very tight follow-up
9 provisions in place in the U.S. study.

10 The review team has attempted to apply the
11 same conservative approach to analysis of the data
12 of the U.S. and the European studies but they have
13 obtained disparate results.

14 Finally, the studies differed in terms of
15 the formulation of acamprosate that was used and
16 the regimen of administration, although the total
17 daily dose was essentially the same.

18 It is not uncommon for an NDA database to
19 have both successful results and results which are
20 not considered positive. In general, the agency's
21 approach to such a situation is to consider the
22 totality of the evidence giving consideration and
23 weight to such factors as the quality of the data,
24 the strength of the effect size, statistical
25 significance and assessment of whether the effects,

1 even in the negative trials, are supportive or
2 trend in the right direction and are not
3 contradictory.

4 If a trial has truly failed--that is,
5 demonstrated an effect that contradicts the
6 remainder of the evidence--an attempt is made to
7 understand the reason for that contradiction and to
8 determine, on balance, which results are more
9 credible. Occasionally, further clinical work is
10 needed.

11 In this NDA, the differences between the
12 studies are clear. The questions that remain,
13 however, are whether these differences can
14 adequately account for the disparate results and
15 whether the failure of acamprosate in the U.S.
16 study was a function of the difference in
17 responsiveness of the U.S. alcoholic population or,
18 perhaps, a difference in manifestation of the
19 disease.

20 Stated differently, can the results of the
21 European trials be generalized to the U.S.
22 alcoholic population? There are other aspects of
23 the drug-approval decision which are not being
24 brought for discussion today. The drug's safety is
25 still under evaluation and is expected to be

1 completed at the end of this month.

2 Both clinical inspections and inspections
3 of the manufacturing site have not been conducted
4 and are expected to be conducted by the end of
5 June. These will both be weighed into the decision
6 for approval and also in the timing of approval.
7 For this reason, the advisory committee meeting
8 today will not be one in which a final approval
9 recommendation is being requested.

10 The FDA is seeking the advice of the
11 Psychopharmacologic Drugs Advisory Committee and
12 experts in clinical research in alcoholism on your
13 assessment of the evidence provided in support of
14 the efficacy of this product. We are inviting the
15 committee to discuss a series of questions probing
16 the issues surrounding the efficacy results and to
17 make recommendations that will ultimately aid the
18 FDA in making its determination once the other
19 aspects of the application are complete.

20 These will lead to the final decision
21 about the approvability of the product for the
22 maintenance of abstinence in chronic alcoholism.

23 Thank you.

24 DR. OREN: Thank you, Dr. McCormick.

25 I would like to ask three more members of

1 our panel who arrived to introduce yourselves, tell
2 us who you are, where you are from.

3 Dr. Cook?

4 DR. COOK: Dr. Cook, University of
5 Chicago.

6 DR. OREN: Dr. Schatzberg?

7 DR. SCHATZBERG: Dr. Schatzberg from
8 Stanford University.

9 DR. OREN: Dr. O'Brien?

10 DR. O'BRIEN: Charles O'Brien, University
11 of Pennsylvania.

12 DR. OREN: We will now move on to the
13 presentations by Lipha. I would like to introduce
14 Dr. Anita M. Goodman, Executive Vice President and
15 Chief Operating Officer of Lipha.

16 Lipha Presentations

17 Introduction

18 DR. GOODMAN: Good morning.

19 [Slide.]

20 I am Anita Goodman of Lipha
21 Pharmaceuticals. I would like to introduce our
22 presentation on acamprosate, a new therapy for
23 maintaining abstinence in alcohol dependence.

24 [Slide.]

25 Alcohol dependence is a medical disorder

1 which afflicts at least 8 million Americans with
2 almost an equal number of alcohol abusers. The
3 cost to society of alcohol dependence are enormous,
4 both in terms of medical and hospitalization costs,
5 losses and economic potential from reduced
6 productivity and premature death, and costs related
7 to incarceration and judicial process.

8 Beyond the obvious economic implications,
9 costs cannot be attributed to the significant
10 emotional toll this disorder extracts from families
11 affected by alcohol dependence and for the loss of
12 lives, both the lives of patients often still in
13 their prime and the innocent lives of those killed
14 by drunk drivers.

15 Every person in this room knows and has
16 been touched by at least one person whose entire
17 life has been altered and all too often ruined by
18 alcohol dependence. The effect of that dependence
19 reaches out and extends to everyone who that loves
20 them, that cares about them and that works
21 alongside them.

22 The treatment of alcohol dependence is not
23 easy nor, in its current status, is it uniformly
24 successful. It requires the voluntary engagement
25 and time commitment of the patient, involvement of

1 family members and concerned friends, and a team
2 approach of care providers ranging from self-help
3 groups, social workers, to psychologists,
4 psychiatrists and internists.

5 [Slide.]

6 The role of pharmacotherapy in this
7 disorder continues to be limited by lack of
8 available approved medications and possibly also by
9 some resistance on the part of the treatment
10 community to consider alcohol dependence as
11 amenable to treatment by anything except intensive
12 behavioral and psychotherapy.

13 Furthermore, from a product-development
14 point of view, there is the additional lack of
15 universally accepted outcome parameters. This is
16 undoubtedly one of the areas we will touch on
17 today. In contrast to diabetes or hypertension,
18 for example, where there are universally agreed to
19 and reliably measurable endpoints for the
20 regulatory assessment of the product's
21 efficacy--for example, hemoglobin A1C and blood
22 glucose levels in diabetes, or blood-pressure
23 changes in hypertension--the ideal parameter or
24 parameters for measuring outcome in trials or
25 therapies for alcohol dependence have not been

1 agreed to and, in fact, are still under active
2 discussion both by academicians as well as
3 regulatory agencies.

4 In the studies described in your briefing
5 documents, we have proposed and utilized a group of
6 related parameters linked to self-reported drinking
7 behavior but in the context of a platform of
8 abstinence. The FDA has expressed some concerns
9 about the methodologies in obtaining
10 outcome-related information and we will address
11 this today.

12 Unlike almost every other medical
13 disorder, as Dr. McCormick pointed out, there are
14 only two pharmacotherapies available which are
15 specific for alcohol dependence post-withdrawal,
16 the aversive agent disulfiram and the opioid
17 antagonist naltrexone. Both of these drugs,
18 however, have limitations in their general
19 applicability related to their mechanism of action
20 either because patients may have significant
21 hepatic dysfunction or may slip to drinking.

22 Thus, a medication such as acamprosate
23 that is more encompassing should be welcomed by the
24 treatment community.

25 [Slide.]

1 This morning, you will be hearing about
2 the development of acamprosate and its current
3 global registration status from my French
4 colleague, Dr. Silvie Chabac, who is based at
5 Lipha's headquarters in Lyon, France. Dr. Chabac
6 has been involved with acamprosate clinical
7 research for many years and brings considerable
8 knowledge and experience to today's meeting.

9 In her presentation, Dr. Chabac will
10 describe to you the core acamprosate studies which
11 comprise the registration dossier for this product
12 worldwide.

13 [Slide.]

14 Fourteen double-blind placebo-controlled
15 studies were conducted throughout Europe between
16 1989 and 1995. From these studies, thirteen of
17 which supported the efficacy and safety of
18 acamprosate in maintaining abstinence and only one
19 of which showed no significant treatment effect, we
20 selected three as pivotal for the following
21 reasons.

22 [Slide.]

23 All fourteen studies in the clinical
24 portion of the European dossier were conducted by
25 qualified experts who are alcohol specialists

1 working in specialized centers or departments. All
2 the studies were performed according to existent
3 standards of good clinical practice. They all
4 followed specific protocols and have existing
5 retrievable case-report forms as well as electronic
6 databases.

7 However, the three studies considered by
8 Lipha to further qualify as pivotal, had the
9 following additional characteristics. The study
10 centers were still active and the source documents
11 and other medical records were still largely
12 accessible, thereby permitting an on-site FDA audit
13 as is required for a new drug application.

14 You have to keep in mind that collectively
15 the archival requirements for retaining documents
16 had been exceeded for the majority of these
17 European studies.

18 [Slide.]

19 In addition, for these three studies, the
20 clinical research organizations or CROs which had
21 managed the trials were still active and also had
22 some of the original trial management
23 documentation. The final point would be that two
24 of these studies looked at two dose levels of
25 acamprosate and they also, thereby, provide some

1 suggestion of dose responsiveness.

2 [Slide.]

3 Following Dr. Chabac will be a
4 presentation by Dr. George Koob, Professor and
5 Director of the Neuropharmacology Division of the
6 Scripps Research Institute in La Jolla. Dr. Koob
7 is the recipient of this year's Distinguished
8 Investigator's Award of the Research Society on
9 Alcoholism and the recipient of this year's award
10 from the American Society on Addiction Medicine.

11 Dr. Koob has worked in the area of animal
12 models and mechanisms of alcohol dependence for
13 many years and has provided significant insight
14 into the way in which acamprosate exerts its
15 activity. He is the author of more than 500
16 peer-reviewed articles largely on addiction.

17 This morning, Dr. Koob will discuss
18 acamprosate's preclinical effects, its purported
19 mechanism of action and will also briefly cover
20 acamprosate's pharmacokinetic profile.

21 [Slide.]

22 Dr. Karl Mann, Professor and Chairman of
23 the Department of Addictive Behavior and Addiction
24 Medicine at the University of Heidelberg in Germany
25 and also an investigator in one of the pivotal

1 studies will then review for you the efficacy
2 results from the three pivotal European clinical
3 trials.

4 Dr. Mann has the unique distinction of
5 holding the only Chair of Addiction in Germany. He
6 is the European editor of the journal Alcoholism,
7 Clinical and Experimental Research and is the
8 author of more than 200 scholarly papers in the
9 area of clinical research on alcoholism.

10 Because, as Dr. McCormick has mentioned to
11 you, the safety review of acamprosate is still
12 ongoing, we cannot present safety data today, so
13 Dr. Mann's focus will be on efficacy only. As you
14 know from the documents you have received, the FDA
15 has convened this committee and its invited experts
16 to consider the persuasiveness of the data from
17 these European studies for the proposed indication.

18 I would like to point out that we, Lipha,
19 always intended to rely heavily on the substantial
20 European database for this new drug application in
21 our overall development strategy. But we also felt
22 that it was very important to conduct a safety and
23 efficacy study of acamprosate in alcohol-dependent
24 patients in the United States.

25 At the recommendation of the division,

1 very broad admission criteria were used. The
2 results of the American trial called U.S. 96.1 in
3 your document which may, at first, appear to be at
4 odds with the conclusions of the European studies
5 which Dr. Mann will describe has, however, afforded
6 us the opportunity to gain further insight into how
7 acamprosate works best.

8 [Slide.]

9 Dr. Barbara Mason, Professor of Psychiatry
10 and Behavioral Sciences and Director of the
11 Substance Abuse Division at the University of Miami
12 as well as overall principle investigator for the
13 American study, U.S. 96.1, will present data from
14 the study and the understanding that it has
15 brought. Again, at the division's request, the
16 discussion will focus on efficacy.

17 Dr. Mason has extensive experience in
18 clinical alcohol research and has been the
19 principle investigator of many NIH-funded clinical
20 trials involving medication development in
21 alcoholism. She serves on the Scientific Advisory
22 Council of the National Institute on Alcohol Abuse
23 and Alcoholism and is field editor for the Journal
24 of Neuropsychopharmacology.

25 Dr. Mason has published extensively

1 including in such journals as the Archives of
2 General Psychiatry and the Journal of the American
3 Medical Association.

4 [Slide.]

5 Following her presentation, I will then
6 make some concluding comments and answer or
7 redirect questions you may have.

8 [Slide.]

9 As Dr. McCormick has enumerated, we have
10 been asked by FDA to address the following issues.
11 Why were the efficacy results for the ITT
12 population in the U.S. trial inconclusive in
13 contrast to the consistently positive European
14 studies? Were the methodologies appropriate and
15 are European and American alcohol-dependent
16 populations comparable?

17 In the next hour, our presentations will
18 bring clarity to these issues.

19 Thank you. Dr. Chabac will now speak.

20 European Development Program
21 and Current Registration Studies

22 DR. CHABAC: Good morning.

23 [Slide.]

24 My name is Silvie Chabac. I was the
25 doctor responsible for the European Development of

1 Program of acamprosate. I would like to give you
2 an overview of these programs along with the
3 current registration status of acamprosate.

4 [Slide.]

5 The story of acamprosate began in France
6 in the early 1980s. The French pharmaceutical
7 company, Laboratoires Meram, decided to investigate
8 amino-acid neuromediators as a new research
9 project. During the screening tests, one compound
10 was particularly noted for its outstanding
11 pharmacological properties, calcium acetyl
12 homotaurine, now best known as acamprosate.

13 Based on animal work that Dr. Koob will be
14 describing shortly, Meram then decided to
15 specifically develop this compound for alcohol
16 dependence. In 1987, the 333 milligram acamprosate
17 tablet was authorized for marketing authorization
18 in France. It has been commercially available
19 there since 1989.

20 At that stage, Meram transferred the
21 license for acamprosate to its sister company,
22 Lipha, for worldwide development.

23 [Slide.]

24 The same year, Lipha began an extensive
25 clinical program throughout European for

1 registration purposes. Over 4000 alcohol-dependent
2 patients were randomized in fourteen double-blind
3 placebo-controlled studies conducted in ten
4 different European countries. This
5 clinical-development program included long-term
6 studies, two phase II and twelve phase III, with
7 the treatment period ranging from 3 to 12 months.

8 [Slide.]

9 Based on the solid efficacy and safety
10 results of this development program, Lipha began
11 the worldwide registration of acamprosate. Today,
12 it is registered in 30 countries on five continents
13 where alcohol dependence is recognized as a disease
14 and a major public-health problem. Since 1995,
15 worldwide registration has been ongoing, first in
16 Europe where it is now approved for marketing in
17 nineteen countries including Scandinavian countries
18 and Eastern Europe, then, in South and Central
19 America and in Mexico. Three years ago,
20 acamprosate was registered in Australia, Singapore
21 and Hong Kong, then last year in South Africa.

22 Finally, to complete the process, Lipha
23 submitted an NDA for acamprosate in the United
24 States of America last December. In every country
25 where it is marketed, acamprosate has a specific

1 labeling; maintenance of long-term abstinence in
2 patients with alcohol dependence who have been
3 withdrawn from alcohol.

4 Acamprosate should be prescribed in
5 conjunction with counseling for a recommendation
6 treatment duration of one year. To date, around
7 the world, there have been 1.5 million patient
8 years of exposure. This group of patients had the
9 opportunity to benefit from the treatment with
10 acamprosate for alcohol dependence.

11 Now, we would like to make that
12 opportunity available to patients in the United
13 States.

14 Thank you very much.

15 Acamprosate: Mechanism of Action,
16 Preclinical Effects and Pharmacokinetics
17 DR. KOOB: Good morning.

18 [Slide.]

19 I am George Koob. I have been consulting
20 with Lipha Pharmaceuticals since 1990,
21 approximately eleven or twelve years, on their
22 preclinical program.

23 [Slide.]

24 Acamprosate or calcium acetyl homotaurine
25 is the calcium salt of acetylated homotaurine.

1 Homotaurine is a homolog of the naturally occurring
2 amino acid taurine and does not readily cross the
3 blood-brain barrier. The acetylation of
4 homotaurine makes the compound more lipophilic and
5 allows penetration of the blood-brain barrier by
6 this compound.

7 I am going to discuss with you, very
8 briefly, this morning the neuropharmacological
9 mechanism of action of acamprosate, its
10 pharmacokinetics and its interactions with other
11 drugs or, shall I say, its lack of interaction with
12 other drugs.

13 [Slide.]

14 The neuropharmacological mechanism of
15 action of acamprosate has been elucidated by
16 extensive use of animal models. Animal models of
17 alcohol have evolved significantly over the past
18 twenty years and have a high degree of face and
19 predictive validity.

20 [Slide.]

21 The animal models for understanding the
22 actions of acamprosate can be understood in terms
23 of excessive drinking, excessive drinking that is
24 driven by dependence, abstinence and relapse. I am
25 going to give you one clear example of the actions

1 of acamprosate preclinically in an animal model of
2 excessive drinking.

3 [Slide.]

4 Before I do that, let me just review with
5 you very quickly the evidence that was accumulating
6 on acamprosate through animal models. It is
7 critical for you to understand that, in all of
8 these models, the animals were producing an
9 excessive amount of alcohol intake by a variety of
10 means. Acamprosate decreases alcohol drinking in
11 rats that were selected for excessive drinking. In
12 one of the earliest studies, acamprosate decreases
13 alcohol intake in dependent animals. This is
14 another one of the early studies done by Le Magnin
15 group. Acamprosate reverses the preference for
16 alcohol and the increase in drinking in dependent
17 animals during withdrawal.

18 I am going to show you an example from our
19 own laboratory where acamprosate eliminates the
20 alcohol deprivation effect in rats under
21 free-drinking operant limited-access conditions.

22 [Slide.]

23 Rodents, like human beings, and this
24 speaks to the face validity of the animal models,
25 don't like the taste of alcohol so, to induce a

1 rodent to drink alcohol, one starts with a sweet
2 solution. We, in our laboratory, use saccharine,
3 and fade in alcohol and ultimately fade out the
4 saccharine. These animals are in limited-access
5 situations where they drink alcohol once in the
6 evening. They have a lever that they press to
7 obtain 10 percent alcohol or water. By the end of
8 a two- or three-week period, these animals are
9 drinking pharmacological amounts of alcohol in this
10 30-minute session.

11 [Slide.]

12 You can see that the alcohol intakes range
13 from about 20 to 80 milligram percent which is
14 equivalent to what you or I would have from one
15 glass of wine. In doing this kind of a procedure,
16 you can reliably have a baseline drinking of
17 alcohol but you can also make manipulations that
18 will produce increases in drinking that at least
19 have face validity and some predictive validity for
20 the human condition.

21 [Slide.]

22 In this slide, what I am showing you is if
23 you stop the animal's availability to alcohol for a
24 series of days, what you see is an increase in
25 alcohol intake that is quite dramatic when the

1 animal is reinstated. This is called the alcohol
2 deprivation effect in rodent models. It is
3 equivalent to the abstinence violation effect in
4 human alcoholics.

5 What you can see from this slide is that
6 the animals that have three, five, seven or
7 fourteen days of abstinence between their
8 self-administration show a dramatic increase in the
9 amount of alcohol. They show a dramatic increase
10 in their blood-alcohol levels, jumping from
11 30 milligram percent, on average, to approximately
12 80 milligram percent.

13 What you can also see is, that on a
14 baseline condition, the behavior is very stable in
15 this model. You can also see here that there is no
16 effect of the alcohol deprivation effect on water
17 intake.

18 [Slide.]

19 Acamprosate dose-dependently, as in other
20 animal models of excessive drinking, decreases the
21 alcohol deprivation effect. There are a couple of
22 very important points from this slide from the
23 point of view of the animal models and the
24 preclinical effects of acamprosate.

25 One is that acamprosate has no effect on

1 baseline drinking at these doses. Higher doses
2 will affect baseline drinking. The other issue is
3 that acamprosate has no effect on water intake.
4 Both of these argue to the selectivity of the
5 effect on excessive drinking and the selectivity of
6 the effect from the point of view of other
7 behavior.

8 [Slide.]

9 It is also important to note what
10 acamprosate does not do in animal models. What
11 this slide addresses is that acamprosate does not
12 produce what we would call anxiolyticlike effects
13 or anticonflict effects in animal models of
14 anxiety. The other points on this slide just
15 simply illustrate the fact that acamprosate has no
16 abuse potential in preclinical animal models.

17 Acamprosate does not substitute for
18 alcohol. It does not block the discriminative
19 stimulus properties of alcohol. It doesn't have
20 any reinforcing or aversive effects on its own and
21 it doesn't interact with other drugs of abuse.

22 [Slide.]

23 The neuropharmacological mechanism of
24 action of acamprosate is thought to focus on three
25 major areas as depicted in this slide. Acamprosate

1 is thought to modulate glutamate receptors as
2 illustrated by No. 1 here. Acamprosate is thought
3 to modulate voltage-dependent calcium channels and
4 acamprosate may also have long-term effects on
5 intermediate early gene products that can
6 ultimately change subunit expression of glutamate
7 receptors. Glutamate, as you know, is the major
8 excitatory neurotransmitter in the brain.

9 [Slide.]

10 More specifically, the
11 neuropharmacological effects of acamprosate can be
12 shown in the following way. Acamprosate has been
13 clearly shown to inhibit neuronal hyperexcitability
14 by decreasing presynaptic release of the excitatory
15 neurotransmitter, glutamate, and by decreasing
16 postsynaptic excitability of glutamate receptors.

17 Acamprosate, as I mentioned, inhibits
18 calcium influx through the NMDA glutamate receptor
19 possibly through an interaction with the polyamine
20 site on the NMDA receptor. This is very important
21 for understanding its action because this is a
22 modulatory effect. It is thought to be an
23 allosteric interaction. It is not a direct
24 receptor action. Acamprosate is not MK801, for
25 those of you versed in this. That means that it is

1 not a noncompetitive antagonist to the glutamate
2 receptor. It does not interact directly with any
3 receptor component of the glutamate receptor that
4 would lend it to toxicity.

5 Acamprosate also inhibits calcium influx
6 through voltage-dependent calcium channels. Just
7 to add to its profile as an antihyperexcitability
8 agent, acamprosate also increases the synaptic
9 availability of the inhibitory neurotransmitter
10 taurine, the work of Philip De Witte and his
11 colleagues.

12 [Slide.]

13 What does this mean? What it means, very
14 simply, is that acamprosate acts a partial
15 coagonist at the glutamate receptor through an
16 allosteric interaction with the polyamine binding
17 site on the NMDA glutamate receptor complex.

18 What does this translate to? It
19 translates to a normalization of the receptor
20 system that has become disregulated by the chronic
21 administration of alcohol. That statement, itself,
22 has all the key elements there. It is the
23 normalization of a disregulated receptor system and
24 neurotransmitter system that has been disregulated
25 by chronic alcohol and chronic withdrawal and

1 repeated alcohol and repeated withdrawal.

2 So neuropharmacological consequences are
3 to enhance activation of the glutamate receptor
4 when endogenous levels of the activators such as
5 glutamate are low but, most critically, to inhibit
6 activation when levels of the endogenous activators
7 are high such as during alcohol withdrawal.

8 [Slide.]

9 This lead to further observations of great
10 scientific interest that acamprosate also has
11 neuroprotective actions. I am not going to go
12 through the details but simply to say that, in a
13 number of in vitro and preclinical models,
14 acamprosate has been shown to have
15 neuroprotective-like effects.

16 [Slide.]

17 From the point of view of the
18 pharmacokinetics, I thought I would go through this
19 and spend a little time on this. Acamprosate does
20 have bioavailability and that has been adequately
21 demonstrated presumably because of the
22 modifications of the molecule to make it more
23 lipophilic. That is 11 percent in humans, 16
24 percent in rodents.

25 It has an elimination half-life of 18

1 hours in humans. Similar, a little longer, in
2 rodents. The time-to-steady-state plasma levels is
3 five to seven days, a critical issue in regards to
4 the design of preclinical studies and clinical
5 studies. There is no protein binding of
6 acamprosate in the blood.

7 The most critical point on this slide is
8 that the elimination of acamprosate is by renal
9 excretion. It is not metabolized and, thus,
10 hepatically compromised patients do not have to
11 worry about taking acamprosate.

12 The lethality in humans, there is no known
13 lethality. In rodents, the dose that has produced
14 lethality is 6 grams per kilogram. This is several
15 log units higher than the effective dose. It is
16 way out there.

17 [Slide.]

18 Acamprosate has basically no interactions
19 with any alcohol. Other drugs that are used for
20 the treatment of alcoholism and other
21 psychotherapeutic drugs with the exception that
22 there is data in press--Dr. Mason has a paper in
23 press in Neuropsychopharmacology showing that
24 naltrexone actually increases plasma levels of
25 acamprosate by about 25 to 30 percent depending on

1 what measure you are using.

2 The mechanism for that increase in plasma
3 acamprosate levels by naltrexone is not known but
4 probably has something to do with its pericellular
5 mechanism of absorption.

6 [Slide.]

7 So I would like to stop now just with this
8 slide to reiterate the neuropharmacologic mechanism
9 of action of acamprosate. This
10 neuropharmacological action of acamprosate, as I
11 said earlier, has three major components. The
12 bottom line is that acamprosate normalizes the
13 hyperexcitability in the brain associated with
14 alcohol dependence, notably alcohol withdrawal and
15 protracted abstinence.

16 Acamprosate does this by modulating the
17 glutamate receptor as a partial agonist which is a
18 very effective pharmacological way of returning the
19 brain to a normal state. It also modulates
20 voltage-dependent calcium channels and it also
21 interacts with the taurine neurotransmitter which
22 is an inhibitory neurotransmitter also decreasing
23 neuronal hyperexcitability.

24 Thank you.

25 Efficacy Results from Three Pivotal Clinical Trials

1 DR. MANN: Good morning. I'm Karl Mann.
2 I am working at the University of Heidelberg. It
3 is my pleasure to share some of the data that we
4 gained about ten years ago in these European trials
5 with acamprosate. Apart from my academic
6 affiliation, I also run a hospital with inpatient
7 and outpatient treatment for alcoholics where we do
8 treat patients with acamprosate on a day-to-day
9 basis so we could share also some of the
10 experiences that we have been gaining there with
11 you today.

12 [Slide.]

13 I am going to talk about these three
14 studies which were done in Europe about ten years
15 ago. Their objective was to look at the safety and
16 efficacy of acamprosate versus placebo in
17 maintaining long-term abstinence in alcoholics
18 following alcohol withdrawal.

19 [Slide.]

20 These studies were done in Belgium, in
21 Germany and in France. They were all multicenter,
22 like twelve centers in this study and twelve
23 centers in the German study, 31 centers in the
24 French study with a large number of patients
25 included which wound up to almost 1,000 patients in

1 these three studies.

2 [Slide.]

3 As I said, they were double-blind
4 randomized and placebo-controlled, all three of
5 them. They were multicenter. Two of them used two
6 dosage levels like the Pelc study and the Paille
7 study in France. They had one arm with a medium
8 dose of acamprosate and one arm with about 2 grams
9 of acamprosate per day whereas the German study had
10 only one arm of medication versus placebo.

11 The Pelc study was done over a period of
12 three months, twelve weeks, and there was no
13 after-care after that whereas the other two studies
14 were over a period of a whole year, so a whole year
15 of study. Then, in the German study, another
16 twelve months of investigation of looking how the
17 patients did afterwards. In the Paille study in
18 France, this was six months.

19 It is also important to note that the
20 psychosocial therapy that was provided to the
21 patients was site-specific. There was not one
22 psychosocial treatment for everybody across all
23 sites. But, of course, within the sites, those
24 patients who received acamprosate or placebo also
25 received the same kind of psychosocial treatment.

1 [Slide.]

2 We had male and female patients, of
3 course, in these studies. We had a lower and an
4 upper age limit so no patients who were older than
5 65 years were allowed. They were all DSMIII or
6 DSMIII-R, positive alcoholics. They all, and this
7 is another important point, had detoxification
8 prior to the entry into this study.

9 This is something you can see here. The
10 Pelc study required at least five days of clear
11 abstinence before they could enter the study. In
12 the German study, this was between two weeks and
13 four weeks, the window in which they could enter
14 the study. In the French study, this was one week
15 up to about four weeks, also.

16 [Slide.]

17 Here are the methods for collecting data,
18 drinking data, in these three studies in Europe.
19 Of course, there is self-report on alcohol
20 consumption at each visit done by the patient.
21 Then, of course, also, there is confirmation
22 looking at biological markers such as gamma GT,
23 liver-function test, MCV, CDT and also
24 breathylizing at each single visit. So each most
25 of these things were done at each of these single

1 visits.

2 Then, of course, the investigator who
3 either was a trained psychologist working in this
4 field or who was a doctor working in this field,
5 they had to make and give their clinical global
6 impression about the drinking status of the
7 patient.

8 These were in addition to their
9 professional training. They were also trained
10 prior to the studies in collecting the data using
11 the interviews and the material that was provided
12 in these studies.

13 Then, finally, family members or other
14 caretakers such as the private doctor or the family
15 doctor of the patient was also involved in trying
16 to find out what the drinking status of this
17 patient was. This was done, the integration of all
18 this material, or all this information, by the
19 investigator who had then to say, well, he is
20 abstinent or he is drinking and he did resume
21 drinking ten days ago, for instance.

22 Whenever there was a discrepancy between
23 those variables, then we said, okay, we are going
24 the conservative way. Then we say he was drinking.

25 [Slide.]

1 Here is the number of patients. You can
2 see we had about 1,000 who were randomized. This
3 is the ITT population. Then the completion of the
4 study you can see here. That is, to me at least, a
5 very important point. You can see that in the
6 acamprosate arms, we retained much more, or many
7 more, patients than we did in the placebo arm.

8 Also this is not, and was not, an outcome
9 criteria in the first place. To me, as a
10 clinician, as a psychiatrist, this is a very
11 important issue because as long as I have and see
12 the patients, I can do something about them. So,
13 for me, clinically, this is a very meaningful and
14 positive figure here.

15 So then, conversely, of course, we have
16 these figures of the patients who discontinued the
17 study.

18 [Slide.]

19 The reasons for discontinuation were
20 different. We had, as you have seen already, 46
21 percent who discontinued while being on acamprosate
22 and 60 percent being on placebo, for instance,
23 because of lost-to-follow-up or treatment failure
24 or other reasons such as patient refusal, et
25 cetera. So, there again, we meet these figures

1 that I have shown to you before. More patients
2 stay in treatment when they are treated with
3 acamprosate.

4 [Slide.]

5 Here are the demographics of these
6 studies. Of the patients in these studies, we had
7 85 or 80 percent males, more or less. We had a
8 mean age of 42, 43 years, 70 kilograms of body
9 weight. We had a mean duration of alcohol
10 dependence of about ten years throughout these
11 studies.

12 Then these are the consumption data from
13 which you can see that many of those people, like
14 around 80 percent or 70 to 80 percent, had had,
15 like, ten shots of whiskey a day, which is a lot,
16 or 40 ounces of wine a day or 80 ounces of beer a
17 day.

18 All of them had been detoxified prior to
19 the entry of the study. That is, again, something
20 we have already touched upon. So almost all were
21 abstinent at baseline. So that was the same across
22 all three European studies which I am presenting to
23 you here.

24 [Slide.]

25 Here are the treatment exposures in weeks

1 within these studies. You can see the Pelc study
2 which lasted 13 weeks, the average was 10 to 11
3 weeks on treatment. The German study--by the way,
4 this acronym stands for Prevention of Relapses in
5 Alcoholics with Acamprosate. That is what PRAMA
6 stands for--48 weeks, and we had about 32 weeks on
7 treatment in the acamprosate group and less on
8 treatment in the placebo group, and then, again,
9 the Paille study, 35 in the low-dose acamprosate,
10 37 in the high-dose and 31 in the placebo group.

11 [Slide.]

12 Compliance. This was based on pill count,
13 the pills that were turned in by the patients when
14 they came to the visits. So we have about 97
15 percent in the Pelc study. Because these are much
16 longer, of course, we have a lower but still
17 satisfactory compliance of 81 percent in the German
18 study, 82 to 88 percent in the French study.

19 [Slide.]

20 Here are the outcome criteria that were
21 used throughout these three European studies.
22 First of all, of course, was time to first drink.
23 So whenever someone had a relapse, we counted, or
24 we measured the time when this occurred and this
25 was entered into this analysis. Then we did a

1 Kaplan-Meier statistics on this.

2 Then, the second outcome criterion was
3 rate of rate of complete abstinence which meant the
4 percent of patients completing the study without
5 consuming any alcohol. Of course, these two are
6 very conservative measures and you certainly--or,
7 let's put it another way. There is more
8 information in this data than just the time when
9 someone had his first relapse because these are
10 relapses to drinking at all. That is different
11 from the studies which were done at the same time
12 in the U.S. where you had return to heavy drinking.
13 This is return to the first drink.

14 If you do this, you might lose someone who
15 had one drink or maybe two days of drinking and
16 then he was abstinent again and he is always
17 counted as a failure.

18 So, what we did in order to try to pick up
19 this additional information is we looked at
20 something that was called cumulative abstinence
21 duration in percent. That is the time on the study
22 where a patient is reported to be abstinent no
23 matter whether they had a relapse or not at some
24 time during the study.

25 [Slide.]

1 So here are the results. First, the
2 Kaplan-Meier for the first drink in the Pelc study.
3 You see the placebo group in blue. They are having
4 relapses. Of course, the other patients have
5 relapses. The difference between the two groups is
6 statistically significant if you take dropouts as a
7 failure.

8 There is no difference between the two
9 dosages. The low and high dosage of acamprosate
10 did not produce a significant difference between
11 those two but the other one compared with placebo
12 was clearly significant.

13 [Slide.]

14 The same is true for the PRAMA in Germany,
15 again, time to first relapse. Those on placebo,
16 they tended to relapse earlier than the patients on
17 acamprosate.

18 [Slide.]

19 The Paille study; again, we have a
20 difference between placebo and the two treatment
21 arms with acamprosate which, again, between the two
22 arms, there was not a difference in the Paille
23 study time to first relapse.

24 [Slide.]

25 The second outcome criterion, you

1 remember, was complete abstinence or rate of
2 complete abstinence. Here is the Pelc study,
3 again, after only three months of treatment. Those
4 on placebo had about 14 percent whereas the others
5 who were treated with acamprosate were at about 40
6 percent abstinent after twelve weeks.

7 After one year in the German study, we
8 have here 12 percent versus 29 percent, again a
9 very clear-cut 2.4-fold advantage for acamprosate.
10 In the Paille study, there is a significant
11 difference between placebo and the high dosage of
12 acamprosate, also. So, I think, also they are
13 clear results.

14 [Slide.]

15 Now this percentage of abstinent days, or
16 the CAD percent. Again, in the Pelc study we have
17 a difference between placebo and the two treatment
18 arms. In the German study, we have the same. In
19 the Paille study, placebo also is different from
20 the high-dosage of acamprosate.

21 [Slide.]

22 Here is the summary. First outcome
23 criterion, time to first relapse, a clear
24 indication that acamprosate works better with about
25 a factor of two to three times longer stay with

1 relapse than in the placebo group.

2 The complete abstinence rate, it is the
3 same result, between 1.7 and 2.7 times greater or
4 better with acamprosate compared with placebo.
5 Also, for this third outcome criteria, we have an
6 advantage in favor of acamprosate versus placebo.
7 These were the results of these three pivotal
8 studies which were done in Europe.

9 [Slide.]

10 With my final slide, I would like to show
11 you again where I work and I might see you again at
12 one of these occasions. Thank you.

13 Analysis of the U.S. Study Results

14 DR. MASON: Good morning.

15 [Slide.]

16 I am Dr. Barbara Mason and I served as
17 overall principle investigator for the U.S.
18 acamprosate trial.

19 [Slide.]

20 In this section, I am going to first be
21 covering these points for the U.S. multicenter
22 trial. I will conclude by integrating the U.S. and
23 European acamprosate clinical trial experience in
24 outpatients with alcohol dependence.

25 [Slide.]

1 The U.S. multicenter trial had two
2 overarching and somewhat competing objectives. The
3 first objective was to provide FDA with the
4 requested reassurance about the safety of
5 acamprosate in the typical American outpatient with
6 alcohol dependence who was considered to be more
7 likely to abuse other drugs and have less access to
8 inpatient detoxification services than their
9 European counterparts.

10 Additionally, because acamprosate is not
11 metabolized and it is eliminated unchanged by the
12 kidneys, there was interest in examining the safety
13 of acamprosate without any restrictions on study
14 admission because of serum-creatinine level or
15 liver-function-test abnormalities or patient age as
16 opposed to the European studies.

17 One implication, of course, of no upper
18 age limit is greater chronicity in a progressive
19 disorder and, likewise, no upper limit for
20 liver-function test may admit patients with more
21 severe alcohol dependence.

22 [Slide.]

23 The second objective related to the
24 sponsor's interest in evaluating the efficacy of
25 the standard therapeutic 2 grams per day dose of

1 acamprosate but given as two 500 milligram tablets
2 twice a day in contrast to the European dosage
3 schedule of two 333 milligram tablets three times a
4 day.

5 These two dosing schedules had previously
6 been shown to be bioequivalent in the multidose
7 crossover pharmacokinetic study. In addition,
8 given the safety and tolerability of the standard 2
9 gram dose of acamprosate, there was interest in
10 evaluating a higher 3 gram daily dose on an
11 exploratory basis in a smaller group of subjects.

12 [Slide.]

13 We developed two strategies specified in
14 the study protocol and case-report form to control
15 for factors generally associated with reduced
16 alcoholism treatment efficacy. The study was
17 particularly vulnerable to the influence of these
18 factors because of the broad admission criteria
19 which had been requested by the FDA for their
20 safety evaluation.

21 First, as in many pharmacologic studies
22 involving drugs with prolonged time to steady
23 state, an efficacy evaluable population was defined
24 that included those subjects who took medication
25 for the seven days needed to reach acamprosate

1 steady state and who were at least 75 percent
2 compliant with medication thereafter.

3 Additionally, this efficacy evaluable
4 population excluded those whose urine tested
5 positive for illicit drugs at any study visit. A
6 second strategy was to include standardized
7 baseline measure of variables identified in the
8 alcoholism-treatment literature as reliably
9 associated with poor outcome such as severity of
10 dependence or comorbidity or treatment goal of
11 nonabstinence.

12 These variables were to be examined in
13 relation to outcome as potential covariates in
14 order to reduce residual variation in the analyses
15 and to off set the influence of random imbalances
16 of baseline variables, particularly for subgroups
17 of interest.

18 [Slide.]

19 As in the European pivotal trials, the
20 U.S. study was double-blind, placebo-controlled
21 with random assignment to treatment and all
22 subjects met DSM criteria for alcohol dependence.
23 Unlike the European pivotal trials, the U.S. study
24 did not exclude substance abusers or those over
25 65 years of age and did not require detoxification

1 nor an abstinent interval prior to randomization.

2 In the European pivotal trials, as Dr.
3 Mann mentioned, all subjects received whatever
4 supportive psychosocial therapy was routinely used
5 by the center or investigator. Conversely, in the
6 U.S. trial, a standardized behavioral therapy
7 program that included a scripted therapist manual
8 and patient handout materials was provided to all
9 study participants.

10 [Slide.]

11 There is no gold standard for determining
12 drinking occurring between study visits or office
13 visits. Therefore, self-report with multiple
14 sources of corroboration whenever possible is the
15 current state of the art, both for alcoholism
16 pharmacotherapy trials as well as in treatment
17 settings.

18 European pivotal and U.S. trials all
19 relied on self-reported drinking gathered under
20 specific conditions shown to enhance accuracy of
21 self-report including eliciting the drinking data
22 by an alcoholism expert and providing written
23 assurance of confidentiality of the data.

24 All data were collected in clinical or
25 research settings which encouraged honest reporting

1 as opposed to probation offices or other settings
2 which might have legal or punitive ramifications
3 for disclosure of drinking.

4 Three of the four trials provided diaries
5 that were collected at each study visit either to
6 aid recall or to provide information on general
7 clinical status. Only the U.S. study included a
8 daily drinking calendar using standard drink icons
9 to enhance precision of self-reported quantity and
10 frequency of drinking, as shown in the next slide.

11 [Slide.]

12 Standard drinks were defined on the basis
13 of alcohol content with a beer equal to a glass of
14 wine equal to a shot of hard liquor. Although
15 standard drinks in the U.S. study contained
16 approximately 15 grams of pure alcohol, a bit more
17 generous than shown here, I am showing you these
18 12-gram icons because for today's presentation and
19 for your briefing document, all drinking
20 information is based on the smaller European
21 12-gram standard drink.

22 [Slide.]

23 All pivotal trials included multiple
24 biochemical measures to confirm validity of
25 self-report of abstinence or drinking. All trials

1 used gamma GT. Both the PRAMA and U.S. studies
2 breathalyzed patients at each study visit, and Pelc
3 II and U.S. trials tested for alcohol in urine as
4 well.

5 Additionally, PRAMA, Paille and the U.S. trials
6 verified patient self-report with a close friend or
7 relative specified by the patient at multiple time
8 points.

9 In all trials, if there were discrepancies
10 between patient self-report and the corroborating
11 information, typically the most negative outcome
12 would be assumed accurate. The drinking intervals
13 assessed in each trial were of sufficient duration
14 to capture infrequent drinkers and were consistent
15 with methodologic studies confirming the validity
16 of self-report for intervals of these durations.

17 [Slide.]

18 The primary study outcomes in the European
19 pivotal trials were informed by an
20 abstinence-oriented treatment tradition with all
21 patients undergoing detoxification and beginning
22 study participation in an abstinence state.
23 Therefore, the first information obtained from
24 participants in these trials at each visit was did
25 they or did they not drink since their last study

1 visit.

2 Four patients who did report drinking, an
3 effort was made in all three European pivotal
4 studies to categorize the amount of alcohol
5 consumed and the number of drinking days since
6 their last study visit as per a case-report form.
7 However, all study primary outcomes, time to first
8 drink, complete abstinence rate, point prevalence
9 of abstinence, were related to abstinence or
10 nonabstinence.

11 Consistent with clinical practice and
12 research involving alcoholism, patients who
13 discontinued prematurely due to alcohol-related
14 reasons, or patients for whom follow-up information
15 was not available were considered treatment
16 failures and as nonabstinent for the remaining
17 treatment period.

18 [Slide.]

19 Conversely, the time-line follow-back
20 method used for data collection in the U.S. trial
21 was a research tool originally developed to assess
22 continuous variables associated with controlled
23 drinking as a study outcome as opposed to the
24 categorical outcome of abstinence/nonabstinence.
25 It involves a more rigorous emphasis on

1 retrospective estimates of daily drinking through
2 the use of calendar-based memory aids and standard
3 drink icons to enhance recall.

4 The tradeoff for the increased precision
5 of the time-line follow-back method is that it
6 requires more time to administer thereby increasing
7 the burden on the subject in clinic personnel.
8 This may result in increased attrition rates and
9 may be inappropriate in a clinical setting where
10 time is at a premium unless more precision on
11 drinking behavior is needed.

12 In U.S. clinical practice, the time-line
13 follow-back is not used for these reasons. U.S.
14 clinical practice more directly reflects the
15 drinking data collection methods of the European
16 studies.

17 Additionally, the time-line follow-back
18 method used in conjunction with the daily drinking
19 diary, as in the U.S. study, may, in itself, reduce
20 drinking. This impact on outcome has been shown
21 for self-monitoring techniques and other
22 indications; for example, Weight Watchers.

23 One can note that, in a double-blind,
24 placebo-controlled trial, the impact of study
25 procedures should be equally distributed across

1 treatment groups. Nevertheless, if study
2 procedures have a therapeutic influence, then the
3 study is actually comparing background treatment
4 plus placebo to background treatment plus
5 acamprosate and the presence of the background
6 treatment might reduce the effect size for
7 potential improvement that acamprosate could
8 provide.

9 [Slide.]

10 The U.S. study was a three-armed trial
11 with subjects randomized in a 3 to 3 to 1 ratio to
12 placebo, acamprosate 2 grams a day or acamprosate 3
13 grams a day. 741 patients were screened and, of
14 these, 601 outpatients with alcohol dependence
15 representing 81 percent of those screened were
16 randomized to 6 months of treatment.

17 After the treatment phase, patients were
18 followed for an additional two months
19 off-treatment. In my discussion of the U.S. study,
20 I am going to focus on the comparison between
21 acamprosate 2 grams and placebo since that
22 comparison forms the basis of the sponsor's NDA.
23 The 3-gram group was an exploratory dose group of
24 smaller size, as you can see and I won't address it
25 further this morning.

1 [Slide.]

2 As I mentioned before, in comparing the
3 methodologies of the U.S. and European studies, in
4 the U.S. study, all patients were provided with a
5 brief standardized behavioral-therapy program at
6 every study visit. The program was based on
7 principles of motivation enhancement with the goals
8 of abstinence and methodology compliance and was
9 delivered by experienced nurses or counselors with
10 a bachelor's degree or higher.

11 Patients were provided with informational
12 handouts about alcohol and acamprosate. There were
13 also tips for quitting drinking and ongoing
14 self-assessment and interactive exercises
15 pertaining to their drinking behavior such as the
16 treatment goals work sheet and the treatment
17 progress summary.

18 The components of this program are
19 currently used in conjunction with acamprosate in
20 Europe--I have some of the materials here and am
21 happy to share them--and will shortly be available
22 on line at Acoweb, the Lipla website. In the U.S.
23 trial, the behavioral therapy was implemented
24 across psychiatry, alcoholism-specialty and
25 internal-medicine settings.

1 [Slide.]

2 The 21 participating treatment centers
3 were located throughout the United States as shown
4 in this map.

5 [Slide.]

6 As in the European pivotal trials,
7 patients were in their mid-40s at their time of
8 study entry although, in the U.S. trial, the age
9 ranged from 22 to 72 years with about 10 percent of
10 patients in their 60s and early 70s. Compared to
11 the three pivotal trials in Europe, there was
12 somewhat greater representation of females in the
13 U.S. trial. Racial distribution was roughly
14 equivalent to U.S. population norms.

15 The 2 gram acamprosate group included more
16 individuals living alone with fewer subjects
17 employed full-time and more individuals with a
18 significant psychiatric history than the placebo
19 group.

20 [Slide.]

21 Just to orient you, the clinical global
22 impression was a summary by the investigator of the
23 patient's current alcohol dependence severity with
24 7 being most severe. A score of 22 or greater on
25 the alcohol dependence scale indicates subjects

1 with substantial to severe lifetime alcohol
2 dependence severity.

3 For the measures shown here and the
4 measures of psychosocial support shown on the
5 previous slide, although generally comparable
6 across the two treatment groups, you might notice
7 that, for each variable, the 2 gram group has
8 evidence of slightly greater severity of alcohol
9 dependence than the placebo group.

10 [Slide.]

11 There was a higher proportion of patients
12 in the placebo group having a baseline goal of
13 total abstinence and a higher proportion in the 2
14 gram group requiring medicated detoxification prior
15 to study entry. Accordingly, in the aggregate,
16 subjects assigned to the 2 gram group appear to
17 have entered the trial relatively disadvantaged.

18 [Slide.]

19 As you can see, approximately
20 three-quarters of the sample reported lifetime
21 experience with illicit substances with
22 approximately one-third reporting illicit substance
23 abuse in the year prior to randomization.

24 [Slide.]

25 Slightly less than half of the population

1 were current smokers and between 6 and 8 percent
2 had positive urine for cannabinoids at screening.

3 [Slide.]

4 You have seen the formal patient
5 disposition in your briefing document. I would
6 like to highlight certain features of patient
7 participation that may be relevant for
8 understanding efficacy. You will note high rates
9 of methodology compliance across all treatment
10 groups. However, the 2-gram group had fewer weeks
11 on study and a lower rate of study completion than
12 the placebo group. In an effort to understand this
13 further, a blinded panel of experts evaluated all
14 premature terminations in terms of alcohol
15 relatedness taking into account all available
16 information.

17 Of those patients terminating early, the
18 reason was more likely to be alcohol-related in the
19 placebo group than in contrast to the 2 gram
20 acamprosate group. There was no difference in the
21 percentage of patients across the groups for
22 terminations due the adverse events.

23 [Slide.]

24 As the FDA pointed out in their
25 information package, in contrast to the European

1 studies, half the U.S. study population was still
2 drinking at randomization. Therefore, the plan for
3 European-based variables such as time to relapse
4 and rate of complete abstinence became relatively
5 meaningless.

6 Similarly, as pointed out earlier, the
7 fact that the 2 gram group had briefer time on
8 study would negatively impact on their cumulative
9 abstinence duration with missing time accounted for
10 as drinking time. Furthermore, the unfavorable
11 baseline imbalances for the 2 gram group were also
12 found to meaningfully influence study outcomes.

13 [Slide.]

14 The variables that we chose to measure in
15 a standardized manner at baseline in the
16 case-report form included a brief screen of major
17 psychopathology as greater psychiatric severity has
18 been reliably associated in the literature with
19 poor alcoholism treatment outcome.

20 Although subjects with current dependence
21 in illicit substances were excluded from study
22 admission, subjects with substance abuse including
23 those with urines positive for cannabis at
24 screening at baseline were admitted to the study.
25 Given the well-known association of drug abuse with

1 premature treatment termination and poor alcoholism
2 treatment outcome, the illicit drug use index
3 developed by the National Institute on Drug Abuse
4 was used to characterize severity of substance
5 abuse.

6 Additionally, the Fagerstrom test of
7 nicotine dependence was used to capture current
8 severity of nicotine dependence.

9 As with psychiatric and substance-abuse
10 comorbidity, greater severity of alcohol dependence
11 has generally been associated with poor treatment
12 response especially for outpatients. In the
13 American study, current severity of alcohol
14 dependence was assessed with the investigator's
15 clinical global impression and lifetime severity
16 with the Alcohol Dependence Scale.

17 [Slide.]

18 Fewer social supports result in worse
19 treatment response generally but especially in the
20 case of outpatient treatment of alcoholism.
21 Readiness to change emerged as the strongest
22 predictor of long-term drinking outcome in Project
23 MATCH and, as in Project MATCH, was measured, in
24 this study with DiClementi's stages of readiness to
25 change.

1 Initial commitment to complete abstinence
2 has been shown to predict higher rates of
3 abstinence among alcoholics, opiate users and
4 cigarette smokers. In contrast, subjects having a
5 goal of minimizing a slip or having other drinking
6 goals are typically more likely to relapse.

7 Treatment goals were assessed at baseline
8 in the U.S. study with a standardized treatment
9 goals check list which I will be showing you.
10 Compliance with prescribed treatment has been
11 significantly associated with drinking outcome in
12 both behavioral and pharmacological clinical
13 trials.

14 In the U.S. study, methodology compliance
15 was estimated on the basis of pill count from
16 returned blister packs at every study visit.
17 Ingestion of acamprosate was verified by plasma
18 acamprosate levels at week 1 and end of study
19 although results were not available until after
20 study unblinding.

21 Importantly, and finally, as Babour and
22 colleagues have pointed out, these factors may be
23 most meaningfully used in combination to create a
24 multidimensional model to understand alcoholism
25 treatment outcome.

1 [Slide.]

2 The FDA has requested that we provide an
3 analysis to reconcile the findings of the U.S. and
4 European trials and to further our understanding of
5 how acamprosate would be beneficial in American
6 alcoholics. Given that missing data are attributed
7 to relapse in study-outcome calculations, in order
8 to better understand the efficacy of the 2 gram
9 group, a standard panel of covariates relating to
10 baseline measures of psychosocial support and
11 alcoholism severity and treatment exposure were
12 uniformly applied to all outcome measures.

13 Statistical modeling associated early
14 termination with baseline variables relating to
15 psychosocial support and disease severity rather
16 than to treatment group assignment.

17 [Slide.]

18 The actual chest list used in the case
19 report form to capture patients treatment goals at
20 baseline is depicted in this slide. In the FDA's
21 analysis, patients with the goal of abstinence were
22 grouped together with those acknowledging that they
23 could have a slip and the difference in results may
24 serve to emphasize the importance of complete
25 commitment to abstinence at treatment onset to

1 optimize acamprosate efficacy.

2 [Slide.]

3 Because the first dose of study
4 methodology was an observed dose given in a clinic,
5 all 601 randomized patients were included in the
6 safety population. The intention to treat, or ITT,
7 population represented all randomized patients for
8 whom any follow-up efficacy data were available. I
9 have already described to you the a priori defined
10 efficacy evaluable population.

11 As Sharon Hall and colleagues at the
12 University of California and Stephanie O'Malley and
13 colleagues at Yale University have reported,
14 commitment to total abstinence is related to a
15 lower risk of returning to use of alcohol as
16 opposed to goals that include slips, controlled
17 drinking or other levels of alcohol consumption.

18 One of the DSM-IV diagnostic criteria for
19 alcohol dependence specifically relates to the
20 tendency to drink more than originally intended.
21 Consequently, complete abstinence is the treatment
22 goal recommended by NIAAA and other expert groups.

23 Because a treatment goal of abstinence was
24 so strongly associated with positive U.S. study
25 outcomes, subjects within the ITT and efficacy

1 evaluatable population who, at baseline, identified
2 their treatment goal as total abstinence were
3 looked at as additional subpopulations in order to
4 better understand acamprosate efficacy in the U.S.
5 population.

6 We have called these subpopulations
7 respectively the motivated ITT population and the
8 motivated efficacy evaluatable population.

9 [Slide.]

10 Cumulative abstinence duration or percent
11 of abstinence time on study was the only original
12 outcome parameter which was still applicable to the
13 U.S. study population since it does not involved
14 censoring of data at the time of the first drink.
15 In the original European-based analysis plan for
16 the calculation of this outcome parameter, the
17 number of abstinent days were divided by the total
18 duration of the trial.

19 Given the precision of the U.S. data
20 collection and follow-up methods in the revised
21 analysis the denominator remained the total trial
22 duration unless patients were censored for leaving
23 the trial for reasons unrelated to alcohol.

24 Also, as stated earlier, in order to
25 better understand the efficacy of acamprosate in

1 the U.S. population, a standard panel of baseline
2 and treatment exposure covariates would uniformly
3 applied across outcome measures in order to reduce
4 residual variation and offset the imbalances in
5 comparisons between acamprosate and placebo.

6 This adjustment enables the supportive
7 identification of trends with p less than 0.05 in
8 favor of acamprosate 2 grams relative to placebo in
9 the ITT group. The extent of these favorable
10 trends increases as one moves to the more defined
11 populations mainly because of the larger increase
12 in cumulative abstinence duration percent in the
13 acamprosate group than in the placebo group.

14 Abstinence time was about 6 percent longer
15 with acamprosate 2 grams in the ITT population
16 while for patients in the efficacy evaluable
17 population who had total abstinence as their
18 treatment goal, abstinence time was about 16
19 percent longer with acamprosate 2 grams relative to
20 placebo.

21 This supports the premise that motivation
22 to be abstinent merits consideration in the
23 interpretation of acamprosate efficacy in the U.S.
24 population.

25 [Slide.]

1 Furthermore, the previously noted trends
2 with acamprosate were maintained in the 2 gram
3 group relative to placebo during the two months
4 post-treatment follow-up phase again most markedly
5 in those subjects with a baseline motivation of
6 total abstinence.

7 [Slide.]

8 As support analyses of cumulative
9 abstinence duration, covariate adjusted odds ratios
10 were calculated for the likelihood of good response
11 with acamprosate relative to placebo. Good
12 responders were defined as those subjects with a
13 cumulative abstinence duration of 90 percent or
14 more. This is highly relevant from a clinical
15 point of view.

16 For the motivated efficacy evaluable
17 population, the adjusted odds ratio for good
18 response with acamprosate versus placebo
19 supportively had p less than 0.05 and corresponded
20 to about three times higher odds for good response
21 with acamprosate 2 grams than with placebo.
22 Conversely, poor response was defined as those
23 subjects having a cumulative abstinence duration of
24 10 percent or less.

25 The adjusted odds ratio for poor response

1 for acamprosate 2 grams relative to placebo had p
2 less than 0.05 and showed a decreasing pattern of
3 lower odds for poor response for acamprosate 2
4 grams across the subgroups.

5 [Slide.]

6 A final support analysis of abstinence
7 looked at the likelihood of a subject being
8 abstinent during the interval prior to their last
9 treatment-phase visit. This outcome may have
10 clinical relevance in that a subject's behavior at
11 the end of study may be predictive of behavior off
12 study.

13 There was a trend for subjects treated
14 with acamprosate 2 grams to have a high odds for
15 being abstinent at the end of study participation
16 compared to placebo with compliant and motivated
17 patients having more than twice the odds to be
18 abstinent at this key time point in the 2 gram
19 group.

20 [Slide.]

21 Now I am going to turn to a secondary
22 outcome that involves quantity of drinking on
23 study. The calendar method of drinking data
24 collection in the U.S. study permitted the most
25 detailed examination to date of whether acamprosate

1 reduces alcohol consumption in nonabstinent
2 subjects during the study.

3 You will recall that all subjects received
4 a standardized alcohol-specific behavioral therapy
5 and, as this slide shows, all patients, including
6 the placebo group, showed substantial reductions on
7 study from baseline levels of drinking. However,
8 particularly in those subjects motivated to be
9 abstinent, the covariate adjusted analysis showed a
10 larger reduction with acamprosate 2 grams than with
11 placebo.

12 Again moving from ITT to the more defined
13 subpopulations, there was a further reduction of
14 only approximately 3 percent in the placebo group
15 compared to almost 20 percent in the acamprosate 2
16 gram group. This provides further support for an
17 association between motivation to be abstinent and
18 trends in favor of acamprosate relative to placebo
19 in the U.S. population.

20 [Slide.]

21 As seen in this slide, all treatment
22 groups showed an improvement in mean levels of GGT
23 at study endpoint relative to the elevations in
24 mean values seen at baseline. Mean endpoint values
25 were normal or near normal in this predominantly

1 male study population further attesting to the
2 improved status of patients in all groups and the
3 validity of self-report in this study.

4 [Slide.]

5 As requested by the FDA, the U.S. study
6 population was much more inclusive than seen in
7 most clinical trials in alcohol dependence in order
8 to assess the safety of acamprosate in patients
9 with polysubstance abuse, hepatic and renal
10 dysfunction and the elderly.

11 As a result of the U.S. study's broad
12 admission criteria, 81 percent of screened patients
13 were randomized supporting the external validity of
14 the study. I want to emphasize that, in contrast,
15 in an ongoing large multicenter trial in
16 alcohol-dependent patients, only about 25 to
17 30 percent of screened patients were randomized.

18 The rate of compliance with medication
19 exceeded 88 percent in all treatment groups lending
20 support to the acceptability of both acamprosate
21 and the divided dosing schedule.

22 [Slide.]

23 Controlling for baseline variables in
24 treatment exposure, the U.S. study results support
25 the efficacy of acamprosate 2 grams relative to

1 placebo particularly in patients with a baseline
2 goal of abstinence. This treatment group had
3 increased cumulative abstinence duration and
4 increased likelihood of good response, a decreased
5 likelihood of poor response and an increased
6 likelihood of being abstinent at study termination.

7 In addition, although all groups showed
8 improvement in drinking behavior on study relative
9 to baseline, the 2 gram group had a greater
10 decrease in both the quantity and frequency of
11 alcohol consumption compared to placebo.
12 Self-reported drinking were confirmed by
13 accompanying changes in GGT. A consistent
14 association was found between trends in favor of
15 acamprosate and a baseline goal of total abstinence
16 across study outcomes.

17 This observation has implications for
18 healthcare providers prescribing acamprosate for
19 their outpatients with alcohol dependence.

20 [Slide.]

21 Integrating the U.S. and European
22 pivotal-trial exposure with acamprosate, overall,
23 acamprosate 2 grams per day showed significant
24 effects on abstinence outcomes in almost 2000
25 alcohol-dependent outpatients participating in

1 double-blind, placebo-controlled trials up to one
2 year in duration.

3 Additionally, acamprosate showed continued
4 efficacy during off-treatment follow-up periods of
5 as long as one year.

6 [Slide.]

7 European and U.S. data suggest that
8 acamprosate does not induce abstinence in
9 unmotivated drinkers. In Europe, patients had to
10 make a commitment to abstinence-oriented treatment
11 that began with formal detoxification typically
12 inpatient. Thus, their treatment goal at the onset
13 of the clinical trial was implicitly total
14 abstinence and treatment effects may have been
15 easier to discern because of the resultant
16 homogeneity.

17 In contrast, the U.S. study population did
18 not typically undergo detoxification and was quite
19 heterogeneous in their expressed baseline treatment
20 goals. Through examination of subpopulations,
21 defined by the presence of total abstinence as a
22 treatment goal, the U.S. data suggest that it is
23 not necessary to undergo formal detoxification in
24 order to obtain therapeutic benefit from
25 acamprosate provided patients are motivated for

1 total abstinence.

2 [Slide.]

3 Uniformly, high rates of compliance across
4 the pivotal trials support the acceptability of
5 acamprosate in the twice daily and three times
6 daily dosing schedules used in these studies. The
7 pivotal trials spanned a range of countries and
8 clinical settings. You may also recall that the
9 European studies, by design, did not include any
10 uniform behavioral therapy. Thus, the efficacy of
11 acamprosate is supported across a broad range of
12 treatment orientations.

13 Closing Remarks

14 DR. GOODMAN: Ladies and gentlemen,
15 members of the committee, I would like to spend
16 these final few minutes of our presentation on the
17 issues set forth by the division for your
18 consideration.

19 [Slide.]

20 In our briefing document and in our
21 presentations this morning, we have described to
22 you three European double-blind, placebo-controlled
23 studies of acamprosate that meet all the FDA
24 criteria for approvability. As we are all aware,
25 the process of drug development is a long one, more

1 often than not. The European studies on which we
2 are relying as evidence of efficacy were conducted
3 starting in 1989 and were completed for the most
4 part by 1995.

5 Although the FDA has characterized these
6 studies as older, in fact, the trials were
7 conducted by qualified clinical experts in the
8 field of alcoholism. They meet the FDA criteria of
9 being clinically generalizable to the target
10 population in the United States and the trials were
11 conducted in a manner consistent with good clinical
12 practice and are auditable.

13 [Slide.]

14 Despite differences of opinion about the
15 most appropriate methodology for assessing outcome
16 in clinical trials of alcohol dependence, and, in
17 fact, despite the actual methodologies applied,
18 those of Lipha or those of the FDA, the three
19 European pivotal trials showed consistently
20 significant and clinically relevant effects both on
21 parameters selected as primary, as shown here, as
22 well as various secondary parameters described in
23 your briefing document.

24 These studies, along with the others
25 described in the documents provided to you, served

1 and continue to serve as the basis of regulatory
2 approvals around the world, most recently in
3 Australia and South Africa. The results of the
4 European trials are applicable to approvability for
5 the United States because there is no biologic or
6 pharmacokinetic reason to believe that drug
7 response in alcoholic patients will differ between
8 Europe and the United States.

9 As Dr. Koob has pointed out, the drug is
10 not metabolized. Nor is there any reason to
11 believe that the nature of alcohol dependence
12 differs in European and American alcoholic
13 patients.

14 [Slide.]

15 In a letter to the FDA, at their request,
16 from the National Institute on Alcohol Abuse and
17 Alcoholism specifically addressing this issue, the
18 concluding comments from NIAAA are the core illness
19 of alcohol dependence is similar in the United
20 States and Europe.

21 The conclusion is based on several
22 considerations. First, the diagnostic methods for
23 coding alcohol dependence are very similar in the
24 United States and Europe. Most of the clinical
25 trials of acamprosate in Europe used the Diagnostic

1 and Statistical Manual of Mental Disorders III-R,
2 the DSM III-R, for verification of alcohol
3 dependence, the version which was available and
4 used in both Europe and the United States at the
5 time these studies were conducted.

6 Second, an international conference, held
7 in Germany in September of 1999 to determine if
8 cross-national studies could be conducted,
9 concluded that, while there are cultural
10 differences between the U.S. and Germany,
11 cross-national collaboration was feasible because
12 the alcohol-dependent populations were similar.

13 Finally, a comparison of the cardinal
14 symptoms of the alcohol dependence syndrome in U.S.
15 and Soviet populations revealed virtually identical
16 characteristics.

17 [Slide.]

18 Dr. Barbara Mason has shown you, through
19 analyses using an informed set of baseline
20 variables and treatment exposure that the American
21 study results are not in conflict with the European
22 experience when baseline differences among the
23 treatment groups are controlled for. In fact,
24 these analyses have led to a further understanding
25 of the sorts of patients who might ultimately

1 benefit from acamprosate, namely patients who are
2 motivated to total abstinence without a slip.

3 These data are offered to you not as a
4 justification of the methods and the results but,
5 instead, as an explanation for what happened in the
6 very broadly inclusive U.S. trial and as a means of
7 assuring you that the populations are, indeed,
8 similar.

9 Dr. Mason has presented to you the
10 interpretation of these additional analyses which
11 showed that acamprosate increased the percentage of
12 abstinent time on study, increased the likelihood
13 of remaining abstinent for 90 percent or more of
14 the time on study and, as shown in your briefing
15 document, also impacted favorably on alcohol
16 consumption in those patients who did drink.

17 [Slide.]

18 Taken as a whole, the acamprosate clinical
19 data submitted to the FDA for the indications shown
20 here which are being considered in the context of
21 an accelerated review more than meet the FDA's
22 criteria for approval and do not warrant additional
23 safety and efficacy trials.

24 It would unduly penalize that percentage
25 of alcoholic patients who may benefit from

1 acamprosate as well as their families and the
2 community in general if approval were to be delayed
3 while we all await further studies and analyses.

4 We acknowledge that acamprosate is not the
5 magic bullet we all seek for just about any medical
6 condition you could describe. However, the overall
7 picture is, indeed, clear enough both from the
8 perspective of acamprosate's efficacy and safety to
9 proceed further with the approval process.

10 [Slide.]

11 The FDA agreed that acamprosate deserved
12 an expedited review when our NDA was filed and
13 their ongoing review of the extensive data
14 submitted has been very thorough in this
15 therapeutic area in which they are practically
16 pioneers.

17 The paucity of available therapies for the
18 treatment of alcoholism and the continued enormity
19 of the personal and economic costs of alcoholism
20 mitigate, however, for action now rather than
21 later.

22 Thank you very much.

23 Questions from the Committee

24 DR. OREN: We now turn to the portion of
25 meeting where the members of the committee have the

1 opportunity to question Lipha about their
2 presentation or anything else with regard to
3 today's questions.

4 Given that there are millions of Americans
5 who may be affected by our recommendation, I
6 encourage our committee members not to be shy but
7 to be very vocal in coming up with questions.
8 Anyone wish to begin?

9 Dr. Keck?

10 DR. KECK: I know our task is mostly
11 around efficacy today but I have some questions
12 just about safety. It is likely that a lot of
13 people, say, with bipolar disorder who have high
14 rates with alcoholism could take this drug. What
15 do we know about drug interactions with lithium or
16 NSAIDs or other drugs that are renally cleared?

17 DR. GOODMAN: I can tell you that, from a
18 formal point of view, we have not conducted any
19 pharmacokinetic interaction studies with those
20 classes of drugs and there could be some reason to
21 suspect, mechanistically, that they might interact.
22 But we don't have the information to date.

23 I don't know, Dr. Chabac, if you are aware
24 of any patients in our postmarketing
25 pharmacovigilance database that might have been

1 exposed to lithium?

2 DR. CHABAC: As I told you, we have 1.5
3 million patient year exposure. You know well that
4 those patients probably have high comorbidity and
5 were treated with these kinds of products. On
6 postmarketing surveillance, we had no specific
7 problem, specific interaction with those drugs.
8 But, as Dr. Goodman told you, we didn't investigate
9 all possible drugs to be associated with
10 acamprosate.

11 DR. GOODMAN: I might add one thing, but I
12 don't want to go out of the boundaries of our
13 restricted discussion of efficacy. But we did look
14 at NSAIDs or analgesics in general in terms of
15 adverse-event occurrence in the U.S. study. My
16 recollection is that there was no difference in
17 pattern of adverse events or increased incidence.
18 But that is just based on--we have been focussing
19 on efficacy both for the preparation of this
20 meeting and so I would want to verify that. It's a
21 good point.

22 DR. KECK: Just one other basic
23 pharmacokinetic question. It was unclear to me in
24 how many of the studies the recommendation was that
25 the drug be taken with food. But that struck me as

1 curious since, if I am reading the data correctly,
2 food decreases the absorption and bioavailability
3 of a drug that already has limited bioavailability.
4 Can you help me understand that?

5 DR. GOODMAN: It's a good point. My
6 interpretation of that would be, again, that this
7 is not a drug that you are taking acutely such as
8 you might use an NSAID for a headache or joint pain
9 or whatever. It is something that is chronically
10 administered.

11 So I think the food effect really is of
12 minimal importance over the long haul once a person
13 is at steady state. Dr. Porte may have some
14 thoughts about that as well. She is our
15 pharmacokineticist from Lyon.

16 DR. PORTE: To answer your question, the
17 food interaction study was performed for a single
18 dose administration. This does not correspond to
19 the dosing schedule recommended in the labeling.
20 So we expect that this food interaction will not
21 impact on the clinical efficacy of this compound
22 even though the bioavailability is already
23 limited.

24 DR. GOODMAN: As far as the clinical
25 trials are concerned, and Karl Mann may have some

1 comments on that, in many instances, the drug was
2 taken with meals as a reminder for taking--

3 DR. OREN: Dr. Winokur?

4 DR. WINOKUR: I wanted to ask a question
5 related to difference between the populations
6 included in the European trials and the U.S. trial.
7 If I remember data from the packet, which I don't
8 think was commented on, a considerably higher
9 percentage of subjects in the European trials had
10 histories of very high drinking histories, for
11 example greater than ten drinks a day. I just
12 wondered if some additional comment about that
13 aspect of different profiles--we have talked about
14 differences, for example, that there was other drug
15 use in the U.S. trial but I was interested in the
16 analysis of the history of drinking frequency in
17 the U.S. trial.

18 DR. GOODMAN: I will just comment. It
19 was, I won't say misrepresented in the briefing
20 document, but, in fact, the calculations presented
21 for the European data were based on drinks per day
22 for patients who did drink whereas the U.S. data
23 was shown as drinks per day for all patients,
24 whether they drank or not. So the data that Dr.
25 Mason presented in her demographics, in fact, was

1 the correct representation for the purposes of
2 comparison because they are basically they same.

3 DR. HUGHES: First of all, before I make
4 my comments, I just want to clarify that the
5 University of Vermont was the site of the U.S.
6 study but I did not participate in that.

7 What I wanted to ask was if there is a
8 subset of more motivated patients that acamprosate
9 works in, two things to judge post hocs on are
10 reproducibility and plausibility. So the two
11 questions I have are are there any instances,
12 either with alcoholism or other drug dependencies,
13 where a subset of more motivated patients changes
14 not the outcome but the odds ratio. That is the
15 first question. So is there a precedence for this.

16 The second question is what would you
17 maintain is the behavioral or biological mechanism
18 by which being more motivated would change, again,
19 not the outcome but, by being more motivated, it
20 would change the relative efficacy of acamprosate
21 to placebo. So, again, what is the reproducibility
22 of this and what is the mechanism?

23 DR. MASON: John, the two papers that I
24 pulled which Sharon Hall and colleagues at the
25 University of California and Stephanie O'Malley's

1 naltrexone study didn't calculated odds ratios.
2 They just are descriptive statistics. So I don't
3 know that I have information that would be helpful.

4 DR. HUGHES: My recollection of those
5 papers was that the more motivated did better but,
6 by being more motivated, it didn't change your
7 response to the treatment. Is that correct?

8 DR. KOOB: The more motivated did better
9 without changing their response to the treatment

10 DR. HUGHES: If you had some measure of
11 active to placebo in a study, I agree with you,
12 being more motivated is going to take your
13 abstinence rates up. But my worry is it going to
14 take them both up and not change the relative rates
15 of outcome because active and placebo.

16 I am trying to think of a prior study in
17 which, if you took a more motivated group, it
18 changed the differences between active and placebo.
19 I was wondering if you know of one.

20 DR. MASON: In the O'Malley study, which I
21 am more familiar with, it depends on what outcome
22 you look at because in the group that had the
23 behavioral therapy in which a slip was considered
24 likely, permissible, et cetera, they did have more
25 days on which drinking occurred as opposed to

1 patients in the behavioral therapy group that were
2 told, you must be completely abstinent.

3 Then that was crossed with naltrexone. So
4 you did have the influence of the instruction to be
5 abstinent or have a slip interacting with an
6 outcome parameter and drug. Does that help?

7 DR. HUGHES: Any thoughts about mechanism?

8 DR. MASON: George has a thought. Good.

9 DR. KOOB: I think the animal data
10 suggests that acamprosate--and this is part of the
11 pharmacokinetic issue as well. Acamprosate takes a
12 while to reach steady state. It is five to seven
13 days. Any mechanism, whether it is cognitive or
14 whether it is induced by the European studies where
15 a person had the detox, that lengthens the time
16 between when an individual has stopped drinking and
17 the onset of steady state blood levels of
18 acamprosate is going to facilitate the
19 normalization of the neurotransmitter systems that
20 it works on.

21 So my answer to that question would be
22 anything that lengthens the time that the organism
23 is without alcohol, and in that alcohol deprivation
24 study where we see a large effect, those animals
25 are not allowed to drink during the period that

1 they are getting acamprosate, you see a bigger
2 effect of acamprosate.

3 DR. OREN: Dr. Ortiz?

4 DR. ORTIZ: My question is Dr. Mann
5 mentioned that the European studies all had
6 psychosocial treatment programs. Dr. Mason just
7 briefly mentioned something about behavioral
8 treatment in the American study, and I am wondering
9 if we can get a little bit of elaboration on that.

10 DR. MANN: In the European studies, there
11 were not psychotherapies or psychosocial treatment
12 which was manual based. It was the treatment that
13 was, at that time, given at these different centers
14 and this might have different--within the study,
15 from center to center. So it was the center-based
16 treatment approach like counseling or, in some
17 centers, behavioral treatment. In others, it might
18 have been something else.

19 So there was not a manual-based treatment
20 in the European studies and that was different in
21 the U.S. study.

22 DR. MASON: In the U.S. study, there was a
23 manual that actually had a script in it for the
24 therapist to model and there was a training video.
25 It was based on principles of motivation

1 enhancement, particularly the manual developed by
2 the National Institute on Alcohol Abuse and
3 Alcoholism from Project MATCH and it also included
4 elements of the National Institute on Alcohol Abuse
5 and Alcoholism brochure for primary-care providers
6 in their approach to treating alcoholism.

7 It was really conceptualized as something
8 that could fit easily into a variety of treatment
9 settings. In fact, we deliberately included
10 internal-medicine sites. It was brief. It was
11 about twenty minutes. It could be delivered by a
12 nurse or an experienced counselor with a bachelor's
13 degree.

14 It involved handouts to the patients that
15 gave them information, let them do self-monitoring
16 exercises and really built on the patient's own
17 experience, what has worked for you in the past,
18 what hasn't worked. Then, if there is a report of
19 a drinking episode, what worked, what didn't work,
20 what do you see as the obstacles to your meeting
21 your treatment objectives.

22 Also, information like GGT levels were
23 shared with the patient so that they received
24 feedback about the progress that their efforts were
25 having in terms of the effect on their health. For

1 example, one of the motivation-enhancing
2 strategies, the time-line follow-back, quantifies
3 the amount of drinking that occurs in a week, for
4 example

5 Each standard drink roughly is equivalent
6 to 100 calories and people were drinking, on
7 average, about 40 drinks a week. So, when you do
8 that multiplication, people are kind of horrified
9 about how many calories are being consumed in
10 alcohol.

11 Also, another strategy is multiplying the
12 number of drinks per week by the cost. If you are
13 drinking in a bar and paying, like, \$5.00 a drink,
14 people then get thunderstruck at how much they are
15 paying for alcohol. So those are some of the
16 motivation-enhancement characteristics of the
17 standardized therapy that are tracked in the
18 treatment progress summary at each visit which
19 occurs on a monthly basis.

20 Initially patients are seen one week after
21 starting medication, then, in two weeks, and then
22 they switch to the monthly schedule.

23 DR. OREN: Dr. Schatzberg.

24 DR. SCHATZBERG: This is a question for
25 Barbara Mason and George Koob. When you are

1 looking at the U.S. study versus the European
2 studies and you are going to a new formulation, and
3 the fact that if you look at the average weight in
4 the U.S. study, it is about 10 percent higher than,
5 let's say, in the German study that Dr. Mann talked
6 about.

7 Are we sure that we just haven't
8 underdosed in the U.S. and have you looked at
9 acamprosate levels to ascertain whether, in fact,
10 we have an effective dose in Europe in 1998 that
11 may not be effective in the U.S.

12 DR. GOODMAN: I am going to just intervene
13 even though I am not Dr. Mason. I do want to
14 correct one thing that might be a misperception on
15 the part of the committee members. These are not
16 different tablets. The only thing that is
17 different--there is no difference in the
18 formulation. They are identically formulated
19 except for the tablet strength. So there is no
20 difference in the tablet formulation.

21 As I believe Barbara pointed out in her
22 talk, there was a pharmacokinetic study,
23 multiple-dose pharmacokinetic crossover design, of
24 these two schedules which were shown to be
25 bioequivalent. So we feel, from the basis of that,

1 that the dosing is equivalent.

2 With regard to the question about the
3 heavier, huskier American population, I would say
4 that the Germans probably aren't too far off from
5 the American population. If you noticed in the
6 demographics, they weighed a bit more, on average,
7 certainly, than the French. So there could be a
8 comparability there.

9 We did do blood levels of acamprosate,
10 blinded of course, in the U.S. study one week after
11 starting treatment and then again at the time of
12 termination. Those blood levels were consistent
13 with steady-state levels in PK studies in our
14 dossier.

15 DR. OREN: Dr. O'Brien?

16 DR. O'BRIEN: My question also concerns
17 psychotherapeutic intervention. One of the
18 difficulties in interpreting efficacy studies in
19 any behavior disorder, whether it is depression,
20 anxiety or alcoholism is that the patients are
21 always getting two effective treatments; namely,
22 psychotherapy and a potentially effective
23 medication.

24 We have some evidence from other evidence
25 from other forms of substance abuse that there is a

1 dose-response curve for psychotherapy. In other
2 words, if you randomly assign people to various
3 levels of psychotherapy, it doesn't matter very
4 much which type of psychotherapy, so it is not
5 specific to, say, supportive-expressive versus
6 cognitive-behavioral. But the quantity is a
7 factor.

8 In clinics, there is a tendency, when a
9 patient is doing badly, you don't know whether they
10 are on drug or placebo but to enhance the amount of
11 time that is given to them, more frequent visits,
12 perhaps, or spending a little more time with them
13 or helping them a little bit more because you are
14 trying to help the patient.

15 I just wonder whether in either the
16 European, or any of the European studies or the
17 American study, whether there was an effort to
18 measure the quantity of psychotherapeutic
19 interaction.

20 DR. GOODMAN: I think I can answer and say
21 yes, there was. But, Barbara, maybe you want to
22 address it more specifically and Karl as well.

23 DR. MASON: I will just tell you that, in
24 the U.S. study, patients were allowed only two
25 emergency visits in addition to their monthly

1 visits. That was the protocol. If they required
2 more help than that, they were terminated as
3 treatment failures.

4 The treatment was proscribed to be twenty
5 minutes. It was very defined in the manual, the
6 procedures, and involved completing things and
7 reviewing things together. That was the parameter
8 of the therapy. It was adhered to.

9 DR. MANN: I think that is a very, very
10 important point which may, indeed, help to
11 understand the differences because, in the European
12 studies, the doses of psychosocial treatment was
13 extremely low. We gave very little, only a few
14 visits throughout the whole year; for instance, in
15 Germany, I think eight or nine visits.

16 So one per month in the first three months
17 and then only one every third month which is really
18 very little. So the doses which we applied were
19 really small. If you give much more--we have seen
20 this in other studies, at least we have the
21 impression that if you have a very high placebo
22 response because you give a lot of psychosocial,
23 then the drug has a harder time showing an effect.

24 If I may add something to the other
25 question earlier about the difference between the

1 treatment sites or the centers, we have looked,
2 because there were different forms of psychosocial
3 treatments, the differences in outcome between
4 these centers and we didn't find any difference
5 there.

6 Also, there was a difference maybe in the
7 approach psychosocially. It didn't affect the
8 overall treatment outcome. I forgot this earlier.

9 DR. GOODMAN: Barbara may want to address
10 something about the phase IV European studies, the
11 Need Project.

12 DR. MASON: There was a large
13 multinational open-label study of acamprosate that
14 was conducted specifically to look at acamprosate
15 efficacy across five major types of psychotherapy,
16 group therapy--Silvie, do you remember what some of
17 the other components were? This was in Europe.
18 There was no change, no significant difference in
19 acamprosate efficacy across the five major models
20 of psychosocial treatment that were studied.

21 This involved approximately 1200
22 outpatients with alcohol dependence all of whom
23 received acamprosate. The varying factor was the
24 co-occurring psychosocial therapy.

25 DR. OREN: Dr. Rudorfer?

1 DR. RUDORFER: If I could go back to the
2 pharmacokinetics for a second, given acamprosate
3 18-hour half-life, I wonder why some of the
4 European studies used three times a day dosing.

5 DR. PORTE: Actually the absorption
6 process of acamprosate is very slow so when you
7 measure the half-life, it corresponds to the end of
8 the plasma profile. Indeed, it does not correspond
9 in the case of acamprosate to pure elimination but
10 there is still some remaining absorption of
11 product. Therefore, to find a dosing regime for
12 acamprosate, we should more look at the elimination
13 half-life for the intravenous dose which is from
14 five to seven hours.

15 DR. OREN: Dr. Leon?

16 DR. LEON: In designing and implementing a
17 clinical trial, we typically take many safeguards
18 to minimize the bias of the treatment effect. What
19 we usually focus on are randomization and blinding
20 and statistical strategies. What I am struck by
21 here is it appears another strategy that is very
22 important in minimizing bias is that we prespecify
23 our primary dependent variable, our efficacy
24 measure, and prespecify our primary data analytic
25 technique.

1 I don't see any examples of that in these
2 four trials. It looks as if the primary data
3 analytic technique that was specified in the
4 protocol was not adhered to nor was the primary
5 efficacy measure.

6 If those measures and techniques are
7 prespecified, then anyone who looks at the data
8 will get the same answer. But when they are not
9 prespecified and changed after the data have been
10 collected, that objectivity or agreement across
11 independent assessors is jeopardized.

12 I wondered if you have a comment on that.

13 DR. G. COOK: Gary Cook. I am a
14 consultant to Lipha. I will probably need Dr.
15 Goodman's help on this. I believe that for the
16 European studies there was some type of reasonable
17 statistical plan and that the analyses that were
18 done to support the efficacy of those studies was
19 reasonably consistent with that plan.

20 There might be some further clarification
21 as to exactly what the plans were, but my
22 understanding is that there was a plan, that the
23 results were consistent with that plan and then a
24 variety of additional analyses have been done to
25 further support the robustness of the analyses of

1 those studies.

2 Now, the U.S. study, the issues are
3 totally different. But we need to sort of deal
4 with this in two steps so could you first clarify
5 what would have been the response to this question
6 with respect to the European studies.

7 DR. GOODMAN: I would make two points, and
8 there may be additional members of our group
9 especially from Europe who could say other things.
10 But, first of all, with regard to the total
11 protocol design, as the FDA has pointed out in
12 their document as well, the design requirements are
13 not as detailed and specific and uniform as they
14 are now with the international harmonization
15 guidelines.

16 So, if the European studies were to be
17 done today, there would be very detailed analytical
18 statistical analysis plans included in the
19 protocol.

20 I believe, as Dr. Chabac also pointed out,
21 that the purposes of the studies globally were for
22 registration purposes so there was a common plan
23 for analysis of the data and that is why these
24 variables, all of which we consider to be related
25 because they are all another way of looking at