

1 Nonetheless, many patients cannot take
2 naltrexone. Some develop intolerable
3 gastrointestinal side effects that prevent its use.
4 Methadone-maintained patients and chronic-pain
5 patients on long-term opioid therapy with
6 co-occurring alcoholism cannot take naltrexone.
7 Finally, despite dosages of 100 to 200 milligrams
8 daily, some patients continue to experience both
9 craving and relapse.

10 I have carefully reviewed the European and
11 North American literature on acamprosate. There is
12 extensive documentation of its superiority to
13 placebo in promoting enhanced abstinence and early
14 recovery. Acamprosate has an excellent safety
15 profile and there is some suggestion it may have a
16 neuroprotective effect. Studies have shown
17 acamprosate and naltrexone, taken together, have an
18 additive effect in promoting abstinence.

19 I urge the panel to consider the millions
20 of lives that will benefit from the addition of
21 such an effective new treatment for such a
22 devastating disease and approve acamprosate.

23 Thank you.

24 DR. OREN: Thank you.

25 Any other general comment from the public?

1 Charge to the Committee

2 DR. OREN: I will now call upon Dr.
3 Cynthia McCormick to deliver the charge to the
4 committee.

5 DR. McCORMICK: Thank you, Dr. Oren. This
6 morning, you have heard from Lipha and from the FDA
7 on the four clinical trials in question. I would
8 like to remind you that this advisory committee
9 meeting today will not be one in which a final
10 approval recommendation is being requested.

11 Recall that there are other aspects of the
12 drug-approval decision which are not being brought
13 for discussion today. The drug safety, as I
14 mentioned earlier, is still under evaluation and is
15 expected to be completed by the end of this month.
16 Both clinical inspections and inspections of the
17 manufacturing sites have also not been done yet.
18 In fact, one of our inspectors is here today and
19 will be leaving for France this afternoon to begin
20 his inspection of some of the European sites.

21 So these will both have to be weighed into
22 the decision for approval and in the timing of
23 approval, potentially.

24 We are asking you to assist the FDA in
25 assessing the weight of the evidence provided in

1 support of the efficacy of this product. A number
2 of exploratory analyses have been performed in an
3 effort to understand or explain the discrepant U.S.
4 results both by the FDA and by Lipha. You should
5 regard these analyses not as definitive but as
6 hypothesis-generating.

7 The FDA, in the end, does not accept the
8 results as positive nor feel that they should be
9 weighed in the decision for approval nor does the
10 FDA have an explanation for the failure of the
11 trial. So where does that leave us? It leaves
12 with questions about whether the populations are so
13 different that the European results may not apply,
14 about whether the differences in methodology alone
15 account for the successes of the European studies
16 and, therefore, whether the effect was real.

17 The effectiveness standards for approval
18 of a new molecular entity include at least two
19 adequate and well-controlled studies that
20 demonstrate a significant effect on the outcomes
21 that have been determined to demonstrate a
22 clinically meaningful result regardless of the
23 trial's origins, European or U.S., of course with
24 the caveat, as I mentioned earlier today, that the
25 sites are those that can be inspected. So the fact

1 that the bulk of the experience, the efficacy
2 experience, is European is not a problem for the
3 FDA.

4 The standards require a certain level of
5 quality such as the existence of a prospective plan
6 to assure data quality, availability of source
7 documents that can be used to verify the quality of
8 the data and the accuracy of the data and conduct
9 of the study following the standards of good
10 clinical practice. As is the agency's practice,
11 there will be inspections, as I mentioned, to
12 evaluate the veracity of the data.

13 As alluded to earlier, there is the
14 question of the credibility of the approach of
15 using highly imputed data in the European studies.
16 This should be carefully considered when assessing
17 the value of these studies. We will ask you to
18 reflect on all that you have heard, consider the
19 totality of evidence giving consideration and
20 weight to such factors of quality of data, strength
21 of the effect size and, most importantly, whether
22 the results that are positive are credible.

23 At the end of the day, the FDA must have
24 confidence that its decision will be based on
25 information that cannot be questioned.

1 So, in returning to the meeting, we ask
2 you to deliberate on the following questions, and I
3 will read them to you. Given the conflicting
4 results between the European studies and the
5 American study, is there sufficient evidence of the
6 efficacy of acamprosate in the treatment of
7 alcoholism to warrant approval? In this, consider
8 not only the quantity but also the quality of the
9 evidence provided in support of the effectiveness
10 claim.

11 How can the discrepant results be
12 reconciled or do they need to be? Finally, do the
13 data support any conclusions regarding subgroups of
14 patients more likely to benefit from acamprosate?
15 Please discuss that.

16 Thank you very much.

17 Continuation of Discussion

18 DR. OREN: Before the committee begins its
19 open discussion, I have a few questions that I
20 wanted to ask of the sponsor to help eliminate some
21 of our discussions. Could you, perhaps, clarify
22 what was your NDA strategy for this drug?

23 DR. GOODMAN: As I mentioned earlier this
24 morning, our NDA strategy was always planning to
25 use the European dossier as a substantial part of

1 our database. We always intended to use at least
2 two of the European studies as fulfilling the
3 requirements that Dr. McCormick has just mentioned,
4 adequate and well-controlled, and, in addition, we
5 felt it incumbent upon us to also preform a study
6 in the United States to confirm both the efficacy
7 as well as get further information on safety in a
8 broader population.

9 When the U.S. study results for the ITT
10 population did not show a difference between
11 treatment and placebo, our strategy was redefined
12 in terms of the amount of European data that we
13 were going to use in that we decided to add an
14 additional study to what we considered to be our
15 pivotal study.

16 The remaining studies that were submitted
17 as "supportive" studies, it did not mean that, in
18 our opinion, any of these studies could not also
19 have been pivotal from the point of view of their
20 design being adequate and well-controlled, having
21 case-report forms, electronic databases, and so on,
22 but it was more a question--in some instances, the
23 study centers were not available anymore or the
24 practitioners who were there weren't available.

25 So the three studies that we

1 identified--and we identified those from the very
2 beginning, the PRAMA and Paille study, and we added
3 the Belgian-French study, the Pelc II study. These
4 were always going to be--or at least the first two
5 were always going to be part of our pivotal
6 database.

7 We did not submit, in the NDA, the U.S.
8 study as a pivotal study and we really think it is
9 misconstruing to say that we thought this was a
10 pivotal study. We didn't. We feel as interested
11 as the committee and the FDA in understanding why
12 the results weren't the same as the European
13 studies for the ITT population, but we think we
14 have done a good job in terms of trying to get an
15 interpretation on a subgroup that could really
16 benefit from the drug.

17 DR. OREN: Given that the European studies
18 are a key to our discussion of efficacy, could you
19 also clarify further or tell us more about the data
20 structure in those studies and the capacity of
21 those specific studies to provide valid endpoints
22 for us.

23 DR. GOODMAN: If I could, I would like to
24 ask Dr. Cook to address that point with Dr. Mason's
25 help, perhaps.

1 DR. G. COOK: The European studies had
2 assessments at specific time intervals. My
3 understanding is that those assessments would be
4 considered sufficient to identify departures from
5 abstinence, that, if a patient had a departure from
6 abstinence, it would be likely to be a major
7 departure and, through the various reporting
8 mechanisms, one would have been able to have
9 captured such a departure.

10 Now, that simply means that when you focus
11 on an abstinence-oriented endpoint, things are
12 fairly straightforward, whether it is complete
13 abstinence throughout the time period in the study
14 or time to first departure from abstinence or even
15 the number of assessments in which abstinence was
16 reported.

17 Certainly, the FDA has correctly
18 identified some difficulty in a calculation of
19 number of days with abstinence because that
20 involves some assumption about the time interval
21 between the assessments. I think the spirit of the
22 sponsor's categorization of all days subsequent to
23 an assessment of nonabstinence as drinking days was
24 simply based on the principle that if a patient had
25 a departure from abstinence, they would be

1 considered a drinker until the data structure
2 proved that they were no longer a drinker.

3 Again, that was probably based on the
4 philosophy that a departure from abstinence is not
5 something that just occurs for a few hours or a day
6 or two but that it actually is a total return to
7 the alcoholism for which they originally were being
8 cared for.

9 Whether that assumption is right or wrong,
10 I can't really comment on. I was just trying to
11 give some clarification as to why the sponsor,
12 potentially when they developed this strategy--why
13 they basically called all days after a nonabstinent
14 day a drinking day following essentially a
15 last-observation-carried-forward principle.
16 Perhaps my colleagues here can comment on it
17 further. But, regardless of how you choose to deal
18 with that intervening interval, I believe that
19 abstinence was accurately characterized by the data
20 structure because, again, I think my colleagues can
21 reinforce the point that if a patient had a
22 nonabstinent episode, that data structure was
23 probably adequate to capture it.

24 So I would like Dr. Mann and Dr. Mason,
25 perhaps, to comment on these points further.

1 DR. MASON: In terms of the importance of
2 a slip or a drinking episode, as I had mentioned
3 earlier, one of the diagnostic criteria for alcohol
4 dependence is going on to--when the person with
5 this disorder, one of the ways they are
6 characterized is by their going on to drink much
7 more than they originally intended.

8 They may go to the wedding reception
9 planning on having just one drink and wake up a
10 case of beer later. That is one of the hallmarks
11 of the disease. All of the intervals that were
12 used as assessment intervals in the European trials
13 were of sufficient duration as demonstrated by
14 Sobell and others working as methodologists in the
15 area of alcohol dependence. They were of
16 sufficient duration to capture these important
17 episodes of abstinence and nonabstinence and long
18 enough to capture episodes of infrequent drinkers.

19 If you have a very quick rating period, it
20 is possible that you would miss a drinker because
21 the drinking just hadn't occurred in a narrow
22 interval. You do need an interval of sufficient
23 time to capture the infrequent drinkers who have
24 more of the binge-type pattern.

25 A final point that I would like to make

1 about the duration of the intervals that the
2 European data collection used and the method in
3 which the drinking data were collected in Europe is
4 how closely it follows U.S. clinical practice. I
5 believe that, given how the methods and the
6 intervals follow clinical practice, and the
7 benefits shown with acamprosate in this type of
8 setting and under this level of inquiry will
9 likewise benefit U.S. patients with alcohol
10 dependence that was diagnosed under exactly the
11 same set of criteria as those patients with alcohol
12 dependence in Europe.

13 DR. MANN: I certainly agree with what has
14 been said about a slip and how a slip is a short
15 return to drinking in general mounts up to what is
16 a full-blown relapse in 80 to 90 to 95 percent.
17 So, in taking into account a slip and counting it
18 as a relapse until the next visit, I think that was
19 the most conservative and the most valid way of
20 looking at these data.

21 I would also like to mention one more
22 point. The German study, the PRAMA study, was
23 published in the Archives of General Psychiatry in
24 1996 and that would say something about the
25 validity of the self reports using gamma GT,

1 figures that we have not heard yet today.

2 There we state that between 81 and 100
3 percent of the patients who self-reported relapses
4 had higher gamma GT levels in both groups, so there
5 was no difference between both groups, and also
6 that the gamma GT values above the normal reference
7 range also corresponded with the number of patients
8 who had had relapses, again in both groups.

9 So I think there is some solid evidence
10 that these self reports are validated by external
11 sources.

12 DR. OREN: We will now turn the discussion
13 over to the committee for us to discuss amongst
14 ourselves. Dr. Titus reminds me that we can also
15 feel free to ask the FDA, ask the sponsor,
16 questions that are of relevance to our discussion
17 to further us along.

18 Obviously, the three questions we have
19 been charged with are all interrelated with each
20 other but, perhaps, we can start with one and try
21 and focus on one and move towards the other. The
22 first one is how can we reconcile discrepant
23 results between the older European studies and the
24 more recently concluded American study?

25 Dr. Hamer?

1 DR. HAMER: First of all, I want to say
2 that I am less than impressed by the argument that
3 the assessment methodology in the European trials
4 followed closely the clinical practice in the
5 United States. That seems to me to be an analogous
6 argument for not using the Hamilton Depression
7 Scale in our depression studies because, after all,
8 in clinical practice, we don't use the Hamilton
9 Depression Scale to assess our patients.

10 DR. OREN: Dr. Fuller?

11 DR. FULLER: My comment is somewhat
12 related and it was already made earlier by two
13 individuals. One was Dr. Hamer. That is the issue
14 that if you do several clinical trials, you will
15 get discrepant results. One, perhaps, is just by
16 chance. Another could be different methodologies.

17 But we have already mentioned the
18 depression studies where this is not an uncommon
19 occurrence, at least as reported in Science last
20 year. Even with effective therapies, you will get
21 some studies where the medication is no better than
22 the placebo.

23 But the comment I wanted to make was more
24 of a historical nature and that has to do with
25 aspirin for preventing myocardial infarction in

1 people who have myocardial infarction. This is
2 considered very important by cardiologists and
3 groups such as Medicare who pays for healthcare.
4 Yet, there was a similar situation where there were
5 two positive studies and then there was a large
6 negative study that involved 2000 individuals.
7 Then there was a fourth study.

8 On the basis of three positive studies,
9 one negative study, people undertook metaanalysis
10 and it has become faith that people who have had a
11 myocardial infarction ought to have aspirin and
12 even those who don't should have it. I just wanted
13 to bring that historical vignette in.

14 What I was leading up to was this
15 sometimes happens, these discrepant results.
16 Others here may have insight into why they happen,
17 but we may not be able to reconcile the discrepant
18 results. But they do occur.

19 DR. OREN: Dr. Winokur?

20 DR. WINOKUR: To begin to address the
21 issue of the discrepant results, we certainly heard
22 a lot of discussion this morning about some
23 important differences in the populations included.
24 One important point that was mentioned and
25 acknowledged by the FDA is the request to broaden

1 the scope of patients including polysubstance use
2 for safety assessment, and that clearly may have
3 changed the composition of the population
4 considerably.

5 But picking up on a comment that Dr.
6 O'Brien made, I also wanted to raise the question
7 as to whether there may be a change in the
8 treatment of alcohol dependence and whether this
9 changed the nature of patients available for
10 studies that occurred earlier in the European
11 studies which were, as we have mentioned, over a
12 decade ago with the more recent studies.

13 Again, the other major difference that we
14 are really grappling with is the issue which was
15 unexpected of the substantial number of patients in
16 the U.S. study who were not abstinent at the time
17 of start of treatment. I know we heard from the
18 FDA that they are willing to accept studies from
19 Europe as a basis for approval but I wonder if
20 there is a reason to discuss whether situations may
21 have changed not necessarily with the illness but
22 the environment in which people are not carrying
23 this illness and are being treated such that the
24 population being studied more recently really
25 represents a different cross-section.

1 DR. OREN: Do you want to say more? I
2 think that is an intriguing thought.

3 DR. WINOKUR: I was really hoping to get
4 some input from people that really work in the
5 field with this population which I certainly don't.

6 DR. OREN: Dr. O'Brien?

7 DR. O'BRIEN: Just to continue on the
8 theme of Dr. Winokur, actually is it what Dr.
9 Winchell said. There are clear differences that,
10 in the populations, in terms of--first of all, the
11 environment, the availability of detoxification is
12 a major difference. The number of people who
13 started off not being detoxified. That is a big
14 difference in all the addicting drugs that we
15 study.

16 The coincidence of other kinds of
17 substance abuse at the same time makes for a more
18 heterogenous population. We haven't said much
19 about comorbid other diagnoses but we know that
20 there is a very high comorbidity of anxiety
21 disorders and affective disorders in alcoholics.
22 That has tended to vary both in different countries
23 and in different sites.

24 For example, some questions were raised
25 earlier about what is the percentage of alcoholics

1 who have substance abuse or who have one thing or
2 another. It really depends on whether you are
3 talking about a community program, a V.A. program,
4 an HMO, a private program. Every environment that
5 you go to is different.

6 So you have all of these environmental
7 factors. Of course, the time. For example, if you
8 did these studies in Germany or France today, you
9 might find a lot more comorbid substance abuse
10 because I believe that there are a lot more street
11 drugs available over there now.

12 But, in addition to all of these factors,
13 you have the biological differences in alcoholism.
14 We all know that there are different ways of
15 categorizing alcohol and the current ones are Type
16 1, Type 2, A and B. But none of these really
17 capture what are probably endophenotypes that,
18 among people who may use the same amount of grams
19 of alcohol per week but they are biologically very
20 different.

21 For example, if we give them alcohol in
22 the laboratory, one difference that is
23 extraordinary is the fact that some people get a
24 huge increase in plasma beta endorphin and other
25 people don't. They also get a different response.

1 It is either activation from alcohol or sedation
2 from alcohol.

3 When we give them the other drug that has
4 been mentioned here, naltrexone, some people, it is
5 just life-saving in the sense that they say that,
6 gee, it has really turned my life around and they
7 get a tremendous benefit from it and, if we stop
8 it, they relapse to alcoholism. So there is no
9 doubt in the mind of the patient and the person
10 treating the patient that the drug is active.

11 But, on the other hand, there are other
12 patients for whom you give the drug and there is no
13 benefit whatsoever even though, according to the
14 usual classification of alcoholism, they might be
15 identical. So we haven't come to the point in
16 alcoholism where we can make a diagnosis like, for
17 example, with anemia. We can take two people with
18 an hematocrit of 30 percent but we know that, by
19 doing hemoglobin electrophoresis, they may have
20 totally different kinds of anemia and you would
21 treat them totally differently even though their
22 symptoms are very similar.

23 We maybe someday--I hope, someday--will be
24 able to do that with alcoholism but to have
25 complete lack of divergence across clinical trials

1 would be totally unreasonable today since we are
2 lumping together people who are very heterogeneous
3 not only according to the environment things that
4 Dr. Winokur brought up but also according to the
5 biology of the illness.

6 DR. OREN: Dr. Rudorfer?

7 DR. RUDORFER: Just to follow up Dr.
8 O'Brien's comments, in addition to some of these
9 cross-sectional issues, I just want to remind us
10 about the longitudinal aspect of this disorder.
11 Several of us have made references to mood
12 disorders, a similar kind of chronic relapsing
13 recurrent disease.

14 It seems to me that, just to kind of
15 restate something we have been saying from a
16 different perspective, there are certainly
17 different phases of the illness of alcoholism and I
18 fear that sometimes those have gotten lumped
19 together here today just in terms of talking about
20 treatment of alcoholism.

21 The issue with the percent of patients
22 abstinent at baseline I think is important in terms
23 of considering the phase of the illness so that the
24 European data really point to efficacy in the
25 prevention of relapse in patients who are already

1 abstinent, and not just already abstinent but
2 abstinent following an inpatient detoxification.
3 That is a particular stage of this illness and many
4 people may go through that multiple times during
5 their lifetime or not at all but to intervene at
6 that particular point, I think, is simply not the
7 same as intervening at another point.

8 So, to a certain extent, I see a certain
9 amount of apples and oranges in the European and
10 the U.S. trials.

11 DR. OREN: Dr. Hamer?

12 DR. HAMER: I think it is unfortunate that
13 the U.S. trial was almost an effectiveness study
14 rather than an efficacy study because what was
15 probably needed was an additional efficacy study in
16 the U.S. In terms of the decision we are being
17 asked to make, I think that, regardless of the way
18 that the sponsor presented the data and regardless
19 of the way we listen to it, it is clear from the
20 FDA's charge and from the things that have been
21 said elsewhere that, except for the issue of trying
22 to reconcile what happened in the U.S. study versus
23 the European studies, that the decision to approve
24 and probably, thus, most of our deliberations to
25 that part of addressing efficacy ought to be based

1 on the European studies, and the U.S. study ought
2 to be viewed as simply an additional failed study
3 and we should attach no more and no less weight to
4 that then we would in similar situations.

5 Having said that, the data the sponsor
6 presented showing efficacy of a sort in the U.S.
7 study depended upon what might appear to be a
8 carefully crafted set of covariates figured into
9 the analysis post hoc. Evidence that those
10 covariates are useful and meaningful and, in fact,
11 mean something in the course of the U.S. study
12 would be useful to us.

13 One way to address that might be to take
14 those same covariates or ones as similar as you can
15 obtain in your database and apply them in the
16 European data and see if they improve the effect
17 size. I wonder if you have done anything like
18 that.

19 DR. LEHERT: My name is Philip Lehert from
20 the University of Brussels and the World Health
21 Organization. I have examined, as a third party,
22 the whole database coming from acamprosate from the
23 European and the American data. I have done
24 exactly what you said.

25 I have examined 4,500 patients on the

1 basis of initial motivation, whether they drink or
2 not, and ten or fifteen different covariates. I
3 found exactly the same covariates in European as in
4 the United States. In using the same covariates on
5 the 4,500 patients in my model, I just used the
6 interaction between the United States, yes or no,
7 and the treatment.

8 I found a significant effect of these five
9 covariates and no significant effect of the
10 interaction. This is just telling you that what I
11 have done is justification of these five covariates
12 all around the world.

13 DR. HAMER: Although, depending on which
14 model we are talking about, there were either six
15 or seven covariates used in the U.S. trials.

16 DR. OREN: Could you identify those
17 covariates?

18 DR. LEHERT: Yes. The first I have,
19 unfortunately, not slides of that but I would just
20 like to say that this would belong to part of the
21 dossier. The first was whether or not the patient
22 was motivated. I would like to stress that
23 motivation was part of the European data but just I
24 had to take this data on the CRFs, themselves.

25 The second was the most important variable

1 I found for all the five. This was whether or not
2 the patient was drinking at baseline. I would like
3 to stress that the FDA has done the same analysis
4 of the American study but just on the seven first
5 days.

6 I did it on the basis of time-line
7 follow-back for Day 0, just Day 0. In other words,
8 I am able to look at all the patients that were
9 drinking at baseline and I found this very
10 surprising and very interesting medically speaking
11 results that the interaction of acamprosate and
12 abstinence at baseline was more important than the
13 acamprosate main effect only. This means that
14 before being treated by acamprosate, a patient must
15 be good willing to heal and not drink at baseline.

16 My first impression in the United States
17 data is that when I just look at those patients who
18 are not drinking at baseline, I found different
19 results in line with the European results.

20 I have a very last thing to say which is
21 the four other main effects were medication
22 compliance, and I would like to stress that it is
23 not compliance during the trial but the compliance
24 measure at the beginning of the trial and it is
25 just at the first three days we had this question.

1 My question was to know whether or not, in
2 using the compliance in the beginning, would should
3 have some image of the motivation because you know,
4 in the European data, I had no motivation of the
5 patient. In other words, I had to find another way
6 of measuring the motivation of the patient and I
7 found that in two things.

8 The first was that whether or not they
9 were drinking at baseline and second if they were
10 good willing to be compliant for the three first
11 days. That is what I found. And I finish in
12 saying that a moderate baseline I will call
13 dependency severity I suppose that everyone can
14 understand that the severity of the illness can be
15 of some importance in the predictive model. At the
16 end, just living with a partner and a child was the
17 thought.

18 I am happy to tell you that on my 4,500
19 patients, I was able to collect more than 35
20 percent of the whole variance which makes that my
21 model is somewhat explanatory, something that never
22 happens even in the World Health Organization in my
23 predictive models. I was very happy to have that.
24 And, at the end, what I was able to see is that
25 there was no interaction when I put that out

1 between the U.S. and the non-U.S. data.

2 In other words, there was no interaction
3 between the country, the trials and the product,
4 itself. In other words, my selection of my four
5 different endpoints was probably favorable for
6 explaining exactly. This is what we call a
7 metaanalysis based on individual patient data.

8 Thank you.

9 DR. OREN: Dr. McCormick.

10 DR. MCCORMICK: I would just like to
11 caution the committee that these are not analyses
12 that we have had the opportunity to review and to
13 comment on. In fact, we haven't seen most of the
14 sixteen trials in detail that you have used in this
15 reanalysis. So I would caution the committee not
16 to rely too heavily on something that we have not
17 had the opportunity to review carefully.

18 DR. OREN: As committee members, we are
19 also at the same level of ignorance as far as
20 awareness.

21 Dr. Hughes?

22 DR. HUGHES: Just a quick yes/no question.
23 When you did your analysis, did you look at just
24 abstinence as a covariate and get an
25 interaction--not the full four, just abstinence,

1 because clinically no one is going to say, well, if
2 you got a, b, c and d, I will give you the drug.
3 The most we can get is, perhaps, one thing. So,
4 with just abstinence did you find an interaction?

5 DR. LEHERT: I just used the fact on the
6 TLFP that I had abstinence in drinks every day and
7 I just looked at Day 0 and the very beginning of
8 Day 1. Then I repeat. I apologize to come back to
9 the study, if you allow me that, that this variable
10 was by far the most important predictor of success.
11 I think it was so important that I put that.

12 DR. HUGHES: But I am just asking if you
13 just had the model with just abstinence as the only
14 other thing in the model, did you show an
15 interaction of abstinence with treatment
16 assignment?

17 DR. LEHERT: Yes; I did

18 DR. HUGHES: Thank you.

19 DR. WINCHELL: Just to clarify, this was
20 the European database combined with the American
21 database that you analyzed this way?

22 DR. LEHERT: I analyzed in a metaanalysis
23 file all the data together including the American
24 study. That's right.

25 DR. WINCHELL: So the only subjects who

1 were not abstinent at baseline in your 4,500
2 patients were from the American study and then a
3 few in the U.K. study; correct?

4 DR. LEHERT: Yes; that's correct.

5 LIPHA: Just as a point of clarification,
6 that was submitted as a part of the integrated
7 summary of efficacy.

8 DR. WANG: Can I just add? This is Sue
9 Jane Wang from the FDA. In the analysis for the
10 U.S. study when just the abstinence goal was
11 included in addition to treatment in the center
12 that was included the model, I get the p-value of
13 0.431 of the medium dose compared to placebo. But
14 this is just for the U.S. study.

15 In other words, if you adjust for that
16 prognostic covariate, I do not see a treatment for
17 the medium dose.

18 DR. OREN: Dr. Rudorfer?

19 DR. RUDORFER: A question for the sponsor.
20 We have been discussing today studies that lasted
21 from six to twelve months. I am wondering if you
22 had any secondary measures in terms of function of
23 quality of life that would help us understand the
24 efficacy data better?

25 DR. GOODMAN: We did not include anything

1 regarding quality of life in the NDA. I know that
2 Dr. Lehert has done such an analysis of the
3 European data but it has not been submitted with
4 the NDA.

5 DR. OREN: Dr. Hamer?

6 DR. HAMER: I just wanted to confirm; in
7 the metaanalysis of individual patients that you
8 did, you used all the U.S. and European subjects.
9 So what you don't have is confirmation in the
10 European data alone that the same predictor--that
11 is, abstinence--is predictive in the European data
12 alone as it was or was not in the American data and
13 that also, since basically you had all abstinent
14 patients in the European data, that variable really
15 is largely confounded with the European versus
16 American studies; right--since half the U.S.
17 patients were not abstinent and none of the
18 European patients were--excuse me; half of the
19 American patients were not abstinent and none of
20 the European patients were not abstinent.

21 DR. LEHERT: The U.K. patients are
22 included into this data file metaanalysis and I
23 think, and I presume, that everybody's view of
24 statistics will assume that it would be doubtful to
25 make at least an analysis on only U.K. What I did

1 was that every time I assessed my model, I used a
2 defined protocol for analyzing the interaction of
3 the first order and then every time this
4 interaction was found, I included it in the model.

5 What I found was that only the interaction
6 between abstinence and the treatment was present in
7 my data. But I have done that exactly as you said.

8 DR. OREN: Dr. Hughes?

9 DR. HUGHES: Dr. Hamer, I am thinking very
10 differently than you here. The FDA said that when
11 they had abstinence, they didn't find anything. So
12 if he is finding in the full dataset, it must be a
13 whopping effect in the U.K. to swamp out the lack
14 of interaction in the U.S. Am I thinking right
15 here?

16 DR. HAMER: Or suppose there was no
17 abstinence effect in the U.S. study, that half the
18 patients in the U.S. were abstinent and also in the
19 U.S. study, abstinence didn't make a difference and
20 also in the U.S. study, we didn't show much of an
21 acamprosate effect. In the European studies, let's
22 suppose exclusive of the British study because that
23 is a small portion of the patients they have there,
24 everyone was abstinent and there was an effect,
25 therefore the difference you find in sort an

1 acamprosate effect versus a nonacamprosate effect
2 is fairly confounded with the U.S. versus European
3 studies and also fairly confounded with abstinent
4 nor nonabstinent. So that is not surprising.

5 I don't think I sort of asked my question
6 adequately. What I would have liked to have seen,
7 since they presented three European studies as part
8 of the NDA, would have been an independent
9 confirmation in the data from those three studies
10 alone, not including the U.S. data and not
11 including any of the other European data, that the
12 same set of covariates showed prediction in those
13 data as well, in the same way as they did in the
14 U.S. data.

15 DR. G. COOK: I think I understand what
16 your question is. I think that those analyses have
17 not been done. I think they mainly have not been
18 done because the direct analyses of the European
19 studies, regardless of covariate adjustment, do,
20 indeed, show significant results. The analyses
21 that the sponsor has done with the U.S. study are
22 largely explanatory. They are not being done to
23 prove anything because they couldn't prove anything
24 even if they found something that looked
25 attractive.

1 They are simply an attempt to see whether
2 or not they can identify trends that seem to be
3 consistent with the findings in the U.S. study. A
4 rather key part to the analyses they did along
5 those lines is to hone in on the motivated group
6 and the motivated group that you have to work with
7 for that purpose is the group that is motivated to
8 be abstinent in the strictest sense.

9 You also have to do the analysis that, in
10 the denominator, uses all days, if people dropped
11 out for an alcoholism-related reason and use days
12 up to time of discontinuation if they dropped out
13 for some other reason and that other reason was
14 considered credible.

15 But these analyses are more to identify
16 trends. They are not necessarily analyses that are
17 intended to produce attractive p-values. You don't
18 get attractive p-values that are durable in the
19 U.S. study. You can find suggestions in the U.S.
20 study that some of you may find reassuring but you
21 need to make your decision on the basis of your
22 confidence in the efficacy shown in the European
23 studies with whatever reassurance you are finding
24 from the U.S. study, recognizing that finding that
25 reassurance may be hard.

1 DR. OREN: Dr. Schatzberg?

2 DR. SCHATZBERG: This bears on that. This
3 is for the sponsor. If you look at the dropout
4 rates on the U.S. study, the dropout rates on
5 active drug are pretty high, particularly on the
6 2000 milligram per day dose. They run about 60
7 percent. I am just wondering how you reconcile
8 that kind of dropout with Dr. Mann's comment about
9 the PRAMA study, the German study, in which staying
10 in was seen as a good thing.

11 What kind of assurance can you have that
12 this doesn't mean that this isn't really a kind of
13 a really very fallible, very flawed study where
14 nobody stays in and 60 percent of the patients
15 dropping out. You can't have it both ways in the
16 argument. If you are the sponsor, you can't say,
17 yeah, people stayed in, it's great and then, in a
18 very large-scale trial, you have a very, very poor
19 completion rate.

20 So I don't know how you reconcile the two
21 arguments in the same presentation.

22 DR. GOODMAN: I don't plan to answer that
23 directly but I think that we were trying to
24 demonstrate, and again, just from an interpretation
25 as to how to explain our results in the ITT

1 population, I believe what Dr. Mason was trying to
2 do when she reviewed the demographics was to show
3 you that, collectively, we considered this 2-gram
4 group to be somewhat disadvantaged in a variety of
5 demographic measures, or baseline measures, relate
6 to drinking.

7 Barbara, I don't know if you want to say
8 anything more.

9 DR. MASON: It wasn't just their
10 disadvantage in relation to drinking. It was the
11 fact that they also had fewer psychosocial supports
12 like full-time employment, living with someone.
13 These are all aspects of rootedness and structure
14 that contribute to stability and staying in
15 treatment. Also, in general, in terms of the high
16 rate of dropouts, that is something that has been
17 demonstrated very nicely by the group at the
18 University of Connecticut where they looked at
19 dropout rates across clinical trials involving the
20 addictions, primarily illicit drug use, relative to
21 dropout rates involving clinical trials for other
22 psychiatric disorders.

23 The difference in the rate of dropouts
24 were very marked, particularly as one gets into
25 illicit substance use. So I believe that that

1 probably also colored the dropout rates of the U.S.
2 study that was so characterized by illicit drug
3 use.

4 DR. OREN: Dr. Leon?

5 DR. LEON: Let me follow up on what Dr.
6 Mason just said. The slide that she showed, each
7 of those differences at baseline looks very
8 trivial, 2 or 3 percent. Certainly, none of them
9 were statistically significant so I don't think we
10 should overstate the importance of that. They are
11 on the slides on Page 8 of your handout for anyone
12 that wants to see.

13 I want to say a couple of other things.
14 The intent-to-treat principle was referred to in
15 the analysis. The sponsor referred to that for the
16 pivotal trials. It is my understanding, though,
17 the that intent to treat was applied in an
18 unconventional way where the last observation was
19 carried forward, imputed for all data after
20 subjects dropped out of the trial.

21 In other words, the treatment and
22 assessment were very tightly linked. As soon as
23 someone stopped receiving treatment, they stopped
24 being assessed. Is that correct? Before I get the
25 answer, I look at the intent-to-treat principle to

1 be more tightly interpreted, to mean that, whether
2 or not somebody is receiving treatment, the
3 assessments are continued for the duration of the
4 trial.

5 DR. G. COOK: So that would mean you would
6 only be confident in a trial that had zero
7 dropouts.

8 DR. LEON: No. I just wouldn't call it an
9 intent-to-treat analysis. I wouldn't call what
10 they refer to as an intent to treat invoking the
11 intent-to-treat principle. They are imputing data
12 with the last observation carried forward.

13 DR. G. COOK: So you are saying that you
14 can only do intent to treat when there are zero
15 dropouts.

16 DR. LEON: No; that is not what I am
17 saying. That is what you are saying.

18 DR. G. COOK: But if what they did as an
19 analysis of all randomized patients is not an
20 intent-to-treat analysis, then it can only fail to
21 be not intent to treat because it imputed a failure
22 status to a dropout.

23 What it basically did was it had a certain
24 number of patients complete and, in the European
25 trials, you would have had a status of the patient

1 at the time of completion. The patients who
2 dropped out were basically managed as treatment
3 failures.

4 Now, the FDA did analysis in which they
5 managed those dropouts in other ways. There was
6 also an attempt to look at time to first departure
7 from abstinence as well. That was the
8 time-to-event analysis. That tried to deal with
9 the data. But, to avoid a semantic difficulty,
10 whatever the sponsor called intent to treat, I
11 believe was simply referring to all randomized
12 patients or all randomized patients with a few
13 exceptions who may not have taken at least one dose
14 of treatment. But that was only a small number, I
15 think, in Dr. Mann's presentation.

16 DR. LEON: Just so I understand this, this
17 was all randomized subjects were included and
18 assessed until they dropped out but none, or very
19 few, were assessed after they stopped taking their
20 treatment; is that correct?

21 DR. G. COOK: That's correct. There is
22 not a retrieved dropout.

23 DR. LEON: Although an alternative
24 strategy, assessment strategy, would be to continue
25 to assess the patients after they stop taking their

1 drug.

2 DR. G. COOK: Yes. And that is very much
3 recommended in today's environment although, again,
4 my understanding from Dr. Mann and others is that a
5 patient who drops out when they are being treated
6 for alcoholism is a patient who is very, very
7 likely to relapse, that these patients are very
8 fragile and, to some extent, dropping out is almost
9 tantamount to treatment failure.

10 Perhaps Dr. Mann would want to comment on
11 that further, or Dr. Mason.

12 DR. MASON: Andy, a point I would just
13 like to make in dealing with this population is
14 that once they are gone, they are really gone. It
15 is very hard to track them after they have lost
16 control of drinking. That is why this type of
17 intervention is so critically important just to
18 keep them involved in treatment.

19 Then, if there is a relapse, as long as
20 they are involved, as long as they remain engaged
21 for whatever reason, you can get them through the
22 relapse. I believe that the label for acamprosate
23 says to continue administering during a relapse.

24 But in a clinical trial involving
25 outpatients with alcohol dependence, once they are

1 gone--it is not like where you can very practically
2 say, you are going to continue research assessments
3 even though they have left the treatment arm of
4 involvement. It just tends to go when you have
5 someone really lose control in that way.

6 DR. OREN: Dr. Cook

7 DR. COOK: This is for the FDA. Did you
8 find evidence that they had documented how they
9 were going to handle failures in the
10 analysis--predefined, of course?

11 DR. WANG: For the European trials

12 DR. COOK: Maybe I can make a comment in
13 terms of how I am thinking about the questions.
14 The U.S. trial was failed.

15 DR. WANG: Also, the algorithm was
16 prespecified

17 DR. COOK: Pardon me? So now my question
18 is about the European trials because what I am
19 really trying to focus on is do we have evidence
20 for more than one adequately conducted controlled
21 trial for efficacy? The U.S. trial is not going to
22 be it. The sponsor acknowledges that. But I hear
23 questions about the three European trials.

24 I keep coming back to the point of
25 predefined analysis endpoints, et cetera, and how

1 failures are handled.

2 DR. WANG: My understanding is, for the
3 European trials, the definitions of dropouts, who
4 they are going to evaluate, as I showed in all the
5 slides, I distinguished between dropout as is and
6 as relapsed.

7 DR. COOK: So my question is what did the
8 sponsor predefine as the way they were going to
9 handle dropouts?

10 DR. WANG: I guess maybe we can go trial
11 by trial. The Pelc II trial was a three-month
12 study. Because we weren't very sure about those
13 imputations for the CAD data, cumulative abstinence
14 duration, the way to analyze these data, we can
15 only say the way they do the imputation on the
16 dropout patients, in some trials, they used the
17 worst-case analysis, worst-case here, I mean they
18 would impute all the dropout patients as patients
19 who relapsed.

20 But they don't do this consistently across
21 the three trials.

22 DR. COOK: Let me clarify because I think
23 we are getting into a little bit of an metaanalysis
24 of all the studies instead of coming back to the
25 principle that Dr. Leon pointed out that, to me, is

1 what we have to adhere to. If the three are
2 slightly different but within reason, I want to
3 know what was the analysis they prespecified.

4 Did they write that down? Is that a
5 document that we can verify and did their primary
6 specified analysis show a difference? We have
7 gotten confused. One page would be more helpful
8 than hundreds.

9 DR. WANG: For the three European trials,
10 we really don't know. That is why we are
11 struggling with presenting two ways of dropout as
12 is versus as relapsed. We have trouble with the
13 definition of what is the primary efficacy outcome.
14 It was not really stated.

15 DR. OREN: I would like to, at this point,
16 use this as a segue in our discussion to move away
17 from the first question, which was how can the
18 discrepant results be reconciled and to summarize
19 that.

20 We have heard at least that there may have
21 been different outcome endpoints between the
22 American study and the European studies. There are
23 certainly different levels of rigor. Randomness
24 may play a role and just this happened to be an
25 unlucky American study, different times, ten years

1 ago versus two years ago, different populations,
2 European versus American, different populations as
3 far as comorbid substance abuse, whether people
4 were drinking at the time of entering the study.

5 We have just heard about a metaanalysis
6 that suggests that maybe they can be easily
7 reconciled. I sort of feel like it is the old
8 Perry Mason show where a surprise witness comes in
9 at the end except in this case I am no judge. But
10 we don't have the full evidence to be able to
11 consider it at this point.

12 But this is, I think, at least the
13 background. At this point, this might be a good
14 time to move to the central question of, given the
15 results that we have seen today, and it seems
16 predominantly the European studies that we are
17 interested in, is there sufficient evidence of the
18 efficacy of acamprosate in the treatment of
19 alcoholism to warrant approval.

20 Again, we will take a vote whether to
21 recommend on the efficacy question, to make a
22 recommendation to FDA on how to act in that regard.
23 In that vote, I will go person-by-person through
24 the entire committee asking everybody to register
25 their vote, yes, no or abstain.

1 But, before that, we have open time for
2 discussion and I would certainly invite everyone,
3 in the course of this discussion, to make your
4 viewpoint known if you like.

5 Dr. Fuller?

6 DR. FULLER: I think my question bridges
7 both Question 1 and Question 2 in that we were just
8 discussing whether there were predetermined
9 endpoints in the European studies. I can be
10 corrected if I am wrong, but when I read this
11 document, I thought two of the three European
12 studies did have predetermined endpoints. I
13 believe--I think, analysis, but the predetermined
14 endpoints, as I read them was in the Pelc study was
15 sustained abstinence and in I will call it the
16 German study was time to first drink. I think that
17 is what they had decided initially to use as
18 endpoints.

19 Then I believe that there was also an
20 endpoint for all three studies added on slightly
21 later, the cumulative abstinence days. I think I
22 am speaking correctly.

23 DR. LEON: I am working from this
24 document. I will show you the page numbers.

25 DR. WINCHELL: Which document?

1 DR. LEON: The FDA background document.
2 If you turn to page 32 of the medical record from
3 Dr. Winchell's report, the evaluation of endpoints,
4 Section 5314, the prespecified main criterion of
5 judgment listed in the protocol was, "the
6 consumption of alcohol, no a prior strategy for
7 transforming the data collected into an overall
8 assessment of alcohol consumption was identified."

9 Also, on that page, as long as we are on
10 that page, there is no explicit data-analysis plan.
11 That is the next big paragraph down.

12 If we turn to the Paille study, Page 13 of
13 the statistics in the FDA document, the last
14 paragraph on Page 13, the first sentence, says that
15 no statistical-analysis plan was included here and
16 the protocol-dependent variable is also on that
17 page, the primary efficacy endpoint is here. The
18 number of abstinent days is right above that
19 paragraph, but this is not the one that was used in
20 the analyses that were presented.

21 As long as we are on this trial, I do want
22 to quote from the sponsor's report that there was
23 not a significant difference between 1332
24 milligrams and placebo. I think that has been lost
25 in the discussion today. In the Paille study, the

1 sponsor's report said there was not a significant
2 difference between placebo and the 1300 milligrams.

3 If you want to see where I got that, that
4 is in FDA report, Page 18, of the statistics
5 report.

6 DR. OREN: Although, since the protocol is
7 for approval for 2000, is that still a problem?

8 DR. LEON: Oh; if we are going to ignore
9 all studies that didn't test 2000, we would knock
10 out some other European data, wouldn't we? We
11 would knock out a third of the data from Pelc and
12 what else?

13 The other dependent variable, though, as
14 long as we are going through these, in PRAMA, was
15 time to relapse. That was defined on Page 61 of
16 the medical record from the FDA. That was time to
17 relapse and that was the day on which alcohol
18 consumption started again.

19 So that is my point of clarification on
20 the dependent variable.

21 DR. G. COOK: I think you are identifying
22 some of the same kinds of considerations that the
23 FDA reviewers identified in the course of their
24 review which is that studies that were launched in
25 the late 1980s and the early 1990s did not have

1 detailed statistical statements in their protocols
2 and they may not have had detailed statistical
3 analysis plans that were formally written prior to
4 unblinding.

5 Because of that, it becomes important for
6 analyses of the data structures that those studies
7 produced to be relatively consistent and robust.
8 So that is why it was somewhat important for the
9 FDA, in their reanalyses under any number of
10 conventions, to find similar significant results to
11 what the sponsor found in their analyses. It is
12 much more critical that the majority of analyses
13 agree with one another in terms of p-values below
14 0.05 when you do not have detailed plans that are
15 identified up front.

16 That is why the robustness from both the
17 FDA analyses as well as the sponsor looking at
18 several things all pointing in the same direction
19 was something that had some discussion.

20 DR. OREN: Dr. McCormick?

21 DR. McCORMICK: I tend to agree with Dr.
22 Cook in his assessment of the quality of
23 prospective strategies in some of the older
24 studies. I think, in our frustration when we
25 reviewed these studies, of not having carefully

1 laid out primary endpoints and statistical analyses
2 plans and so forth, led us to take probably the
3 most rigorous approach we possibly could take.

4 So we basically looked at these trials
5 with the perspective of what is the highest bar we
6 could set for these studies and it was complete
7 abstinence. We felt that the studies made it on
8 that criteria.

9 Our discomfort, as I mentioned this
10 morning, is--I think we have almost moved past this
11 problem of not having the prospective strategies
12 before us and that is really dealing with the issue
13 of this imputed data. Do we believe it or not? Is
14 it really credible? Three months of really no
15 ascertainment, can we know what really happened or
16 not?

17 If I were to summarize the crux of our
18 discomfort, it has to be that.

19 DR. MANN: That is something I understand.
20 I think, in looking back at these in our early
21 days, we have the same kind of discomfort. But,
22 fortunately, we have also other data, the ones that
23 were shown by your statistician, which is
24 abstinence rate per visit. Only one day, and you
25 take all the information that you can get and you

1 say someone is abstinent or is not abstinent.

2 You are not computing back or forth or
3 anything. You just say, today is abstinent or nor
4 abstinent. If we do that, then we also have a very
5 clear-cut difference in favor of acamprosate versus
6 placebo. So we do not only rely on these things
7 that make us have some kind of discomfort.

8 We could show it to you. It is in
9 different studies, even. Abstinence per visit is
10 clearly significant in favor of acamprosate as has
11 been shown.

12 DR. G. COOK: Could you comment on how
13 many departures from abstinence might have been
14 missed because of the visit schedule? Do you have
15 a reasonable degree of confidence that the study
16 captured the vast majority of departures of
17 abstinence?

18 DR. MANN: That is, of course, something
19 which I cannot give you exact figures on. This is
20 more what you would call a gut feeling or clinical
21 experience. I think, and you have to be aware of
22 the fact that these patients were not just
23 outpatients which you see maybe three or four or
24 five times. But you have seen them for a week or
25 for two weeks or for three weeks as inpatients and

1 you know all about it, and they have already told
2 you how it was and how bad it was and they have
3 already confessed, more or less, that they had all
4 these terrible experiences.

5 Also, their relatives come in. We have
6 talked to their relatives so we know. They don't
7 have anything to hide anymore. If we see them
8 again after six weeks or after twelve weeks, we
9 know that these feelings of guilt and of shame of
10 admitting that you have a relapse, that is
11 something that we have already talked about in the
12 past.

13 If we miss it, then the spouse called us,
14 "How come you don't pick up that he is drinking for
15 the last two weeks?" That is what is happening, or
16 we have this kind of information in 30 to 40
17 percent of our patients throughout the year.

18 So I think we are fairly confident that we
19 picked up most of the relapses during the year and
20 I am very sure that we did not have a difference in
21 picking up those relapses or not between
22 acamprosate or placebo. The same margin of error
23 certainly is true for both groups.

24 DR. OREN: Dr. Hughes

25 DR. HUGHES: I just want to comment on the

1 last part that you said which is when we get
2 imprecision, which is the word FDA keeps talking
3 about is precision, you don't worry about it as
4 long too much as long as it is not systematic
5 because what it does is it introduces noise. So
6 what the imprecision does it makes it such that
7 those prior studies had to have a bigger effect in
8 order to detect it.

9 So I almost use the imprecision as an
10 argument that those European trials had a bigger
11 effect and we only found this much of an effect.
12 So, actually, the imprecision doesn't bother me
13 very much.

14 DR. KECK: This is sort of jumping on the
15 same bandwagon, but I think this is the beauty of
16 randomization. It is what randomization should
17 control for especially in a study or studies of a
18 drug that is, from what I can tell--I have never
19 seen anybody in such a trial--virtually
20 indistinguishable from placebo.

21 So the likelihood of unblinding or some
22 kind of systematic, as Dr. Hughes said, bias
23 contributing to the results despite the imprecision
24 of methods I think is pretty small.

25 I guess what I am hung up on a little bit,

1 and I would actually appreciate some input from
2 people like Dr. O'Brien and other people who
3 actually done trials in alcoholic patients is Dr.
4 Mason set out a nice table in her slide kit on Page
5 4 comparing the different methods involved in the
6 U.S., which I think is so different than the
7 European studies it is not worth obsessing about
8 anymore, but in the three European studies, how
9 good are these methods because my gut reaction is,
10 in totality, they are not bad.

11 But I want to be comfortable with the .

12 DR. FULLER: You may disagree with me. I
13 don't think they are that bad. Let me try and
14 justify that. It is not uncommon in alcoholism
15 treatment trials, depending on the length of the
16 trial, to interview the person every two or three
17 months. Granted, ideally, you would like to
18 interview them every day, but that is not feasible.

19 Some day, we will have a little wristwatch
20 you can wear that will measure alcohol and we won't
21 be having these discussions. But, until that day
22 arrives, you follow the patient, you track them,
23 you interview them. It is always, then, a
24 retrospective report.

25 Now, the advantage to the time-line

1 follow-back is that, hopefully, it improves the
2 accuracy of that or in that patients are given
3 prompts, holidays as indicators of certain days.
4 They are shown these pictures of quantity. So you
5 may get a better frequency, quantity report but,
6 basically, they are both capturing the data, in a
7 sense, retrospectively. The time interval is two
8 to three months.

9 So I think what was done in the European
10 studies was fine. It could have been improved a
11 little bit by current standards.

12 The other comment I will make has to do
13 with randomization. Even if there was somewhat
14 more imprecision in the data collection in the
15 European studies, this should have been randomly
16 distributed across the treatment groups. So I
17 think the data collection is okay.

18 DR. OREN: Dr. O'Brien?

19 DR. O'BRIEN: I really agree with what Dr.
20 Fuller just said. I should tell you all that I
21 have never had any kind of relationship with Lipha,
22 not a consultant or anything like that, but I do go
23 to Europe a lot and I have read all these trials
24 when they first came out and I have heard them
25 presented, both in English and in French. I have

1 discussed them when they were fresh.

2 I always was aware of the differences in
3 methodology between the European--as a matter of
4 fact, I have slides of their trials that I have
5 used to compare the kinds of studies we have done
6 here and there. I have used these for years,
7 actually, not just recently, because it has always
8 been very obvious.

9 Then a couple of years ago, I was involved
10 with a group that included Dr. Mann to plan some
11 joint American and European studies of alcoholism
12 using the other medication that has been talked
13 about here, naltrexone, a depo form of it. So I
14 think we had people representing many of the
15 European countries where these studies were done.

16 We arrived at combined protocols. But, in
17 the past, they really were different. But, at the
18 same time, I was always impressed and I still am,
19 that there is an effective drug there and that,
20 while I always had problems with the design of the
21 studies, the way they originally were done, I still
22 felt that there was some efficacy there. That is
23 also borne out by my talking with clinicians in
24 Europe who, in fact, believe, for what it is worth,
25 that the drugs are effective.

1 DR. OREN: Dr. Schatzberg?

2 DR. SCHATZBERG: I have a question for the
3 FDA staff. In terms of the PRAMA study, which had
4 longer intervals going out, were you folks
5 satisfied that, in the first 120 days where you had
6 more frequent interviews of the patients, that the
7 drugs separated in terms of either time to first
8 drink, as was presented earlier by Dr. Mann, or in
9 terms of total abstinence because I think if there
10 is an effect still at the 120 days, which is a
11 reasonable length of time for these folks, that
12 would connote substantial benefit for the large
13 group of patients and would still be within that
14 time of frequent assessment so you wouldn't have to
15 worry about whether you are, in fact, having some
16 sort of systematic effect in terms of recall.

17 DR. WINCHELL: I didn't look at 120 days.
18 I know that Dr. Wang replicated the
19 time-to-first-relapse analysis.

20 DR. SCHATZBERG: You did?

21 DR. WANG: As she showed you on her slide,
22 there is a delay of the time to first relapse that
23 comes out statistically significant.

24 DR. SCHATZBERG: Even if you just go to
25 120 days?

1 DR. WINCHELL: Oh; I don't.

2 DR. WANG: I didn't specifically look at
3 120 days, either, but what I would like to point
4 out for the PRAMA study is time to first relapse is
5 the prespecified primary efficacy endpoint. This
6 is the only study that prespecified and had a
7 result coming out consistent with other endpoints.

8 What I am really struggling with was there
9 was a question asked from the committee whether the
10 company used the same model to do the European
11 studies. Because I did so many different analyses
12 in trying to understand what is going on, if what
13 we are seeing here from the U.S. trial is true,
14 which means that the acamprosate median dose has a
15 shorter treatment exposure, more dropouts, by that
16 kind of modeling adjustment, it to make the worst
17 outcome to be better.

18 If this logic applies, then the European
19 trials, using the same kind of definition, it
20 should be in favor of placebo, logically.

21 DR. OREN: Sometimes, the wisest people
22 are silent. I know, Dr. Porrino, you haven't said
23 much today. I wonder if you might share some of
24 your thoughts on this efficacy question.

25 DR. PORRINO: Part of my silence really

1 comes from the fact that I am a basic scientist who
2 is now starting to dabble in looking at human
3 patients and, in particular, alcoholics. I don't
4 conduct clinical trials, so I consider this a
5 remarkable learning experience for me and I
6 appreciate the opportunity to be a part of this
7 because I have learned a tremendous amount.

8 But one of the things that keeps coming
9 up--there are two things that I could comment on.
10 One of them is the discussion of motivation,
11 motivation as an important variable, and the
12 difference between motivation to completely stop,
13 to remain completely abstinent, and those that are
14 willing to slip a little.

15 In our experience, and this is not just
16 experience with alcoholics where I have much less
17 experience, but with marijuana users where I have a
18 tremendous amount of experience. We have looked at
19 subjects at that point and we have asked them sort
20 of that very question, although not exactly phrased
21 that way, and then we have done some brain
22 imagining.

23 I will say that there is a large
24 difference between the brains of those individuals
25 who are willing to slip occasionally and those that

1 are really trying. So motivation is a very
2 important variable and I don't think it should be
3 underestimated nor do I think that combining the
4 two is necessarily appropriate.

5 So I appreciate that it sounds the same
6 and very often is the same, but, actually, in our
7 hands, it looked quite different. Their brains
8 looked quite different so I was quite interested in
9 putting those two together versus separating them
10 which I think is a more appropriate thing to do.

11 The other thing that I can comment on is
12 the fact that, in the patients that I have seen and
13 the alcoholics that I have seen, there is a
14 tremendous desire to have aids and any possible
15 chances to try and remain abstinent. They want to
16 get better, at least many of the ones that I see.
17 And there are no ways to help them.

18 So acamprosate, although it may not be the
19 perfect drug, may certainly work for some where
20 other drugs don't work. I think we need to
21 consider that very importantly.

22 DR. OREN: Dr. Malone?

23 DR. MALONE: I don't really work with
24 drugs and alcohol either, but, in looking at the
25 result of the American study, I think the problem

1 that it didn't find any result, I guess, makes us
2 look more closely at the European studies. So it
3 seems that they were using older methodologies and
4 they didn't have preplanning which is troubling.

5 Then I think you start thinking about the
6 way we deliver medical care now and you wonder
7 whether the results from those older studies will
8 be applicable in the way we deliver care in the
9 United States right now for efficacy.

10 DR. OREN: Beyond that, as a child
11 psychiatrist, there is no data presented with
12 regard to alcoholism in youth. Do you have any
13 thoughts on that?

14 DR. MALONE: We study conduct disorder. I
15 guess maybe these children might go on to drink.
16 They might drink now and we don't really know. We
17 have the same problems with following out
18 populations. Half of them never come back to the
19 studies.

20 But I think one of the things that we did
21 learn is that it seems to me that some of the
22 treatments work better in one setting than another.
23 So, for instance, you might have a treatment that
24 works pretty well in an inpatient controlled
25 setting, but when you take it to the outpatient

1 setting, it doesn't seem to work as well.

2 So this is really the problem I have with
3 the older European data is that it really is about
4 a treatment for a different setting. The only data
5 we have in the current American setting is negative
6 data. Overall, I think that does cast some doubt
7 on the efficacy of using that dataset to say
8 whether the drug will work the way it is used in
9 the United States, the way it would be used, people
10 not getting detoxed, and maybe being on drugs,
11 polydrugs, when they start the treatment.

12 DR. OREN: Dr. Winokur?

13 DR. WINOKUR: I had wanted to come back to
14 the issues that I had raised before but directed to
15 the FDA representatives, Dr. McCormick or Dr.
16 Winchell, and Dr. Malone came back to that
17 beautifully. So I just wanted to follow up on
18 that.

19 One possibility might have been that we
20 have had data from the U.S. study that supported
21 efficacy and then we could put that together with
22 the European studies that were done a bit ago, but
23 also have some data supporting efficacy and look at
24 them together. As it has happened, we generally
25 agreed that we are going to have to primarily look

1 at the European studies and think through how
2 convincing we find the efficacy data to guide our
3 thoughts.

4 We have heard from Dr. McCormick that
5 there is precedent or openness to consider data
6 from the European trials to form an opinion for
7 approval, but, I guess the concern that I had
8 thought about, and Dr. Malone expressed, is if
9 there are differences between the clinical
10 circumstances in the European studies in this case
11 done a while ago and what we have heard to be the
12 case currently in the U.S., and we are talking
13 about a U.S. approval, does that represent a
14 problem from the agency's point of view in terms of
15 that being the exclusive basis in terms of efficacy
16 data?

17 What I am explicitly thinking about is the
18 use of the inpatient detox as a lead-in to having
19 abstinent patients to begin the trial which was
20 done in Europe we have heard is rarely possible in
21 the U.S. We have seen that when a study was
22 launched in the U.S. with the intention of having
23 abstinent patients, there was a very high degree of
24 lack of success in achieving that.

25 So I would like to hear some response from

1 the FDA.

2 DR. McCORMICK: I don't believe that that
3 would be a problem. There are ways to abstinence
4 that are nonpharmacologic. So I guess that is
5 another question that we have to you. I guess that
6 is really the essence of the third question, are
7 there subsets that we could identify that might be
8 more responsive and is abstinent prior to
9 initiation of treatment necessary.

10 But the approval of this product, based on
11 European data, given a different set of medical
12 conditions, would not preclude our approval of this
13 product.

14 DR. OREN: Dr. Schatzberg?

15 DR. SCHATZBERG: It would seem to me that
16 the only positive data you have are in abstinent,
17 fully abstinent, detoxified patients so that there
18 are no data that we have seen that it works,
19 particularly in the U.S. trial--that if you are not
20 detoxified, it will have any effect. So I would
21 think that that one group would have to be there
22 because I think it would be misleading to imply
23 that to the public that you could just sort of hand
24 it out in your office to an actively drinking
25 subject and you are going to have any efficacy that

1 is true.

2 Just a couple of comments because I am
3 going back to the West Coast. I think the FDA has
4 done a service, in a way, to the sponsor in going
5 that extra mile to look at the European database to
6 see if there is something that can be common across
7 the studies in terms of looking at abstinence and
8 brought some clarity.

9 From a consultant's end, we can't comment
10 on the quality of the data because we don't have
11 the books. We really don't know what they look
12 like, but fact that there is some assurance that
13 two or three of the trials, with the drugs
14 separated on a very highly conservative measure,
15 that does have public-health significance and
16 really ought to count in spite of the fact that you
17 have a failed or a negative U.S. trial where you
18 can't say anything except that it didn't work and
19 there was a high placebo-response rate and a high
20 dropout rate, which are two kisses of death, I
21 think, for clinical trials.

22 But I think you and your staff ought to be
23 given some kudos for really trying to bring clarity
24 on this problem although I am not sure that any of
25 us, either as consultants or people on the

1 committee, can tell you what the data looks like.

2 You have got those data right there.

3 DR. McCORMICK: Thank you.

4 DR. OREN: Dr. Ortiz, I know you have been
5 on the left so I haven't always looked straight at
6 you. Is there anything you might want to
7 contribute?

8 DR. ORTIZ: No. I actually had just
9 written down some thoughts. Since we had left
10 Question No. 1, although it seems like we seem to
11 be moving in a direction that the differences can't
12 really be reconciled very well, and we were on
13 Question No. 2, I had come to the same conclusion
14 that Dr. Schatzberg had addressed, that we clearly,
15 I think, seem to have evidence that it is an
16 effective medication for abstinent alcoholic
17 patients.

18 DR. OREN: Dr. Hamer?

19 DR. HAMER: For me, I think the U.S. study
20 is sort of off the table. I think that the
21 decisions need to be based on the European studies.
22 Also, with respect to American study, I want to
23 drag in some really trite, elementary statistics
24 and just remind everyone that failure to reject the
25 null hypothesis doesn't prove the null hypothesis

1 is true.

2 So, merely because, in that U.S. study, we
3 failed to show that acamprosate beat placebo
4 doesn't prove that it doesn't beat placebo. All
5 the noise in the world will just make it look
6 worse. That doesn't carry as much weight. I am
7 reassured that the reanalyses that the FDA carried
8 out with some fairly hard endpoints in a
9 conservative way, in a relatively precisely defined
10 group, as Dr. Schatzberg mentioned, seems to
11 indicate that this at least beats placebo in those
12 trials, and, therefore, as an additional weapon in
13 the armamentarium that is fairly sparse right now,
14 might have some use in medical practice.

15 DR. OREN: Dr. Fuller?

16 DR. FULLER: I second those comments. I
17 am persuaded--I think, from the European data, that
18 acamprosate has some efficacy and it is really
19 based somewhat on the literature. Some of these
20 studies were published before. Of course, the
21 problem with the literature, I recognize you don't
22 have the full report, also, by the material that
23 was presented here, and Dr. Winchell's summary of
24 those reports.

25 So I would second the last two comments,

1 that the European data do indicate efficacy.

2 DR. OREN: Dr. Mehta. Then we are going
3 to one-by-one through everyone to ask you to
4 register your opinion.

5 DR. MEHTA: Just a comment to what Dr.
6 Malone said. Dr. Goodman showed a slide which
7 showed that the core illness for alcohol dependence
8 is similar in the U.S. and in Europe. This was
9 shown based on a letter written to FDA by NIAAA.

10 DR. OREN: Dr. Malone; you have a
11 question?

12 DR. MALONE: No; the study populations
13 were very different, though, because the European
14 one did not really include people who had abusive
15 drugs and it didn't include people who were
16 drinking. So even if just alcoholism is the same,
17 the study populations were very different.

18 DR. OREN: We have a little more time for
19 commentary, it turns out. Dr. Hughes

20 DR. HUGHES: You know, the thing that is
21 hanging me up, and let me try to put it as an
22 analogy. It seems to me the analogy is it is like
23 Lipha is a guy who--let's say a baseball player and
24 he has hit a home run thirteen times in a row, and
25 he comes to somebody else and he says, "I can hit a

1 home run." And the other person says, "Well, I
2 don't know about that."

3 And the guy says, "Well, I tell you what.
4 I will prove it to you. I will do it right now."
5 And he tries to do it right now and he doesn't hit
6 the home run. We know he has hit it thirteen times
7 in a row but he put himself at risk by saying, he
8 can prove it to you to you that next time.

9 So what I am hung up on is, as a result of
10 this trial, I am less confident that this drug
11 works than I was at the get-go. So I am a little
12 bit worried about the precedent. In other words,
13 what would have Lipha had to have done in this
14 trial to disprove it. I am not sure what they
15 would have had to have done for us to say, "You
16 can't have approval."

17 Then, as a result, I worry about the
18 precedent there; that is, that it seems to me that
19 if you make an agreement, that you agree that you
20 have to show your drug works in a subset before you
21 are going to get approval and then you don't get
22 it, that is what we used to call going back in your
23 word.

24 So that is where I am hung up.

25 DR. OREN: Or, to use your baseball

1 analogy, perhaps when a ball player was younger in
2 the different town, he could hit home runs. But it
3 a few years later and he is in a different city and
4 time has passed a little.

5 Dr. O'Brien, did you want to say
6 something?

7 DR. O'BRIEN: Before the baseball, we were
8 talking about detoxified patients. I just wanted
9 to point out that, while it is the mode right now
10 to not admit people for detox or even pay that much
11 for outpatient care, if, indeed, there were
12 evidence about the state of a patient--in other
13 words, if this is emphasized that the people should
14 be drug free before they start on the medication,
15 then this probably would be cost-effective--in
16 other words, to invest something in a
17 detoxification, to start them off clean--because
18 what you would pay at the outset, even if you had
19 to admit them for a few days would be more than
20 offset, if you were an HMO, by the savings over the
21 next few years.

22 We already heard that Kaiser Permanente is
23 using another drug which is reasonably expensive
24 and they must be doing it because it is
25 cost-effective. I think there are data showing

1 that it is cost-effective.

2 So I think that we needn't worry about the
3 fact that, in the American trial, there weren't a
4 lot of people who were abstinent at the beginning
5 because there could have been if, in fact, that had
6 been a requirement.

7 DR. HAMER: I just want to continue the
8 baseball analogy a little bit. I think what has
9 happened here might be that the baseball player hit
10 thirteen home runs and then made the wager with his
11 friend. Then, after they agreed, the friend said,
12 "Oh; by the way, for this at bat, we are using a
13 smaller baseball, you are getting a lighter bat and
14 the pitcher is a foot and a half taller and has
15 been lifting weights for the last five years."

16 DR. OREN: Dr. Malone?

17 DR. MALONE: Back to what Dr. Hughes said,
18 the problem was that the American trial was
19 negative. Was the American trial necessary? They
20 could not have come forward with just the European
21 trial? I don't quite understand.

22 DR. OREN: Do you want to repeat the
23 question?

24 DR. MALONE: Back to what Dr. Hughes was
25 saying. You have these positive trials and now

1 you, somehow, come here to the FDA and you do
2 another trial and it is negative. I would think
3 that would put you in a worse position unless that
4 trial was somehow not necessary.

5 DR. McCORMICK: I guess, to go back to the
6 baseball analogy, we don't expect all home runs.
7 As I mentioned this morning, we frequently do see
8 development programs in which there are trials
9 which may trend in the right direction but are not
10 statistically significant on the primary endpoints
11 and, occasionally, we see some that really show no
12 effect at all.

13 We try to understand why that is the case.
14 We try to assure ourselves, as we are in this case,
15 that the studies that we are relying upon, or the
16 studies that are positive, aren't fallacious.

17 First of all, let me just set the record
18 straight. There aren't thirteen home runs. Let's
19 just say the three pivotal studies that we have
20 reviewed may be characterized as home runs. I see
21 a difference of opinion which we would like to hear
22 from, but the fact that there is a negative study
23 doesn't trouble us. It is not a preclusion to
24 approval.

25 DR. OREN: Dr. Malone?

1 DR. MALONE: Was the purpose of the
2 American study for efficacy or really just safety
3 in the different sample that you get in the United
4 States?

5 DR. WINCHELL: The purpose of the American
6 study, as we understood it when we first met with
7 the company, was because they wanted to make a
8 change from marketing the 333-milligram tablet to
9 the 500-milligram tablet. So, since there were no
10 studies on the 500-milligram tablet, what we agreed
11 to do was accept a marketing application that
12 consisted of a single study using the 500-milligram
13 tablet with a nominally very similar total daily
14 dose of 2 grams, although we didn't expect that
15 complete bioequivalence, as we define it, would be
16 established.

17 We said, okay; if you can do one winning
18 study with the 500-milligram tablet, the other
19 stuff you have got here on the 333 milligrams, two
20 tablets TID, will serve as your supportive evidence
21 of efficacy, your confirmatory evidence. That is
22 how this whole story began.

23 DR. McCORMICK: If I can just add another
24 word. We did conceive of this as an efficacy study
25 and a safety study and it was designed to obtain

1 efficacy information and proof of efficacy.

2 DR. OREN: Dr. Cook

3 DR. COOK: I want to refer to the thirteen
4 home runs again. First of all, there are three
5 studies submitted besides the U.S. study, so there
6 can only be three home runs. Number two, some that
7 are not submitted were not positive, at least one.
8 Number three, I count three studies. Based on the
9 analyses, number one, you could consider none of
10 them at bats on the basis of no
11 prospective-analysis plan.

12 So, to go beyond that is to bend over
13 backwards, I think. I don't care if it was 1988,
14 if we were in the clinical-research center at any
15 major university, if you didn't have a prospective
16 data-analysis plan, the study wouldn't go through.
17 This study would not have been approved for funding
18 at most institutions.

19 Then, if we look at the analysis, two
20 studies seem to be positive, the Pelc II and the
21 Paille. Dr. Wang I think was fairly convincing
22 that, unless you look at it just the right way, the
23 Paille was not. Again, you have to be conservative
24 if you didn't prespecify the analysis.

25 Now we have two studies. That is enough

1 in the analogy that two hits out of four is a
2 pretty good batting average or the idea that more
3 than two well-conducted studies have been positive

4 Now, I have already said I have a problem
5 with well-conducted. But, seeing that this hasn't
6 been monitored, anything in the monitoring that
7 doesn't show that randomization was perfect, that
8 everything was on the up-and-up, in me, may be
9 based on what we have that is tentative and not
10 fully monitored. But, it is very slippery.
11 Anything that is weaker than it already is in those
12 studies is a problem.

13 I worry about the differential dropout
14 rate with placebo in those studies. That is why I
15 am concerned about randomization.

16 DR. OREN: I am going to try and move on a
17 little bit. Before we go on a person-by-person
18 vote, I just wanted to ask the members of the
19 committee if any of you wanted to make any general
20 statement before we each register our opinions.

21 What I will do is I will go
22 person-by-person asking you to say yes, no, or
23 abstain. If you wish, you can argue at that point
24 or share some of your rationale for your vote if
25 you would like. But, before we register those,

1 does anybody want to make any additional point from
2 the committee or from the guests?

3 What I would like to do is, for the
4 nonvoting members of the committee, I just want you
5 to say if you were voting, please share with us how
6 you might vote and why you might do that, although
7 you are obviously not voting.

8 Dr. Mehta?

9 DR. MEHTA: I just wanted to make a
10 comment that I don't know why we are hung up about
11 the prospective plan for analysis. These studies
12 were done 1998 in Europe. That was the state of
13 the art. Probably these are designed a couple of
14 years earlier. If I go back and look at my own
15 studies in this country and major pharmaceutical
16 companies submitting across all the divisions,
17 these are not very different than what they have
18 done.

19 Maybe in clinical research centers, it
20 would be different. Maybe at different places, it
21 might be different, but certainly not in drug
22 trials, particularly submissions. I have never had
23 any comments from FDA statisticians which says
24 that, look, this protocol or analysis is not
25 acceptable. No. That is absolutely not true.

1 DR. OREN: So if you were going to be
2 voting, how would you vote, the question being, is
3 there sufficient evidence of the efficacy of
4 acamprosate in the treatment of alcoholism to
5 warrant approval.

6 DR. MEHTA: Just one additional comment.
7 In another division, the Cardiorenal Division,
8 there was a major ace inhibitor approved for heart
9 failure. The only major and important study was in
10 the United States. It was totally negative. Bob
11 Temple said they had tried, just like what you have
12 done, about twenty different ways of looking at the
13 data to find out if there was some redeeming
14 feature in that study. There was none.

15 Nevertheless, based on the two or three
16 European studies, the drug was approved and it is
17 on the market. Subsequently, several years later,
18 there was an American positive study.

19 All right. Coming back to this drug, I
20 would approve it because there are three studies
21 which have been shown that the drug is clearly
22 different than placebo. The U.S. study, I would
23 just ignore it. It is three to one, batting
24 average.

25 DR. OREN: Thank you.

1 Dr. Hughes, if you were voting, what would
2 you tell us?

3 DR. HUGHES: Vote for approval.

4 DR. OREN: Any additional comment? No?

5 Dr. Porrino?

6 DR. PORRINO: I vote for approval.

7 DR. OREN: Dr. O'Brien? You are obviously
8 influential in the field of alcoholism and whatever
9 you think will clearly have a great impact. So,
10 although you are not voting, tell us how you would.

11 DR. O'BRIEN: Well, first of all, I would
12 like to say that I was extremely impressed with the
13 material that the FDA gave us to prepare for this.
14 I was already familiar with most of these papers.
15 I had reviewed some of them for publication. This
16 was the best exposition I had seen. Drs. Winchell
17 and Wang gave just beautiful presentations this
18 morning.

19 I think they were correctly very rigorous.
20 So certainly I will have to say that, if I had been
21 asked this question before I got these materials
22 and heard them, I would have been much more
23 positive about the drug. But I still feel, and it
24 is hard for me to separate the three studies from
25 what I know about the other group of studies, I

1 would consider two of the other studies not to be
2 positive and all the rest of them, for various
3 reasons, I don't have to go into here--but, in
4 other words, the vast majority were positive.

5 To me, it is remarkable that they were
6 positive because of the imprecision involved, I am
7 critical of some of the design, and also because of
8 all of the problems with studying this. When we
9 have situations where, with antidepressants, there
10 is evidence that 50 percent of the trials fail to
11 show an advantage for a so-called active drug over
12 placebo. We had a debate on this at ACNP a couple
13 of years ago.

14 So, anyway, the fact that you could get
15 this much positive with alcoholism must mean that
16 there is efficacy there. So, based on the evidence
17 that we have, if I had a vote, I would have voted
18 positive.

19 DR. OREN: Thank you.

20 Dr. Fuller, you do have a vote, so please
21 tell us.

22 DR. FULLER: I am going to make this five
23 or six hits in a row. I find, I think as I
24 expressed earlier, the European data are reasonably
25 credible. I think the method of collection of data

1 was reasonably standard. I believe in many of the
2 studies they did breath alcohols at the time of the
3 interview and these are little tricks that are done
4 to try and improve the quality of data.

5 The differential dropout rate in the
6 European studies actually I think is in favor of
7 the medication. My thinking is along these lines.
8 I think the placebo patients felt that they weren't
9 getting something out of the treatment so they were
10 more likely to drop out of treatment.

11 Now, one can always think of caveats.
12 Certainly, if there were problems
13 post-randomization that are not apparent from the
14 material that was given, that would influence me.
15 But, taking it as a whole, the material that was
16 given with its pros and cons, with the summaries
17 prepared by Drs. Winchell and Wang, and based sort
18 of on my clinical and other research experience,
19 weighing all these, I think the European data
20 indicates there is some efficacy for acamprosate
21 and it should be approved.

22 DR. OREN: Dr. Cook

23 DR. COOK: I have one general comment that
24 I can't leave without stating. I don't want to
25 minimize the importance of motivation in treatment

1 but I don't want patients who participated in
2 trials as described as less than motivated because
3 my view is, whether people are abstinent or not,
4 they are motivated to stop this.

5 I particularly want to point out whether
6 people's goal was different. The issue is how they
7 answered the question. The question was, I seek
8 total abstinence versus I seek total abstinence but
9 realize I may slip. I realize I may not be
10 perfect. That actually may be a step in the right
11 direction to somebody who is recognizing they don't
12 have complete control over themselves.

13 Had the question been, my goal is complete
14 abstinence, or my goal is complete abstinence with
15 a few slips, that is a different question. So, I
16 have struggled with this, obviously a lot, and I
17 guess I said before, I do see two positive studies,
18 Pelc and PRAMA, no matter how it is looked at and
19 the only question is verification.

20 So I guess I say yes with that caveat.

21 DR. OREN: Dr. Ortiz?

22 DR. ORTIZ: I am very appreciative of the
23 FDA staff for bringing this confusing picture to us
24 from around the country and to the public to
25 consider what to recommend for the American public

1 given some of this confounding data and confusing
2 data.

3 I was very confused at home going over the
4 data. But I also realize, again having the
5 gentleman from Kaiser that represents, basically,
6 the working alcoholic in the United States that is
7 insured and their willingness to use new
8 medications for this group, in thinking about my
9 population from New Mexico which is a rural
10 population with lots of Hispanics and Native
11 Americans, I guess, again, again going back to the
12 American study, I am concerned that it doesn't
13 represent what the American alcoholic is like.

14 It seems that the issue is really what is
15 shown by the European studies and I also concur
16 that they do appear to show efficacy.

17 DR. OREN: Let's go down to the other side
18 of the table. Dr. Leon?

19 DR. LEON: I have expressed my concerns
20 about the methodology, the prospective--I mean,
21 getting to the home-run analogy, I feel like the
22 fence was moved after the ball landed, as you have
23 heard me say that many times today.

24 So I vote against it. I think there is a
25 need for another study with more rigorous,

1 prospectively defined--that is, defined before the
2 first subject is enrolled--more rigorous
3 methodology using the assessment procedures of the
4 U.S. study.

5 DR. OREN: Dr. Keck?

6 DR. KECK: I am not going to use the
7 baseball analogy. I am actually going to limit my
8 remarks because they have already been well
9 expressed by Drs. Fuller and O'Brien. I will vote
10 in the affirmative.

11 DR. OREN: Dr. Hamer?

12 DR. HAMER: I hate to disagree slightly
13 with my colleague Dr. Leon, but in terms of the
14 prespecified endpoint, I am reminded of an incident
15 four or five or six years ago in cardiorenal in
16 which a clinical trial was stopped early because so
17 many fewer patients were dying with placebo than
18 with drug and then the sponsor had a great deal of
19 trouble getting it approved because death was not a
20 prespecified endpoint.

21 We need to be rigorous, but I think we
22 need to put a great deal of thought into it. I
23 especially complemented the FDA reviewers earlier
24 in person and I want to complement them publicly on
25 the absolutely thorough coherent job they did with

1 this material. My vote would be in favor of
2 efficacy.

3 DR. OREN: Dr. Winokur?

4 DR. WINOKUR: I also vote in favor of
5 efficacy based on the European studies. I echo all
6 the comments about the extremely high quality of
7 their review and presentation by the FDA reviewers.

8 I guess my other comment is, even though
9 I, and many of us, have stated the opinion that the
10 data available do meet our standards for
11 demonstration of efficacy, it is also clear, and
12 especially in the discussion of the U.S. trial,
13 that there is an awful lot more to be learned. I
14 would hope that the sponsor and the investigators
15 in the field would continue to work forward to
16 understand more about the complex variables that
17 are related to effective use of this agent.

18 DR. OREN: Dr. Malone?

19 DR. MALONE: I think everything taken
20 together, I would say that it seems to be
21 efficacious in the sample who undergo detox and are
22 abstinent at the time of starting the drug. But I
23 think, for other samples, you don't have any data
24 for efficacy. So, for that one sample. And the
25 American sample might really end up being different

1 because maybe the alcohols in the United States
2 tend to use what seemed, from the data, a lot of
3 drugs and they are not going to be abstinent when
4 they start taking the medicine.

5 DR. OREN: Actually, we will come to
6 samples as a part of our last question.

7 Dr. Rudorfer?

8 DR. RUDORFER: I would like echo what Dr.
9 Malone just said. I am troubled by the American
10 study in that it seems to have been the best
11 conducted one and I think Dr. McCormick used the
12 term this morning about the targets of the drug,
13 were it to be approved and the U.S. study actually
14 consisted of the real targets.

15 Having said that, I am persuaded that at
16 least two of the European studies did show efficacy
17 under narrowly defined conditions. Patients who
18 were medically detoxified, and even if it is hard
19 to do inpatient nowadays in the U.S., it can be
20 done on an outpatient basis and people who were
21 abstinent on entry to the study, I believe did
22 benefit from the drug. So, overall, I would vote
23 in the affirmative.

24 DR. OREN: For my vote, just so Dr. Leon
25 won't be alone, I will join you in voting in the

1 negative although that is the minority vote. I
2 think that it is not unreasonable to hold a drug to
3 current standards even if the data are from the
4 past. About fifteen years ago, I bought a
5 townhouse from a chronic alcoholic who was one of
6 the designers of the Challenger space shuttle that
7 crashed. If we were trying to evaluate a new
8 proposal for a space-shuttle design and we were
9 being submitted with the original standards because
10 they were good enough in that time, I am sure that
11 we would not accept that because we have learned
12 something since then.

13 I think it behooves us to try and take the
14 latest knowledge and use it and make the best
15 possible use of it. So, although the narrow
16 circumstances of the European studies, I hear them,
17 I am not fully persuaded by them.

18 Having said that, if the FDA
19 were--clearly, there is a strong sense of a
20 majority opinion to encourage the FDA to approve
21 the drug, my encouragement, and this was be the
22 segue into the last question for us to talk about
23 which is do the data support any conclusions
24 regarding subgroups, I didn't hear the sponsors
25 describe the drug as being a home-run hitter.

1 It wasn't described as a panacea. It
2 wasn't a lithium, a penicillin, a fluoxetine. So I
3 think it would be very important that, if the drug
4 were to be approved, that the indications for it be
5 very clearly identified and we should talk about
6 what those indications might be.

7 I would encourage, certainly, the FDA to
8 not be reticent about describing those indications
9 and not hesitate about the marketing of the drug,
10 that its limited value be not overstated in the
11 marketing.

12 So maybe this would be a good time to turn
13 then to the last question which is do the data
14 support any conclusions regarding subgroups and
15 this might give the FDA some guidance in--

16 MS. TITUS: I just want to do a formal
17 vote into the record so there are no phone calls
18 back to me later on what the formal vote was. It
19 was eight yesses, two nos and, of the eight yesses,
20 there were several conditions attached to that
21 which you will see in the transcript when it comes
22 through.

23 DR. OREN: Okay. On the last question,
24 does anybody want to offer some comments or
25 suggested answers

1 Dr. Hughes?

2 DR. HUGHES: I think it would be very
3 important that the FDA replicate the analyses on
4 the 4500. I thought the way the FDA went through
5 the different hypotheses of subgroups, is it
6 severity, is it behavior therapy, is it motivation,
7 is it abstinence, et cetera, that if we did that
8 same sort of analysis with this larger sample size,
9 that would be a very good way to decide on any
10 subgroups.

11 DR. WINCHELL: We would need that efficacy
12 data. We do have the integrated safety data but I
13 don't believe we have got the efficacy data.

14 DR. McCORMICK: We do have the efficacy
15 data on the three European studies that we have
16 been discussing, so that would be feasible.

17 DR. HUGHES: I guess, since I am not a
18 member of anything, I would really encourage Lipha
19 to provide the data of the 4500 patients so that
20 you can replicate that or perhaps some third
21 disinterested party could replicate that, I think
22 would be very important because I think that is
23 your best data source for deciding whether or not
24 to restrict the use to a subgroup.

25 DR. OREN: Dr. Leon?

1 DR. LEON: A point of clarification. I
2 know in one of these documents, it not only
3 mentioned that the indication was for the
4 maintenance of abstinence but also for they
5 recommended one year of treatment. Is that part of
6 this vote, or part of this discussion? It is?
7 Okay. I just want to point out, in my looking at
8 the data which I did, I notice that actually none
9 of the trials treated anyone for a full year. One
10 of them came close, 48 weeks.

11 That was the PRAMA trial. In that, only
12 79 subjects out of the subjects who were enrolled,
13 on active medication completed the trial. So I
14 don't think there is a lot of data there supporting
15 one year of treatment.

16 There is actually no data there supporting
17 one year of treatment and there are 79 subjects
18 that went 48 weeks.

19 DR. HUGHES: If I could comment on that.
20 It is often with medications, physicians use longer
21 durations than are labeled, so, especially with
22 drug-dependent patients in which oftentimes many
23 clinicians feel like a longer duration is
24 warranted, I would hope there would be some
25 flexibility around that duration because I know, in

1 my field, I have done a lot.

2 There was, early on, a statement that you
3 should not use agonist therapy beyond a certain
4 point, should not do this. I think that has been
5 somewhat harmful to field. I would rather see use
6 beyond some point at the discretion of the
7 prescribing physician.

8 DR. OREN: Dr. Rudorfer?

9 DR. RUDORFER: Just another comment and
10 then maybe a question to the FDA related to that.
11 We are specifically not addressing safety issues at
12 this meeting but, in real life, if the drug were
13 approved, of course, physicians would need to
14 consider the benefit-to-risk ratio which I would
15 assume that issues like duration of treatment
16 should be considered at that time.

17 So, for instance, if there are adverse
18 effects that only appear after six or eight or ten
19 months, then that may well influence the length of
20 treatment.

21 DR. McCORMICK: You are absolutely right.
22 We are looking at that and will have that
23 information within the next few weeks.

24 DR. OREN: Two of the predictors, or
25 positive predictors, of good response from the drug

1 were someone being detoxified before starting the
2 use of it and being committed to abstinence. Does
3 the committee accept these particular subgroups and
4 should this be something that the FDA should,
5 perhaps, encourage in its labeling or in terms of
6 marketing or indications?

7 Dr. O'Brien?

8 DR. O'BRIEN: The one about abstinence is
9 something which is physiological. You can think of
10 a lot of other situations in which a recommendation
11 about the use of a drug is dependent upon a
12 particular state that someone is in. So I think it
13 is pretty clear-cut and you can even verify it with
14 the appropriate tests.

15 The one about the motivation is much more
16 difficult because, with all due respect to the
17 questionnaires that were used, no one would really
18 expect that an alcoholic or any other person who
19 has been diagnosed with a substance-use disorder
20 has any consistent level of motivation.

21 We actually have motivational scales that
22 we use that would get at it more specifically, but
23 ambivalence is one of the hallmarks of this
24 disorder so that a person may tell you one minute
25 that, I am totally motivated to be abstinent for

1 the rest of my life and walks out of your office
2 and starts drinking again.

3 This happens all the time. It is not that
4 they were lying in one case. It is just that they
5 are impulsive and things change. So I am not so
6 sure that we would gain very much by that, but I am
7 in favor of recommending that people not use the
8 drug until they achieve abstinence and then it is a
9 drug for maintaining abstinence rather than helping
10 to induce abstinence.

11 DR. OREN: Dr. Malone?

12 DR. MALONE: It seemed also from that data
13 that they would have to be abstinent from other
14 substances, so it wouldn't just be alcohol. You
15 shouldn't be abusing other substances, it seemed to
16 me, at least, comparing the American and European
17 data, that was one of the key differences, was
18 using other substances.

19 DR. OREN: Dr. Winokur?

20 DR. WINOKUR: Just to reinforce that, I
21 think it is important to point out that the only
22 data that we had a chance to look at where we did
23 see efficacy was under circumstances where
24 abstinence was the case at the time of instituting
25 treatment, and the study that didn't go that way,

1 there was a more complicated situation.

2 So, until we have other data to broaden
3 our understanding, that really has to be the
4 starting point.

5 DR. OREN: Dr. O'Brien?

6 DR. O'BRIEN: I think it has been
7 mentioned but it might be worth highlighting that I
8 believe that one of the studies that most people
9 would--that was negative in Europe was the U.K.
10 study where there was a lot of nonabstinence when
11 they started on the medication. So, in a sense,
12 that certainly supports the conclusion that might
13 draw from the American study and it suggests sort
14 of two-for-two, when they were not abstinent, the
15 results were not better than placebo.

16 DR. OREN: Any additional comments from
17 the committee? Do the FDA staff want us to address
18 any other particular aspects?

19 DR. McCORMICK: No. I would like to thank
20 you. This discussion this afternoon has been
21 extremely helpful for us. You have answered,
22 really, all the questions that we have had. Thank
23 you.

24 DR. OREN: I would like to thank the
25 public who has been here for us, the sponsor for

1 presenting their data and, of course, all of
2 members of the committee for your time. I will
3 call this meeting to adjournment. Thank you.

4 [Whereupon, 4:00 p.m., the meeting was
5 adjourned.]

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