

1 abstinence or drinking that these are appropriate.

2 DR. CHABAC: I just want to add something.

3 Remember that we designed all our European studies
4 using a core protocol. That means the same study
5 design. In our protocol, we specified which were
6 our primary criteria, mainly time to first relapse
7 since we were seeking for an indication to maintain
8 long-term abstinence. So it was our primary
9 criteria very well described in our protocol and it
10 is in the NDA.

11 DR. LEON: Can I just follow up? In my
12 reading of the documents, it looked like the time
13 to alcohol was not specified as a primary dependent
14 variable either in Pelc or in the second one,
15 Paille.

16 DR. GOODMAN: Right; I think that is
17 correct. They varied slightly between the studies
18 but what I am saying is that the information that
19 was obtained allowed one to do an integrated type
20 of analysis where you could use the information and
21 look at it for a similar outcome parameter. As I
22 said earlier, and I think we all agree, there is
23 not really a methodology, a statistical
24 methodology, people certainly agree on but the
25 outcome measures for this, especially when Lipha

1 was working with acamprosate, naltrexone was not
2 available in Europe and just became available there
3 recently. So Lipha was really pioneering this area
4 and the types of outcome parameters that were used
5 were, by that very nature, something that could be
6 gleaned from the information gathered.

7 I think probably each country had their
8 own kind of slant on what they thought, more or
9 less investigator-driven types of endpoints.

10 DR. G. COOK: The primary objective,
11 relatively clearly abstinence.

12 DR. GOODMAN: Yes; exactly.

13 DR. G. COOK: So, even though there may
14 have been variations on how abstinence was looked
15 at, whether it was time to first drink or complete
16 abstinence or number of abstinent days, the focus
17 was on abstinence and the conclusions across those
18 multiple criteria were pretty much the same.

19 I think the analyses the FDA has done
20 pretty much agrees with that so there are not
21 really any major inconsistencies that I have seen
22 if you basically say the real objective of those
23 studies was abstinence.

24 DR. LEON: But I still haven't heard you
25 say that the data analyses that were presented

1 today corresponded directly with that that was
2 described before the data were collected. It seems
3 like the primary efficacy measure and the data
4 analytic techniques in all four of the studies are
5 different than those specified in the protocols.

6 DR. G. COOK: But, for the three European
7 studies, your earlier point, which is consistency
8 of findings across a variety of ways of looking at
9 the data, was, indeed, supported. Now, the U.S.
10 study is going to be a totally different phenomenon
11 which we will get to shortly.

12 Essentially, the structure of the European
13 studies, particularly at the time they were done,
14 had a reasonably clear objective of abstinence and
15 the criteria that were looked at were all criteria
16 that were relevant to abstinence. The conclusions
17 across those criteria by the different ways of
18 looking at them, whether by the sponsor or the
19 agency, were pretty much the same.

20 It would be important that they were the
21 same because if it had turned out that the analyses
22 of abstinence in the Europeans had varied according
23 to measure or method, that would be an issue with
24 respect to the European studies. So, the fact that
25 there is consistency across those different ways of

1 looking at the data, even though they have
2 different conventions for how you deal with
3 intervals between visits, is important to the
4 robustness.

5 With respect to the U.S. study, I think
6 there was, at one time, interest in the time to
7 first drink or abstinence. That was a goal of the
8 U.S. study. But that was basically defeated
9 because the patients weren't abstinent at baseline.
10 In other words, unlike the European studies, you
11 did not have abstinent patients at baseline. So
12 the notion of looking at time to first drink or
13 total abstinence broke down. That is why other
14 things had to be looked at.

15 Now, the role of the U.S. study here is to
16 try to understand consistency; is there information
17 in the U.S. study that more or less fits with what
18 was proven in the European studies. The U.S. study
19 doesn't prove anything. It is possibly
20 inconclusive. It possibly raises doubt about what
21 was seen in the European studies.

22 So the role of all of the explanatory
23 analyses--we don't call them confirmatory anymore
24 for the U.S. study; we call them explanatory--is to
25 try to understand whether there is information or

1 trends in the U.S. study that fits with what was
2 proven in the European studies. That is what Dr.
3 Mason tried to share with you all.

4 So the original planned analyses didn't
5 work because we didn't have an abstinent population
6 at baseline.

7 DR. OREN: Dr. Hamer?

8 DR. HAMER: Actually, I have a related
9 question. I have very little experience in
10 substance abuse but I do have a great deal of
11 experience in depression studies and schizophrenia
12 studies and a variety of other psychiatric studies.

13 If a sponsor came in with four depression
14 studies of which three were positive and one
15 wasn't, basically, I think both the FDA and this
16 committee would tend to sort of shrug our shoulders
17 and say, you know, we have failures in depression
18 studies. Three out of four is not bad. Sounds
19 like a good drug to me.

20 So, as a statistician, I never want to
21 underestimate the pure properties of randomness.
22 So I may not feel as compelled as the FDA seems to
23 feel to seek explanatory reasons for why the U.S.
24 study, unfortunately, failed.

25 Now, there are other issues with the

1 European studies having to do with the time frame
2 and conditions under which they were designed and
3 the fact that they didn't have this rigid
4 prespecified endpoints and analyses as the ones we
5 would design now are.

6 But I do agree with Dr. Cook that what we
7 really should be pulling out of the
8 nonprotocol-specified reanalyses of the U.S. data
9 is that these analyses are possibly explanatory.
10 They are hypothesis-generating. They are not
11 hypothesis-confirming. I hope that the sponsor is
12 not claiming that these hypotheses in the U.S.
13 study indeed confirm that acamprosate promotes
14 abstinence in patients who are already abstinent
15 and I would hope we don't interpret it that way.

16 So I would say that our task, in some
17 sense, is, using the standards that we are
18 accustomed to using, in a sense, to look at the
19 European studies and decide whether those provide
20 sufficient evidence of safety and efficacy.

21 DR. OREN: If I could just ask you, since
22 we just have a few more minutes for this
23 segment--we will have an afternoon discussion
24 section to weigh all the different points. So if
25 we could just focus on the specific questions for

1 the company to answer.

2 DR. HAMER: In that case, I will postpone
3 things.

4 DR. OREN: Okay. Dr. Keck?

5 DR. KECK: This is a belated follow up to
6 Dr. O'Brien's point about psychosocial influence on
7 outcome. I am just, again, trying to understand
8 the many reasons why the U.S. study failed. In a
9 way, it doesn't surprise me that a study in which
10 you had ambivalently motivated people many of whom
11 were not abstinent to participate in the trial with
12 poly drug abuse didn't do so well in this study.

13 But one other embedded reason I wonder
14 about in the design is it seems to me that patients
15 had not only one but potentially two psychosocial
16 treatments here because of the--I'm getting the
17 terminology here--the time-line follow-back method
18 which, again, coming not as a substance-abuse
19 researcher but doing research in other
20 impulse-control disorders, any time you put a diary
21 into a study as a treatment-outcome measure, you
22 invariably introduce, I think, subtly, a form of
23 behavioral therapy by completion of the diary,
24 itself.

25 So I guess I am saying it seems to me you

1 had two psychosocial interventions or behavioral
2 therapy interventions which I think made it even
3 more difficult to find a drug-placebo difference.

4 Does that sound fair to say?

5 DR. MASON: It sounds quite fair and
6 accurate, and the placebo response rate was high in
7 the U.S. study. I completely agree with you that
8 the data-collection methods, in themselves,
9 probably raised the threshold of what was perceived
10 by the patient as therapeutic activity, in addition
11 to the twenty minutes that they were officially
12 assigned.

13 DR. OREN: Dr. Hughes

14 DR. HUGHES: I wonder if you could respond
15 to my rationale here. The notion is that, with
16 increased psychosocial treatment, you decrease the
17 odds ratio between active and placebo. That is the
18 notion I hear being proposed.

19 If increased psychosocial is--the typical
20 way you test that is you take the response of the
21 placebo group and does it correlate with the odds
22 ratio. It is a standard metaanalytic treatment.
23 So the notion is studies that have high placebo
24 responses should have low odds ratios.

25 I did this before I came down. When I

1 look across the fourteen studies, that is not the
2 case in the fourteen acamprosate studies. So my
3 rationale is the data don't suggest that high
4 placebo rates lead to lower odds ratios. But maybe
5 I am thinking wrong.

6 DR. GOODMAN: I am certainly far from a
7 statistician but I would just comment that, if you
8 are looking across the European studies and, if I
9 understood your comments correctly, you were
10 talking about behavioral therapy and I gathered
11 something rather substantial that was, as Dr. Mann
12 has pointed out, that was not the case in Europe.
13 It was not consistent and it varied and it was
14 more--the term that was used in the European
15 dossier was "naturalistic."

16 Maybe I didn't understand what you were
17 saying.

18 DR. G. COOK: This is Gary Cook, again. I
19 am not sure how to answer your question. I think
20 when the placebo rate is higher, that can make it
21 more difficult to show a difference in rates
22 because the amount of room for change may be
23 affected.

24 Odds ratios are complicated kinds of
25 things, so their ability to be large or small is

1 related to the base rate that you are working with
2 so an odds ratio of 90 percent versus 95 percent is
3 2. If you have 90 percent compared to 95 percent,
4 the odds ratio there is about 2 whereas if you are
5 comparing 50 percent to 67 percent, the odds ratio
6 is 2.

7 So I think it is very difficult to try to
8 actually project what you think an odds ratio might
9 do as you change the base rate. If you do have
10 high placebo rates, it may make it more difficult
11 to show a substantial difference in response rates
12 because the amount of room for improvement may be
13 less.

14 But I think, really, it is uncertain in
15 these kinds of things. Also, again, the U.S.
16 population and European populations were different
17 from one another, so extrapolating across the two
18 populations will have its difficulties.

19 DR. OREN: To conclude this segment, Dr.
20 Rudorfer and then I will ask one question after
21 that.

22 DR. RUDORFER: Thanks. It certainly can
23 be challenging to do an effectiveness study such as
24 the U.S. study where one broadens inclusion
25 criteria to try to better reflect real-world

1 populations. I think the American investigators
2 did a very good job of responding to the FDA
3 request to, say, have a broad age range and include
4 comorbidities.

5 But what concerns me is they are sort of
6 going back to basics. If we are discussing the
7 efficacy of a drug for "maintenance of long-term
8 abstinence from alcohol," I still don't understand
9 why abstinence was not an inclusion criterion.

10 DR. GOODMAN: I will let Barbara address
11 that, but I think our assumption in designing the
12 protocol was that patients would understand that
13 they were to be abstinent at the study onset. It
14 was not explicitly stated, but that was our
15 expectation. So, of course, it was quite a
16 surprise to find out that half these people were
17 not abstinent.

18 I think we had been quite--what would I
19 say--just really tuned into the European
20 populations as starting from this abstinence
21 without appreciating that that would not be the
22 case in our study.

23 But, Barbara, you might--we also had the
24 steady-states idea.

25 DR. MASON: Your point is well taken. The

1 behavioral therapy was abstinence oriented,
2 complete abstinence. The admission criteria was
3 people had to have a minimum period of time with no
4 hazardous drinking, which is no more than one drink
5 a day for women, two drinks a day for men, so that
6 they would have decreased to that level so we
7 wouldn't have to deal with withdrawal symptoms on
8 study.

9 But, because acamprosate takes the time
10 that it does to reach steady state, and the animal
11 literature was indicating that there may be some
12 benefit in alcohol withdrawal, our idea was to
13 start drug as soon as possible in the process to
14 help these patients become and stay abstinent.

15 That is why the admission criteria were
16 what they were. We did no interim analyses or
17 peaks or anything and so that is why it was the
18 surprise that it was in terms of the rate of
19 nonabstinence.

20 DR. OREN: My question is for Dr. Mann.
21 In the European studies in support of the efficacy
22 of acamprosate, you mentioned that the completer
23 rates were higher in the active group than in the
24 placebo group. Was that a statistically
25 significant difference and what kind of statistic

1 was used?

2 DR. MANN: It was a significant
3 difference. I think we could pop up one of these
4 extra slides, but I know there was a significant
5 difference between those two groups but I don't
6 recall what kind of statistics we did. But we
7 could find out and then deliver that information
8 later if you want. Sure.

9 DR. OREN: We will now take a ten-minute
10 break and then reconvene to hear from the FDA.

11 [Break.]

12 DR. OREN: We are now at the point for FDA
13 presentations. I will call upon Dr. Celia
14 Winchell, Medical Team Leader for Addiction Drug
15 Products.

16 FDA Presentations

17 Clinical Issues on Efficacy

18 DR. WINCHELL: I am Celia Winchell from
19 the FDA and I am going to speak to you this morning
20 about the clinical review of the efficacy of
21 acamprosate.

22 [Slide.]

23 I want to let you know that we approached
24 this data hopefully. We knew before the
25 application came in that the American trial hadn't

1 worked out. But it isn't unusual for an
2 application to contain some trials that worked and
3 some trials that weren't able to show a difference
4 from placebo.

5 But this time, we had some older, perhaps
6 less rigorous, foreign studies that worked against
7 a recent domestic and really good study that
8 didn't. It was hard to overlook that.

9 We had some reservations about the conduct
10 of the European trials but we looked at them at
11 them a few different ways and we were able to find
12 encouraging results. Then both the statistical
13 reviewer, Dr. Wang, and I dug into the American
14 trial data. We really hoped there would be some
15 explanation for the outcome that would have some
16 face validity and could tell us something about
17 circumstances in which acamprosate works and
18 circumstances in which it doesn't and that would
19 give us confidence that we could accept the
20 European studies.

21 For about the next half hour, I am going
22 to take you through the process of looking at the
23 efficacy data and show you where it led us.

24 [Slide.]

25 The questions on this slide are the ones

1 you have been asked to consider this morning. You
2 have heard some comments from Lipha on the matter
3 and, before I begin, I will point out that there
4 are two ways of casting the questions.

5 It was suggested in the materials that we
6 reviewed that the reason the European trials were
7 able to demonstrate the effect of acamprosate and
8 the American trial wasn't is primarily that the
9 populations differed. The European subjects, as we
10 have heard, all randomized to treatment after
11 completing an inpatient detox. There were few
12 polysubstance abusers in the European studies and
13 the European studies either assumed or required a
14 high level of motivation for abstinence.

15 Lipha was able to identify a subset of the
16 American population they presented to us as being
17 most like the European subjects and they feel that
18 this group did demonstrate the effect of
19 acamprosate. So you could put the questions on the
20 slide this way. Given the positive findings
21 throughout Europe, how would we weigh the results
22 of the United States trial upon consideration of
23 our explanatory analyses based on population
24 differences?

25 But, on the other hand, I found a number

1 of the aspects of the European data presentation
2 that gave me pause during my review and I was
3 completely unable to find a way to explain the
4 results of the American trial.

5 As you saw in the materials provided in
6 the backgrounder, I defined a number of population
7 subsets that I thought could account for the
8 differences. For statistical reasons, I restricted
9 myself to use of prerandomization characteristics
10 and, no matter how I sliced it, there was no
11 treatment effect of acamprosate at the proposed
12 dose. It was not a matter of failure to reach
13 statistical significance due to small sample size.
14 There was really no difference and occasionally
15 there were differences that trended in the wrong
16 direction, in the direction of favoring placebo.

17 So I would be inclined to put the
18 questions this way. In view of the failure of the
19 carefully conducted American trial, which we are
20 unable to explain through analyses directed at
21 various subpopulations, can we accept the findings
22 of the European studies knowing the data was
23 collected less systematically.

24 [Slide.]

25 In the next few minutes, I am going to

1 take you through the review of the efficacy data
2 that was submitted to the FDA for review. The
3 emphasis in the material submitted to us for the
4 purpose of an integrated efficacy analysis was on
5 the cumulative abstinence duration. So I will
6 cover how we concluded that this outcome variable
7 identified for the European pivotal trials couldn't
8 really be viewed with confidence.

9 Then I will give you the good news about
10 what we were able to make out of those trials and
11 then I will walk you through the American trial
12 which wasn't able to show an effect of acamprosate
13 and our attempts to resolve the discrepancies
14 between these bodies of data.

15 [Slide.]

16 So, first, what is my problem with
17 cumulative abstinence duration. As I mentioned,
18 the primary outcome variable emphasized in the
19 integrated analyses in the European pivotal trials
20 was cumulative abstinence duration, which is
21 measured in days, or what was called corrected
22 cumulative abstinence duration which amounts to
23 percent days abstinent.

24 In your briefing book, you read that we
25 rejected this variable on review. I will remind

1 you that these studies were complete at the time
2 the IND was open. We never discussed the design
3 and analysis of these trials prospectively, so
4 there wasn't an opportunity to comment prior to the
5 NDA review.

6 Let me make the point that I have no
7 problem with these measures in theory. They are
8 attractive because they capture the picture of
9 drinking behavior even for those subjects who don't
10 abstain for the entire observation period which we
11 know is most of them.

12 The problem with the use of these measures
13 in analyzing the European studies is that they
14 amount to a false precision. These studies
15 collected the drinking data in a somewhat
16 nonsystematic way at widely spaced visits and used
17 various data-handling rules to convert the data so
18 collected into number of days of abstinence and
19 days of drinking.

20 On examining the protocols, the
21 case-report-form fields and the data-handling
22 rules, I concluded that the CAD in the three
23 pivotal European trials, actually in all the
24 European trials, the ten additional ones other than
25 the British study, seem to be a highly imputed

1 value that went beyond the precision of the data
2 actually collected.

3 I will walk you through the three pivotal
4 studies to show you what I mean.

5 [Slide.]

6 We have already heard about these studies.
7 The first study is Pelc II. This was a short-term
8 study with 90 days of treatment. This study had
9 seven on-treatment visits. These visits were close
10 together, one to two weeks. At each visit, the
11 investigator estimated the subject's average daily
12 consumption on drinking days and average frequency
13 of consumption. It wasn't a systematic approach to
14 this, like the time-line follow-back method.

15 The real problem, though, is in the
16 data-handling rules. Anyone who had any number
17 other than 0 listed for frequency and amount for
18 the purposes of the CAD calculation was considered
19 to have been drinking during the entire inter-visit
20 interval. So any number between one drinking day
21 and 15 drinking days was transformed to 15 drinking
22 days.

23 If a visit was missed, drinking days were
24 imputed all the way back to the previous visit. So
25 this method collapses a fairly wide range of

1 responses into two possibilities, 0 or 15. I find
2 this troubling because the result was then
3 mathematically summed, a mean was calculated to the
4 tenth place and comparisons were made
5 statistically.

6 [Slide.]

7 The Paille study, somewhat more
8 problematic, had a one-year treatment period but
9 only nine visits on treatment so the interval was
10 as much as 60 days between visits. At these
11 visits, the investigator again came up with an
12 estimate of the number of days of nonabstinence and
13 the drinks per drinking day without a systematic
14 technique for reconstructing the data.

15 But, unlike the Pelc study which used this
16 very conservative approach, the Paille study
17 handling rules took that estimate on its face and
18 put it into the calculations of CAD. I am just
19 skeptical about the precision.

20 [Slide.]

21 The PRAMA study had only six visits over
22 48 weeks of treatment. For half the visit, the
23 intervisit interval was three months. At these
24 visits, there was a global assessment by the
25 physician and then the physician was also supposed

1 to determine if a relapse occurred, classify it as
2 short-term or long term, try to figure out when it
3 happened, and then there were data-handling rules
4 for the calculation of CAD which are so complex
5 that I have put them on a separate slide which is
6 still too small to read.

7 [Slide.]

8 I know you can't read this but I am just
9 trying to make the point that there is such a
10 complicated set of mathematical rules here to
11 transform what is a rough estimate about what has
12 happened for the past three months into a specific
13 number of days of drinking versus abstinence. I
14 just felt that is a false precision that goes
15 beyond what was really known. That was the bad
16 news.

17 [Slide.]

18 But the good news was we looked at the
19 datasets and tried to see what we could conclude
20 based on the data collected. You have heard that a
21 considerable amount of effort went into
22 establishing abstinence versus nonabstinence.
23 There were blood-alcohol levels taken,
24 breathylizers. There were collateral informants.
25 There were other external informants. There was a

1 lot of effort here. So we could place some
2 credibility on that.

3 I considered how many people were assessed
4 by the investigator as continuously abstinent. I
5 realize that is a very high standard and doesn't
6 really capture all of the clinical effect that
7 would be considered relevant so I wanted a way
8 other than CAD to look at periods of abstinence
9 even if they were interrupted by periods of
10 drinking.

11 So I went through and I counted how many
12 people had zero visits at which they were assessed
13 as abstinent, how many had two, and so on, and
14 compared across treatment groups. Now, with an
15 intervisit interval of 90 days, binary assessment
16 of abstinence versus nonabstinence, maybe a little
17 suspect but we talked about all the effort that
18 they went to do this; right?

19 If the subject can convince the
20 investigator he hasn't had a drink in three months,
21 that probably does mean something.

22 [Slide.]

23 Here I have laid out the results of the
24 continuous abstinence analysis. This lists the
25 number of percent of subjects in each treatment arm

1 who were assessed as continuously abstinent
2 throughout the treatment period. In each of these
3 studies, acamprosate, at the dose proposed for
4 marketing, was superior to placebo and the
5 differences were statistically significant.

6 Here Pelc is clear. Here this one is kind
7 of marginal and it depends on what analysis you do.
8 Mine came out with a p-value of 0.042 for this
9 pairwise comparison. Then here I will just
10 clarify. This says 1998 per day. Actually these
11 patients were allocated by weight so that heavier
12 patients got 1998 per day and later patients got
13 1332 per day. But it turns out there were only
14 thirteen people who got 1332 a day. So, for
15 convenience, I am just calling it 1998 a day and
16 this is also statistically significant.

17 [Slide.]

18 I also wanted to look at the results that
19 included noncontinuous abstinence as clinically
20 relevant. So I tabulated for each study how many
21 subjects were assessed by the investigator as
22 abstinent at zero visits, one visit, two visits and
23 so on. I am going to show the tables for each
24 study one-by-one on the next few slides. I will
25 just tell you that the differences come out

1 statistically significant in favor of acamprosate
2 1998 milligrams per day in all the studies.

3 If you look very closely, it seems that,
4 for the most part, the superiority in this analysis
5 continues to be driven primarily by the subjects
6 who were continuously abstinent. But there is, in
7 some studies, a little greater tendency for the
8 placebo subjects to have very few abstinent visits.
9 In other studies, the subjects who have many but
10 not all abstinent visits strengthen the finding.

11 So this first slide shows you the results
12 from Pelc II. There were supposed to be nine
13 visits but, for some reason, there are no subjects
14 with nine abstinent visits. But these numbers
15 here, this 26, 26, 9, these are the same numbers
16 that come up for the continuously abstinent
17 analysis. I haven't been able to explain this. It
18 may have to do with handling of missing data.

19 In any case, you will see here that there
20 is a greater tendency for placebo subjects to have
21 zero, one or two abstinent visits as compared to
22 people assigned to active condition.

23 Of course here you will see this is
24 consistent with the continuous abstinent analysis.
25 There are just a lot more people assigned to active

1 who had eight visits compared to placebo.

2 [Slide.]

3 Here is the analysis for the Paille study.

4 There were nine visits, these 85 people here.

5 These are 85 people who were continuously

6 abstinent. They are shown as having nine visits

7 assessed as abstinent.

8 This study was the one that had the most

9 marginal results when you look at continuous

10 abstinence. But you can see that if you add in the

11 people who had eight abstinent visits, that

12 strengthens the finding because you end up with 44

13 in each of these groups which is 24 to 25 percent.

14 In the placebo group, you end up with 22,

15 which is only 12 percent. At the other end of the

16 spectrum, the least successful end, the difference

17 is less obvious. 54 percent of the placebo group

18 has two or fewer abstinent visits--I am adding

19 these together--compared to 47 percent of the

20 acamprosate low-dose group and 40 percent of the

21 acamprosate 1998 milligram group.

22 [Slide.]

23 Here is the data from PRAMA. There were

24 only six visits in this one-year study and, as Dr.

25 Wang will discuss, there were many dropouts and

1 dropouts occurred at different rates across
2 treatment groups. Missing visits couldn't be
3 assessed as abstinent visits. They were missing.
4 So this analysis is vulnerable to the dropout
5 problem. We understand that many fewer placebo
6 subjects actually attended six visits so,
7 obviously, they have many fewer opportunities to be
8 assessed as abstinent.

9 So we have to look at this analysis with
10 caution in view of that phenomenon. But here you
11 see that the superiority of acamprosate over
12 placebo at the most successful end of the spectrum
13 is clearly driven by the subjects with six
14 abstinent visits. There is no difference at four
15 or five.

16 But the difference between treatments is
17 also apparent at the other end of the success
18 spectrum. 63 subjects, or 46 percent in placebo
19 group, had zero or one visit at which they were
20 assessed as abstinent as compared to 39 which is
21 just 29 percent of the acamprosate group.

22 [Slide.]

23 So, in summary, it does look as if the
24 three European studies indicate an effect of
25 acamprosate in maintaining abstinence after

1 detoxification.

2 [Slide.]

3 Let's turn to the American study. As you
4 have already heard, this was a multicenter study
5 involving 601 subjects at 21 centers throughout the
6 United States, 260 subjects randomized to placebo,
7 258 on acamprosate 2000 milligrams a day and 83 to
8 the exploratory arm, acamprosate 3000 milligrams a
9 day.

10 We have discussed that the study used a
11 different formulation from the one in the European
12 trials. In those studies, there was a 333
13 milligram tablet. Subjects took two tablets three
14 times a day with meals. This study used a
15 compositionally proportional 500 milligram tablet.

16 The subjects actually took three tablets
17 QAM and QHS3. So everybody, including the 3 gram
18 exploratory arm, would have to take three tablets,
19 the 2 gram got two active and one placebo and the
20 placebo arm got three placebo.

21 We have already discussed the
22 pharmacokinetics and the TID dosing isn't essential
23 to maintaining steady state. So BID is not a
24 concern. And we have already touched on the food
25 effect. The effect of food is to lower systemic

1 exposure so, if anything, we think that the dosing
2 schedule in the American study would have exposed
3 the American subjects to a higher total daily dose
4 even though the nominal dose, 2 grams and 1998
5 milligrams, are essentially the same.

6 This was a carefully conducted and closely
7 monitored study. The features included six months
8 of treatment with eight on-treatment visits most of
9 which were at four-week intervals. Subjects
10 brought drinking diaries to each visit which were
11 used to help reconstruct day-by-day drinking data
12 using the time-line follow-back method.

13 Breath alcohol was measured at each visit
14 and collateral informant data was also collected at
15 intervals. This information was used to modify the
16 drinking data when it conflicted with the subject's
17 information and, in addition, as we have heard, the
18 subjects received a standardized brief psychosocial
19 therapy oriented to reinforcing medication
20 compliance.

21 [Slide.]

22 The primary outcome measure was the
23 percent of study days which were non-drinking days
24 referred to in the study report as corrected
25 cumulative abstinence duration. The number of

1 non-drinking days was calculated from the time-line
2 follow-back data as modified by other information
3 in the breath alcohol collateral informant and
4 there was an algorithm prespecified for assigning
5 values to missing days that occurred prior to
6 discontinuation or lost to follow up.

7 There was also a fairly rigorous protocol
8 for locating subjects to minimize the amount of
9 data that had to be imputed. My understanding is
10 that, in the calculation of a CCAD,
11 discontinuations were evaluated by a blinded panel
12 of raters and, if they were related to drinking,
13 all the days after discontinuation were considered
14 drinking days. But if a discontinuation was not
15 considered related to drinking, the denominator was
16 then adjusted so that the days after dropout were
17 not considered in this calculation of percent days
18 abstinent.

19 You might think that that is very
20 conservative and unfair to people who drop out
21 early as the result of drinking, so we actually
22 looked at people's baseline level of drinking to
23 see, if they got worse, maybe they would go back to
24 how bad they were before they came into the trial.

25 It does probably overestimate but over

1 half the subjects were drinking six or seven days a
2 week. About a quarter of them were drinking four
3 or fewer days a week. So it is an overestimate but
4 it is not horrendous.

5 [Slide.]

6 These are the results that I get from the
7 sponsor's datasets that were submitted to us for
8 review. Considering the entire intent-to-treat
9 population, the mean percent days abstinent for the
10 placebo group was 51 percent. The small group that
11 was randomized to 3 grams a day, about the same, at
12 50 percent. And the group that got the recommended
13 dose of acamprosate 2 grams a day had a mean
14 percent days abstinent of 46 percent.

15 Looking at the medians, placebo also
16 outperformed acamprosate. Why did this happen? If
17 acamprosate worked in the European studies why
18 didn't it seem to work here?

19 [Slide.]

20 Here were the simplest and most attractive
21 explanations presented to us from even before the
22 NDA was submitted. First, the European subjects
23 had been detoxed and were abstinent at baseline but
24 the American subjects were not required to undergo
25 detox probably as a consequence of the current

1 climate in our medical-care delivery system. Only
2 about 10 percent of them got it.

3 Furthermore, by the time the
4 study-medication treatment began, about half the
5 subjects were already actively drinking. So, the
6 first idea that springs to mind to all of you is
7 that acamprosate is just a relapse-prevention
8 agent. It keeps alcoholics from taking the first
9 drink but it can't seem to put the brakes on if
10 someone is actively drinking.

11 So, of course, I looked at the subset that
12 was abstinent at baseline which is about half the
13 subjects.

14 Now, the second difference was level of
15 motivation. Some of the European studies actually
16 required, as a condition of entry, that the subject
17 be committed to abstinence. Others didn't, but it
18 has been assumed the subjects must have been
19 motivated because they were willing to go through
20 detox.

21 Now, I am not sure about that because I
22 don't know about the healthcare delivery system in
23 Europe, either now or at the time these studies
24 were done over ten years ago. It is possible
25 inpatient detox was pretty standard and readily

1 available and that willingness to go into the
2 hospital for three days wasn't really a marker for
3 a high level of motivation.

4 But let's say it was. In the American
5 study, as you heard, subjects were asked to
6 indicate at screening what their goal was for
7 treatment and they could choose from a list that
8 ranged from total abstinence to no goal. You saw
9 that it included temporary abstinence, controlled
10 drinking. You also saw there was another option on
11 there; total abstinence, but I realize a slip is
12 possible.

13 This wasn't, "I think a slip is okay," or,
14 "My therapist has told me, you will probably slip."
15 That's okay. Let's talk about what we are going to
16 do about it. This was just, my goal is total
17 abstinence but I realize a slip is possible. It
18 was multiple choice.

19 I regard that as just as motivated but a
20 little more realistic. And I put those two
21 together. That is actually 72 percent of the
22 subjects and evenly distributed once you add them
23 together, evenly distributed across treatment arms.

24 Finally, the high rate of polysubstance
25 abuse in the American trial was striking,

1 especially given that a positive urine tox for
2 anything other than marijuana was exclusionary.
3 Now, only PRAMA of the European studies gave us
4 information about other substance-abuse history
5 and, in that study, on 20 percent of the subjects
6 had any history of other substance abuse.

7 In contrast, the United States population,
8 only 20 percent did not have a history of illicit
9 drug use.

10 [Slide.]

11 As you have heard, Lipha was able to find
12 a subset they thought resembled the European
13 population. It was defined by some
14 post-randomization variables, post-randomization
15 compliance with visits and medication. In
16 addition, a treatment goal of complete abstinence.

17 In this group, the acamprosate arm had 70
18 percent days abstinent and the placebo group had 63
19 percent. But the problem here is that it appears
20 to be that this is the only population that
21 demonstrates an effect of acamprosate. It is
22 defined primarily by post-randomization behavior
23 such as medication compliance and observed use of
24 substances. All post hoc analyses make us
25 uncomfortable because if you do enough of them, you

1 are bound to find one that comes out significant
2 which actually makes it particularly troubling that
3 we couldn't.

4 But subset analyses, whether post hoc or
5 planned, that rely on groups defined by
6 post-randomization factors are particularly
7 troubling. Finding that a drug was particularly
8 effective in a group with a certain set of
9 post-randomization behaviors really doesn't give us
10 any information that we can use for patient
11 selection.

12 What's more, this population definition
13 doesn't even take into account the issue of
14 abstinence at baseline which the proposed label
15 indication now indicates is the important feature
16 of patient selection. So I am not convinced by
17 this finding. I am not convinced by this
18 population definition.

19 As you read, I conducted a series of
20 subset analyses of my own using populations that
21 seemed to make sense to me.

22 [Slide.]

23 I am going to go over for you my analysis
24 populations and how I hit upon them. I analyzed a
25 subset of subjects that were abstinent for at least

1 five days at baseline. That is fairly
2 straightforward. The subset that identified a goal
3 of abstinence, whether or not they indicated that
4 they realized a slip was possible. And I tried to
5 figure out the best way to define the
6 nonpolysubstance-abusing population. So let me
7 take you through some of the things I considered.

8 First, there was something called an
9 illicit drug use index calculated for each subject.
10 If they had no history whatsoever of illicit drug
11 use, that was zero. So I looked at that group, but
12 it was very, very small. It was 20 percent of the
13 randomized population.

14 So then I thought, well, maybe past-year
15 drug use was probably a reasonable indicator of
16 current active polysubstance abuse. So I looked at
17 the group with no illicit drugs in the past year
18 which enlarged the subset to about 40 percent of
19 the randomized population.

20 But, because subjects were allowed to
21 enter the study if they had a tox screen positive
22 for marijuana, if I looked at the group that had no
23 past-year drug use other than marijuana, I actually
24 got as many as 80 percent of the randomized
25 population. Now, I will acknowledge that that is

1 our fault. We asked Liphia to broaden the inclusion
2 criteria to allow for a positive tox for marijuana
3 at entry because we are concerned that the actual
4 target population has a pretty high prevalence of
5 polysubstance abuse and it seems like we were
6 right.

7 Even though people were screened out, if
8 they had current dependence on any other substance
9 and screened out if they had a positive urine tox
10 at screening for anything other than marijuana, the
11 enrolled population still has a 14 percent history
12 of opiate use and 49 percent history of cocaine
13 use. This is what American alcoholics look like.

14 I also looked at the group defined by the
15 results of urine toxes during the study. But I am
16 actually not at all convinced that this is useful.
17 With monthly study visits, tox screens are unlikely
18 to pick up all the illicit drug use in the study
19 and also nothing can be predicted about the results
20 of urine-tox screens that weren't done because the
21 subject dropped out of the study.

22 So if you select subjects who just don't
23 have urine-tox evidence of drug use, it doesn't
24 mean you have a population that didn't use drugs.
25 It also especially means you don't have a

1 population that is prone to use drugs after they
2 drop out. Also, there were only urine-tox data for
3 525 subjects, so I didn't use this.

4 Ultimately, I decided to focus on the
5 subjects whose only illicit drug use in the past
6 year had been marijuana. So, from now on when I
7 say no past-year illicit drug use, what I am
8 talking about is actually the subjects who had no
9 past-year illicit drug use other than marijuana.

10 Then I put together the subset that was
11 abstinent at baseline, motivated and had no
12 past-year illicit drug use, a very small group,
13 only 20 percent of the randomized population.

14 [Slide.]

15 These are my results. This is using the
16 sponsor's corrected cumulative abstinence duration
17 in the dataset. Here is motivated. I don't have a
18 slide for this but I did look. I looked at
19 motivated, total abstinence versus total
20 abstinence, but I believe a slip is possible. And
21 they are exactly the same. They are the same.

22 Here is abstinence. Here is the no
23 history whatsoever of drug use. These are very
24 small numbers. No illicit drugs and here is not
25 illicit drugs other than marijuana. This is the

1 last time you are going to see these guys. You
2 will see that these are all actually going the
3 wrong way.

4 I have to say that, going into this, I was
5 really hoping that the rubber was going to meet the
6 road somewhere. I was going to be able to say,
7 ah-ha, it only works in pure alcoholics, or, see,
8 as long as you are abstinent at baseline, it works.
9 But these analyses just don't bear out any
10 conclusion about patient selection that suggests
11 why acamprosate didn't work in this study.

12 [Slide.]

13 Looking at the subset that was abstinent
14 and motivated and the subset that was abstinent,
15 motivated and had no past-year illicit drug use, I
16 still could not find an effect of acamprosate.

17 [Slide.]

18 I looked at other measures, too. Complete
19 abstinence wasn't very useful because there were so
20 few subjects, 33 to be exact, who were abstinent
21 for the entire trial and 20 of them were on
22 placebo.

23 There was a categorical analysis of good
24 response which looked at how many subjects had 90
25 percent days abstinent or more. This was

1 interesting because the motivation ITT population
2 defined by the sponsor did show the acamprosate
3 group tied with the placebo group and then the
4 sponsor defined motivated efficacy evaluable
5 population showed acamprosate beating placebo, but,
6 as it turned out, my analysis populations do not
7 fare as well and the placebo group did better than
8 the acamprosate group in all the populations that I
9 tried.

10 [Slide.]

11 So next I looked at fairly liberal
12 definition of success. There was a dataset in
13 which relapse was flagged if the patient relapsed
14 into having at least five drinks a day for five of
15 the next seven days.

16 So we looked at how many subjects never
17 had a relapse as so defined. Obviously, success by
18 this criterion is fairly common. In this slide,
19 you will see the ITT population looks a little bit
20 promising but neither the abstinent subset, the
21 motivated subject, the no-past-year-illicit drugs
22 or the group that met all three criteria show an
23 effect of acamprosate on this measure. But the
24 sponsor motivated efficacy evaluable does.

25 [Slide.]

1 Just in case I missed something, I pored
2 over the demographics from the different trials to
3 find another explanation. I was so enthusiastic
4 about this that I misinterpreted this data and I
5 confused the number of drinks per drinking day with
6 the average number of drinks per week and I was
7 under the misimpression that there were more heavy
8 drinkers in the European data.

9 But, just in case you were wondering, this
10 analysis doesn't work either.

11 [Slide.]

12 In summary, the European studies indicate
13 an effect of acamprosate on either a continuous
14 abstinence or noncontinuous abstinence while the
15 American study does not demonstrate the efficacy of
16 acamprosate in any subset defined by
17 prerandomization variables that would be useful for
18 patient selection.

19 [Slide.]

20 So I will put the questions back up here.
21 I have gone through some of the concerns about the
22 data from the European trials; relatively
23 nonsystematic data collection, low frequency of
24 study visits and then some of the ways in which the
25 European-trial populations differed from the

1 American population.

2 Then I went through the exploratory
3 analyses I undertook to try to select the subgroup
4 from the American study who resembled the European
5 population on important measures such as level of
6 motivation, baseline drinking status and
7 polysubstance abuse and I showed you that I was not
8 able to identify any population that demonstrated
9 the effect of acamprosate on measures including
10 percent days abstinent, categorical good response,
11 or even the fairly low bar of surviving the trial
12 without five heavy drinking days in a single week.

13 So I will reiterate my way of looking at
14 the questions we have posed to you. In view of the
15 failure of the carefully conducted American trial
16 which we were unable to explain through analyses
17 directed at various subpopulations, can we accept
18 the findings from the European studies knowing that
19 the data was collected less systematically?

20 I am going to turn the microphone over to
21 Dr. Sue Jane Wang for the statistical presentation.

22 Statistical Perspective of Acamprosate Experience

23 DR. WANG: Good morning, everyone. I am
24 Sue Jane Wang from Statistical Discipline of FDA.

25 [Slide.]

1 In this presentation, I would focus on the
2 statistical perspective of my acamprosate review
3 experience. [Slide.]

4 Here is the outline of today's
5 presentation. First, I will discuss the dropout
6 issue in the three European trials followed by
7 proper interpretation of the efficacy results. I
8 will spend most of the time on the U.S. trial
9 because the drinking data was much more credible in
10 this well-controlled study but knowing that the
11 differential dropout problem still exists in the
12 U.S. trial making it very difficult to interpret.

13 Finally, I would bring to your attention
14 on the conflicting analytical issues we faced
15 during review in the U.S. trial and the European
16 trials.

17 [Slide.]

18 Since you have heard several
19 presentations, I will just use the following
20 notations for the four dose arms that consist of
21 these four different studies: first, the placebo
22 arm; acamprosate, low dose, only studied in the
23 European; acamprosate, medium dose studied in both
24 different places; and the high dose, 3 grams per
25 day.

1 [Slide.]

2 The Pelc trial was a multicenter
3 double-blind, randomized, placebo-controlled
4 three-arm study. The objective of this study was
5 to explore the effectiveness and tolerance of
6 acamprosate in helping to maintain abstinence in
7 the weaned alcoholic patient population. Although
8 the main criteria of judgment was the consumption
9 of alcohol, the drinking data was based on
10 respective collections from clinicians. The Pelc
11 II study was the shortest, about three months study
12 duration.

13 [Slide.]

14 The number of patients in this study was
15 about 60 for each treatment arm. Among this
16 percent of patients who discontinued study early
17 was the highest with placebo, 48 percent, and lower
18 but similar for the low-dose and medium-dose
19 acamprosate, about 30 percent. Time to
20 discontinuation from the study was similar among
21 the three groups.

22 To analyze the percent of patients with no
23 relapse, two analysis results are presented. Let
24 me explain the two analyses first. For the dropout
25 of this analysis, patients who did not complete the

1 study and did not relapse will be considered as a
2 good outcome or a success. So the numerator is the
3 number of patients who did not relapse but who may
4 or may not complete the study.

5 This is the traditional
6 last-value-carried-forward analysis. Often, the
7 additional trial considers dropout patients as a
8 bad outcome. However, in light of very different
9 dropout patterns between the U.S. and the European
10 trials, we think it is important to show these
11 analysis results.

12 The other one, see the row of as relapsed.
13 Only patients who completed the study and did not
14 relapse is considered as a good outcome. Although
15 a patient may discontinue the study and did not
16 have any relapse at the time of discontinuation,
17 but in this analysis they would be considered as
18 relapsed.

19 As shown in this table,
20 acamprosate-treated patients had more than twice on
21 the percent of no relapse as compared to placebo
22 using either the dropout-as-is analysis or the
23 as-relapsed analysis. In addition, the finding of
24 the time to first relapse was consistent with the
25 percent of no-relapse rates. All showed convincing

1 evidence of acamprosate effect.

2 [Slide.]

3 The Paille was a multicenter double-blind,
4 randomized, placebo-controlled study with three
5 arms. Although the low dose and medium dose were
6 included in this trial, the main objective was
7 really to study the low dose not the medium dose in
8 the alcohol patients who were followed as
9 outpatients after withdrawal.

10 In this 360-day trial, patient size was
11 about 180 per arm. Similar to the Pelc II trial,
12 significantly more dropouts occurred in the
13 placebo-treated patients compared to the two
14 acamprosate groups, 65 percent versus 55 and 48
15 percent. But the treatment exposure time was the
16 shortest with the placebo, about eight months,
17 followed by the low-dose acamprosate of 10.5 months
18 and the high dose, 11.8 months.

19 When the LVCF type analysis was
20 performed--that is, the dropout-as-is
21 analysis--there was no statistically significant
22 percent of complete abstinence between acamprosate
23 and placebo although a numerical trend was
24 observed, 23 percent in placebo, 27 in acamprosate
25 low dose and 20 percent in the high dose. The

1 p-value was 0.285, not significant.

2 In contrast, when the as-relapsed analysis
3 was performed, twice higher in the percent of
4 complete abstinence was observed with acamprosate
5 as compared to placebo with a nominal p-value of
6 0.044. Interestingly, the sponsor reported that
7 the percent of complete abstinence using 340 days
8 as the cutoff instead of 360 days of the trial
9 period possibly related to the visit window in
10 counting the number of days.

11 [Slide.]

12 In this analysis, as you can imagine, it
13 lies between the dropout-as-is analysis and the
14 as-relapsed analysis giving a nominal p-value
15 somewhere in between, in this case, 0.096, not
16 significant.

17 A closer look using the time to first
18 relapse outcome showed that the time to first
19 relapse was twice longer with the medium dose but
20 not the low dose when compared to placebo, two
21 months versus one month. It is noted again that
22 the trial objectively planned to study the low dose
23 but not the medium dose. Thus the low-dose effect
24 cannot be conclusively shown and the medium-dose
25 effect observed was exploratory but was consistent

1 with the Pelc II trial.

2 [Slide.]

3 This is the third study for the European
4 trials. The PRAMA trial was a 48-week multicenter
5 double-blind randomized placebo-controlled two-arm
6 study studying acamprosate versus placebo. The
7 objective here again is to help maintain abstinence
8 after detoxification in the alcoholic patient
9 population.

10 [Slide.]

11 I would like to point out here that the
12 primary efficacy outcome for this study was
13 prespecified and that was time to first relapse.
14 Here, the relapse included short-term relapse,
15 long-term relapse and continuous relapse.

16 [Slide.]

17 In this 48-week trial comparing
18 acamprosate versus placebo, there were 136 patients
19 per group. Again, significantly higher dropout
20 rates were observed in placebo, 60 percent, versus
21 42 percent in acamprosate and had about half the
22 time on trial. It appeared that more placebo
23 patients dropped out because of patient refusal.

24 The percent of abstinence was higher in
25 acamprosate, 51 percent, versus 40 percent in

1 placebo when using the dropout-as-is approach. The
2 rates were significantly smaller using the
3 as-relapsed approach as this is more conservative,
4 29 percent in acamprosate and 12 percent in
5 placebo. Note that, in this study, the primary
6 efficacy endpoint prespecified was the time to
7 first relapse. Using the sensory indicator based on
8 either dropout-as-is or as-relapsed, the results,
9 based on time to first relapse clearly showed a
10 significant acamprosate effect.

11 [Slide.]

12 In summary, the three European trials had
13 the drinking data retrospectively collected and the
14 dropout rates were higher in placebo than in drug.
15 The effect of the medium dose was shown in percent
16 complete abstinence in Pelc II, in PRAMA,
17 confirmatory. In Paille, though, exploratory.

18 By the way, the medium dose is the
19 sponsor's proposed to-be-marketed dose. The effect
20 of the low-dose acamprosate was not shown in the
21 Paille trial. I would like to point out that these
22 trials were planned and conducted in the late '80s
23 and early '90s, about a decade ago.

24 [Slide.]

25 Now I would like to turn to the U.S.

1 trial. Subjects who were alcohol-dependent or who
2 had been withdrawn from alcohol or who had
3 completed medicated detoxification within two to
4 ten days of study entry were studied. This was a
5 multicenter, double-blind, randomized,
6 placebo-controlled study.

7 I would like to point out that the
8 randomized allocations of patients to the three
9 treatment arms were well balanced. The alcohol
10 measurements were rigorously collected according to
11 alcohol time-line follow-back schedule.

12 [Slide.]

13 For the U.S. trial, the primary objective
14 was to confirm the safety and efficacy of this
15 medium-dose acamprosate. The secondary objective
16 was to explore the efficacy and safety of the high
17 dose. The exploration was only planned for
18 one-third of the patients; that is, 83 patients
19 compared to 260 patients of the other two treatment
20 groups.

21 The treatment phase was 24 weeks or six
22 months and was conducted much more recently,
23 between '97 and '99.

24 [Slide.]

25 There was an apparent difference in the

1 percent of patients who dropped out of the study
2 early. Noticeably, the medium dose, or, say, the
3 to-be-marketed dose proposed by the sponsor,
4 appeared to have about 60 percent of patients who
5 discontinued study early but less so in the other
6 two arms, 45 percent placebo, 48 percent in the
7 high dose. The difference was primarily that the
8 medium-dose acamprosate group had more patients
9 dropped out due to patient decision, due to
10 patients lost to follow up.

11 There was also a difference in the time to
12 treatment discontinuation, about one month shorter
13 in the medium-dose acamprosate compared to the
14 other two arms.

15 [Slide.]

16 Here are the protocols specified by
17 primary efficacy outcomes that you are now familiar
18 with.

19 [Slide.]

20 Here are the results of the five primary
21 efficacy endpoints extracted from the sponsor's NDA
22 report and confirmed by us. For the comparison
23 between the medium-dose acamprosate and the
24 placebo--that is, the main objective--the percent
25 of patients who relapsed to drinking were similar,

1 92 percent with medium-dose acamprosate and 89
2 percent with placebo.

3 The median time to first drink was four
4 days in both groups and the median time to first
5 heavy drinking days was only a two-day difference.
6 For these three outcomes, the p-value were between
7 0.85 to 0.9 as for the cumulative abstinence
8 duration outcome, or the percent of cumulative
9 abstinence duration.

10 I would like to make a point of this
11 notation here that the sponsor used because I will
12 be referring to that later. CAD, cumulative
13 abstinence duration, in days; CCAD, percent of days
14 abstinence--in other words, alcohol free. As you
15 can see from this table, it appeared that the
16 medium dose had borderline evidence of fewer days
17 of acamprosate, of complete abstinence based on
18 either the mean days or the median days.

19 Using the median as an example, you have
20 56 days for the medium dose compared to 78 days for
21 placebo having cumulative abstinence duration.
22 Similarly, for the percent of that, 38, much lower
23 compared to placebo. I will refer to these numbers
24 later.

25 Taken together, the total evidence based

1 on the five efficacy endpoints, there was no
2 evidence of medium-dose acamprosate effect on any
3 of the endpoints nominally although the high-dose
4 acamprosate appeared to perform better numerically
5 in the time to first heavy-drinking days.

6 [Slide.]

7 Thus, based on the prespecified primary
8 efficacy outcome, the result indicated that there
9 was no statistical evidence of this medium-dose
10 acamprosate. There were exploratory or supportive
11 analyses prespecified in the protocol. We
12 performed these analyses and could not find an
13 acamprosate medium dose effect.

14 [Slide.]

15 Right before the NDA, new drug
16 application, submission, the sponsor met with the
17 agency and acknowledged that the medium-dose
18 acamprosate failed to show a statistically
19 significant effect and submitted a new statistical
20 analysis plan. The highlight of this new plan
21 included the definition of the CAD was modified
22 post hoc. The algorithm of imputation on the
23 dropout patients was changed and the newly
24 considered outcome was percent abstinence duration.

25 Interestingly, the endpoint actually used

1 in the NDA submission was percent abstinence
2 duration but adjusted for treatment discontinuation
3 which appeared to be shorter in this medium-dose
4 acamprosate; that is, the variable, ALCCAD. This
5 endpoint was not included in the revised
6 statistical analysis plan although it was presented
7 at the pre-NDA meeting with the agency.

8 [Slide.]

9 What you have seen presented by the
10 sponsor is based on this Model No. 1. It contains
11 the seven covariates that Dr. Mason had explained.
12 I would like to just point you to the one
13 particular problematic variable, treatment
14 exposure. This model was discussed at the phase II
15 pre-NDA meeting but this model was not part of the
16 revised statistical analysis plan submitted at that
17 time.

18 [Slide.]

19 The sponsor was asked to also analyze the
20 data without that treatment exposure for Model No.
21 1, we just saw. The sponsor labeled it as Model
22 No. 2. Let's call it the six-covariate model.

23 Here, the treatment exposure was
24 calculated by multiplying the treatment compliance
25 and the treatment duration and then normalizing

1 into percent. It is worthwhile to note that the
2 treatment exposure so defined is potentially
3 treatment-related because that medium dose had a
4 higher percent of dropout rate and a shorter time
5 to discontinuation compared to the other two
6 groups.

7 In addition, such defined treatment
8 exposure variable is different from the baseline
9 variable and is not affected by the treatment
10 administration and the treatment outcome. But the
11 treatment exposure defined here would heavily
12 depend on when the treatment administration is
13 ended and whether patients comply with the
14 treatment assigned and why patients discontinue the
15 study.

16 [Slide.]

17 The CCAD outcome was the endpoint
18 discussed at the pre-NDA meeting. It was
19 prespecified but post defined. Of the two models
20 presented here, Model No. 1 and Model No. 2, using
21 the CCAD modified outcome, there were no
22 statistically significant findings of medium-dose
23 acamprosate.

24 Even if you don't do any adjustment, you
25 don't find anything either. Let us see how these

1 results can be drastically changed using the
2 post-hoc-defined primary-efficacy endpoint, ALCCAD.
3 Again, percent abstinence duration but adjusted for
4 treatment discontinuation.

5 [Slide.]

6 Here are the results using the
7 post-hoc-defined statistical model, the No. 1 and
8 No. 2 row, versus this model without further
9 covariate adjustment, the other four rows. Let's
10 look at the row labeled as mean No. 1 which was
11 based on seven covariates including the treatment
12 exposure, the problematic variable.

13 A nominal borderline statistical
14 significance was observed for the medium-dose
15 acamprosate compared to placebo, a p-value of
16 0.044. But when excluding that treatment exposure,
17 which is Model No. 2, such an acamprosate effect
18 disappeared, a p-value of 0.296. In contrast,
19 without this covariate adjustment, the unadjusted
20 mean showed a numerical trend of increased percent
21 abstinence duration from placebo to medium dose to
22 high dose, the third row here.

23 That is an adjusted mean. You can also
24 see on an adjusted median, the percent is
25 essentially the same between the medium dose and

1 the placebo of 59 percent.

2 I would like to bring to your attention
3 and clarify what the sponsor called an adjusted
4 mean or an adjusted median really is. As I just
5 mentioned, both the mean and the median was
6 adjusted for treatment discontinuation. In other
7 words, it rests strongly on treatment
8 discontinuation. Particularly, it was differential
9 among the three arms.

10 The truly unadjusted outcome was the CCAD,
11 the last two rows. As you can see, both the raw
12 mean and the raw median for acamprosate medium dose
13 was worse compared to placebo.

14 Let's put the high-dose acamprosate.
15 There was a numerically higher percent of
16 abstinence duration after adjustment for treatment
17 discontinuation. The high-dose effect appeared to
18 be shown nominally with the six covariate model and
19 was evident using the seven covariate model. These
20 better results did not hold up when we use the CCAD
21 outcome for the modeling.

22 [Slide.]

23 The sponsor considered four patient
24 populations to demonstrate the post hoc model. So
25 chosen, they were very consistent across the

1 patient population defined. As you have heard,
2 these are the four different patient populations;
3 the ITT, evaluable, multivariate ITT and
4 multivariate evaluable.

5 By showing this table, the nominal p-value
6 based on the seven covariate No. 1, all showed
7 statistical significance ranging from 0.044
8 borderline evidence to 0.008 significant evidence.
9 However, such evidence could not be supported when
10 the six covariate model No. 2 was applied to all
11 the four patient populations. None of them showed
12 statistical significance.

13 If a post hoc model is to be chosen
14 between Model No. 1 and Model No. 2, a less biased
15 analysis or a more persuasive analysis will
16 consider Model No. 2 without the treatment-exposure
17 variable. In addition, if these covariates are
18 really prognostic, including a fewer number of
19 covariates should still demonstrate some kind of
20 acamprosate medium-dose effect and should be
21 consistently reported in the literature cited by
22 the sponsor. But it did not.

23 [Slide.]

24 One might wonder what was the rationale
25 for the Model No. 1 chosen by the sponsor which was

1 not provided a priori. As previously shown, it was
2 the model with seven covariates that demonstrated
3 an acamprosate medium-dose effect but not the other
4 which excluded treatment exposure.

5 [Slide.]

6 This, of course, makes our job tougher.
7 We performed a few exploratory analyses. The idea
8 here was to understand how robust the results were
9 based on Model No. 1 chosen by the sponsor in the
10 NDA submission but not in the original protocol
11 analysis plan.

12 The exploration went on to include models
13 that always have the center in there or having one
14 variable at a time, or some combination of those.
15 This consisted of more than 30 models that we
16 tried. Other than the one model that the sponsor
17 identified, we found that there was no
18 statistically significant acamprosate medium-dose
19 effect from these various reasonable explorations
20 but there was one that works, which is the one that
21 included the abstinence goal and the
22 treatment-exposure variable together but not
23 individually.

24 [Slide.]

25 I would like to show you that, of the

1 seven covariates chosen by the sponsor, two of them
2 indicated potential imbalance between the three
3 treatment arms, namely treatment exposure and
4 abstinence goal.

5 As shown in this table, median exposure
6 was shorter in acamprosate medium-dose group
7 compared to the other two. This was consistent
8 with the shorter time to treatment discontinuation,
9 15 versus 20 or 21. In addition, there was a trend
10 in patient's baseline abstinence goal for the
11 treatments received as mentioned by the sponsor.

12 It appeared that numerically,
13 placebo-treated patients was more desirable to be
14 complete abstinence than acamprosate-treated
15 patients, 45, 40, 32. In contrast, if one
16 considered a more realistic goal of a slip is
17 possible versus others, the reverse numerical trend
18 was observed, 28, 31 to 39. It is the reverse
19 trend of the complete abstinence goal.

20 As pointed out by Dr. Winchell, when one
21 does not distinguish between complete abstinence
22 goal and the goal of allowed a slip is possible,
23 then there was essentially no imbalance among the
24 three treatment arms, as you can see, 73 percent,
25 71 percent.

1 [Slide.]

2 Here is a different way to look at the
3 data. In the following two figures, I will be
4 using green color to represent the medium dose,
5 darker blue for placebo and coral color for high
6 dose. For heavy drinking days, when the data was
7 summarized at each visit alone on the observed
8 data, as shown in this figure, it appeared that
9 acamprosate medium-dose group, the green color on
10 the top, showed a consistently larger number of
11 mean heavy-drinking days as compared to placebo.

12 Although the high dose had only one-third
13 of the patient size compared to the other two, an
14 apparent fewer number of heavy drinking days across
15 all the visits appeared to be evident and the
16 separation of the curve was consistent from Week 8
17 to Week 24, the end of the trial.

18 [Slide.]

19 In contrast, the distribution of any
20 drinking days at each visit was comparable among
21 the three treatment arms.

22 [Slide.]

23 From these various results shown, can we
24 conclude that the medium-dose acamprosate is
25 effective? First of all, the U.S. trial was

1 sufficiently powered to study the efficacy of this
2 dose but, clearly, there was no evidence of
3 medium-dose acamprosate when only one covariate was
4 accounted for. Even suppose that one covariate is
5 the potential outcome-related treatment exposure
6 alone. It didn't reach any statistical
7 significance.

8 To appropriately account for the
9 covariates, that should be unrelated to treatment
10 or outcome; that is, when that treatment-exposure
11 covariate is excluded from the model, we have shown
12 from a few example models, out of a total possible
13 128 models, the medium-dose acamprosate effect was
14 not found.

15 In addition, a numerically higher number
16 of heavy-drinking days relative to placebo at each
17 visit was observed.

18 [Slide.]

19 In fact, the 10 percent medium-dose effect
20 was highly dependent on post hoc selection of
21 covariates that were included in the model; for
22 example, a model including just two covariates, the
23 abstinence goal and the treatment exposure, or that
24 one model having all the seven covariates
25 coexisting in that model.

1 We have pointed out the problem with
2 models including the treatment-exposure covariate
3 because it could not be obtained until after
4 randomization of treatment assignment, after
5 treatment compliance and after treatment
6 discontinuation. An even more serious concern in
7 this exercise is the potential multiplicity
8 problem. In other words, could it be that the
9 sponsor performed analysis using only this
10 post-hoc-defined seven covariates or using many
11 more models to pick up this specific Model No. 1;
12 namely, what is the chance that one is going to
13 find a statistical significance after analyzing the
14 data using so many different models.

15 We all know that if one tests the same
16 parameter 100 times, five times are going to show
17 statistical significance simply based on chance
18 alone. Here, we found two out of 128.

19 [Slide.]

20 In this U.S. trial, the study was not
21 sufficiently powered to study this high-dose
22 effect. Rather, this dose was included to explore
23 the efficacy and safety. In a previous slide
24 showing mean heavy-drinking days, you have noticed
25 a numerically superior effect of acamprosate high

1 dose relative to placebo was seen at the later
2 visit of the treatment period and was consistent
3 throughout the end of the trial.

4 In addition, this high-dose effect
5 appeared to be seen if the adjustments always
6 included the abstinence goal but not otherwise. If
7 a model was performed using ALCCAD but not the
8 CCAD, we could not tell whether such finding was
9 real or by chance alone since the sample size was
10 only one-third of those powered for studying an
11 acamprosate effect.

12 [Slide.]

13 Here I would like to summarize the U.S.
14 experience. The medium-dose acamprosate appeared
15 to have worse dropout characteristics. The effect
16 of this medium dose was not shown based on the
17 protocol-specified primary efficacy outcome
18 although post-hoc-defined primary efficacy endpoint
19 of CCAD.

20 For the acamprosate medium dose, the
21 sponsor's post hoc chosen Model No. 1 or, for that
22 matter, Model No. 2, can be problematic as
23 statistical significance must rely on which
24 particular post hoc baseline defined covariates
25 and/or post randomization defined variables were

1 included in the model. The finding was very
2 fragile because the carefully chosen model showing
3 statistical significance could not hold its
4 significance after multiplicity adjustments.

5 [Slide.]

6 As for the high-dose acamprosate, the
7 exploratory analysis is suggested in the effect in
8 the time to first heavy drinking days and in the
9 mean heavy drinking days at each study visit over
10 the treatment period. Such heavy drinking days do
11 not adjust for treatment discontinuation like
12 ALCCAD.

13 It is emphasized, however, that the
14 finding in the high-dose acamprosate is simply
15 hypothesis generation as it didn't have sufficient
16 sample size for the study and had lack of safety
17 information for the dose level. The small sample
18 size prevented us from better understanding this
19 high-dose acamprosate treatment effect.

20 [Slide.]

21 So what is the difference between the
22 European and U.S. trials in terms of efficacy
23 outcomes? Why are we getting conflicting evidence
24 given randomizations were properly done. From the
25 statistical perspective, the biggest problem, in my

1 view, is the issue of differential dropout from the
2 study in terms of the time to discontinuation, in
3 terms of percent of dropouts and also in terms of
4 the distribution of reasons of dropouts.

5 We immediately face the problem of
6 differential dropouts in the opposite direction.
7 In other words, what have we found on the proposed
8 to-be-marketed acamprosate 2-grams-per-day effect?
9 We saw in the European trials, patient treatment
10 with acamprosate tended to stay in the trial longer
11 and less dropouts, but it was reversed in the U.S.
12 trial.

13 The sponsor had defined how they would
14 handle the missing data or data needed for the
15 dropout patients a priori but realized that it
16 didn't work and modified the definition after the
17 data had been collected when meeting with the
18 agency at the pre-NDA meeting and then modified
19 this outcome again as ALCCAD further by adjusting
20 for patient discontinuation.

21 Further data dredging was to include
22 treatment compliance and treatment duration to
23 create a variable called treatment exposure. That
24 can only be collected after the treatment
25 randomization. We believe that it is important and

1 there is a need to have a well-thought prespecified
2 algorithm for handling dropout patterns rather than
3 post hoc defined and redefined.

4 This concludes my review experience.

5 Thank you.

6 Questions from the Committee

7 DR. OREN: It is now time for the
8 committee to ask questions of the FDA regarding the
9 previous two presentations. Does anybody wish to
10 begin?

11 Dr. Rudorfer?

12 DR. RUDORFER: A question for Dr.
13 Winchell. We heard that about 10 percent of the
14 U.S. patient sample had undergone medical detox
15 before enrollment. Did you look at that subgroup
16 specifically?

17 DR. WINCHELL: I didn't because there were
18 so few of them. But I think that that was one of
19 Lipha's prespecified analyses so they may be able
20 to address that.

21 DR. GOODMAN: The statisticians can
22 correct me if I'm wrong, but I don't believe that
23 we had a prespecified plan for looking at the detox
24 patients. What we plan to do, patients were
25 stratified according to whether or not they had

1 undergone detox before they were randomized. But,
2 again, this was a surprising finding to us. We
3 expected that at least a third of the patients, if
4 not more, would undergo detox but, in fact, it was
5 only, as you saw, about 10 percent of patients.

6 DR. OREN: Dr. Hughes.

7 DR. HUGHES: Does anybody know, of all the
8 patients who come in for alcohol treatment, how
9 many of them are already abstinent at the time they
10 come in? Is there any kind of health-resources
11 database on that? Celia, do you know of any or do
12 the Lipha people know? Is that 90 percent of the
13 patients or 20 percent?

14 DR. WINCHELL: The best data I have ever
15 seen on that question was from Dr. Mason who
16 presented some very interesting data, I think from
17 this study, showing that people are really bad off
18 until they make the call to enter treatment and
19 then, between making the call and actually entering
20 treatment, they seem to do a little better.

21 But I think we have got lots of experts
22 here from NIAAA and Dr. Mason who may know
23 something about that.

24 DR. OREN: Dr. O'Brien?

25 DR. O'BRIEN: I think Dr. Winchell alluded

1 to the fact about the current American healthcare
2 system. In fact, it has really changed. We began
3 studying discontinuation in the 1970s and, at that
4 time, there were a lot of inpatient alcohol
5 detoxification programs and we actually did random
6 assignment between inpatient and outpatient in a
7 randomized clinical trial.

8 Nowadays, it is very difficult for us to
9 study this because it is so expensive. We have to
10 get an NIH grant to pay for the inpatient days
11 because there aren't any available through any
12 other system. So I think that things have really
13 changed and the modal method now is for alcoholics,
14 in the United States, at least, to come to us with
15 blood-alcohol levels fairly significant, sometimes
16 incredibly high because they are so tolerant and
17 they just walk in or drive up despite huge alcohol
18 levels.

19 Then we have to figure out how to get them
20 detoxed. Depending on what the protocol is, we may
21 have to find an inpatient program which is, as I
22 said, difficult or we do an outpatient detox.

23 DR. OREN: Any further questions from the
24 committee to the FDA? Dr. Schatzberg?

25 DR. SCHATZBERG: I have a question for Dr.

1 Winchell and Dr. Wang. It seems that, on your
2 reanalysis, that the European data are pretty
3 convincing in terms of what you would agree would
4 be a reasonable criterion for efficacy, I gather
5 from what you concluded.

6 But just as something for the committee or
7 for my edification, these studies were done a long
8 time ago, obviously. How do you feel about, in a
9 way, changing what is the specified outcome
10 criterion in a post hoc analysis in that way. In a
11 sense, are we doing something contradictory? We
12 are sort of, on the one hand, saying, in the U.S.,
13 we are going to throw out the EFF data because it
14 is post hoc, and whatever.

15 There are issues, there, granted. Yet we
16 are still sort of doing that except it is our own,
17 or the FDA's, reanalysis. What kind of criteria
18 would you use or would you recommend for what
19 should constitute a reanalysis and is part of it
20 just that these are so old in terms of the studies?

21 DR. WINCHELL: I will start and then I
22 will let Dr. Wang respond. First of all, the
23 difference between an efficacy evaluable post hoc
24 analysis and some of the other types of subset
25 analyses we did, as I mentioned, it has to do with

1 whether the subsets can be defined by
2 prerandomization variables.

3 The real problem with post hoc analysis,
4 the reason people tend to dismiss it, is that there
5 is the risk of multiplicity, the risk that, simply
6 by chance, if you do enough of them, you will get
7 one coming out statistically significant, as you
8 know.

9 Nevertheless, we do these types of
10 analyses to see whether there is differential
11 effect in women and men, differential effect by age
12 or by race. Usually, the studies are not powered
13 to generate a statistically significant difference
14 in any type of subset. They are powered just big
15 enough to demonstrate an effect in the ITT
16 population.

17 So we don't expect these analyses to come
18 out with a statistically significant result. We
19 expect them to give us some trends or some
20 understanding or just to shed some light on who in
21 the population is particularly prone to benefit of
22 not to benefit.

23 We do these routinely. Rarely one might
24 take as the body of evidence supporting an
25 application some type of post hoc reanalysis of

1 data as supportive. If you had one or two very
2 strong studies, you might look retrospectively at
3 existing datasets in a way that was not anticipated
4 at the time the data was collected and say that
5 this analysis generates supportive, confirmatory
6 evidence that helps to complement the other results
7 and complete the body of evidence necessary for
8 regulatory decision making.

9 So it is not uncommon to look
10 retrospectively at older sets of data. Usually, we
11 get a little uncomfortable if that is the only
12 basis on which the efficacy can be concluded. I
13 think of this, and I know Dr. Wang maybe thinks of
14 this differently because she is a statistician and
15 I am a medical officer, but I think, in some ways,
16 of approaching this European data the way one might
17 approach a literature-based application where there
18 is this large body of data. I have got the actual
19 data. I can look at it various ways.

20 I think what we hoped to get when we first
21 met with Lipha was what I described, that we would
22 have one American trial that was successful but
23 that could not stand alone--it was not
24 replicated--and that we would accept as
25 confirmatory evidence analysis of older European

1 data notwithstanding the fact that it was a
2 different dose and a different dosage regimen and
3 that those pieces together would form the basis of
4 our decision.

5 Ultimately, we were faced with going
6 forward without that successful American study and
7 we still tried to make what we could out of the
8 European data.

9 I don't know if that addresses your
10 question. I will also ask Dr. Wang to talk about
11 how she sees it statistically and I see that my
12 boss wants to tell you what she thinks of it. So I
13 will let her go first.

14 DR. McCORMICK: Thank you. I guess,
15 really, the crux of your question is how is it that
16 we can go into the U.S. dataset and do these post
17 hoc analyses ourselves and not accept what the
18 sponsor has given us in terms of their post hoc
19 analyses, and yet we are taking the European
20 dataset and saying we are all going to do a post
21 hoc analysis here, and that is going to be the
22 basis of our regulatory decision.

23 Yes, that does give us some discomfort.
24 Let me first say that, as far as the U.S. post hoc
25 analyses are concerned, I think both on the part of

1 the sponsor and ourselves, is that these are purely
2 hypothesis-generating. We are looking to try to
3 understand this information, not to draw any
4 conclusions about it, because we feel quite
5 comfortable that we cannot use the United States
6 study in making a regulatory decision.

7 That leaves us with the bulk of the data
8 from Europe, or all of the data from Europe, to
9 make our decision about. Yes; it does give us some
10 discomfort in seeing trials in cases where we
11 haven't had prespecified primary-outcome measures
12 and we have to reconstruct them based upon what the
13 trial objectives were.

14 Yet, when we take the most conservative
15 approach, even more conservative than what was
16 probably originally intended, looking at complete
17 abstinence, it is consistent across all the
18 studies.

19 This, truly, is something that we would
20 like to bring to the table, though. But I think
21 even beyond having done that and taking the more
22 conservative approach, looking at complete
23 abstinence as an outcome, our even greater level of
24 discomfort and, really, the reason for having this
25 meeting is not so much have we chosen a post hoc

1 analysis to do on this dataset but what is the
2 credibility of the dataset, itself.

3 Can we rely upon, for example, a one-year
4 study in which there have been only six visits,
5 where the data is largely imputed? Can we believe
6 that and can we base our regulatory decision on
7 these studies? That is the crux of the matter.

8 DR. WANG: I am going to talk about from
9 the statistical perspective. In terms of the
10 timing of the European trials versus the U.S.
11 trial, yes, we are going to say these are all post
12 hoc analyses. What you see from the European
13 studies, you have all the consistencies across all
14 the outcomes that you looked at.

15 When there is a problem of differential
16 dropout between the acamprosate and the placebo, it
17 is in the direction, you believe the drug works.
18 However, in the U.S. trial, the troubling thing is
19 the post hoc nature of it.

20 First of all, if the drug works, if the
21 prespecified analysis works, we don't need to talk
22 about the post hoc. So, going to post hoc, you
23 already failed the first step. In that post hoc
24 situation, yes, we accept some kind of post hoc
25 evaluation. But, you start with one covariate

1 adjustment. It was believed by the sponsor that
2 the abstinence goal was a very prognostic one. If
3 you have a model, just include treatment center and
4 that covariate of complete abstinence goal, you
5 don't find the statistical evidence.

6 If you then say, all right, let me look at
7 treatment center and the slip is okay, because that
8 is also differential in the opposite direction,
9 still you did not see the statistical evidence.
10 Even if you adjust for just one covariate,
11 treatment exposure, it is not there either.

12 So this post hoc nature was trying to
13 explain what is going on. You would expect that if
14 the effect is really there, then, using a fewer
15 number of covariates should still give you some
16 kind of treatment-effect size. But it wasn't in
17 this case.

18 So the post hoc nature, in this particular
19 situation, is very troubling.

20 DR. OREN: Dr. Schatzberg?

21 DR. SCHATZBERG: I appreciate the answer.
22 It was really more kind of a structural--as Dr.
23 McCormick raised. But let me ask one other
24 structural one, if I might, because of something
25 that Robert raised before, and that is, while this

1 is somewhat of a different division, I guess, of
2 the FDA from the psychopharm group, is there
3 concern in the agency that recommending approval
4 based on the European portfolio and without U.S.
5 data would not jive or go with other efforts on the
6 part of this committee.

7 I am not a member of the committee so I
8 just raise that as a precedent, or is that just
9 because they are different illnesses and different
10 agencies and different criteria?

11 DR. McCORMICK: To answer your question,
12 there really are no concerns on the part of the
13 agency about making a regulatory decision based on
14 purely European data. As long as they are rigorous
15 and credible and the studies have been done using
16 good clinical practices and they are in sites where
17 we can do inspections.

18 In this case, there are. There have been
19 precedents where European data has been relied
20 upon. That is not an issue.

21 DR. OREN: Dr. Leon?

22 DR. LEON: Are there standards that the
23 agency uses for maximum dropout rate in clinical
24 trials? I mean, these dropout rates typically were
25 never less than 35 percent but, typically, 50 or 60

1 percent dropout.

2 DR. WINCHELL: These are not unusual
3 dropout rates for addiction-treatment trials. If
4 we had standards for unacceptable dropout rates, I
5 don't think we would be able to do
6 addiction-treatment trials that lasted more than
7 two weeks.

8 DR. OREN: Dr. Winchell, I wonder if you
9 could just say a little more, just specifically
10 focussing on the European studies and not focussing
11 right now on the broader question of approval but
12 just specifically on the efficacy of acamprosate in
13 the European studies? How would you summarize your
14 analysis?

15 DR. WINCHELL: Well, let me say that,
16 based on the data that I had available to analyze,
17 the very short three-month Pelc study certainly
18 showed an effect of acamprosate on complete
19 abstinence. The Paille study was more marginal on
20 that and the PRAMA study showed an effect if you
21 imputed failure to all the dropouts and not
22 necessarily if you didn't.

23 So, on complete abstinence, it looks
24 promising but it is not a blockbuster. In my own
25 made-up, what else can I do besides cumulative

1 abstinence duration analysis, there is a difference
2 between the dose proposed for marketing and placebo
3 in favor of acamprosate in all the studies. As I
4 mentioned, that is again driven primarily by the
5 completely abstinent subjects who, in this
6 analysis, have failure imputed after dropout.

7 So I can certainly get a good result.
8 But, obviously, I have some reservations about how
9 much I should believe my own analysis. I don't
10 mean to sound disrespectful about these studies.
11 All I know is that the American study reported 100
12 volumes and some of the European study reports are
13 one volume.

14 So I just have so much more detail
15 available for my scrutiny for the American study.
16 That is what we are accustomed to, actually, is
17 something on the order of the 100 volumes per
18 study. I should say that the case-report forms
19 were submitted electronically as were the
20 case-report tabulations so those weren't even
21 included in there.

22 That is the type of thing we are
23 accustomed to having available for our examination
24 and we didn't have that for the European data. So
25 that is why we are here.

1 DR. OREN: Dr. Cook

2 DR. COOK: I think you have covered this,
3 but just to clarify for me. If you took the
4 predefined outcome variable and the predefined
5 analysis by the sponsor, number one, were those
6 defined? Is there any doubt about whether they
7 were defined? In other words, do you have a
8 document that clearly specifies it. And, for those
9 three trials, what happened with those primary
10 hypotheses and their primary analyses?

11 DR. WANG: Are you specifically talking
12 about just the European studies?

13 DR. COOK: Yes; just the European studies.

14 DR. WANG: As Dr. Winchell mentioned, the
15 European-study information given to us was limited.
16 So that is why, in my presentation, I only based it
17 on percent complete abstinence and not others. So
18 I cannot make too much out of what I have--I mean,
19 in addition to what I have

20 DR. COOK: Okay. But, by limited, do you
21 mean that, in each trial, you couldn't see in their
22 documents that they had written a document before
23 the study started about what the predefined
24 analysis would be and what the predefined outcomes
25 were and did you have the data to see whether those

1 trials were positive given that standard.

2 DR. WANG: I think, from our internal
3 discussion while we were doing this priority
4 review, we had a discussion as to how much can we
5 believe in the European data in terms of the number
6 of days that the patients were abstinent.

7 As Dr. Winchell presented, there were--if
8 you are talking about Pelc II, it is biweekly
9 visits. But, for others, is a one to three months
10 kind of difference. So if you are doing
11 imputation, there is big chunk of time that you can
12 impute by days. Therefore, it was believed that
13 the quality of the data with those were
14 questionable and that was the reason of the focus.

15 DR. WINCHELL: I have something else I can
16 say to address your question. At least one of the
17 studies--I am thinking it is Pelc II--it said that
18 the primary outcome variable, the main criterion of
19 judgment, would be abstinence. But what it didn't
20 have in the protocol was any operationalization of
21 how that would be evaluated.

22 As you have seen, if your main criterion
23 of judgment is abstinence, you could look at time
24 to first drink, time to first heavy drink, time to
25 relapse, cumulative abstinence duration or any

1 number of other measures of abstinence. So then,
2 appended to the protocol, we then had a statistical
3 report. In the statistical report, it was set
4 forth what analyses were done. At least one of
5 them was a blinded analysis. I can say that much.

6 So one could assume that the statistician
7 decided what to do first. It is unclear. But it
8 is not like what we are accustomed to seeing in an
9 American NDA in 2002.

10 DR. WANG: I would like to add to that is
11 the difficulty in analyzing the Paille study. In
12 fact, the patient's dropout reasons were
13 reclassified even though those data were used to
14 have a European approval. By using the new defined
15 reasons of dropout and looking at the three
16 treatment-arm comparisons, you can get a different
17 result.

18 DR. OREN: Dr. Mehta?

19 DR. MEHTA: One way to look at it would be
20 that there are very few areas of medicine where you
21 do fourteen placebo-controlled studies and you turn
22 out to be a winner fourteen times. What the
23 sponsor has done is, in European, twelve or
24 thirteen times, rolled the dice against placebo and
25 it came out as a winner.

1 By the law of averages, I would have
2 expected the next trial will be negative and what
3 they did is essentially ably demonstrated the law
4 of averages works.

5 DR. OREN: Dr. McCormick?

6 DR. McCORMICK: I would just like to point
7 out that we were only given full study reports of
8 three of the European studies. We know that they
9 haven't all succeeded and I don't believe that they
10 all had complete abstinence as an outcome.

11 DR. OREN: I think we will take Dr.
12 Rudorfer with the last question and then we will
13 take our lunch break.

14 DR. RUDORFER: I am sorry to have to
15 compete with lunch. Just a couple of questions.
16 We have all been talking about the fact that
17 European studies are a decade old. I am wondering
18 if we have learned anything in the interim. For
19 instance, are the postmarketing data available that
20 might be informative just in terms of do people
21 actually refill their prescriptions over a year's
22 duration, issues like that?

23 DR. WINCHELL: Obviously, Lipha has much
24 more information than we do, but I just know
25 recently looking at some of their materials, that

1 it said market research shows that typical duration
2 of use was, like, three to six months. So it
3 doesn't sound like people are typically using it
4 for a year or more. But, certainly, I will let--I
5 see heads shaking but I did read that in the NDA
6 yesterday.

7 DR. CHABAC: I just want to remind you
8 that alcohol-dependent patients are very badly
9 compliant patients. To keep them treated for six
10 months with the treatment, I think it is a very
11 good sign that this drug could be beneficial to
12 them.

13 I told you that we have 1.5 million
14 patient years experience with the product. That
15 means that there are a lot of patients treated with
16 acamprosate. We have the experience with the NEED
17 Program where we treated nearly 2000 patients in
18 Europe. Dr. Mann can tell me if I am wrong, but I
19 think there is a benefit using that drug. It is
20 not a magic product but I just want to remind you
21 that the two drugs available on the market to treat
22 these kinds of patients have neither a very huge
23 rate of efficacy and that if we can bring something
24 safe to treat, to help, those patients, this is
25 something.

1 DR. MANN: I think to understand these
2 figures, the recommendation in Germany, at least,
3 is to give it for six months. All the doctors know
4 it would be given for six months and not for a year
5 or more which is now something that is recommended.

6 So if you have figures that show that it
7 is taken five or six months, this shows compliance
8 of the doctors, if you want.

9 DR. OREN: Dr. McCormick?

10 DR. MCCORMICK: Just a word of caution
11 that I would like to insert and that is while it
12 may be important to understand how a drug plays out
13 in the postmarketing period, we would not accept a
14 postmarketing uncontrolled experience as evidence
15 of a product's efficacy as part of our making of a
16 regulatory decision.

17 DR. OREN: Before we break for lunch, I am
18 reminded to remind each member of the committee
19 that, because this is a public hearing, over the
20 one-hour lunch break, we are not supposed to talk
21 about any of this particular material because it is
22 out of the public forum. There will be plenty of
23 time later this afternoon to continue and we will
24 be back in one hour.

25 Thank you.

1 [Whereupon, at 12:15 p.m., the proceedings
2 were recessed to be resumed at 1:15 p.m.]

1 studies.

2 The Research Society on Alcoholism
3 appreciates the opportunity to present its views
4 about the importance of finding effective
5 pharmacological treatments for individuals
6 suffering from the psychological, social and
7 biomedical consequences of abusive drinking.

8 The RSA is a professional scientific
9 society of over 1400 members who are committed to
10 understanding and intervening in the negative
11 consequences of alcohol abuse through basic
12 research, clinical protocols, psychosocial research
13 and epidemiological studies. About one-third of
14 RSA members are also clinicians actively involved
15 in the treatment of individuals with
16 alcohol-related problems.

17 As we heard this morning, the cost of
18 alcohol abuse and dependence on American society
19 and individual lives is staggering. The cost to
20 the nation is estimated at approximately \$185
21 billion annually. Not only are the fiscal costs
22 real and powerful, but alcohol misuse is costly in
23 many ways.

24 Estimates of alcohol-use disorders ranging
25 from abuse through dependence from the National

1 Longitudinal Alcohol Epidemiological Survey
2 indicates that about 7.5 percent or 14 million
3 Americans are affected. Further, a Robert Wood
4 Johnson Foundation report indicates that more than
5 700,000 people receive alcoholism treatment on any
6 given day. Approximately only 15 percent receive
7 inpatient treatment and these patients often have
8 the most severe form of alcohol problems.

9 The remaining patients receive outpatient
10 treatment from a variety of different treatment
11 providers including psychiatrists, primary-care
12 providers, psychologists, social workers and
13 self-help groups such as Alcoholics Anonymous.
14 Based on Project MATCH data, approximately 40 to 50
15 percent of those in outpatient treatment are able
16 to abstain in the first week of therapy but many
17 relapse shortly thereafter.

18 Although the combination of behavioral
19 therapies and currently available medications such
20 as disulfiram and naltrexone help 40 to 70 percent
21 of persons with alcoholism either reduce their
22 alcohol consumption or maintain abstinence up to
23 six months following treatment.

24 The relapse within one year of treatment
25 still ranges from 30 to 50 percent. The primary

1 reason for relapse to abusive drinking is
2 noncompliance with both the pharmacologic as well
3 as the behavioral treatment.

4 Importantly, and I think this is something
5 that has not been mentioned this morning to date is
6 a significant number of adolescents and young
7 adults are frequent consumers of large amounts of
8 beverage ethanol with disastrous consequences.
9 These are individuals that also would benefit from
10 new therapies.

11 A recently released report on college
12 drinking sponsored by the National Institute of
13 Alcohol Abuse and Alcoholism reveals that 1400
14 college students between the ages of 18 to 24 die
15 each year from unintended alcohol-related injuries.
16 An additional half a million students per year
17 between the ages of 18 to 24 are unintentionally
18 injured under the influence of alcohol. The
19 majority of these individual have not developed
20 physical dependence as discussed in some of the
21 studies this morning and typically do not seek
22 treatment. But, still, these are individuals that
23 would benefit from new therapies.

24 Alcohol abuse and alcohol dependence are
25 cites as major causes of medical morbidity, mental

1 retardation, accidental death and injury, homicide,
2 suicide, lost productivity and disruption of
3 family. Further, frequent and prolonged heavy
4 drinking contributes to illness in each of the top
5 three causes of death, heart disease, cancer and
6 stroke.

7 Chronic alcohol abuse is linked to nearly
8 half of all cirrhosis deaths, the tenth-leading
9 cause of death in the U.S. For some special
10 populations of American society such as Native
11 Americans and African Americans, the costs
12 associated with alcohol misuse are
13 disproportionately higher and may be directly
14 linked to some of the major health problems in this
15 group such as hypertension and diabetes.

16 The Indian Health Service estimates that
17 age-adjusted alcoholism mortality for American
18 Indians is 63 percent higher than the rate for all
19 other ethnic groups in the U.S. Overall, alcohol
20 mortality rates are particularly higher among
21 African-American men even though alcohol use tends
22 to be moderate for African Americans compared to
23 Caucasians and Hispanics.

24 Given the range and diversity of the
25 severity of alcohol problems across the general

1 population of the U.S., the number of available
2 medical treatments is extremely limited. As we
3 heard this morning, there were only two types of
4 medications and, in fact, only two medications that
5 are FDA approved, and that includes disulfiram
6 which is an aversive agent available since the
7 early 1950s and, more recently, naltrexone which is
8 the first medication approved by the FDA for
9 alcoholism treatment in nearly 50 years.
10 Compliance with both these medications is a problem
11 but, when combined with behavioral therapy, both
12 have been shown to be useful in reducing drinking
13 in selected but not all patient groups.

14 However, medication is not without its
15 limits in relation to safety of use. Neither
16 disulfiram nor naltrexone, for example, are
17 recommended for individuals with significant liver
18 injury or liver disease such as cirrhosis or
19 hepatitis C. Given that alcohol is a known
20 hepatotoxic agent, many individuals who desperately
21 need to quit drinking in order to improve their
22 health are not candidates for these medications.

23 Alternative treatments that are not
24 hepatotoxic and that can be safely used by
25 medically compromised patients are critically

1 needed. A larger number of medical treatments are
2 required given that no one pharmacological
3 treatment is strongly effective and probably helps
4 only a subgroup of patients.

5 Currently, members of the RSA and other
6 scientists are conducting both basic and clinical
7 trials on a number of promising compounds to
8 identify effective pharmaceutical agents to treat
9 individuals with alcohol dependence or those who
10 chronically abuse alcohol. The RSA asks that you
11 give careful consideration to the current proposal
12 for approval of acamprosate as the currently
13 available clinical armamentarium is quite sparse
14 and is really insufficient to address the very
15 needs of the treatment providers across the
16 spectrum of alcohol-related problems that they are
17 asked to treat.

18 Thank you for the opportunity to present
19 our views.

20 DR. OREN: Thank you.

21 Has Dr. Johnathan Chick arrived? No?
22 Then we will go on. The next Open Public Hearing
23 presenter is Dr. Steven Mirin, Medical Director of
24 the American Psychiatric Association.

25 DR. MIRIN: Thank you, Mr. Chairman,

1 members of the advisory committee. I am Steve
2 Mirin, Medical Director of the American Psychiatric
3 Association, a medical specialty society
4 representing more than 38,000 psychiatric
5 physicians nationwide.

6 I commend the FDA and this committee for
7 undertaking a review of the efficacy of acamprosate
8 for the treatment of alcohol dependence. I have no
9 association with any pharmaceutical company that
10 develops or distributes this drug.

11 I come before you not as an expert on the
12 pharmacology of acamprosate but as the
13 representative of 38,000 care-givers concerned
14 about the public-health need for more effective
15 treatment for alcoholism. Alcohol, as you know,
16 remains the commonly abused drug by youth and
17 adults alike in this country. About 14 million
18 Americans meet medical criteria for the diagnosis
19 of alcohol abuse or dependence and 40 percent of
20 Americans have direct family experience with the
21 illness.

22 The financial burden of alcohol abuse and
23 dependence is estimated at \$185 billion a year, 52
24 percent greater than the estimated cost of all
25 illegal drug use and 21 percent greater than the

1 estimated cost of smoking-related problems. More
2 than 70 percent of this amount is attributable to
3 lost productivity and lost earnings, but the
4 medical costs are also staggering. Up to 40
5 percent of patients in urban hospital beds are
6 there for the treatment of conditions caused by or
7 exacerbated by alcohol including diseases of the
8 brain and liver, certain forms of cancer, accidents
9 and violence.

10 These data underscore the need for more
11 effective clinical interventions in people
12 suffering from alcoholism. In this context,
13 approval of the use of acamprosate, a drug shown in
14 numerous international studies to be effective in
15 the maintenance of abstinence and relapse
16 prevention in patients with a history of alcohol
17 dependence would be, in our view, in the interests
18 of this large patient population and an important
19 new tool for the practitioners I represent and for
20 other healthcare providers across the country

21 As you know, acamprosate is currently
22 approved for use in 39 countries and about 1.5
23 million persons with alcohol dependence have been
24 treated worldwide. The drug appears to be well
25 tolerated with no serious adverse side effects and

1 no evidence of abuse potential or rebound effects
2 when discontinued. It can be used safely in
3 patients with liver disease and it does not impair
4 performance on motor tasks like driving. It has a
5 very high margin of safety.

6 Multiple controlled clinical trials have
7 demonstrated the efficacy of acamprosate in
8 reducing craving for alcohol and helping maintain
9 abstinence in previously dependent patients. This
10 is not a trivial finding. It can reduce the time
11 to first drink. There is a higher rate of complete
12 abstinence, a greater percentage of abstinent days
13 while on medication and these effects are sustained
14 over post-treatment follow-up periods for as long
15 as one year in some studies.

16 There are fewer hospitalizations for
17 detoxification and diminished need for
18 rehabilitation in institutional settings and a
19 diminished rate of relapse to heavy drinking or
20 even sporadic drinking. As one of the
21 investigators in the early studies of naltrexone, I
22 can well appreciate the need to avoid slips in
23 alcoholics. Slips are not trivial events. They
24 are the forerunner of relapse.

25 Not surprisingly, a study conducted in 600

1 outpatients with alcohol dependence in this country
2 indicated that patients who were not motivated to
3 be abstinent are not as likely to benefit from
4 acamprosate whereas those who were significantly
5 more likely to meet their treatment goals when
6 compared to folks given placebo. This suggests
7 that, as in other addictive disorders,
8 psychotherapy is just one aspect of a successful
9 treatment program.

10 In summary, we believe that on the basis
11 of the findings to date, acamprosate has
12 demonstrated efficacy in the treatment of alcohol
13 dependence and has provided a cost-effective
14 treatment for these patients. Given the high
15 prevalence of alcoholism in this out and the
16 medical, economic and emotional costs of these
17 disorders, approval of acamprosate can have
18 important benefits for millions of our citizens and
19 for our society as a whole.

20 Thank you for the opportunity of
21 presenting this testimony.

22 DR. OREN: Thank you, Dr. Mirin.

23 Our next public speaker is Dr. Edward
24 Eder, Medical Director of the Comprehensive
25 Addiction Treatment Program, Fairfax, Virginia.

1 DR. EDER: Good afternoon, Mr. Chairman
2 and panel members of the advisory committee. I
3 appreciate the opportunity to speak on this
4 subject.

5 My name is Edward Eder. I am an internist
6 with twenty years practice predominantly in the
7 field of addiction medicine. I am a consultant to
8 Fairfax County's Alcohol and Drug Services, a
9 member of the American Society of Addiction
10 Medicine and Medical Director of the Comprehensive
11 Addiction Treatment Services.

12 As an internist and Medical Director of
13 the Comprehensive Addiction Treatment Services
14 affiliated with INOVA Fairfax Hospital, I have been
15 aware of the high risk of relapse in patients with
16 alcohol dependence despite involvement in
17 well-designed outpatient treatment or in sober
18 structured environments. With the advent of
19 greater understanding of the neurochemistry of the
20 addicted brain, I share the hope that
21 pharmacological agents would become available to
22 assist patients in maintaining abstinence.

23 Our current list of medications to reduce
24 relapse is very limited and acamprosate would be an
25 important addition to therapeutic options. There

1 are three specific categories of patients who would
2 most benefit from acamprosate in terms of our
3 clinical practice. One, patients on opioids who
4 are not candidates for naltrexone and would benefit
5 from an agent that would assist alcohol abstinence.
6 In methadone-maintenance programs, up to 50 percent
7 of patients have alcohol-dependence or alcohol-use
8 disorders for, instance.

9 Also, patients with hepatotoxicity
10 excluding Child Class C category who may not
11 qualify for disulfiram or naltrexone as well as
12 patients who might benefit from the neuroprotective
13 effect of acamprosate such as individuals with
14 alcohol-withdrawal seizures.

15 The addition of acamprosate to the
16 available medicines for treatment of alcohol
17 dependence would allow for future combinations that
18 may afford greater efficacy. Given the novel
19 pathways which acamprosate appears to act upon, the
20 potential for additive or, perhaps, synergistic
21 effects is promising.

22 I believe that there is a strong clinical
23 justification for a medication such as acamprosate
24 and believe multicenter trials in Europe appear to
25 confirm both efficacy and safety. I urge the panel

1 to consider the approval of the medication for the
2 treatment of addiction.

3 Thank you very much.

4 DR. OREN: Thank you, Dr. Eder.

5 Since this is an Open Public Hearing, I
6 wanted to ask if there is any member of the general
7 public here who wishes to make a statement in
8 regard to the topic at hand.

9 Please. Do you want to introduce
10 yourself?

11 DR. PUBLICKER: My name is Mark Publicker.
12 I was actually on the comment list. I am the Chief
13 of Addiction Medicine for Kaiser Permanente in the
14 MidAtlantic Region. I am also President of the
15 Virginia Society of Addiction Medicine.

16 I am speaking on behalf of the Chiefs of
17 Addiction of Addiction Medicine for Kaiser
18 Permanente nationally. We provide care to over 10
19 million Kaiser Permanente members coast-to-coast.
20 I am also speaking on behalf of Virginia's
21 addiction-medicine specialists. I am also speaking
22 on behalf of my alcoholic patients many of whom are
23 desperate for an effective medical treatment for
24 this disabling behavioral disorder.

25 Following the lead of earlier speakers, I

1 should hasten to add I have no financial interest
2 in Lipha and, quite frankly, I don't have any
3 investments that will help me pay for my daughter's
4 college education next year. So I am clean.

5 Since its FDA-approved indication for the
6 treatment of alcoholism, I and my local partners
7 have prescribed naltrexone to thousands of
8 alcoholic patients. I am proud to say I appear to
9 hold the record. We have found it to be very
10 effective in combination with behavioral therapies
11 and decreasing craving and relapse allowing our
12 patients to focus their energies on psychosocial
13 treatments rather than on white-knuckling their
14 recovery.

15 We have found that patients are grateful
16 for such psychotherapy much in the same way that
17 chronic heartburn sufferers are grateful the first
18 time they are prescribed proton-pump inhibitors. I
19 have received many phone calls of the same quality.
20 I would like to also add that I have a number of
21 patients who schedule follow-up visits with me
22 every six months for the last few years checking on
23 the status of acamprosate because they are getting
24 incomplete relief when they are on their
25 naltrexone.