

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

PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE
NDA 21-253: ZYPREXA (olanzapine IM, Eli Lilly, Inc.)

Wednesday, February 14, 2001

8 o'clock a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

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Carol Tamminga, M.D., Chairperson
Sandra Titus, Ph.D., Executive Secretary

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Abby J. Fyer, M.D.
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Irene E. Ortiz, M.D.
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Matthew V. Rudorfer, M.D.

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GUESTS

Jean Barbey, M.D.
Edward Pritchett, M.D.

FDA

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Robert Temple, M.D.

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

2 Call to Order

3 DR. TAMMINGA: I would like to call the meeting to
4 order, please. This is the Valentine's Day Meeting, 2001,
5 of the Psychopharmacology Drug Advisory Committee. My name
6 is Dr. Carol Tamminga. I am from the University of Maryland
7 and the Chair of the committee.

8 First, I would like the committee to introduce
9 themselves. Perhaps we can start with you, Dr. Barbey, and
10 go right around the room.

11 DR. BARBEY: Hello. I am Toby Barbey from
12 Georgetown University. I am a cardiologist and a clinical
13 pharmacologist and do a lot of tilt testing and autonomic
14 testing, and I believe that is perhaps why I am here.

15 DR. PRITCHETT: I am Ed Pritchett from Duke
16 University and I am a cardiologist and clinical
17 pharmacologist.

18 DR. GRUNDMAN: I am Michael Grundman. I am a
19 neurologist at the University of California, San Diego.

20 DR. BANISTER: I am Gaurdia Banister. I am a
21 psychiatric nurse right here in Washington, D.C. I am the
22 consumer representative.

23 DR. GRADY-WELIKY: I am Tana Grady-Weliky from the
24 University of Rochester, School of Medicine and Dentistry.
25 I am a member of the committee.

1 DR. TITUS: Sandy Titus. I am the administrator
2 for this committee. I am with the FDA therefore.

3 DR. MALONE: I am Richard Malone. I am a child
4 psychiatrist from MCP Hanneman University.

5 DR. FYER: Abby Fyer, research psychiatrist from
6 Columbia University in New York.

7 DR. ORTIZ: Irene Ortiz. I am a member of the
8 committee. I am a geropsychiatrist from the University of
9 New Mexico in Albuquerque.

10 DR. RUDORFER: Matthew Rudorfer. I am a member of
11 the committee. I am a psychiatrist at the National
12 Institute of Mental Health.

13 DR. LAUGHREN: Tom Laughren, Team Leader for
14 Psychopharm at FDA.

15 DR. KATZ: Russ Katz, FDA, Neuropharm Drugs,
16 Division Director.

17 DR. HAMER: I am Bob Hamer. I am a statistician
18 at the University of North Carolina.

19 DR. TAMMINGA: On line, we have Dr. Oren. Would
20 you like to say hello to us?

21 DR. OREN: Yes. Hi everyone. I will see you in
22 person tomorrow. I am Dan Oren. I am a member of the
23 committee and I am in the Psychiatry Department at Yale
24 University.

25 Conflict of Interest Statement

1 DR. TITUS: I am going to read the conflict of
2 interest statement related to this meeting. The following
3 announcement addresses the issue of conflict of interest
4 with regard to this meeting, and is made a part of the
5 record to preclude even the appearance of such at this
6 meeting.

7 Based on the submitted agenda for the meeting and
8 all financial interests reported by the participants, it has
9 been determined that all interest in firms regulated by the
10 Center for Drug Evaluation and Research which have been
11 reported by the participants present no potential for a
12 conflict of interest at this meeting, with the following
13 exceptions: In accordance with 18 USC 208, full waivers
14 have been granted to Drs. Carol Tamminga, Gaurdia Banister
15 and Robert Hamer. A copy of these waiver statements may be
16 obtained by submitting a written request to the FDA's
17 Freedom of Information Office, Room 12A-30 of the Parklawn
18 Building.

19 In addition, we would like to disclose that Drs.
20 Michael Grundman, Richard Malone and Robert Hamer have
21 involvements which do not constitute a financial interest in
22 the particular matter within the meaning of 18 USC 208, but
23 which may create the appearance of a conflict. The agency
24 has determined, notwithstanding these interests, that the
25 interest of the government in the participation of Drs.

1 Grundman, Malone and Hamer outweighs the appearance of a
2 conflict. Therefore, they may participate fully in all
3 matters concerning Zyprexa.

4 In the event that the discussions involve any
5 other products or firms not already on the agenda, for which
6 an FDA participant has a financial interest, the
7 participants are aware of the need to exclude themselves
8 from such involvement and their exclusion will be noted for
9 the record. With respect to all other participants, we ask
10 in the interest of fairness that they address any current or
11 previous involvement with any firm whose products they may
12 wish to comment upon. Thank you.

13 DR. TAMMINGA: Dr. Katz?

14 Welcome

15 DR. KATZ: Thanks. I just want to give you a very
16 brief welcome and thank you for coming. Thank you for the
17 work you have done already in preparation for the meeting
18 and for the work you will do over the next couple of days.

19 Once again, we have put you in the position of
20 having to help us define a clinical entity for which no drug
21 has been previously approved, and to help us figure out what
22 the best development program for such an indication should
23 be. That is not an easy thing to do, and we appreciate it.
24 We have put you in that position many, many times in the
25 past. I hope some day we will bring you a straightforward

1 antidepressant application or an anxiolytic where you can
2 just tell us what you think the data mean, but that is not
3 today. So, it is a hard job. We appreciate your efforts and
4 thanks for coming. And, I will turn it over to Tom.

5 Overview of Issues

6 DR. LAUGHREN: I would also like to welcome
7 everyone. There are really two parts to the meeting today.
8 The discussion that we would like to have this morning is
9 going to focus on actually what is needed to develop a
10 parenteral form of an antipsychotic. Once we have had that
11 discussion, this afternoon we will begin dealing with the
12 two specific applications for such products, Lilly's
13 application this afternoon and the Pfizer application
14 tomorrow.

15 Now, obviously we have parenteral forms of
16 antipsychotics available for some of the older drugs. We
17 have none for the newer drugs. I think if there is one
18 issue that is probably not controversial, that is the issue
19 of clinicians believing that they need additional parenteral
20 forms of antipsychotics, particularly the newer drugs. I
21 think there is almost no controversy about that.

22 The question is how you develop those products,
23 and that is what I want us to talk about this morning. Now,
24 one approach, and actually this was the approach that was
25 used for the older products, is to say you don't need any

1 efficacy data. The oral forms are already approved for an
2 indication. One approach might be to simply gather some
3 pharmacokinetic information. You want to characterize the
4 product, get some safety data and say that is enough. The
5 problem the FDA has with that is that it involves making an
6 assumption that the rate of absorption doesn't make a
7 difference. The fact is the parenteral form and the oral
8 form are not bioequivalent. The Cmax and the Tmax are quite
9 different for those two products. So, we would have to make
10 the assumption that that doesn't make a difference.

11 We haven't been willing to make that assumption in
12 other settings. For example, for sustained release
13 formulations of drugs we have always required at least one
14 clinical trial to support that claim. So, that is not an
15 attractive option for us, although we are willing to listen
16 to arguments about that.

17 In any case, because there is an interest in
18 developing the parenteral forms, we have had discussions
19 with companies in recent years, and the first advice we have
20 given them is that they have to do efficacy trials. So,
21 then the question is, well, efficacy for what? What are you
22 going to focus on as a clinical target?

23 There are two basic approaches that have emerged
24 in those discussions. The first one is to take the approach
25 that you focus on the clinical entity for which the product,

1 the oral product, is already approved, in this case
2 schizophrenia. In fact, that approach I think is consistent
3 with the views of some clinicians that, when they give the
4 intramuscular form of these medications, they are beginning
5 treatment of the psychosis; that is the first step towards
6 treating the psychosis. They understand, of course, that
7 the switch to the oral is going to occur quickly and that
8 the antipsychotic effect is probably not going to be
9 achieved for some time after the switch to the oral. But
10 they view that as the initiation of treatment.

11 Now, if you were going to take that approach, the
12 question is what kind of a trial would be needed to support
13 that claim? I think one could modify the usual approach in
14 that you would basically test the strategy of initiating
15 treatment with an intramuscular form and then very quickly
16 switching to the oral. You would still be looking down the
17 road at five to six weeks at the endpoint of an
18 antipsychotic effect, but you would be testing that strategy
19 versus placebo. So, that would be one approach to doing
20 this.

21 The alternative view is that you are not really
22 treating the psychosis per se when you are giving the
23 intramuscular form. Rather, you are treating some other
24 phenomenon that occurs as part of that exacerbation, a
25 phenomenon that generally has been referred to as agitation,

1 and the goal here would be to obtain very rapid control of
2 that agitation. This, obviously, has some advantages in
3 terms of drug development because one would hope to be able
4 to do that in a very short-term trial.

5 The question then, however, becomes what is
6 agitation? And, there are a number of definitions of
7 agitation. In Dorland's Medical Dictionary, agitation is
8 defined as exceeding restlessness associated with mental
9 distress. It goes on to define the adjective "agitated" as
10 marked by restlessness and increased activity intermingled
11 with anxiety, fear and tension.

12 Now, DSM-IV also has a definition for what is
13 called psychomotor agitation, which is excessive motor
14 activity associated with a feeling of inner tension. It
15 goes on to say that the activity is usually non-productive
16 repetition and consists of behavior such as pacing,
17 fidgeting, wringing of the hands, pulling of clothes and
18 inability to sit still. Allan Schatzberg wrote an article
19 about a year ago about agitation and he defined it as motor
20 restlessness, such as fidgeting and pacing, associated with
21 an inner tension.

22 So, there is a common theme in all of these
23 definitions of some kind of excess motor activity, along
24 with some kind of inner tension or inner dysphoria. Also, I
25 would note that these are fairly general definitions which

1 obviously would apply to the type of agitation that you
2 might see in a number of different clinical states, in other
3 words, associated with a number of different kinds of
4 diseases -- schizophrenia, bipolar and so forth. There are
5 other definitions as well. Some definitions emphasize more
6 the aggressive aspects that are seen in these patients.

7 Now, one distinction that I think might be worth
8 noting and I would like to have the committee discuss this
9 morning is a possible distinction between what might be
10 called acute agitation and chronic agitation. I think this
11 came up in the context of the meeting we had about a year
12 ago when we were talking about various behavioral
13 disturbances associated with patients with dementia. In
14 that discussion, I had the sense that what was being
15 referred to as agitation in that context referred to a much
16 broader array of behaviors than what we are usually talking
17 about when we are talking about, for example, a
18 schizophrenic patient who is having an acute exacerbation.
19 Behaviors like pacing and wandering, and excess verbal
20 behavior, stereotypic behavior, all of those according to
21 some writers and investigators in this area, are referred to
22 as agitation. So, I am wondering if it is worth thinking
23 about a distinction between those kinds of behaviors which
24 are more persistent as opposed to those that are associated
25 with some acute exacerbation of an illness that has

1 exacerbations, like schizophrenia.

2 I want to summarize a couple of other points that
3 came out of the March 9th meeting last year that I think are
4 of relevance today. Again, there was a lot of discussion of
5 the concept of agitation. However, I didn't think that
6 there was any real consensus that came out of that meeting.
7 Some of the discussants at that meeting felt that the
8 agitation that you see with Alzheimer's disease is fairly
9 specific to Alzheimer's disease. Others argued that it is a
10 more general phenomenon and can be seen, in some sense, as a
11 non-specific finding. In any case, there wasn't any
12 consensus about how to define it. So, I didn't think there
13 was any common view coming out of that meeting about how to
14 develop a drug for agitation.

15 As some additional background information, again I
16 want to make the point that from a regulatory standpoint
17 there are basically two approaches to getting a claim. Most
18 claims are for specific disease entities or syndromes, in
19 this case like schizophrenia or like major depression,
20 rheumatoid arthritis, congestive heart failure, well-defined
21 diseases or syndromes.

22 But there is an alternative approach. We do grant
23 claims for non-specific symptoms like pain and like fever.
24 In those cases, if a company wants to develop an analgesic
25 they have to study it in several different models. That is

1 something to think about here.

2 When we are thinking about whether or not to
3 consider a symptom, a non-specific symptom, there is a
4 thought process that we go through, and I want to just go
5 through some of the things we think about. We like it to be
6 universally defined. We like it to be something which is
7 measured in the same way in whatever disease context it
8 occurs. We like it to respond similarly to medication,
9 again in whatever disease context it occurs. A fourth thing
10 we think about that I think is sometimes controversial is
11 the notion that we would like to have some kind of
12 pathophysiologic understanding of the symptom. Of course,
13 in this area, in psychopharm, we don't have a
14 pathophysiologic understanding of anything that we treat.
15 So, it seems, you know, a bit ridiculous to require that for
16 something like agitation.

17 But, again, I think the bar should probably be set
18 a little bit higher when you are trying to make a claim that
19 something is non-specific because you have to try and tease
20 it apart from the underlying illness. And, people have
21 thought about models of agitation.

22 [Slide.]

23 I don't know if you can see this in the back.
24 This is somebody's model of restlessness. You will notice a
25 lot of arrows and the cortex, and the striatum, and the

1 thalamus, and dopamine, acetylcholine and so forth. You
2 will be pleased outcome know that I am not going to try and
3 talk you through this model. I simply wanted to present it
4 to make the point that people have thought about models of
5 agitation and restlessness, but I don't think we have
6 figured it out yet.

7 Now, another concept that I need to bring up, that
8 I also hesitate to bring up because the concept itself seems
9 to induce agitation, is the notion of pseudospecificity. It
10 comes up in this context because if you are trying to make a
11 case that a symptom is non-specific, it is probably not
12 going to be sufficient to study it in one disease because,
13 by definition, that would be sort of specific. On the other
14 hand, if you are not confident that the symptom is non-
15 specific, then it is probably okay to study it in just one
16 disease. So, that is something that I think needs to be
17 part of the discussion.

18 Whether one is going after a claim that is for a
19 specific disease entity or for a non-specific symptom, in
20 either case there is another requirement and that is that it
21 be well defined and accepted in the community. It has to be
22 something that is recognized. It has to be operationally
23 definable, and it has to identify a reasonably homogeneous
24 population, the latter two, in order to study it. We have
25 to be able to study it and we have to be able to describe it

1 in labeling so that clinicians know how to use the drug to
2 treat the condition.

3 Now, as I mentioned, there are two sponsors who
4 have come forward with programs for parenteral forms of
5 antipsychotics. Later today we are going to talk about an
6 application for Zyprexa intramuscular. We did talk to the
7 sponsor during the development and gave them some advice.
8 We offered them the options of either looking at
9 schizophrenia as a target or looking at something like
10 agitation. They chose to focus on agitation.

11 We also, at the time since that represented our
12 view at the time, we said that it might reasonably thought
13 of as a non-specific symptom, and we advised them to study
14 it in several different models. So, they chose to study it
15 in schizophrenia, bipolar and agitation in dementia. They
16 focused on the excited component of the PANSS as their
17 primary outcome measure, looking at change from baseline
18 after their first dose, after a two-hour period. So, we
19 want you to talk about the efficacy data. Also, there is a
20 safety issue that needs to be discussed for olanzapine, the
21 finding of bradycardia associated with hypotension and then
22 three cases of sinus pause in normal volunteers.

23 Tomorrow we are going to talk about the Pfizer
24 application for ziprisidone IM. Again, we consulted with
25 Pfizer during the development of this product. This

1 consultation occurred earlier than our consultation with
2 Lilly and, at that time, we weren't thinking in terms of
3 agitation as being a non-specific symptom so we did not
4 advise them to study more than one model, and they chose to
5 study it primarily in agitated schizophrenic patients.

6 They developed their own instrument, basically a
7 seven-point scale looking at both agitation and level of
8 consciousness, and we will want you to discuss both the
9 efficacy and the safety data for that application.

10 Now, before we get into discussion, I just want to
11 go through the questions again. So, Steve, if you could put
12 up the questions?

13 [Slide.]

14 The first question is this issue of do you need
15 effectiveness data at all? Might you rely only on
16 pharmacokinetic and safety data, and rely on the
17 effectiveness data for the oral formulation?

18 [Slide.]

19 If you do feel that effectiveness data are needed,
20 what should be the clinical target? In particular, should
21 the focus be on schizophrenia, which is the approved
22 indication for all of these products, or for some other
23 clinical findings that are present during an acute episode
24 of illness that are deemed to require the use of an
25 intramuscular medication?

1 [Slide.]

2 If you consider schizophrenia to be the
3 appropriate target of this development program, what study
4 designs would be optimal to support those claims?

5 [Slide.]

6 If, on the other hand, you feel that agitation is
7 the more appropriate clinical target, how should agitation
8 be defined? What outcome measures would be optimal in the
9 trials? And, again, what study designs would be optimal to
10 support that claim?

11 [Slide.]

12 Then, again, this question of do you think it is
13 worth distinguishing between what might be considered acute
14 agitation and chronic agitation?

15 [Slide.]

16 Then, this important question of, you know, if you
17 do decide that agitation is the appropriate target, is this
18 a phenomenon that is specific to different disease states?
19 In other words, is agitation in schizophrenia unique to
20 schizophrenia? Is the agitation in bipolar unique to
21 bipolar, and so forth? Or, can this really be considered a
22 non-specific symptom in the same sense that you think of
23 pain and fever as non-specific symptoms? If it is
24 considered non-specific, does it need to be studied in
25 different disease models and, if so, which models should be

1 looked at?

2 [Slide.]

3 Finally, at the end of the day for both the
4 specific applications we are going to be asking you the same
5 questions we always ask you, has the sponsor provided
6 evidence from more than one adequate and well-controlled
7 trial that supports the conclusion that either drug is
8 effective for the treatment of agitation? Similarly, have
9 they provided evidence that their product is safe for the
10 treatment of agitation? I am going to stop there. Thanks.

11 Committee Discussion on General Issues of Research on
12 Agitated Patients

13 DR. TAMMINGA: Thank you, Dr. Laughren, for that
14 presentation.

15 As usual, Dr. Laughren laid out very clearly for
16 the committee the questions at hand and the marching orders
17 we have for the morning. What is a little bit unusual today
18 is that we don't start right out with a drug but we start
19 out with a question.

20 Although Dr. Katz thanked us for giving our
21 opinion, nobody usually just asks for our opinions so it is
22 probably kind of a treat to be able to sit and discuss it.
23 This is an important question from a clinical point of view.
24 The discussions that we have today will have a practical
25 impact -- hopefully, will have a practical impact on what

1 the FDA decides to do with these issues, and I think that we
2 should pay attention to offering the broad range of opinions
3 that there obviously are on this particular complex
4 question. Dr. Oren will be on the telephone and can
5 contribute. You are going to have to signal us in some way
6 when you want to make a contribution.

7 This is a question that the committee will
8 discuss, but also we do have experts, both from Lilly and
9 from Pfizer, who will signal when they have a contribution
10 to make, and also other experts in the audience if they are
11 outside of those two camps.

12 Does anybody have some initial comments that they
13 would like to make? Otherwise, I could recommend that we
14 could actually begin the discussion of the questions since
15 the discussion of the questions, as they are laid out, are
16 rather rational in terms of considering the issue.

17 Let's start with the first question which is,
18 actually as I see it, a fairly practical one, are
19 effectiveness data needed to support the approval of a
20 parenteral formulation? I guess the question would be if a
21 company could demonstrate what the kinetic differences are
22 between an oral an antipsychotic medication, is it
23 sufficient to rely on the efficacy data that has already
24 been presented? Matthew?

25 DR. RUDORFER: I am going to make a comment that

1 won't quite be a definitive answer but I think will move us
2 towards that. It occurs to me that, as Tom was speaking, it
3 seemed that intramuscular antipsychotics might be used for
4 at least two different purposes, one, as a drug delivery
5 system to start getting the medication into the system, to
6 be followed by an oral medication where there may not be
7 necessarily an immediate clinical goal, just getting the
8 drug level up.

9 On the other hand, usually there is some acute
10 action that is desired clinically, whether it is treatment
11 of an underlying disease or treatment of a non-specific
12 agitated state. So, in essence, you might say those are two
13 different indications. For instance, hypothetically, if a
14 person has a paranoid ideation around pills and will not
15 take an oral medication but is agreeable to beginning
16 treatment with an intramuscular form, it may be perfectly
17 all right that there be no acute effect at all, other than
18 to get the medication level up and then, at a later point,
19 be switched to oral. So, it is not clear to me that always
20 the effectiveness in terms of an antischizophrenic effect is
21 what is being sought by the intramuscular form.

22 DR. TAMMINGA: I think it would be the usefulness
23 of these compounds in the acute state. Although in both of
24 those states that you are referring to, certainly, the
25 person who is receiving the medication is symptomatic in

1 some way or otherwise the medication wouldn't be given. But
2 I think that we should focus the discussion around your
3 second example.

4 DR. RUDORFER: But there, as Tom pointed out, we
5 are accustomed to thinking that the antipsychotic effect is
6 a delayed one. So, part of the dilemma is that by the time
7 we might clinically expect to see a true, shall we say,
8 antischizophrenic effect the intramuscular form is often no
9 longer being used. So, I think we face a dilemma in terms
10 of looking at antipsychotic efficacy in the drug form that
11 is often used temporarily and then stopped before that
12 action might be seen.

13 DR. TAMMINGA: So, we are working with two drugs
14 now that are both approved for the treatment of psychosis in
15 schizophrenia. And, what you would be saying is that
16 agitation and psychosis is something different.

17 DR. RUDORFER: Yes.

18 DR. FYER: I guess we have been asked for our
19 opinion and this is an area that is outside my personal area
20 of expertise and I will just offer sort of an outside
21 opinion. It seems to me that in the current day and age the
22 question we have to ask is why would you not want to find
23 out how effective this was in a different form of giving the
24 medicine? In other words, why would you not want to find
25 out whether or not the IM form was effective? And, the only

1 situation I could think of where you wouldn't want to get IM
2 efficacy data would be if somebody could provide some
3 scientific explanation for why we were sure in advance that
4 it was going to be effective.

5 I think you could probably give some logistical
6 reasons -- it costs money; it takes time. On the other
7 hand, I think you would prefer to have the money and time in
8 advance than to have a sort of haphazard accumulation of
9 clinical data, especially when you are treating patients who
10 are acutely ill.

11 DR. GRUNDMAN: I think there are many examples of
12 drugs in the neurologic literature where, if you give them
13 parenterally, systemically it is very different in terms of
14 the amount of sedation and type of reaction that you might
15 get if you give it orally. So, I would agree that it would
16 make sense to try to study them using different routes. It
17 just seems like it is common sense.

18 DR. TAMMINGA: Are there examples you can think
19 of, for instance, that would be drugs that are used for
20 neurologic conditions, specific examples of what you are
21 talking about?

22 DR. GRUNDMAN: Well, for example, dilantin can
23 drop blood pressure if you give it parenterally, but if you
24 give it orally it doesn't usually happen. Often you may get
25 dizziness or nausea or vomiting with drugs that are given

1 parenterally but you may not see that if you give them
2 orally; phenobarbital, the same type of situation.

3 DR. TAMMINGA: Dr. Laughren?

4 DR. LAUGHREN: Just to clarify, we would always
5 want safety data. Even if we didn't think it was necessary
6 from an efficacy standpoint, we would always want safety
7 data for a new formulation. The question here really is if,
8 as Mat suggested, we are going to focus solely on the
9 treatment of psychosis and looking at this as a way of
10 initiating treatment, would you need to have efficacy data?
11 Again, FDA's position has been that since the
12 pharmacokinetics are different we are not willing to make
13 the assumption that it is not relevant. So, even if it was
14 for a short period of time, we would still probably argue
15 that we would want to see that strategy, you know, of a few
16 doses of IM followed by a switch to oral studied as a
17 treatment strategy because the pharmacokinetics are not the
18 same as starting from day one with the oral. But we would
19 always want to look at the safety regardless.

20 DR. TAMMINGA: But the idea is on the table that
21 one might not be looking at the antipsychotic effect early
22 on, but one may really be looking at a different target.
23 Therefore, one might need another kind of efficacy study,
24 which gets us into the second question, what might be the
25 clinical target if we decided we needed specific efficacy

1 data?

2 DR. OREN: Dr. Tamminga, this is Dr. Oren.

3 DR. TAMMINGA: Yes, please?

4 DR. OREN: I just wanted to comment on the first
5 question before you do move on to the second one. I think
6 Dr. Laughren has presented us with a very challenging set of
7 questions for today. I am very grateful that the first one,
8 I think, is perhaps a little less challenging than some of
9 the rest.

10 The opinion that the FDA has previously had I
11 think is a very solid opinion as far as requiring efficacy
12 studies for new formulations, or at least one efficacy
13 study. One can think, for example, of a drug outside the
14 psychiatry field, something like minoxidil which, depending
15 upon what formulation one takes and how it is administered
16 to the body, whether it is on the skin or through the GI
17 tract, can have very different primary effects. So,
18 switching from an oral formulation to an IM formulation I
19 think is a compelling reason to require at least one level
20 of efficacy data. Of course, the question then is raised as
21 far as what indication one is looking for, and that is the
22 second question. But for the first question of should there
23 be some efficacy, I think if the formulation is
24 significantly different the FDA's previous position is quite
25 reasonable.

1 DR. TAMMINGA: Thank you, Dr. Oren. There doesn't
2 seem to be very much difference of opinion on this
3 particular question. It seems that the committee is
4 weighing in clearly on the side of yes on the question for
5 efficacy.

6 I have an additional question. The first question
7 that Dr. Laughren asked is really dependent on the
8 assumption that the kinetics are pretty similar between the
9 oral and the IM preparation, and for the two drugs that we
10 are going to consider, although the IM preparation clearly
11 causes higher blood levels earlier, the overall kinetics are
12 rather reasonably similar, and that is in some distinction
13 to our other workhorse, antipsychotic IM oral preparation
14 which is haloperidol where the plasma levels for efficacy
15 are so different with an IM preparation and an oral
16 preparation. As I was going through all the kinetics data,
17 I was wondering about the difference between those, between
18 the current drugs that we are considering today and the
19 older drugs where the IM and the oral kinetics are so
20 different. I am not sure that there is an answer to the
21 question.

22 I think we ought to move on to the second question
23 about the clinical target. We have already pretty much had
24 some suggestions as to what the secondary target might be,
25 which would surely be the agitation that accompanies

1 psychosis. So, I think there is reason to talk about this a
2 little bit more.

3 Clearly, agitation as a concept is different than
4 the other two examples that Dr. Laughren raised, fever and
5 pain. I was trying to think of some examples where fever
6 and pain were not connected to a disease state. Fever and
7 pain are clinical terms and they are almost inevitably
8 connected to a disease state. Agitation is a concept that,
9 you know, all of us have applied to our teenagers and we
10 have oftentimes read about in the newspaper. Agitation is a
11 much broader term than a clinical term, and having agitation
12 be an unmodified target for what we are talking about today
13 seems a little bit too broad.

14 Dr. Laughren also suggested the idea of acute
15 agitation or the agitation of psychosis, or some modifier
16 terms like those that we can consider. Anybody have ideas
17 about those?

18 When you make comments from the audience, if you
19 could use a microphone and introduce yourself.

20 DR. KANE: Thank you. My name is Eric Kane. I am
21 from the University of Rochester. I am here as a consultant
22 for Eli Lilly.

23 I think this brings up a number of issues, and
24 certainly I was a participant on that side of the table at
25 the March 9 meeting last year, and I think we are really

1 talking now about what we are trying to treat in the issue
2 of acute and sustained.

3 Clearly, I think one of the important issues is
4 when is IM medication used. A defining issue is the
5 practical one, and practically it is used in emergency rooms
6 and on inpatient units and in other settings where there is
7 urgent therapy required. Certainly, over the long haul,
8 over five or six weeks, there is no data at this point to
9 suggest that loading with an IM as a delivery vehicle, as
10 you suggested, is going to be preferential to oral
11 medication whenever possible.

12 So, in those settings it is rather non-specific in
13 its use. People come into emergency departments. They are
14 upset. They are threatening. Of course, you are bringing
15 up the issue of agitation really as a continuum, and it is a
16 continuum from the very mild Dorland's definition of a
17 pacing person to the hostile, aggressive, potentially
18 dangerous to self or others person where IM medication,
19 particularly involuntarily, is provided as a way of gaining
20 control and safety in an acute and distressing situation for
21 all involved.

22 Now, as I talk about this, I am talking about it
23 as a non-specific entity or a non-specific symptom. At the
24 same time, I think it is very clear to all of us as
25 clinicians that the agitation that evolves in someone who is

1 schizophrenic with delusions and hallucinations, and is very
2 upset about that, is qualitatively different than the
3 increasing agitation or exacerbations of someone with mania
4 and excitement in the context of mania, or the very uncommon
5 but, nonetheless, at times confrontational dementia patient
6 who needs urgent therapies. Clearly, in the long haul you
7 are not going to use IM medication for any of those
8 conditions if someone has recurrent, sustained or episodic
9 agitation. If we look at the therapies for those long-term
10 conditions or chronic conditions we don't use IM medication.
11 It would be unwarranted and, in fact, probably unethical to
12 not try to find a solution. But, in the short-run the
13 driver is safety.

14 And I think the issue you are bringing up is what
15 is the indication, well, it is the practical, pragmatic one.
16 So, I am trying to use a day-to-day scale or day-to-day
17 sense of things to say you need an acute medicine, but the
18 acute medicine for a non-specific symptom is really quite
19 different from the chronic treatment, which was talked
20 about, where there are very distinctive types of
21 interventions.

22 DR. TAMMINGA: Dr. Kane, if you want to just stay
23 there a minute and consider the question that I actually
24 raised, which was the distinction between clinical and non-
25 clinical agitation. The examples that you used were various

1 examples of clinical agitation. When people use the term
2 agitation more broadly outside of a clinical context, one
3 wouldn't want that confused with what we are talking about
4 today.

5 DR. ERIC KANE: Absolutely, but that is the same
6 as depression and depression. You know, the general
7 population often gets depressed but we don't use
8 antidepressants for everyone. We talk about a much more
9 defined, rigorously characterized situation where clinicians
10 have assessed that there is a need, that there is a
11 functional decrement and, indeed, there may be criteria for
12 those, and whether you wrap the criteria in a scale or you
13 wrap the criteria in a series of words and adjectives --
14 sure, my adolescents -- well, they are no longer adolescents
15 but my former adolescent children certainly became agitated
16 and as young adults they still do. I am not going to give
17 them IM medication, as much as I might have wished to on
18 some occasions but I just took a drink in those instances.

19 [Laughter.]

20 DR. MALONE: I have been thinking about this idea
21 of agitation partly from my experience in treating
22 aggression, and in aggression the treatments I think are
23 dependent upon the diagnosis and maybe the subtype of
24 aggression. So, if you have a schizophrenic patient who is
25 aggressive or becoming more aggressive or agitated, however

1 you wanted to think about it, I think the treatment would be
2 to use an antipsychotic. However, I am not sure that that
3 is true in all sorts of aggression. Aggression is really
4 related often to environment, and even when it is in a
5 psychiatric disorder I think the treatment could be
6 different depending on the disorder.

7 In a sense, agitation is aggression, the type that
8 we are talking about, I think. Probably it is a more acute,
9 explosive form of aggression. But, I think it would be very
10 hard, in my mind, to design studies that would cover all
11 agitation of that type. For instance, probably the most
12 common acute agitation we see in the community is related to
13 substance abuse, or it probably occurs in individuals that
14 we consider aggressive, whether we call them antisocial or a
15 conduct disorder. In many ways, some people might think
16 those are normal.

17 So, when you start considering the safety of using
18 IM medications for a general indication of aggression I
19 think it becomes hard to know who you should look at for
20 safety because once something is labeled for agitation
21 without any qualifications I don't think any of these
22 discussions start occurring, except that it is for
23 agitation. Actually, in terms of adolescents in child
24 psychiatry in patient units, most of the adolescents are not
25 psychotic and they are not demented, but they are agitated.

1 I think that IM medications do get used frequently in these
2 groups that are more akin to, say, personality disorders or
3 other uses in the community.

4 DR. TAMMINGA: Dr. Malone, might you suggest some
5 modifiers for agitation that we could consider?

6 DR. MALONE: Well, whenever I think about the work
7 that we do in aggression, I think the modifier is generally
8 at this point in time the diagnosis that you are treating.
9 So, for instance, we do studies on aggressive conduct
10 disorders where we would say our treatment is for aggressive
11 behavior in conduct disorder but we wouldn't say that our
12 treatment might be for aggression in psychosis. So, I think
13 one of the modifiers would be the diagnosis that you are
14 seeing.

15 Another modifier that we don't have a good way of
16 using in aggression is subtype of aggression. Again,
17 agitation is probably a certain type of explosive,
18 aggressive behavior but at this point I think the modifier
19 would generally be the diagnosis in the studies.

20 DR. KATZ: If I could ask a follow-up question,
21 would you say that you would call something in treatment for
22 aggression in conduct disorders as opposed to aggression in
23 psychosis? Would you do that because you think that the
24 aggression that you are seeing in the context of conduct
25 disorders is fundamentally different, either clinically or

1 in some other way, than the aggression perhaps associated
2 with psychosis? Or, is it because you want to restrict its
3 use to a particular population?

4 DR. MALONE: Well, I would kind of think of the
5 mechanism that started the aggressive behavior and, after
6 having read all these materials, for instance the mechanism
7 for starting aggression in psychosis could be that you are
8 hearing voices, or having some commands to do a certain
9 behavior. I think the mechanism that occurs in conduct
10 disorder is different because they don't hear voices and
11 they are not responding to commands but perhaps they have
12 something else, certain impulsivity or response to
13 environment that you are trying to treat.

14 DR. KATZ: I just want to press a little bit
15 because I think you are getting at some fundamental question
16 when we are talking about aggression but we really want to
17 know about agitation, but we are very interested to know
18 whether or not it is sort of a final common pathway of
19 multiple different mechanisms, and you just see a patient
20 who appears a certain way clinically, and we want to know
21 whether or not you can say, well, yes, we can reliably say
22 that this patient is agitated or, in your case you are
23 talking about aggression, and come up with a treatment that
24 is appropriate for all of those pathophysiologies, or
25 whether or not they need to be specific.

1 So, do you think, even though they may have
2 different mechanisms -- of course, it is not known but they
3 might; it seems reasonable -- do you think there is sort of
4 a final common pathway, or do you think that the aggression
5 looks different clinically, and could you tell if you didn't
6 know the patient's context whether or not this patient is
7 aggressive due to psychosis or conduct disorder? You know,
8 we had talked at the meeting about a year ago and the
9 committee felt that the psychosis of dementia was a specific
10 psychosis associated with Alzheimer's disease. Do we think
11 that is true here, that these are all specific or is there
12 sort of a final common clinical pathway that can be
13 identified and treated successfully?

14 DR. MALONE: Well, I think in aggression there
15 wouldn't necessarily be a final common pathway. For
16 instance, one of the ways that we use the subtype aggression
17 is to look at more planned predatory aggression versus more
18 explosive types of aggression, and I don't think, even
19 though they are both hitting someone, that they have a final
20 common pathway. I think the treatment would be quite
21 different for those two different subtypes of aggression.

22 DR. TAMMINGA: Dr. Barbey?

23 DR. BARBEY: If I may, this may be a preamble to
24 some of the discussion that will take place this afternoon
25 regarding the safety or the relative safety of this compound

1 in normals versus people with a psychiatric diagnosis, it is
2 also tainted by my very different view as a cardiologist who
3 sees haloperidol used fairly indiscriminately in difficult
4 situations, sort of in the CCU. But, in my view, is it
5 possible to distinguish, in other words, the use of
6 olanzapine intramuscularly in people who have reason to
7 believe are already diagnosed or have a problem that will
8 end up requiring long-term oral therapy and, therefore,
9 whatever form of agitation that may be, that seems to me an
10 appropriate use versus the agitation where you suspect there
11 is no underlying psychiatric disorder where you might be
12 dealing more with normals and you don't foresee using the
13 drug in the long term but simply as a chemical
14 straightjacket, and I don't know whether it is possible to
15 make this distinction but my concern would be the use of the
16 drug in the sort of non-specific, non-pathologic states,
17 just sort of agitation.

18 DR. TAMMINGA: I think that physicians could make
19 diagnosis of a psychiatric condition or not a psychiatric
20 condition. It is exactly in this situation that I was
21 wondering about the term agitation since agitation is
22 sometimes connected with a psychiatric diagnosis and other
23 times not connected and, for sure, IM haloperidol is used in
24 ways that psychiatrists don't oftentimes see for agitation
25 that is not connected with a psychosis diagnosis. And, what

1 do you think of that?

2 DR. BARBEY: Well, I guess interestingly, if
3 anything, I have also dealt with acute Q-T interval issue
4 and, if anything, I have seen Q-T prolongation with
5 haloperidol given in the ICU, but my concern would be again
6 with what I know of the compound and other situations that
7 there would be indiscriminate use by psychiatrists, and I
8 don't exactly know how one would get around that but while
9 the efficacy short term may be comparable in terms of
10 achieving sedation or control, I am not sure that the safety
11 profile would be the same. I trust my colleagues here but I
12 don't know about busy physicians should such a drug be
13 available, and I don't know what the experience has been
14 with other drugs in that context.

15 DR. TAMMINGA: I trust that here we are talking,
16 Dr. Laughren, about agitation associated with a psychiatric
17 diagnosis, or should we be talking more broadly, like Dr.
18 Barbey is describing, about agitation associated with
19 anything?

20 DR. LAUGHREN: Well, that is really the question.
21 Is there a general phenomenon of agitation which sort of
22 sits above diagnosis? Can you think of it in the same way
23 you think about pain where you can distinguish it from the
24 underlying pathology of the disease in which the pain
25 arises? Is there a common pathophysiology for something

1 called agitation or is, in fact, agitation different
2 depending on the context in which it occurs? That seemed to
3 be what Dr. Malone was suggesting, that there are different
4 types of agitation. That is really the question.

5 DR. ORTIZ: I would like to argue that we look at
6 agitation a little broadly. I think about patients I have
7 seen in the emergency rooms who were intoxicated with
8 cocaine or heroin, who are extremely difficult to manage and
9 are a life-threatening risk for themselves, and
10 antipsychotics are used. However, the primary medical
11 condition in that case is intoxication of the substance and
12 that has to be addressed. The same thing with the delirious
13 older patient who is delirious from a urinary tract problem
14 or a cardiac condition and, again, you have to address the
15 behavior that may complicate the problem, but the problem is
16 a medical condition that is totally separate from a
17 psychotic condition even if the behavior looks psychotic or
18 psychiatric to the medical management staff.

19 DR. TAMMINGA: Dr. Kane?

20 DR. ERIC KANE: I want to comment on a couple of
21 things. I think it is very clear, and this goes back to
22 what Dr. Malone said, that you have to use environmental
23 controls. Medication shouldn't be thought of as a sole form
24 of intervention in the context of agitation for any cause.
25 I am a little worried that we are getting into an

1 "either/or" situation though when I think both may apply. I
2 think it was Dr. Ortiz who made the comment that the
3 fundamental disorders may be very different but what the
4 clinician is faced with acutely is a rather uniform
5 intervention, and I think that what Dr. Katz is talking
6 about is asking is there a different pathophysiology or is
7 it common and my answer to that is we don't know. We know
8 that benzodiazepines and haloperidol have very different
9 mechanisms of action and they both have utility and are
10 currently used.

11 So, clearly, there are probably underlying
12 biologies that give us different routes into this issue, and
13 what I am really saying is, yes, there are distinctive
14 disorders behind them but in the first 24 hours and the
15 first 20 minutes clinicians are faced with very pragmatic
16 and practical issues, and I think one of the things before
17 the committee is are you going to set up a standard by which
18 real-world activities are tested out in drug development, or
19 are you going to leave it to the community at large to test
20 it out after the drug is released? It seems to me the more
21 you set up studies that are akin to the real world, which is
22 using a compound in different conditions and testing out
23 whether or not it has utility, the better off you are
24 because we know that clinicians are going out there and use
25 it willy-nilly, and I think that the safety data and the

1 other kinds of things are going to be best served, if you
2 are going to talk about agitation at all, by having it used
3 in multiple disorders.

4 DR. TAMMINGA: Dr. Grady?

5 DR. GRADY-WELIKY: I was just going to say
6 something similar to that. I would think it is really
7 important, since agitation is different to define and it
8 does present, at least in my experience, very differently in
9 a schizophrenic patient or a patient with bipolar disorder
10 or an elderly patient who has dementia, since we don't have
11 very good scales yet to measure those differences and there
12 are safety concerns, I think trying to do studies that will
13 target agitation in different settings is very important and
14 not that there is a similar pathophysiology because I don't
15 think we know that yet. I would agree with Dr. Kane.

16 DR. TAMMINGA: Dr. Katz?

17 DR. KATZ: Yes, I had used the expression of final
18 common pathway but perhaps the word pathway was misleading.
19 I acknowledge that we don't know what the pathway is. I
20 really meant a final common clinical presentation that looks
21 the same across all diseases, and this is just restating
22 what Tom has said a number of times already this morning.
23 You know, we have to worry very much about labeling and
24 writing labeling and being able to identify specifically who
25 a drug might be indicated for, and what particular clinical

1 event the drug might be indicated for. We need to be able
2 to reliably come up with a distinction or a definition, if
3 we can, that this drug is useful for these behaviors in
4 these sorts of patients before you have made your diagnosis
5 of psychosis or cocaine abuse. Is there a clinical picture
6 that is common to all of these pathways that we can reliably
7 be able to describe and say these are the people for whom
8 you should use this drug for and this is that is going to
9 work on? Or, do they look different across different
10 disease states, which would imply that we would have to
11 study each individual disease state? This would be not
12 pseudospecific but truly specific. I mean, that is the
13 question on the table.

14 DR. TAMMINGA: The drugs that we will consider,
15 Dr. Katz, today and tomorrow are drugs in which agitation
16 has been studied within the context of a psychiatric
17 diagnosis. So, they are not people that Dr. Barbey was
18 describing before in a medical setting without any
19 psychiatric diagnosis.

20 DR. KATZ: But that is part of the problem or part
21 of the question. If it is, as Tom has asked, a symptom that
22 is at least clinically essentially identical across multiple
23 conditions, how many of those conditions would you have to
24 study in order to be able to say this is a general treatment
25 for the symptom of agitation? The fact that it has been

1 studied only in psychiatric disorders doesn't mean that it
2 might not also be useful in cocaine abuse, or maybe it
3 wouldn't be. As we say, we want to know not only what is
4 agitation but what ought a development program for it look
5 like.

6 DR. LAUGHREN: Just as follow-up to that and the
7 comments that Dr. Barbey made, if it is a general phenomenon
8 and we know it is likely to be used much more broadly than
9 in psychiatric conditions, how broad should the development
10 program be? Should it look particularly at safety in non-
11 psychiatric populations if we have a reason to believe that
12 it is going to be used in non-psychiatric populations?

13 DR. FYER: Only two points, one with respect to
14 what Dr. Katz said. I think about most human phenomena and
15 how similar things are has to do with how closely we look at
16 them and, you know, I think one could look at substance use
17 related agitation and psychotic related agitation and see
18 them as being completely similar if you didn't do a thorough
19 enough mental status to see if the person was having
20 hallucinations or delusions. So, I think we have to be
21 careful when we think about this whole idea of a common
22 picture because it depends on what the lens is that you are
23 looking at and the fact is that we don't know a whole lot
24 about pathophysiology.

25 The second thing has to do with what Dr. Kane was

1 saying about real-world situations, and I agree with him in
2 the sense that we should try to make things as real world as
3 possible because that is where drugs are used. But I think
4 there are two separate things. One is what situations you
5 study the drug in and the second has to do with what kinds
6 of indication and labeling information the FDA requests the
7 sponsor to give.

8 I think that things should be studied in broad
9 populations, knowing that things are going to be used nilly-
10 willy, as somebody said, but the indications of labeling
11 have to take into account two things. First of all, it is
12 our responsibility to make sure people are treated as safely
13 as possible and I think indications have to reflect that.
14 It may be possible to use these things because they may work
15 but they may be a lot safer for an adolescent who is
16 agitated secondary to drug abuse or something to have
17 something else, and we have the responsibility for knowing
18 that people will take what is at hand and, you know, we need
19 to indicate to people an educational function, that is, to
20 label things so that people will be most likely to use the
21 safest kinds of things, and people can always use the other
22 things under the clinical practice allowance that doctors
23 work under. So, I would be conservative in my approach to
24 indications on this since these are drugs with potential
25 serious side effects.

1 DR. MALONE: I am going to make a few comments
2 about the real-world and labeling because I think we are
3 talking about agitation kind of unqualified. I think there
4 are even more examples in medicine to suggest that there are
5 different underlying causes for the same phenomenon,
6 agitation. If I recall from when I was an intern in ICUs, I
7 think most of the agitation that we saw in ICUs, or a lot of
8 it, was related to things like pain and anoxia. And, that
9 agitation might look similar or the same, but I think the
10 treatment would clearly be different and I think the safety
11 issues would be quite different. So, if you labeled
12 something for agitation alone, I mean, this would then take
13 it quickly out of the realm of psychiatry.

14 DR. RUDORFER: If I could take that a step
15 further, I think what we are all saying is that agitation
16 has certain clinical features in common but most clinicians
17 do see distinctions depending on the underlying condition.
18 I don't know that that is necessarily unique even when we
19 are using the non-specific example of fever and pain and,
20 yet, we know that a clinical description of pain, whether it
21 is chronic or intermittent, location and diurnal variation
22 and so on, would differ across different conditions.

23 I think what is different about agitation, it
24 sounds to me, is that it is more linked to the underlying
25 disorder, at least in terms of the mental disorders, and I

1 am more comfortable thinking in terms of agitation
2 associated with specific disorders, and I think that
3 labeling for agitation, where there is not necessarily a
4 diagnosis of any mental disorder at all necessarily, might
5 be more broad than we need or should consider.

6 DR. TAMMINGA: Well, we are talking now about
7 agitation as being a clinical phenomenon that spans
8 diagnostic categories, including medical conditions as well
9 as psychiatric conditions. Are we recommending that the FDA
10 require studies in non-psychiatric diagnoses of agitation
11 since we would all acknowledge that the use in those
12 conditions is rather broad?

13 DR. RUDORFER: Well, I would argue that even
14 though it is clear, as was pointed out earlier that we know
15 little about pathophysiology in mental disorders, it would
16 seem, on the face of it, that where there are clear organic
17 factors, whether it is a medical condition or anoxia, as Dr.
18 Malone pointed out, or substance abuse, it seems on the face
19 outcome it to suggest that the pathophysiology there would
20 be different from that seen in agitation associated with
21 schizophrenia or different mental disorders. It would seem,
22 to my mind, evident and, therefore, I would think that
23 before labeling was so broad as to encompass organic
24 etiologies that specific studies of efficacy and safety be
25 done.

1 DR. GRUNDMAN: Just getting back to the clinical
2 phenotype or the common presentation, I think we can say
3 that these patients as a whole are hyperexcitable. They
4 look like they are under stress. They have excessive motor
5 activities which seem to be a problem with regard to safety.
6 Or, they are either threatening or aggressive. I think
7 there has been general agreement that these intramuscular
8 forms of acute treatments are really focusing on people who
9 are a danger either to themselves or to people around them,
10 or who are destructive to the environment because of this
11 hyperexcited state. So, I think that if we sort of focus on
12 that clinical phenotype that might help us try to define
13 something that we could define as a treatable entity.

14 With regard to the possible underlying mechanisms,
15 I would agree that hypoxia or other underlying medical
16 conditions can certainly lead to that phenotype. I agree
17 that those are certainly things that need to be treated
18 specifically and not treated non-specifically with, you
19 know, the sort of band-aid approach of an antipsychotic.
20 But, I think that is pretty much what people try to do,
21 although I think in an ICU setting sometimes everything that
22 can be done has already been done or, you know, hypoxia has
23 been checked or metabolic problems that can be corrected yet
24 the person is still agitated and some sort of a treatment is
25 necessary.

1 DR. BARBEY: But, indeed, the risk-benefit ratio
2 in that setting might be different and really needs to be
3 explored if it is going to be used in such a setting. So,
4 if you have a patient who is in septic shock and agitated
5 for that reason, he or she may not necessarily be given any
6 old drug that would be a problem. So, if it is going to be
7 used broadly it would seem to me, as a clinician, that the
8 risk-benefit ratio should be established in a broader set of
9 circumstances.

10 DR. TAMMINGA: We are suggesting that the
11 definition of agitation is fairly broad, probably that
12 reflects clinical practice and use and is much broader than
13 the drug treatments that we will be seeing now. Dr. Kech?

14 DR. KECH: I am Paul Kech, from the University of
15 Cincinnati, here today as a consultant to Pfizer. I just
16 wanted to make some comments about some of the comments made
17 today so far.

18 I think you are right, Carol, that we are talking
19 about two things really, one, what the definition of
20 agitation is and, secondly, agitation in relation to what.
21 I think, as Dr. Breier said in the March 9th meeting last
22 year, from a clinical standpoint agitation does have very
23 strong face validity. I think anybody who walks into an
24 inpatient psychiatric unit today could immediately spot the
25 agitated patient down the hall. It is something that is

1 unmissable.

2 I also think there aren't any good data to suggest
3 that agitation is a phenomenon and, again, it depends on how
4 we define it, but is a phenomenon that is unique to mania,
5 to schizophrenia or even the acute agitation in someone who
6 has Alzheimer's disease, differentiating that from more
7 chronic states of agitation and wandering. I think if we
8 were to do a study in which we videotaped patients who were
9 manic, schizophrenic or had Alzheimer's disease, obviously
10 matched for age, and blindly asked people to differentiate
11 specific types of agitation among those people, I don't
12 think that could be done.

13 So, I think we have years and years of experience
14 phenomenologically that these syndromes do share a common
15 phenomenology. Now, whether the pathophysiology is similar
16 I don't think anybody knows. But empirically, in some ways
17 it almost doesn't matter. Typically, antipsychotic drugs,
18 benzodiazepines, work by a very different mechanism of
19 action, clearly in a non-specific way, non-specifically
20 reduce or ameliorate a non-specific syndrome that is common
21 among different states, namely agitation. So, in some ways
22 I think the key thing is how we would define agitation and
23 can we operationally define it, and I think the answer to
24 that is yes. I think it has been by the sponsors of both of
25 these applications. Then, also, can we reliably measure it?

1 There is one other distinction I want to make
2 which is I don't think agitation is aggression. I think
3 agitation can often lead to aggression, but I think they are
4 very different things. I think when we are talking about
5 agitation we need to keep those two issues separate.
6 Obviously, one goal of treating agitation is to prevent
7 aggression but I don't think they are necessarily
8 synonymous.

9 DR. TAMMINGA: Dr. Kech, the two sponsors have
10 defined agitation in these two cases in the context of
11 psychiatric diagnoses so that the current presentation of
12 the data that the committee has to look at is really in the
13 context of psychiatric diagnosis. It is not in the context
14 of an ER situation or of an ICU situation.

15 DR. KECH: I think you are exactly right. I think
16 that is what the focus should be narrowly on.

17 DR. TAMMINGA: Sir?

18 DR. ALLEN: I am Dr. Michael Allen, currently at
19 the University of Colorado but previously I ran psychiatric
20 emergency services in Bellevue. I recently reviewed this
21 literature and studies to date have been in mixed
22 populations and actually have not focused much on specific
23 disorders. In those populations no differences have been
24 found in relative efficacy based on the contributing
25 diagnosis. Generally diagnosis was ascertained after the

1 fact so that the decision to enter the person into the trial
2 was made -- this is obviously ancient history but the
3 decision was made to enter the person into the trial prior
4 to a diagnosis having been made. Diagnosis was, you know,
5 made after the fact. In studies of that type agitation was
6 associated with a response to medication but not based on
7 the underlying diagnosis.

8 So, I am personally of the opinion that agitation
9 cuts across various entities and can be reliably
10 ascertained. I think it is different from anger. It is
11 certainly different from aggression. And, it is an
12 appropriate target. I think the concerns that I am hearing
13 from the committee have to do with relative safety in
14 different populations, but I think that, with the exception
15 of possibly one study that comes to mind in HIV delirious
16 patients, efficacy between the benzodiazepines and the
17 antipsychotics has been comparable, with maybe some modest
18 differences in the effect on aggression per se but agitation
19 has generally responded similarly between the
20 benzodiazepines and the antipsychotics.

21 One other thing, it might be useful to reflect on
22 another regulatory train of thought, which is that HCFA has
23 saddled us with a definition of chemical restraint that
24 seems to suggest that chemical restraint is being done prior
25 to assessment, that if you have done an assessment and have

1 a diagnosis and are then administering a treatment pursuant
2 to a plan of care, then it is not chemical restraint. But I
3 think we probably should assume that much of this will be
4 done prior to assessment.

5 DR. TAMMINGA: Dr. Allen, are you saying that
6 studies have been done across all diagnoses, medical and
7 psychiatric, or just across all psychiatric diagnoses to
8 suggest that agitation is the same in those conditions and
9 responds pharmacologically similarly?

10 DR. ALLEN: Well, the answer to that would be in
11 two parts. The studies were done on all-comers. In other
12 words, if you made it to the setting and you were agitated,
13 then you might be entered into the study. So, all kinds of
14 patients have been entered into such studies. However, the
15 power related to rare diagnoses would be low. There would
16 be a small number of patients in the cells that you may be
17 interested in. So, most patients would have had a
18 psychiatric diagnosis, or a substance use diagnosis, or some
19 combination.

20 DR. TAMMINGA: Have studies been done much, Dr.
21 Barbey, in the kind of populations that you are talking
22 about, about these kinds of compounds?

23 DR. BARBEY: I don't know but I was hoping you
24 would know.

25 DR. TAMMINGA: Does anyone on the committee have

1 any familiarity with studies that have cross psychiatric and
2 medical diagnoses? Dr. Kane?

3 DR. ERIC KANE: Clearly, over the last twenty
4 years there have been anecdotal reports in series done in
5 intensive care units by consultation psychiatrists on the
6 relative safety of infusions and those sorts of things,
7 using benzodiazepines and traditional antipsychotics, and
8 that is part of the reason that both haloperidol and
9 droperidol and finally the benzodiazepines have been used in
10 those settings.

11 On the other hand, there has been nothing that I
12 know of that has been done related to drug development
13 marketing indications, and this really goes back to the
14 point of are you going to have compounds that have been set
15 up and actually tested as part of the indication process, or
16 are you just going to leave it to -- how shall I say? -- the
17 postmarketing release for people to do what they are going
18 to do, which, as Dr. Barbey says, they will do.

19 Another issue is when you start to talk about
20 studies in people with dementia of the Alzheimer type or
21 vascular dementia or mixed dementia, you are clearly going
22 to be ascertaining populations with substantial medical co-
23 morbidity and I think one of the things that the committee
24 can look at is whether or not in those contexts there are
25 adverse outcomes that are indicative of potential problems,

1 albeit it is not an ICU population, it is an emergency room
2 population. I think you mentioned ER. And, many of these
3 studies are conducted in emergency rooms. Dr. Allen talked
4 about "the setting." Well, "the setting" certainly in
5 Rochester is the emergency room. So, I think that in those
6 kinds of settings it is an all-comers type of ascertainment.

7 DR. KECH: Just a quick comment, I think one
8 reason why there is so little overall data in this area and
9 why Dr. Barbey was not able to offer any more studies in
10 response to your question is the issue of informed consent
11 and how difficult it is to study people with agitation,
12 particularly in these settings. We end up not being able to
13 study the most severely agitated, potentially aggressive,
14 assaultive people for obvious ethical reasons. So, I think
15 that is one reason why the field has been so constricted so
16 far.

17 DR. TAMMINGA: Actually, there are some settings,
18 Dr. Kech, in which those informed consent considerations
19 have been solved for the greater good of really studying
20 things like this. So, while it is much more difficult, it
21 is still possible in some settings to study agitation in
22 people unable to give full informed consent. Dr. Katz?

23 DR. KATZ: I just had a question for Dr. Grundman.
24 Help me clarify the first part of your last statement
25 related to the severity. You were talking about the

1 patients who are severely agitated or basically a threat to
2 themselves or a threat to others. Were you suggesting that
3 when you look at that end of things we can consider this a
4 sort of non-specific symptom? Or, only in that context?
5 Or, did I get that wrong?

6 DR. GRUNDMAN: Well, again, I think that the
7 phenotype of these hyperexcitable patients who are restless
8 and who are moving around and active can arise from many
9 different disorders. They can be metabolic. They can be
10 neurological. They can be psychiatric. But, I think that
11 they do tend to look alike when they are in their most
12 severe setting. If you go to the ICU and you see them
13 thrashing around in their bed, or you are in the emergency
14 room and patients are coming in and they are thrashing
15 around and they are violent, you know, they are
16 hyperexcitable, they are tachycardic; their eyes are glowing
17 and they look like they are having a flight-or-fight
18 response, and I think that that type of patient might be one
19 that we would consider treating with intramuscular or trying
20 to bring under rapid control.

21 DR. TAMMINGA: The term psychomotor agitation
22 actually might fit that phenotype better than just the
23 simple term agitation because it sort of draws in the brain
24 and the motor system as associated with the agitation.

25 DR. MALONE: I just wanted to comment. You had

1 made a statement about maybe the committee suggesting that
2 studies need to be done in other populations. At least when
3 I was bringing up those examples, I wasn't trying to suggest
4 that. I was just trying to suggest that the labeling for
5 agitation would be more restricted, but not that you would
6 have to study all these examples if you didn't use the term
7 just agitation.

8 DR. GRUNDMAN: I guess the question about how many
9 different states you need to study agitation in is a good
10 question because I think, you know, if you just study
11 psychiatric disorders that probably doesn't tell you that it
12 is safe in the ICU. On the other hand, it might be very
13 effective in the ICU. It might be better than some of the
14 agents that are available now which sedate the patient and
15 the patient doesn't come arousable for hours later after the
16 agent is given, and you lose your examination and you can't
17 really make coherent assessments. So, these drugs might
18 work or they might not but I think that is an empirical
19 question.

20 DR. TAMMINGA: Dr. Fyer?

21 DR. FYER: I find it a little disturbing that we
22 have this sort of idea that everybody knows what agitation
23 is and there is this commonly accepted term. I don't think
24 that is the case. Talking about Dr. Kane's thing about the
25 real world, I think within the psychiatric milieu most

1 people who have done emergency room work in their residency
2 have a pretty clear idea, but the fact is that drugs, by and
3 large, are not dispensed by psychiatrists. The psychiatry
4 community is a small proportion of the medical community and
5 we have to think about those consequences pretty seriously.

6 The second thing is that the fact that you can
7 identify some common characteristics and show a tape of
8 people and not tell them apart really doesn't relieve us of
9 the responsibility of finding out as much as possible about
10 patients and giving them the most specific treatment
11 possible in any particular situation. I think that needs to
12 be taken into consideration.

13 DR. TAMMINGA: It seems like people around the
14 table are suggesting that the term agitation is much broader
15 than psychiatric conditions, diagnoses. Are we recommending
16 further studies be done from a practical point of view? Dr.
17 Pritchett?

18 DR. PRITCHETT: I will take a shot at this,
19 knowing that I am a cardiologist but I will speak
20 generically about the problem of drug development because I
21 feel that innovation in drug development comes not from the
22 FDA but from the pharmaceutical industry and medical
23 community who identify problems that need treatment, and the
24 pharmaceutical industry comes up with compounds that may be
25 useful. I think the FDA has a very important regulatory

1 role and a very, very important early advisory role because
2 they have seen it all. In most cases all of it has not been
3 published. There is a colossal repository of information
4 about what works and what doesn't work at the FDA that isn't
5 in the public domain. So, I think the FDA has an important
6 role there.

7 But, I think that when we talk about writing
8 labeling for a compound what I think you need to look at is
9 the inclusion and exclusion criteria for the clinical trials
10 that were brought forward and that, for the most part, you
11 wind up with indications that mirror what was used in the
12 clinical trials as inclusion and exclusion criteria. We
13 have learned over the years, for example, that in clinical
14 trials of antiarrhythmic drugs we should exclude patients
15 who have arrhythmias due to electrolyte abnormalities. I
16 would assume that similar ideas would apply in the
17 development of drugs for agitation. You don't give these
18 drugs to patients who are agitated because they are hypoxic.
19 So, we aren't talking about labeling that would include
20 that.

21 What I have found over on the cardiology side is
22 that the whole world is divided into lumpers and splitters,
23 and if you want your drug labeled in these three indications
24 do you do three different studies? Or, do you do one big
25 study that includes all three? I happen to be a lumper. I

1 like one big study that includes all three. As a clinician,
2 I want information about the maximum number of patients who
3 benefit from the proposed therapy. I think that is also
4 consistent with the goals of the pharmaceutical industry who
5 want the largest possible market.

6 At the same time, they would be fools to include
7 in their clinical trials a population of patients in whom
8 the drug was known not to work. For example, if you knew
9 that your drug did not work for agitation due to cocaine
10 intoxication, you would be fools to include it. But I think
11 that to a certain extent there is some trial and error
12 involved here and the industry has to pay the price for
13 that. I mean, they are the ones that are developing the
14 drug and if you are a very conservative company you may come
15 up with a development plan that says I am going to very
16 narrowly target a very specific agitation syndrome in a very
17 specific psychiatric diagnosis and get approval for a very
18 narrow indication. If, on the other hand, you are a very
19 creative, risk-taking company you may say I want a broader
20 indication so I am going to include a lot of other patients
21 even though I have less information about them, and you will
22 wind up either with a program that doesn't work or with much
23 broader labeling.

24 So, I think that there are practical issues here
25 that marry the clinical trial development program, the drug

1 development program with the ultimate labeling, and I don't
2 think we can sort it out in kind of a theoretical way here
3 today.

4 DR. TAMMINGA: Labeling certainly doesn't take the
5 place of medical research or medical practice or medical
6 education.

7 DR. PRITCHETT: No, but I think it is important in
8 terms of how we introduce drugs into clinical medicine in
9 the bounds of labeling which they have.

10 DR. RUDORFER: Just to take that one step further,
11 if we are reviewing clinical trials in which people with
12 active substance abuse were excluded, then it seems to me
13 hard for us to justify labeling that would include such
14 patients.

15 DR. PRITCHETT: No, I would argue strongly that
16 they should be excluded. The FDA has lots of ways to say
17 this. The most benign way is to say that this drug has not
18 been studied in patients with agitation due to cocaine
19 intoxication. The other thing you can say is that it is
20 contraindicated. You know, there are all levels of warnings
21 and statements they can make. Tom is going to sort this
22 out.

23 [Laughter.]

24 DR. TAMMINGA: Dr. Laughren?

25 DR. LAUGHREN: I think it is true that you can

1 handle a lot of things in labeling, but a fundamental
2 question here is what is the minimum development that is
3 needed to get a claim for an intramuscular antipsychotic?
4 If I can use the pain analogy again, given the way we view
5 the phenomenon of pain, we would not accept a development
6 program that focused on only one model of pain. Given the
7 way that pain is thought about, that would not be enough.
8 So, the question is what is the minimum amount that is
9 needed to approve an antipsychotic to be able to label it?

10 DR. PRITCHETT: Can I ask you, Tom, if somebody
11 came forward with a drug that had been studied in
12 postoperative pain for surgical incision pain and said we
13 want labeling for surgical incision pain, would you say you
14 can't have that labeling?

15 DR. LAUGHREN: Fortunately, that is not in our
16 division so I don't have to answer that.

17 [Laughter.]

18 My guess is that that would not be enough.

19 DR. KATZ: Yes, it is just this issue of
20 pseudospecificity that Tom talked about. You know, if you
21 study a symptom in only one condition and you label it for
22 that specific condition is what has been called
23 pseudospecific. In other words, if you only study headache
24 in Alzheimer's patients or fever in Alzheimer's patients you
25 wouldn't want us to approve a drug for the fever of

1 Alzheimer's disease. I mean, that is the idea. If it
2 really is non-specific and cuts across, the idea is to show
3 either that it is effective across a number of different
4 models, and that is one of the questions, what ought the
5 models to be? Or, it is not effective in the others; it is
6 only effective in one, in which case you have sort of
7 operationally defined that it is specific, maybe, in which
8 case that would probably be an appropriate claim.

9 Now, these drugs have been studied in psychiatric
10 indications I guess because these are psychiatric drugs.
11 So, there is a natural sort of place to look. But for all I
12 know, as Michael says, these drugs are as effective in the
13 agitation of anoxia or the agitation or cocaine abuse as
14 they are in schizophrenia. So, these are questions you have
15 to grapple with.

16 DR. FYER: I am a little confused by Tom's
17 comments. I wonder if I could ask him more specifically. I
18 mean, could one give an indication that these drugs are for
19 agitation due to the three disorders they have been studied
20 for, which is dementia, schizophrenia and bipolar disease?
21 And, is there a concern that even if you give it with that
22 kind of specificity they will still be more widely used? My
23 sense is that if the FDA is concerned about that, then they
24 ought to require the sponsors to do more extensive studies.
25 If that is what the issue is, or do some forceful

1 exclusionary process for the labeling.

2 DR. LAUGHREN: If there was the belief that
3 agitation in schizophrenia and agitation in bipolar and
4 agitation in dementia were somewhat different things, that
5 agitation should not be thought of in the same non-specific
6 way as pain, that would be an entirely reasonable approach.
7 I wouldn't have any problem with that. I wouldn't have any
8 problem with the company studying it in just one indication
9 if it were the view of the community that that is a
10 legitimate claim, a real claim that can be defined and is
11 not in some sense misleading.

12 It fundamentally comes down to whether or not the
13 labeling is misleading. Again, it gets back to the
14 pseudospecificity issue. If you really think that this is a
15 non-specific thing, in a sense it would be misleading to
16 only study it in one model. But if you don't know the
17 answer, then I think it is legitimate to study it in the
18 different settings and simply write labeling for that. I
19 think that is perfectly legitimate.

20 DR. GRADY-WELIKY: I have a similar question as
21 Dr. Fyer, with the over-arching concern that with a broader
22 label than just agitation without some type of modifier, it
23 would be used in non-psychiatric medical conditions and the
24 safety concerns come up for me.

25 DR. TAMMINGA: I think the concept of Dr. Laughren

1 brought up about it being misleading, what the FDA would
2 have control over is whether or not the label is misleading.
3 What the medical community is going to do the FDA has much
4 less control over.

5 DR. KATZ: Yes, I don't think we would ordinarily
6 write labeling specifically to exclude off-label use in some
7 sense. As you say, we have little to nothing to say about
8 off-label use. The question is whether or not the thing we
9 approve it for is a bona fide clinical entity, and whether
10 or not we can adequately describe it, and whether or not it
11 is misleading to say this is approved for the agitation of
12 schizophrenia when, in fact, it is a global anti-agitation
13 agent.

14 DR. TAMMINGA: So, we have talked a bit about the
15 definition of agitation and the breadth of the term. What
16 do people have to say about the measures? We have read some
17 examples of the two applications that will be presented this
18 afternoon and tomorrow about the measures and the study
19 designs. I wonder what people's opinions are, if any, about
20 the measures that are used for agitation, for psychomotor
21 agitation and for the study designs? What would be the
22 optimal study designs?

23 DR. MALONE: I thought the measures that were used
24 are very similar to the measures that I am used to seeing in
25 aggression studies and they seemed to be, to me, fairly

1 adequate. So, the measures, for me, didn't seem to be much
2 of a problem.

3 DR. RUDORFER: I would echo that and I would add
4 that we need to distinguish rating scales of symptoms from a
5 diagnostic instrument. So, the studies we reviewed dealt
6 with people who at first had a diagnosis of schizophrenia,
7 bipolar disorder or dementia made, and then agitation was
8 rated and the methodology seemed fine to me.

9 My concern might be for the moment the other end
10 of the spectrum, a potential patient without one of those
11 diagnoses. Let's say we use the example of the adolescent
12 hostile, newly admitted patient. If there has not been a
13 diagnosis made and the person is considered agitated, I
14 don't know that we know enough to say whether or not an
15 intramuscular antipsychotic is indicated. I think it would
16 be a mistake to say that, well, if that individual reaches a
17 certain score on the rating scale that provides an
18 individual for a parenteral treatment in the absence of a
19 diagnosis.

20 DR. TAMMINGA: So, in the discussions that we will
21 have this afternoon and tomorrow, your emphasis would be
22 that this is discussing agitation within the context of a
23 psychiatric diagnosis?

24 DR. RUDORFER: Yes, and if I can go back to the
25 pain example for a moment, it occurred to me that that is a

1 very useful example of the non-specific issue but, at the
2 same time, if an effective anti-pain medication is approved
3 the labeling needs to somehow deal with the fact that that
4 is not suggesting that morphine is appropriate for a tension
5 headache.

6 DR. ERIC KANE: I think one of the practical
7 problems that you are bringing up is when do you make the
8 diagnosis. I think in the emergency room you are faced at
9 times with very agitated, hostile -- as Dr. Grundman was
10 talking about, patients who have tremendous psychomotor
11 excitement and are dangerous, and you don't have the ability
12 to make a definitive diagnosis. I think one of the
13 questions that the committee is then challenged with is are
14 the data sufficient, such that a medication can be applied
15 safely and effectively? Clearly, that is done all the time
16 in emergency rooms around the country, in psychiatric
17 emergency rooms where patients are not able to give you
18 information, where there are not adequate medical record
19 available and, therefore, you are dealing with a non-
20 specific phenomenon, akin to what Dr. Kech was talking about
21 before. So, in some sense, you know, we are in the crux of
22 a problem between how do you best design a study and how do
23 you deal with the real world.

24 DR. MALONE: I think the other crux is how do you
25 label it because you can use it any way you want once it is

1 labeled. So, I think the crux is how you label it.

2 DR. FYER: Dr. Kane, are you aware of any studies
3 with either of the sponsors' products that are coming before
4 the committee or that have been done in that setting you
5 just described? If not, what are the issues about doing
6 those kinds of studies? Because I agree with you. I mean,
7 I think they need to be done and it would be extremely
8 helpful to everybody if they could be.

9 DR. ERIC KANE: I can't talk specifically about
10 Pfizer studies. I am not aware of them at all. In terms of
11 the Lilly studies, the emergency room was certainly one of
12 the settings in which people were accrued, and I think there
13 can be more discussion about that this afternoon. But it is
14 very evident, as Dr. Allen alluded to, that the people who
15 come to the setting, these are places where this work is
16 done. Psychiatric inpatient units and other settings are
17 the other kinds of practical real-world places for these
18 things.

19 DR. FYER: This whole issue about in a real-world
20 setting, are you going to have to give people something
21 before you make a diagnosis?

22 DR. ERIC KANE: Sometimes you do, yes.

23 DR. FYER: Yes, everybody knows that. But the
24 thing is that is an issue in terms of this definition of
25 agitation. My personal opinion would be, since there is

1 this off-label clinical use thing that people can always
2 resort to, that the FDA ought to be more conservative in
3 labeling and stick to the facts. But the ideal solution
4 would be for larger studies to be done in that setting.

5 DR. ERIC KANE: Well, I think you are also then
6 bringing up a variety of other confounds and questions. The
7 issue of informed consent although, as you said, there are
8 ways of dealing with this -- the issue of informed consent
9 for the most extreme people, as Dr. Kech mentioned, is
10 really a very, very complex one, especially in an emergency
11 room. The other kinds of questions about how you would do
12 that in an intensive care unit or other kinds of settings
13 becomes even more complicated when you may have
14 fundamentally competency problems beyond anything else. In
15 any case, I am sympathetic to that and I think people can
16 address that. I am not really answering your question.

17 DR. FYER: I think it is a difficult issue. I am
18 really talking about emergency rooms. In ICUs, we have some
19 sense of what most people's diagnosis is. It seems to me
20 that if you want to go for a very broad indication, then
21 either you have to do the studies in a broad way, even if
22 they are difficulties inherent in them -- everybody knows
23 clinical research is difficult and some forms are more
24 difficult -- or there needs to be some consensus that such
25 things are so completely unfeasible that the social benefit

1 of allowing non-empirically based treatment is justified.

2 DR. ERIC KANE: I would argue whenever possible to
3 try to set up a situation where you are going to have
4 multiple diagnoses. You then have to say how many people
5 can I accumulate in a particular diagnostic entity in order
6 to look at whatever you are looking at. I am not even
7 talking about agitation now. I think that there are certain
8 things that are diminishingly rare that you are not going to
9 get them in an emergency room. Clearly, when you start
10 saying, look, I am going to look at schizophrenia, bipolar
11 disorder and mania and dementia of the Alzheimer type you
12 are starting to collect the three largest groups, the fourth
13 being substance abuse, of the kinds of problems that you are
14 going to have with agitation in an emergency room setting.
15 That is the beginning of a process, I think, for trying to
16 address does a particular therapy have utility. I think
17 that it is then up to the regulatory agency and the company
18 to work out how much is enough. I am not a labeling expert
19 so I will stay away from that part of your comment.

20 DR. FYER: I think we are sort of having a little
21 difficulty in that there have been a number of people who
22 have said, well, you really have to be able to give these
23 drugs to people without knowing their diagnosis because this
24 is the real-world situation.

25 DR. ERIC KANE: It happens sometimes.

1 DR. FYER: Of course, and everybody knows that. I
2 guess the thing that needs to be addressed head-on is to
3 what extent is it really that difficult to do that kind of
4 research, and is it justified, given that difficulty, to
5 proceed without empirical basis in terms of drug approval
6 and labeling.

7 DR. TAMMINGA: Dr. Katz?

8 DR. KATZ: As Dr. Fyer says, there are lot of
9 difficulties in doing research, but the question is what is
10 the minimum amount of data that we would need to approve a
11 drug for this thing called agitation? I mean, the committee
12 could decide that we really need a global anti-agitation
13 claim and that you have to study other indications. So,
14 that is the real question here, what is the minimum amount
15 of information that we need to be able to approve a drug for
16 agitation, and is it appropriate to link the claim of an
17 effect on agitation to specific psychiatric diagnoses or
18 other types of specific diagnoses, or does it need to be
19 wider than, let's say, the psychiatric diagnoses? And, if
20 it is appropriate to link it to psychiatric diagnoses alone,
21 as Tom says, because we really don't understand what the
22 different agitations are or what the pathophysiology is,
23 should we require companies to study multiple different
24 psychiatric indications or is agitation one specific
25 psychiatric diagnosis acceptable and, therefore, we can even

1 further narrow the claim to that particular diagnosis? I
2 mean, these are the sort of minimum requirement type
3 questions that we need answered.

4 DR. TAMMINGA: Well, I think the answers to some
5 of those questions or some more considerations will come up
6 in the specific discussions of the request in front of the
7 committee. It would seem to me that most of the committee
8 would readily agree that agitation as an entity is different
9 from psychotic symptoms or manic symptoms or dementia, and
10 that the study designs that have been proposed may be rather
11 appropriate to that condition. There wasn't a lot of
12 discussion about the measures used, except for a positive
13 comment.

14 The question that Dr. Laughren raised before about
15 the acute versus the chronic distinction, sometimes clinical
16 terms aren't as precise as one would wish them to be in drug
17 development, and certainly acute and chronic to characterize
18 one set of things may be different than we mean by acute and
19 chronic here. But acute agitation seems like what Dr.
20 Grundman was describing, whether it is in the emergency
21 room, whether it is a psychiatric condition, whereas chronic
22 agitation is sometimes that is really considerably different
23 from that.

24 I would like the committee to spend a little time,
25 since Dr. Laughren brought that up specifically, talking

1 about the acute versus the chronic distinction within
2 psychiatric diagnoses, for sure, because that is where this
3 distinction originally came from. It also may be
4 appropriate with the medical conditions but it may be less
5 clear there.

6 DR. GRADY-WELIKY: I have a question just in terms
7 of the specific question. I think there is a difference
8 obviously between acute agitation and chronic agitation, and
9 is the question is it worthwhile making that distinction as
10 it relates to IM drug development or IM approval of an
11 antipsychotic?

12 DR. LAUGHREN: It probably mostly has to do with
13 how agitation is characterized in labeling. Again, I think
14 it goes back to the discussion we had about a year ago when
15 my sense was that when experts in dementia talk about
16 agitation, they are talking about something somewhat
17 different than what we are discussing here today. They are
18 talking about a much wider array of behaviors, including
19 more persistent behaviors, than the types of emergent
20 behaviors that we are seeing in psychiatric patients who are
21 having an acute exacerbation. So, I just wanted to get some
22 sense from the committee of whether or not you think it is
23 useful making that distinction because, again, at some point
24 if we approve either of these products we will have to write
25 labeling and we will have to try to define agitation in some

1 way, and anything we can do to make that more precise would
2 be helpful.

3 DR. BANISTER: I guess I have more of a question
4 than a comment because I know some of the discussion earlier
5 talked about when we were looking at the emergency room or
6 the ICU that we were talking about agitation in a very acute
7 setting. I am trying to understand from a consumer's
8 perspective, I guess chronic agitation is certainly
9 something long-term and I guess what I see in my mind is not
10 acute where we are bordering on aggression or violence and I
11 don't want to put the two together. I would like to know
12 what would be some of the reasons we would give an IM
13 injection.

14 DR. TAMMINGA: Would you clarify that just a
15 little bit more? In an emergency room setting?

16 DR. BANISTER: No, what I meant was when I am
17 looking at agitation from an acute or chronic perspective, I
18 can certainly understand the need for an acute kind of event
19 needing to give an IM. I am trying to understand what kind
20 of an event would constitute the need for an IM injection
21 for chronic agitation.

22 DR. TAMMINGA: I am not sure if anybody would
23 support that. Let's find out first if any of the advisers
24 today would support the use of IM medication for a chronic
25 agitation as Dr. Laughren presented it and in the context

1 that we talked about before.

2 DR. FYER: I don't know whether I would support it
3 or not support it but somebody gave an example of a patient
4 who had a delusional resistance about oral medication. I
5 don't think routinely we would, but I think one could
6 imagine situations like that.

7 DR. RUDORFER: I am wondering if the key variable
8 we are thinking about is actually duration of treatment with
9 the IM preparation. In other words, as Dr. Kane pointed out
10 before, IM medication is not designed for long-term
11 treatment. I could see where if a patient is presenting for
12 treatment in the midst of what appears to be a chronic
13 agitation situation in terms of initiating treatment if the
14 patient is unable or unwilling to begin with oral treatment,
15 one could make the case that, well, if one uses an IM
16 preparation for a day or two and relieves their agitation
17 they are more agreeable to switching to oral medication. I
18 could see that scenario but, again, I think when we talk
19 about chronic agitation with a treatment with IM medication,
20 we are not talking about chronic treatment.

21 DR. GRUNDMAN: Maybe the distinction between acute
22 and chronic isn't necessarily the key element that we are
23 thinking about. Maybe it has to do more with how
24 threatening or how much of a danger the behavior is to the
25 patient or to the environment or to other people. It seems

1 to me that in those situations the patient is uncooperative
2 and we need to bring the behavior under control rapidly
3 through some means. If you can talk the patient down, that
4 would be nice. If you can calm them down, put them in a
5 nice, quiet room and have a nice little chat, that would be
6 nice. But that doesn't always work. It seems like that
7 situation is the kind of situation where you might want to
8 give some parenteral form of the medication.

9 DR. OREN: This is Dr. Oren.

10 DR. TAMMINGA: Dr. Oren, would you like to make a
11 comment?

12 DR. OREN: Yes, thank you. I would like to echo
13 the comments of the previous speaker with regard to the
14 real-world scenario. The issue of threatening agitation is
15 a key variable that should be measured in outcome studies
16 because that is what typically defines in clinical practice
17 when one will use an involuntary treatment such as
18 intramuscular injection. This is often associated with
19 patients who are in restraints or about to go into
20 restraints and an IM medication is often considered because
21 of the threatening behavior of the patient, whether it is
22 towards themselves or towards other people. This is perhaps
23 the key distinction between the agitation that one might see
24 in one's teenage child or one might see in situation which
25 you wouldn't treat with medication versus something that

1 requires an intramuscular preparation.

2 I would also add that with regard to the labeling
3 I think that the labeling that the FDA produces is the
4 closest thing to the Bible in medicine, and it is very
5 critical to practitioners that the labeling fit the data
6 available. I think that how far that labeling should go
7 should be based solely on what data is available. If the
8 sponsors choose to investigate in a narrow set of
9 conditions, while the labeling shouldn't exclude other
10 condition, it should only be reflective of those conditions
11 for which the data is available.

12 DR. TAMMINGA: Thank you, Dr. Oren. Dr. Laughren?

13 DR. LAUGHREN: Actually, that is very helpful
14 advice. Ultimately, if we are going to approve either of
15 these products we have to be able to define what we mean by
16 agitation. What both of you have suggested is that
17 threatening behaviors are a key part of that definition.
18 So, it is that kind of specific advice that I think will be
19 very helpful in clarifying for the clinician what population
20 the drug is indicated for. So, if that is a key element,
21 that is very useful information.

22 DR. TAMMINGA: Dr. Katz?

23 DR. KATZ: Yes, I would like to know how the rest
24 of the committee feels about that. There are obviously
25 other definitions of agitation that don't necessarily

1 include the violent or pre-violent behavior. I would like
2 to know whether the committee thinks that if these things
3 are approved they ought to be limited for use in patients
4 who are violent. For that matter, of course, you would want
5 to see studies done looking at that if you were going to
6 restrict its use to that symptom in that patient population.
7 So, I would like to sort of poll the committee.

8 DR. HAMER: Dr. Katz partially expressed what I
9 was about to say, which is if we ask the FDA to make that a
10 part of labeling, then most of the patients in the studies
11 we are going to look at didn't meet those criteria. So, we
12 will be asking them to make a recommendation based on
13 something that we have no data for.

14 DR. KATZ: That might be okay. From our point of
15 view, again, this session is a generic session, so what are
16 we to approve drugs for, what sort of indication and what
17 sort of population. If the committee believes that we
18 should limit the approval for an agitation-related claim to
19 those patients who are dangerous which, by the way, raises
20 its own questions but if that were the advice of the
21 committee, and the natural corollary is that you would have
22 to study patients who are dangerous and assess the effect on
23 that behavior, and if the sponsors that are in front of us
24 today and tomorrow haven't done that, that might be the way
25 it goes. But, that is why this first part is generic.

1 DR. TAMMINGA: I think that the clinicians on the
2 committee would have to consider an answer to a broader
3 question than what you are specifically raising here, that
4 is, I am assuming that IM antipsychotic drugs are used with
5 a lot of indication and a lot of clinical benefit. Is that
6 benefit beyond the group of people who are dangerous to
7 themselves or others or who are threatening? I wouldn't
8 necessarily think that we ought to end up answering the
9 question that would really restrict a lot of very useful
10 clinical use of the drugs.

11 DR. RUDORFER: I agree. I think that would be a
12 mistake. Though agitation that suggests the need for
13 parenteral medication is often threatening, I don't think it
14 is always and there are circumstances, particularly where
15 there is enough of an alliance with a patient who is
16 agitated who can agree, for instance, to receiving an
17 injection to "help you calm down." If that can be
18 introduced before a patient is threatening, that might be a
19 win-win situation.

20 DR. TAMMINGA: Might you suggest a couple of
21 additional modifiers? Certainly, we would all say that IM
22 medications might be indicated in situations of threatening
23 agitation, but when other times might that be indicated as
24 well?

25 DR. RUDORFER: Well, one thing that perhaps we

1 will discuss this afternoon when we look at the data, it
2 occurs to me, is the need for rapid onset of action as an
3 important part of the indication. For instance, even in the
4 example I am giving are there circumstances where using an
5 IM preparation in an agitated person is preferable to an
6 oral preparation? I think we need to look at the data about
7 that.

8 DR. TAMMINGA: Dr. Katz?

9 DR. KATZ: I just want to say something
10 generically. A number of people have made comments about
11 preferable treatments in various settings. Generally
12 speaking, we don't get much involved in that question
13 either. Again, we want to know what is the appropriate
14 design which includes duration of action, or might include
15 duration of action for a particular indication but we don't
16 usually get involved in the question of what is the best
17 treatment available. Many -- not many but certainly some of
18 the conditions for which we have drugs approved could be
19 treated in many other ways. So, we don't usually get
20 involved in that question. We want to know is the drug
21 effective for a particular describable population and
22 describable symptom or condition and is it safe for that
23 use.

24 DR. TAMMINGA: Dr. Kane?

25 DR. JOHN KANE: John Kane, Hillside Hospital,

1 representing Eli Lilly as a consultant. I just wanted to
2 emphasize that although there is certainly a concern about
3 escalating agitation leading to violent and aggressive
4 behavior, I think agitation is one of the most subjectively
5 distressing phenomena that we, as clinicians, deal with and
6 we really shouldn't minimize what the experience of a
7 patient is who is agitated. It does not necessarily always
8 lead to violence or self-harm but it is an extremely
9 distressing situation which can lead to a number of other
10 untoward events.

11 DR. MALONE: I did want to comment on the need for
12 rapid action. We have studied the use of medication in our
13 inpatient units, for instance in children and adolescents,
14 and I think one of the things that always strikes me is that
15 by the time they give the medication for agitation, often
16 the patient is no longer agitated. So, it is hard to
17 describe or specify that you need rapid onset because I
18 think many people who get the medicine are already calmed
19 down by the time they get it.

20 DR. ERIC KANE: I want to go back to the issue you
21 raised before about sustained therapy versus urgent therapy.
22 To me, that is one of the big differentiations we are
23 talking about here. The IM medication is used for urgent
24 therapeutic intervention whether you are talking about rapid
25 onset of action or threatening or escalating behavior that

1 is distressing. The sustained therapies are where the
2 disorders diverge and, clearly, the sustained therapy for an
3 agitated patient with Alzheimer's disease is going to be
4 working with the environment, making sure they are on
5 cholinesterase inhibitors, perhaps looking at things like
6 valproate or carbamazepine or perhaps oral antipsychotics.
7 Very clearly, with bipolar disorder you are talking about
8 dealing with the fundamental mood stabilization, and with
9 schizophrenia you are talking about oral antipsychotics.
10 So, in sustained treatment obviously you have very, very
11 different therapeutic interventions and presumably you are
12 getting at the core problems that relate to agitation. You
13 obviously want to prevent the repetitive, episodic outbursts
14 that lead to the need for IM or urgent therapeutic
15 interventions.

16 So, I think it is a useful thing to differentiate
17 when you are talking about indications. We wouldn't want to
18 see, even when someone is hostile, the repeated use of IM
19 medication for a patient with Alzheimer's disease for
20 failure to set up all the other interventions, or the
21 repeated use of IM medications for failure to get someone on
22 oral treatments. If someone comes in and is fearful of
23 taking oral medications but they need sustained therapy
24 then, obviously, you are going to use some sort of depo form
25 of medication. You are not going to use repeated short-

1 acting IMs. So, I think that we are making a distinction
2 between urgent therapeutics and sustained therapeutics and
3 it is important to separate those out.

4 DR. TAMMINGA: I wonder if there is any more
5 comment from the committee on these issues or questions from
6 the FDA if there are things that you haven't heard us
7 discuss that we need to really go over in greater detail.

8 DR. LAUGHREN: Well, I think some of this will
9 come out in the discussions of the specific applications,
10 but I would like to hear a little more detail about the
11 actual patients who are treated. I think we were on a
12 fairly productive line of thought here in trying to define
13 what specifically the behaviors are that one lead one to use
14 an IM, and I think the threatening behavior is a key issue.
15 I didn't really hear any other modifiers yet discussed so I
16 would be very interested in knowing, you know, more about
17 the actual behaviors in the patients who are entered into
18 these trials. What led the clinicians to define those
19 patients as agitated? As I understand it, and I guess we
20 will get into this, it was really a judgment on the part of
21 the clinicians that a patient was clinically agitated but we
22 will hear more about that. But from our standpoint it is
23 very important that we be able to define in some way what is
24 meant by agitation leading one to need to use an IM in order
25 to write labeling.

1 DR. TAMMINGA: Let me just read the modifiers that
2 I have actually written down that the committee has brought
3 up. Threatening would be one of them; clinically
4 distressing being another; urgent need for rapid action
5 being another. Some of those involve a lot more clinical
6 judgment than you can actually write down in the labeling.
7 So, perhaps if we could oblige Dr. Laughren by being a
8 little bit more specific about what a clinician might mean
9 by this, using rather specific modifiers?

10 DR. MALONE: At least in our studies, we do have
11 criteria for being randomized to medication and it would
12 include actual threats and also some sort of destructive
13 behavior. I don't think you could put this in for agitation
14 but we do have threatening and destructive behavior.
15 Destructive behavior would be another modifier and that
16 would mean someone who is physically aggressive to the
17 environment, others or themselves.

18 DR. FYER: I want to come back to Dr. John Kane's
19 description, and I would urge with him to not exclude the
20 patients who are in horrible subjective distress from this
21 sense of agitation. I think the other Dr. Kane's use of the
22 word "urgent" is a good criterion in the sense of a patient
23 who felt they were urgently in need of some kind of
24 medication to counteract this kind of escalating sense of
25 terrible agitation where people feel this kind of

1 excruciating pain that I think, you know, is available for
2 description in things like Kay Jamison's work, etc. in terms
3 of talking to patients directly.

4 DR. ORTIZ: I would argue against also the
5 inclusion of anything with chronic. I think in older
6 patients and patients who have dementia we are often talking
7 about other phenomena that are going on in addition to the
8 dementia that is causing what looks like a chronic
9 agitation. So, I would argue against including that.

10 DR. TAMMINGA: Dr. Grundman, might you discuss a
11 bit more some of the characteristics of the people that you
12 described?

13 DR. GRUNDMAN: I am not sure what you are
14 referring to but, I mean, I think of situations where there
15 is a safety issue for the patient either in terms of their
16 hyperexcitable state where it might lead to either some sort
17 of destructive behavior or, I guess, you could even think of
18 a situation where they are so tense and excited that if they
19 kept going in such a situation they might exhaust
20 themselves, or if they were so hyperactive they might do
21 something. Again, we didn't study this but, I mean, you can
22 think of people who are in the ICU, for example, who develop
23 rhabdomyolysis from just moving around so much. Certainly,
24 in those sorts of situations you might want to sedate
25 somebody. In psychiatric situations I am sure that you ever

1 reach that point but that would be another case.

2 DR. ALLEN: One comment related to that, I think
3 for me often the issue is that the agitation is an
4 impediment to a proper assessment. So, you are confronted
5 with a situation where something is obviously wrong and the
6 person is in great distress. I completely agree with Dr.
7 Kane that that is a central consideration but you are unable
8 to talk with them in a coherent enough way to establish what
9 the problem is.

10 DR. TAMMINGA: In some situations like that you
11 just come back the next day and in some situations you
12 wouldn't. Could you offer some more objective modifiers?

13 DR. ALLEN: Well, I think if the person is
14 inattentive or so hyperactive that in order to conduct the
15 assessment you would have to follow them around. I think
16 also it is often the case that people just literally can't
17 string two thoughts together because they are so agitated,
18 and in those cases you are often looking for a third source
19 of information but I think in many cases it looks as if you
20 can't wait. You know, something bad is going to happen if
21 you were simply going to wait until the next day. For me,
22 rather than acute/chronic, I prefer transient/persistent.
23 If it looks like the person is in a transient agitated state
24 where I am concerned about what they are going to do as a
25 result of the agitation, and there is some vague perception

1 of danger -- it may not be that the person is directly
2 threatening me or anyone else but it looks like they are so
3 anxious that they are going to do something to themselves
4 perhaps if they don't get some relief from this, then in
5 that situation you intervene in order to conduct an
6 assessment.

7 DR. LEBER: Can I say something?

8 DR. TAMMINGA: Dr. Leber?

9 DR. LEBER: I don't want to pull a Bill Clinton to
10 come back from the past and this is not on behalf of either
11 company but it dawns on me that in most decisions of this
12 sort -- since I am the person who talked about
13 pseudospecificity, I will talk about overspecificity, you
14 can't exhaustively define the states in which you might use
15 a parenteral medication, but the concept of urgency in the
16 clinical judgment of the clinician is, I think, the
17 overriding feature. It overlaps with the acute state and
18 the chronic state. A patient who is a chronically sick
19 patient can have an episode in which they need acute, urgent
20 treatment. I think you are really trying to find the
21 treatment for something for which there is a short-term
22 urgent need for treatment, immediacy. And, to go further
23 than that is going to force you to define a list that you
24 can't really write.

25 DR. TAMMINGA: Additional comments from the

1 committee or from the FDA? Dr. Katz?

2 DR. KATZ: Not specifically about this particular
3 issue but one question that Tom raised that we haven't
4 really heard too much about would be outcome measures.
5 There was little discussion about whether or not outcome
6 measures that the specific sponsors have used are okay, but
7 just from a generic point of view, I am wondering what the
8 committee feels about that, again, in a general sense.
9 Because you can give treatments for agitation that will just
10 snow the patient and they would be asleep or, you know,
11 semi-comatose and they would no longer be agitated. Would
12 that be an appropriate outcome that would be acceptable to
13 support approval of a treatment for agitation, or must the
14 patient still have a normal level of consciousness but be
15 less distressed, for example, if that is a critical part of
16 it? Do you see what I am getting at? I just wonder what
17 the committee feels about that in a general way.

18 DR. TAMMINGA: You clearly wouldn't want a
19 treatment that didn't actually treat the agitation but it
20 just anesthetized the person, so to speak, and as soon as
21 the person woke up the agitation would still be there.

22 DR. KATZ: One can imagine a scenario in which you
23 actually do make a patient unresponsive and then when they
24 do arouse they are not agitated anymore.

25 DR. TAMMINGA: Right.

1 DR. KATZ: So, would that be an appropriate
2 treatment for agitation?

3 DR. TAMMINGA: Those clearly would mirror the data
4 that was built into the assessment for the products that we
5 are looking at this afternoon and tomorrow.

6 DR. KATZ: Right, but we are going to be looking
7 at other products presumably for this indication at some
8 point perhaps, beyond the two that we have in front of us
9 here. So, I am just wondering generically under the heading
10 of what are the standards, what ought the minimum standards
11 to be.

12 DR. GRUNDMAN: I think generically or ideally if
13 such a medication existed, you would bring a person who is
14 behaving uncooperatively, irrationally, and who is a threat
15 and a danger to somebody who is calm and you could have a
16 reasonable discussion, and who is no longer manifesting
17 those behaviors, without necessarily overshooting to the
18 point that you drove them into a semi-stupor or comatose
19 state and thereafter, you know, waking up and being
20 agitated. But I think, again, there is a benefit and a risk
21 and I think you have to weigh whether or not if you don't
22 have the situation that I described in an ideal world and
23 you do have the situation where you overshoot a little bit
24 and the person falls asleep or takes a nap and then wakes up
25 and is better, whether or not that might not be acceptable.

1 I am not sure.

2 DR. MALONE: I am not so sure. In addition to how
3 sedated they are going to get, if you look at this as use
4 for an urgent situation what you might want to follow-up is
5 how many times after using it for that urgent situation it
6 occurs again within a time period. So, you might want to
7 know how many times they need additional IM medication over
8 the next day or the next week as one of the outcome measures
9 for treating an urgent situation.

10 DR. KATZ: For acute treatment you would expect
11 that it would have a persistent effect? In other words, if
12 you are really treating the agitation acutely and not the
13 underlying diagnosis, you would treat an episode of
14 agitation today and would you really expect that it would
15 decrease the number of agitated episodes the patient would
16 have in the future?

17 DR. TAMMINGA: I would think that the answer from
18 clinicians to that question would surely be yes. Am I
19 wrong? I mean, if you expect that there is something
20 emergent about the condition that some medication would
21 actually be effective in quieting.

22 DR. KATZ: But these are acute treatments. You
23 know, it is like migraine treatments. We don't expect that
24 if you treat a migraine successfully you will prevent
25 subsequent migraines. I suppose there could be a treatment

1 that would do that and there is prophylaxis but we are
2 talking about acute treatments.

3 DR. TAMMINGA: I don't hear people talking about
4 treating agitation by itself without giving consideration to
5 the underlying condition that produces the agitation. So,
6 you might try a quiet room. You might try a treatment for
7 the bipolar disorder. You might try a treatment for
8 whatever your underlying diagnosis is but you wouldn't
9 necessarily propose that a treatment for agitation would
10 really wipe out the complex illness or the complex
11 presentation that you were looking at.

12 Additional comments from the committee about our
13 discussions? About agitation? Or additional questions from
14 the FDA?

15 [No response.]

16 In that case, I think we will take a break, 15
17 minutes. We will restart at 10:30 with the presentation by
18 Lilly.

19 [Brief recess.]

20 DR. TAMMINGA: I would like to call the meeting
21 back to order, and continue on with our agenda. After our
22 initial morning discussion of agitation as a clinical
23 condition, we will continue now with the presentation by
24 Lilly of intramuscular Zyprexa in the indication of
25 agitation, and Dr. John Kane will begin by talking about the

1 are some overlaps in phenomenology but obviously it is not
2 one to one. We are going to be hearing later not just about
3 two psychiatric disorders but also a neuromedical condition,
4 Alzheimer's disease or dementia with agitation.

5 [Slide.]

6 Again, we have discussed how agitation can be
7 defined. This is something again that a clinician working
8 in an emergency room or working in an acute inpatient unit
9 is confronted with, making in some cases a very rapid
10 judgment about how to manage the situation.

11 [Slide.]

12 I think Dr. Allen emphasized that in some cases we
13 have to make a very rapid clinical judgment, make a decision
14 to intervene before we have been able to complete a full
15 diagnostic workup. In fact, the clinical intervention that
16 we make at that point is essential to help in facilitating
17 the completion of the diagnostic workup.

18 The extreme personal distress is something that I
19 emphasized earlier and I think if you talk to someone who
20 has had agitation, this is akin to, I think, the most
21 extreme states of pain. In addition, if you talk to someone
22 who has been in a violent or aggressive episode, they are as
23 frightened often as the people around them. The state of
24 being totally out of control is extremely frightening.

25 [Slide.]

1 A survey was done of academic emergency rooms
2 around the country, and of the 50 emergency rooms which
3 responded to that survey, the typical service sees about 400
4 patients per month. If we look at New York State, we are
5 talking about 135,000 psychiatric emergency visits per year.

6 [Slide.]

7 About 8.5 percent in this survey of those patients
8 required mechanical restraint for agitation. Mechanical
9 restraint is something that has received a lot of attention
10 in the lay press, something about which I think everyone is
11 concerned. We would very much like to avoid the use of
12 mechanical restraints.

13 We also really do not consider the use of the
14 treatments that we are talking about today as chemical
15 straightjackets. We really think of them as early
16 intervention for the disease as well as, fortunately,
17 controlling agitated and disturbed behavior. In that
18 respect, I think we are quite fortunate that the drugs can
19 have those dual effects.

20 There has been a lot of concern about the use of
21 restraints and the number of fatalities that have been
22 associated with the use of restraints. Her you see data
23 from New York, over a period of 10 years 111 fatalities.
24 Again, I think if we had better use of appropriate
25 pharmacotherapy we might be able to avoid some of these

1 situations. It is also important to continually emphasize
2 that the use of these treatments is only initiated after
3 other interventions have failed. We try environmental
4 manipulation; we try interpersonal work with the individual
5 but when that fails, then this is the appropriate
6 intervention.

7 [Slide.]

8 The assaults that occur -- again, I want to
9 emphasize that this is not the typical psychiatric patient
10 but these things certainly do occur, and when they do occur
11 it is a medical emergency. The assaults that result most
12 frequently happen to the nurses who work either on inpatient
13 units or in emergency rooms, and these often lead to fairly
14 serious injuries.

15 [Slide.]

16 We also talked about compliance to oral treatment,
17 and we are first going to try to get a patient to take oral
18 medication. If that fails, then this is the next approach.
19 As has been discussed, IM dosing is used really during the
20 very initial phase of management with the attempt to switch
21 to an oral form of medication as rapidly as possible, as
22 soon as is feasible.

23 We talked about sedation a little bit and, again,
24 one cannot view this as a black and white situation. There
25 are some patients who come in to an emergency room who have

1 not slept in 48 hours.

2 You heard some discussion about the dangers of
3 unmanaged excitement. If you look at the old literature in
4 mania, the mortality rate associated with mania was
5 staggering and some people attributed that to manic
6 excitement. Undoubtedly there are other factors
7 contributing to that as well but when you go back and look
8 at some of the old literature it is quite sobering.

9 The current therapies include benzodiazepines and
10 typical antipsychotics. Obviously, these are very widely
11 used, widely used, as you have been discussing, in non-
12 psychiatric conditions as well.

13 [Slide.]

14 There are some limitations associated with these
15 compounds. I think benzodiazepines are generally quite safe
16 but there are some associated problems. The typical
17 antipsychotics we have more concern about I think in terms
18 of acute dystonic reactions and akathisia, and these things
19 are typically seen during the early phases of treatment and
20 can have a very dramatic impact on patients' subjective
21 attitudes towards subsequent treatment -- excessive sedation
22 and neuroleptic malignant syndrome as well.

23 [Slide.]

24 Here we are talking about three different
25 conditions, schizophrenia, bipolar disorder and dementia of

1 the Alzheimer's type. I want to emphasize we have two
2 psychiatric conditions and one neuromedical condition,
3 although there may be some people in the audience who would
4 like to consider that a psychiatric condition. We are
5 fortunate in one sense, that the IM antipsychotics and the
6 benzodiazepines are used in all three of these conditions,
7 yet, when we look at sustained therapies there are some
8 differences. At the same time, in schizophrenia and bipolar
9 disorder antipsychotic medications are part of the standard
10 treatment for many patients. In dementia of the Alzheimer's
11 type we see some use of antipsychotics but other drugs as
12 well.

13 So, in this sense, as we talk about the two
14 different models that have been discussed, we are also
15 talking about treatments that are indicated and effective
16 for the disease at hand. At the same time, we are talking
17 about treatments that have been shown to be helpful during a
18 very rapid need to control agitation. Obviously, there is a
19 lot of discussion about the pain model and how to go about
20 this. I think, as Dr. Leber said, it would be difficult to
21 study absolutely every indication for which a drug will be
22 used. Even with the pain model, I think the tradition has
23 been to study three or four different categories of pain.
24 We would not use the treatment for dental pain to treat
25 migraine headaches. Obviously, there is some clinical

1 judgment involved in that. Here, fortunately, we have seen
2 a series of trials in three different disease entities which
3 are very informative.

4 So, let me stop at that point and turn it over to
5 Dr. Breier.

6 Clinical Development of IM Olanzapine

7 DR. BREIER: Thank you. It is a pleasure to be
8 here. I want to first commend the committee for tackling a
9 complicated issue but a terribly important one. I think all
10 of us who have treated severely ill neuropsychiatric
11 patients have vivid memories of the acutely agitated patient
12 and how important it is to deliver very effective and safe
13 treatment. So, I think tackling this issue is a laudable
14 task.

15 [Slide.]

16 What I would like to do over the next hour or so
17 is take you through the data that supports our olanzapine
18 IM.

19 [Slide.]

20 Before doing that, I would like to give you a
21 little bit of history. We thought about developing an IM
22 formulation of olanzapine many years ago, and at the
23 beginning of that process we laid out for ourselves really
24 what we thought would be the optimal characteristics of an
25 IM. So, that was really our starting point to develop this

1 kind of a model.

2 This is what we came up with. You heard a bit
3 about this already in this morning's discussion, and that is
4 rapid onset of action. These are oftentimes therapies that
5 need to be used very quickly and where control of behavior
6 is mandated to occur very quickly. We heard the term
7 "urgent" used quite frequently this morning and that really
8 is the role predominantly of an IM, to very rapidly calm a
9 patient who is agitated. So, rapid onset of action is very
10 important otherwise an oral medication would be suitable for
11 most instances.

12 Effective response to the first dose -- giving an
13 IM is an invasive procedure. It is a procedure that you
14 would like to maintain good control with the initial dose.
15 An IM is not meant for dose titration. You don't start low
16 and start moving up, but you want a good, solid, safe,
17 effective dose on the first injection. Again, oftentimes
18 the patient is in a crucial situation, a crisis situation in
19 which rapid control is important and it is important to get
20 that control with the first dose if possible.

21 This was also raised today, a calming effect
22 without excessive sedation. Excessive sedation is not going
23 to be a desirable endpoint for any patient. Sleep might be,
24 but unarousable is not. Unarousable will create management
25 problems. More importantly, it can pose its own safety

1 concerns in terms of respiratory function and other sorts of
2 untoward events. So, excessive sedation is undesirable and
3 it gets to Dr. Tamminga's point of analogy to general
4 anesthesia.

5 Low incidence of acute dystonia and other
6 extrapyramidal side effects -- I think perhaps one of the
7 biggest liabilities of haloperidol is its safety profile in
8 this domain. Acute dystonia is an event that commonly
9 occurs with Haldol. It is a very dramatic event. If you
10 have ever seen a case of significant acute dystonia you will
11 never forget it -- a wrenching over of the neck oftentimes.
12 That event alone is not only painful for the patient but can
13 then lead to a history of non-compliance because of a mis-
14 association that they have had some sort of allergic
15 reaction or something of the sort. It also then modifies
16 the use of haloperidol because of the concerns of an acute
17 dystonic reaction and will lead then to perhaps using
18 benzodiazepines or other such agents that will not cause
19 that. So, acute dystonia is a very, very important
20 parameter and I think a very kind of limiting factor
21 associated with haloperidol.

22 Then also, obviously, along the safety continuum
23 ECG abnormalities is another very important concern. As you
24 will see, you get high, fast blood levels. So, safety
25 concerns that could be related to a very rapid peak onset is

1 going to be something that one looks very carefully at with
2 an IM.

3 [Slide.]

4 To begin our development process for an IM we
5 sought consultation with the agency, as Tom Laughren noted.
6 On may 14 of 1998 we met with the Neuropharm Division. We
7 came forward with a desire to develop an IM formulation of
8 olanzapine. We did not see the appropriate kind of
9 precedent-setting material in the literature so we sought
10 guidance.

11 The FDA indicated that IM antipsychotics are used
12 for the control of agitation in numerous disease states, and
13 I don't think anyone would dispute that. At that point, the
14 FDA recommended studies of agitated patients in multiple
15 disease states based on anticipated use. So, as Dr.
16 Laughren mentioned, at that time there was thinking that
17 agitation could, in fact, be non-specific and that invoking
18 the pain model seemed to be appropriate. We took the advice
19 of the agency and then went back and really then thought
20 through how we could develop a clinical program that would
21 meet these kinds of specifications.

22 We had a teleconference on November 12 in 1998,
23 and in that conference we discussed our plan in sketch form,
24 and we proposed at that point four double-blind pivotal
25 trials in three different conditions, schizophrenia, bipolar

1 and dementia, and informally had some general agreement in
2 terms of the direction we were heading in.

3 [Slide.]

4 We talk a lot about the label and I think that is
5 an important point because that is where the so-called
6 rubber meets the road. That is where we can get very, very
7 concrete, and it is probably useful for us to present to you
8 our proposed label now so that as we go through the data you
9 can reflect back on the proposed labeling and see if, in
10 fact, we have fulfilled the requirements for the label.

11 So, the label that we propose is as follows:
12 Zyprexa intramuscular (IM olanzapine) is indicated for the
13 rapid control of agitation. The efficacy of Zyprexa
14 intramuscular for the control of agitation was established
15 in 4 short-term, 24-hour, placebo-controlled trials in
16 agitated inpatients with schizophrenia, bipolar I disorder
17 or dementia.

18 I think as we now go through, we will go in a fair
19 amount of detail of a variety of different pieces of data
20 that I think speak to this label.

21 [Slide.]

22 After our original meeting with the FDA we went
23 back to begin the development of this clinical plan. We
24 realized quite rapidly that we had a bit of a daunting task.
25 It was, indeed, a challenge, and it was a challenge in that,

1 again, there was really no precedent. There was no
2 guidepost that we found that we could use for how to develop
3 a clinical development program that would be specifically
4 targeting acute agitation, and do so in the framework that
5 we talked about. So, this required a lot of consultation, a
6 lot of looking at the literature, and I think probably a lot
7 of innovative kind of work that we will be sharing with you.

8 First, there was no precedent, and in terms of
9 other challenges, we felt that the most powerful design for,
10 let's say, a new indication, acute agitation, would be one
11 that combined two very critical components. One is placebo
12 and the other would be active comparator. So, you will see
13 that in all four of our pivotal trials we have both because
14 we think that both provide useful means of interpreting the
15 data. Placebo obviously is very, very useful from a safety
16 concern, and I think that that was raised today in terms of
17 the importance of looking at an IM and I think that that may
18 be a gold standard, if you will, in examining safety and
19 provides you kind of very pristine information. Also, it is
20 obviously very important in demonstrating an effect without
21 confounds.

22 We think that active comparators are also very
23 helpful in interpreting the data as well because, again, we
24 are going into new ground, and when you are going into new
25 ground you are wondering, well, what is a meaningful effect?

1 How would this compare to standard treatment? I think in
2 the areas where the ground is a little bit more worn this
3 may be a bit less of a critical issue, but in going into a
4 new area, having an active comparator in your studies gives
5 you a barometer, gives you something you recognize and can
6 look to, to help understand the strength of your signal, the
7 signal that is occurring in patients randomized to that
8 treatment arm. I think it can also give you help in terms
9 of a standard for interpreting safety. So, we felt that
10 both of those dimensions would be powerful in the design and
11 we planned to include both.

12 We did a very extensive review of the literature,
13 and I will show you in a bit a very extensive consultation
14 in terms of what should the primary measure be. How do you,
15 if you will, define agitation. Would one primary be
16 appropriate, or would one want to use a battery of agitation
17 scales, etc.

18 Well, we rapidly found out that there was no one
19 gold standard. There was no BPRS total, if you will, for
20 agitation. However, we were impressed that there were a
21 number of very reliable and valid scales in the literature.
22 There is a deep and strong literature on agitation -- the
23 definition of agitation; studies of agitation; and even some
24 clinical trials on agitation. So, we felt that there was a
25 wealth of material in the literature, although no consensus

1 that there is one clear scale that is obvious to be used.
2 But we were at least encouraged that there was a lot of
3 literature.

4 Another challenge was the data capture. We are
5 traditionally used to doing studies over weeks -- six weeks,
6 months. Now we are talking about something that is really
7 trying to capture information over minutes to hours. This
8 is something we had never done before at least in my group.
9 To design clinical trials we are trying to precisely capture
10 information over a very short time interval. That is really
11 going to influence the kinds of assessments you use, the
12 kinds of tools that one might use in terms of capturing the
13 information.

14 This point and the second point, which is related,
15 I think is very important. I think it is important we just
16 put it on the table right out front, and that has to do with
17 enrolling patients with an appropriate level of agitation.
18 We strove in our studies to have criteria that would be
19 meaningful agitation; that would be acute agitation that
20 would span a spectrum, including severe agitation; that
21 would be agitation that would allow generalization to other
22 patients. But I want to be absolutely crystal-clear and
23 very frank, there are patients with extreme agitation that
24 are inappropriate for enrollment in clinical trials. Those
25 patients were not in our trials. There is the severely

1 agitated patient who may be in four-point restraints, who is
2 flailing about, where you would want to use an IM
3 antipsychotic drug that would be appropriate, and there was
4 that subgroup of patients that were not in this trial. So,
5 I think that we are all going to need to kind of look at
6 that and think about that, and think about our level of
7 comfort in extrapolating some of the severe end of the
8 spectrum.

9 But having said that, I think we will be able to
10 show you some data that shows that we did capture a
11 representative group of patients, a rather broad group, and
12 do address some of the issues around the severity end of the
13 continuum with the agent, but just to underline it, I think
14 it is clear that there was a subgroup of patients who were
15 not represented. Perhaps if there is a more wide-ranging
16 discussion, how you would actually study those patients
17 would probably be a useful discussion.

18 Ethical considerations -- every clinical trial has
19 to start there. One cannot go forward with any study in
20 humans without very strong and serious concerns of the
21 ethics, and ethics will trump. There are design features we
22 would love to have had in our study but we felt that they
23 bumped up against ethical guidelines and did not include
24 them. For example, it would have been nice to have had a
25 one-, two-, three-, four-day totally drug-free washout

1 period. We think with an acutely agitated patient who is
2 treatment seeking and needing treatment that would be
3 pushing an ethical bound. Prolonged use of placebo would be
4 another one that we think would be an ethical bound.

5 We had to then develop a way to get strong and
6 meaningful information on safety and efficacy and still
7 consider these very real ethical implications. Again, when
8 you think about the kinds of patients whom you can enroll in
9 a clinical trial, I think you have to have your ethical hat
10 on and consider some of these patients who would be good
11 candidates for an IM but it would probably be unethical to
12 enter them into a trial. So, I think those ethical issues
13 become very important in considering the clinical trials and
14 making those kinds of judgments in terms of evaluating the
15 overall package of information on safety and data.

16 [Slide.]

17 With that as background, why don't we move
18 forward? What I would like to do now is really turn to the
19 data and talk about it in four components, first review the
20 pharmacokinetic profile of IM olanzapine; second, the
21 clinical methodology and rationale; third, the efficacy
22 results; and, lastly, the safety results. Let's go to
23 pharmacokinetics.

24 [Slide.]

25 The pharmacokinetics of IM are rather predictable

1 and they are rather straightforward. We have fairly
2 extensive PK understanding of our oral compound. For those
3 of you who don't know, our oral compound is approved for
4 schizophrenia and for acute mania. It has now been in over
5 six million individuals worldwide. We have a very extensive
6 database on oral olanzapine.

7 There are really two kind of very noteworthy
8 differences in terms PK in terms of IM olanzapine and oral
9 olanzapine. IM olanzapine has a much higher Cmax, much
10 quicker elevation in blood level. That occurs typically
11 between 15 minutes and 45 minutes. The Cmax of oral is much
12 lower, two-, three-, four-fold lower, and its Cmax occurs
13 later. So, its Tmax is later, occurring between three and
14 six hours. So, you are getting a more rapid and a much
15 sharper, although fleeting, peak dropping off, and that is
16 the main issue contrasting the IM with the oral.

17 The AUC is comparable. I think that is an
18 important point. Clearance is similar. Half-life is
19 similar, and volume of distribution is similar as well.

20 [Slide.]

21 Let's look at a figure of this data. This shows
22 you 2 IM injections of 5 mg given 4 hours apart and 1 10 mg
23 oral. You are looking at blood levels. To note, if we look
24 over to this more intensive period of 12 hours you see this
25 fast, rapid peak and then this dropping back down, generally

1 within an hour. Then, the second injection being given 4
2 hours later, again the peak and the coming back down but the
3 area under the curve is very, very similar between the 2
4 drugs. So, that helps you in thinking about comparability
5 between the oral, which I think people tend to be fairly
6 familiar with, and the IM in terms of just sort of the
7 mental calculus of going back and forth between daily
8 dosing.

9 [Slide.]

10 In two of our trials patients could receive up to
11 10 mg -- and I will go into detail in a minute when we come
12 to those trials -- up to 10 mg of IM over a 24-hour period.
13 So, in order to support that database we did a PK study in
14 non-agitated patients to look at the PK profile of the
15 highest dose we would envision in our clinical trials anyone
16 getting over a 24-hour period -- 3 injections of 10 mg.

17 First you see this characteristic very rapid peak
18 and drop-off 4 hours later; second injection, 4 hours later;
19 the third injection. You see a fairly classical stepping up
20 phenomenon that you see with administration of this sort.
21 You don't see a doubling of Cmax but you clearly see a
22 stepping up. It takes about 5 days to get to steady state
23 with the oral medication, by the way. Then you sort of see
24 this half-life that is, again, quite predictable from our
25 oral experience.

1 I think when one is considering PK it is important
2 to think about some of the possible safety implications.
3 What if a patient received the maximal amount, 3 10 mg
4 injections over a 24-hour period, and what would the
5 significance of those blood levels be? Well, we are going
6 to come back to that specific point when we talk about some
7 cardiac issues later in the presentation. So you may want
8 to keep that in mind.

9 [Slide.]

10 But this will give us a bit of a benchmark. Here
11 is the data I just showed you -- first dose, second dose and
12 third dose. Each one of these points is an individual
13 subject's Cmax and then you see the mean and the standard
14 deviations of those Cmax's plotted there.

15 Then, what we have plotted for comparison are the
16 Cmax's of patients receiving 20 mg of oral at steady state.
17 This is from a large sample. This is 474 observations in
18 333 patients. For those who are not aware, 20 mg is the
19 upper dosing level of the recommended dosing range of the
20 oral. The oral is recommended between 5 and 20 per day, and
21 20 is a very commonly used dose of olanzapine.

22 What you see here is a box plot, the mean and
23 standard deviation, same axes of the two studies. This is
24 the 10 percent Cmax at the highest end of the spectrum, and
25 here are the 10 percent at the lowest end of the spectrum.

1 The point that I want to make is that the mean is not that
2 far different, nor is the standard deviation, from what we
3 see in this scenario and all of these data points --
4 granted, the sample size is much smaller than we see here,
5 but all of these data points are falling within the range we
6 see of 20 mg oral, and we have a very extensive safety and
7 efficacy database on these patients.

8 Also, just notice that there is a wide range in
9 blood levels with olanzapine. We have noticed that from day
10 one. It is true as well with the IM.

11 [Slide.]

12 This just summarizes the pharmacokinetic profile
13 of IM olanzapine. Fundamental PK characteristics are
14 similar to oral; similar half-life, clearance and volume of
15 distribution. They follow linear, fairly predictable
16 pharmacokinetics. The key difference is more rapid rate of
17 absorption, a higher Cmax, a Tmax earlier for the IM, as I
18 noted, between 15-45 minutes versus 6 hours for the oral.

19 Maximum IM plasma concentration is comparable to
20 oral steady state. Maximum IM plasma concentration after 3
21 10 mg injections is similar to steady-state plasma
22 concentrations after oral 20 mg. Then there is a similar
23 metabolic profile for oral and IM. It is the same agent.
24 The key difference is rate of absorption.

25 [Slide.]

1 Let's now move to clinical methodology and
2 rationale as we move to a discussion of efficacy and safety.

3 [Slide.]

4 This just sort of is a background that really
5 speaks to the selection of our efficacy measures, again a
6 point of discussion earlier in the morning, and we found
7 that actually quite interesting and helpful. The debate has
8 been useful to be part of.

9 In January through November of '99 we began this
10 very extensive search of the literature that we noted. We
11 had a very, very extensive consultation with experts. This
12 included psychometricians, scale developers of major scales
13 of aggression in psychopathology, academicians and
14 clinicians, clinicians who actually are working in the
15 trenches, so to speak, using IMs, treating a wide range of
16 different psychiatric patients.

17 We convened an international expert advisory panel
18 on agitation specifically to talk about different available
19 scales, and in that meeting were some of the real leading
20 thinkers of scale development and developers of a variety of
21 different scales. The outcome was that there was clearly no
22 gold standard, although you can imagine some of the
23 developers of their own scales were a little partial to
24 their own instrument but we tend to see this in academic
25 debates. But, no clear gold standard. There were, however,

1 very impressive group of clinically appropriate agitation
2 scales. So, again, the literature was deep and there is a
3 significant amount of tools available.

4 What was also striking was the core features that
5 appear to be common. So, there were certain scales that
6 were developed more specifically, for example, for the
7 demential population. There were other scales that tended
8 to be used more in the schizophrenia populations, etc. But
9 when you dug in and looked for core features there was an
10 awful lot of commonness in what these scales were talking
11 about in terms of core features of agitation. I think it
12 gets to Paul Kech's comment that through training you come
13 to know agitation. You walk onto a ward, you look at a
14 patient and there is usually not a lot ambiguity that that
15 person is either agitated or not agitated, and I don't think
16 that is really true for many of the syndromes that we, in
17 psychiatry, have to deal with but I think that agitation is
18 one of those where the maxim is "you'll know it when you see
19 it."

20 [Slide.]

21 We decided, in part because this was a new area,
22 that a prudent approach might be to have a core battery of
23 agitation scales. Clearly, we have a primary and we decided
24 to use the Positive and Negative Syndrome Scale, the Excited
25 Component, as our clearly stated primary. But in all four

1 of our pivotal trials we have three agitation scales. We
2 have our primary obviously and each primary is used
3 essentially the same way. It is powered to show differences
4 from placebo at two hours across all four studies. In
5 addition, we have a scale developed at Lilly called the
6 Agitation-Calmness Evaluation Scale. In the two
7 schizophrenia studies and in the bipolar study we used the
8 Corrigan Agitated Behavior Scale. Then, in the dementia
9 study we used the Cohen-Mansfield Agitation Inventory. So,
10 in all four studies is the PANSS EC. In all four studies is
11 the ACES, the Agitated-Calmness Scale. In the three non-
12 geriatric studies is the Corrigan, and in the dementia study
13 is the Cohen-Mansfield but, clearly, this was our key scale.
14 That was a priori stated primary. That is what we powered
15 the studies on, and that is the most important measure.

16 [Slide.]

17 Why did we select the PANSS EC? First, it
18 contains those common features identified in our review of
19 the literature and from speaking to experts. I will show
20 you what I am talking about in the next slide. The items in
21 the PANSS EC resonated, if you will, with what we were
22 hearing and seeing in the literature. It is what people
23 commonly see in agitation across diverse disease states.

24 This is an established, validated factor by the
25 developers of the PANSS. We consulted with those

1 individuals in selecting this sub-component of the PANSS.
2 The validity was established by us in agitated and non-
3 agitated patients. This included internal consistency,
4 construct and discriminate validity, responsiveness,
5 reliability and reproducibility. The scale performs very
6 well.

7 It has applicability across different populations.
8 Some scales do have a bit of a specialization for certain
9 segments. This scale has the advantage where it would allow
10 us to use it across diverse populations, and we have a very
11 diverse group of patients in our data set. So, we wanted to
12 be able to use the same measure across diverse patient
13 populations so we could look across the different patient
14 populations and help address some of the issues that were
15 raised earlier this morning. These five items in the PANSS
16 are such that you could do that.

17 It is rated by clinician observation. It does not
18 require a verbal response. As you probably know, those of
19 you familiar with the PANSS, some of the PANSS are rated on
20 eliciting a verbal response; other items are not. These
21 five items are not. So, it is based on the clinician
22 observing the patient and that is useful because some very
23 agitated patients are not necessarily predisposed to a
24 structured interview or detailed kind of psychiatric
25 interview and, remember, one of our challenges was to

1 collect data over a short time period which required the
2 rapid use of scales, and that really speaks to this
3 component. So, the PANSS EC was a scale that one could do
4 rapidly over multiple different time points and collect the
5 data.

6 [Slide.]

7 This is in your handout. These are the five
8 items. These are the PANSS definitions of those items. All
9 the items are scored 1-7, absent to extreme -- poor impulse
10 control, tension, hostility, uncooperativeness, excitement.
11 When you were going through your descriptors in your morning
12 discussion, I think you will find many of them in the
13 definitions here. If you do the exercise that we went
14 through in looking at other scales and other kind of
15 conceptual perspectives, you will find those in these
16 definitions. Obviously, hostility was a key component or
17 item that was discussed today and you see the definition
18 here that seems quite consistent with some of the discussion
19 going on earlier today. So, we would suggest that a lot of
20 the key components are really contained here and that all
21 five of these items make contribution to defining and
22 measuring agitation.

23 [Slide.]

24 This was the scale developed by us at Lilly, the
25 Agitation-Calmness Evaluation Scale. It is designed to

1 assess the clinical levels of calmness and sedation. It was
2 really our only measure to get at the point that Dr.
3 Tamminga raised, and that is the concern of excess of
4 sedation. So, we wanted to determine were we calming
5 patients appropriately without inducing excess of sedation.
6 For that, we felt we needed a scale that took a patient
7 literally from an agitated spectrum towards that calming end
8 but then to have anchors that went further into an
9 undesirable state and, indeed, the last item on the scale --
10 it is scored from 1-9 -- is unarousable, which would be
11 clearly an undesirable endpoint for any patient who has been
12 treated for agitation.

13 We did undergo some reliability and validity
14 testing of the scale. I do want to, however, just note that
15 the major emphasis for us was on our primary. Again, this
16 was a scale that we relied largely on for this measure of
17 excessive sedation, although I will show you the efficacy
18 data we gathered as well.

19 [Slide.]

20 I mentioned the Corrigan in the two schizophrenia
21 and one bipolar study. This is a 14-item validated scale.
22 It rates the degree to which specific behaviors are
23 observed. The degree rating is from 1, absent, to 4,
24 extreme. Total scores range from 14-56.

25 It is used in clinical trials of acute agitation

1 across multiple disease states. There is nice literature
2 using the Corrigan. These were in schizophrenia trials,
3 mania, psychoactive substance abuse, brain injury,
4 Alzheimer's disease. There was even one trial in an
5 emergency room setting of psychotic patients undergoing a
6 clinical trial of psychotropic agents focused on agitation.
7 So, there was a useful database in the use of this scale.

8 [Slide.]

9 Lastly, the Cohen-Mansfield, a validated
10 instrument designed to assess agitated behaviors
11 specifically in the elderly. It is used in numerous
12 clinical trials of dementia patient populations. We needed
13 to adapt the scoring for this short-time epoch that we were
14 looking at. The scoring was adapted and shortened, and
15 there were more frequent observation periods. We did
16 consult Cohen-Mansfield in terms of this modification.
17 Behaviors were assessed as absent or present, 0-1, and total
18 scores range from 0-30.

19 [Slide.]

20 Now let's get to how did we select our three
21 patient populations. This is an important area. First of
22 all, the criteria that we set our were as follows: Number
23 one, that the agitation is a common clinical problem. So,
24 agitation commonly occurs but, as was noted earlier today,
25 agitation is a common phenomenon. So, it had to be common

1 but we felt that it also had to be one that presented a
2 particular clinical challenge because, as noted by several
3 people today, IMs are not used across the board. They are
4 used really in specialized circumstances when there is a
5 particular clinical appropriate need for them. So, not only
6 did we ask that agitation be common but that it be
7 clinically challenging to manage.

8 We also wanted to study disorders in which IM
9 medications were frequently used, the benzodiazepines and
10 haloperidol. We went to the IMs data set and these are the
11 three of the neuropsychiatric disorders where IMs today are
12 most currently used, primarily in schizophrenia. Next would
13 be dementia and third would be bipolar mania. So, these are
14 the three neuropsychiatric disorders where IMs are most
15 commonly used today.

16 Then, we wanted to study also a diverse patient
17 population. We wanted to study patients that had a broad
18 range of different characteristics. Again, we wanted to
19 look at safety and efficacy, and to do that best we thought
20 that it made the most sense to cast a relatively wide net in
21 terms of our study populations so that when particular
22 safety issues or efficacy issues came to the fore there
23 might be a database that would allow one to look at some of
24 these very important questions, some of which were even
25 raised earlier this morning.

1 [Slide.]

2 In terms of the diversity of this particular
3 population, just note that the levels of agitation were
4 quite broad when you look across the four pivotal trials in
5 the three populations, ranging from moderate to severely
6 agitated. I will show you that data in a bit.

7 We have both psychotic and non-psychotic
8 individuals. That becomes important because we were
9 developed initially as an antipsychotic drug. One would
10 then wonder is an effective agitation purely a secondary
11 phenomenon of your antipsychotic drug effect? In order to
12 answer that question the best approach, in our view, would
13 be to look at the drug specifically in patients who do not
14 have psychosis in order to try to parcel out the agitation
15 response from the psychotic response.

16 A broad range -- the earliest age you could come
17 into the study was 18 and we did have 18-year olds in the
18 study, all the way up to the very elderly and, as you will
19 see in a moment, we had some very elderly individuals going
20 up into the upper 90s in terms of age. So, we had a very
21 broad range in terms of age.

22 Patients with and without concurrent medical
23 conditions -- I think whenever you do a clinical trial,
24 particularly when it is double-blind, placebo-controlled,
25 you have introduced a change and I think it is always a fair

1 criticism to say that is not real world and, almost by
2 definition, you have deviated from that and I think that is
3 kind of creating the right balance where you can get
4 meaningful information that can be extrapolated to the so-
5 called real world but you have introduced a change from day
6 one.

7 I think one of the things that happens in a lot of
8 trials is that concurrent medical conditions are so
9 carefully screened out it is difficult to ascertain from the
10 clinical trial base how would this drug perform in a group
11 of patients that are more real world. And, we know that in
12 schizophrenia, bipolar and particularly dementia concomitant
13 medical complications are common. So, I think it is helpful
14 to determine the safety profile of a drug when you are
15 studying this kind of diversity in groups.

16 We have both psychiatric and neurologic patients
17 in terms of the psychiatric ones being bipolar and
18 schizophrenia and then the dementias being neurologic. And,
19 differing underlying disease process as well, with the
20 dementias being a neurodegenerative underlying disease
21 process and bipolar and schizophrenia presumably, although I
22 have to put some quotes around that, presumably being non-
23 neurodegenerative. We have good hypotheses of etiology in
24 disease process in these two disease states. We don't know
25 for sure but the most compelling data is that these are not

1 your typical neurodegenerative type disease processes, but
2 probably something more in the neurodevelopmental framework
3 or something along those lines, although that is not
4 conclusively demonstrated.

5 So, again, we think that this adds some strength
6 to the package because of the diversity, and then when you
7 are starting to think about the possibility of extrapolating
8 from your diagnostic types, what we are trying to do is
9 offer more parameters to allow a comfort level in that
10 extrapolation if, indeed, that happens to occur.

11 [Slide.]

12 Now let's get into the study designs of the four
13 pivotal trials.

14 [Slide.]

15 I am just going to take a moment on this slide
16 because I think it is important and as I kind of go forward
17 I won't be going back but so that there is a good
18 understanding of how these trials work.

19 There was a basic template for all four studies
20 and it was that basic template that allowed us to then make
21 some examinations across the studies. But there are also
22 differences in each of the four studies. That is why I am
23 going to take a little bit more time here. These are the
24 four studies. This is how I will identify them from here on
25 out. This is a schizophrenia dose-finding study. This is a

1 schizophrenia study that had larger sample sizes, in part
2 because for a European regulatory request we had a primary
3 of non-inferiority to haloperidol. So, we have larger
4 sample sizes in these two arms. There is a bipolar study,
5 and that is the insignia for bipolar, and then the dementia
6 study. Just note the diagnostic groups. These are DSM
7 criteria and then for bipolar you could be bipolar manic or
8 mixed episode dementia of the Alzheimer's type. Vascular or
9 mixed were allowed.

10 All of the studies were 24 hours in duration. We
11 made a concerted effort to try to bring in as much of the
12 real world as we could to trial designs. We tried to mimic
13 the way we think the drug would most likely be used,
14 therefore, the relatively short interval with that idea of
15 trying to quell agitation and then rapidly move to oral
16 treatment if, in fact, oral treatment is appropriate and
17 indicated.

18 All the treatment groups have placebo, as you see
19 here, and all of the treatment groups have active
20 comparator, haloperidol in the two schizophrenia studies;
21 lorazepam in the two non-schizophrenic studies. Then, note
22 the ranges of doses of olanzapine. In the dose-ranging
23 studies or the dose-finding studies these are all fixed
24 doses of 2.5 ranging up to 10 mg, 10 mg in the schizophrenia
25 studies, 10 mg in the bipolar study and then in the dementia

1 study two fixed arms of 2.5 and 5.

2 The randomizations were even in this study,
3 1:1:1:1. The randomizations were weighted in this study
4 2:2:1 for the active treatment groups and 1 to placebo,
5 again, partly an ethical consideration trying to find that
6 balance of trying to bring forward the most meaningful data
7 and also give consideration to ethics. This study was 2:1:1
8 randomization again partly for the same reason. Then, this
9 was an even randomization.

10 The doses in the dementia study were chosen based
11 on our knowledge of the oral. We know that 10 mg is a very
12 typical, generally a very effective dose for non-geriatric
13 individuals. Remember, we have similar AUCs between the IM
14 and the oral so that 10 seemed to make sense in these
15 studies, and we had some early Phase II study data to
16 support that. What we have learned in our dementia studies
17 of the oral is that lower doses seem to be effective. In
18 general convention, in treating the geriatric populations
19 there is a tendency to use lower doses as well and that is
20 why we have used these two lower doses. So, that is based
21 on our knowledge and a bit of bridging from IM to oral in
22 our dementia versus our non-dementia populations.

23 [Slide.]

24 Let's talk about the rationale for the doses of
25 the comparator. We think that is always a challenge,

1 getting the dose of your comparator right and I think there
2 is always room for some debate on what is the precise or the
3 right dose for your comparator. I will just take you
4 through our rationale.

5 We elected to use haloperidol at 7.5 mg in the two
6 schizophrenia studies. We did that because in looking into
7 the literature and a fairly broad consultation network that
8 was actually global we found that 5 mg and 10 mg of
9 haloperidol were commonly used. So, we thought that 7.5
10 represented an intermediary between these two doses that
11 tend to be commonly used. In addition, to support that
12 there was a dose-response analysis that suggested that doses
13 that exceed 7.5 to 10 do not appreciably increase immediate
14 efficacy -- this was an IM meta-analysis -- but may cause
15 additional side effects. So, as you start going much beyond
16 7.5 you are not getting that much more efficacy but you are
17 getting more side effects. However, there is increasing
18 efficacy up to about that 7.5 to 10 mg range. So, again,
19 7.5 seemed like a reasonable selection for a comparator
20 dose.

21 Now, IM lorazepam -- we elected to use 1 mg as the
22 starting dose in the dementia population and 2 mg in the
23 non-geriatric groups. Again, I will give you our rationale.
24 We wanted to be able to, from a real-world perspective, look
25 at more than one dose, particularly if it was clinically

1 indicated. In order to do that and to match across arms, if
2 we used a higher starting dose of lorazepam there would be
3 some mismatching in doses later because it is recommended
4 that you not exceed 4 mg of IM lorazepam over a 24-hour
5 period.

6 I think the other point is that 2 mg in a non-
7 geriatric group is a common dose. It often comes in the
8 United States in a pre-filled syringe that is 2 mg and it is
9 commonly used as 2 mg. You will find experts that will say
10 that they prefer to use 4 mg. So, I can't tell you that 2
11 mg is the only or the uniformly only starting dose. You
12 will have some people who will elect to use 4 mg as their
13 starting dose and I think that could be a useful discussion
14 point when we look at some of the comparator data.

15 For geriatrics you just tend to use lower doses in
16 a more vulnerable group and that is why we chose to use a
17 lower dose of lorazepam in the geriatric population.

18 [Slide.]

19 Here are the template study designs. All patients
20 underwent a screening period initially that did not exceed
21 24 hours. It could have been as short as 2 hours. Some of
22 these patients were coming in very agitated. It was
23 important to do a very good consent, physical exam, EKG,
24 blood work and assessment but we did not have a long
25 screening period.

1 At the point of randomization the baseline began,
2 and that began with the first injection of study medicine.
3 So, injection number one was given at baseline, double-
4 blind. Then, no other treatments were allowed for the next
5 two hours. This is the most important observational period
6 because this is where we are looking at our primary, our
7 PANSS EC versus placebo, in all four trials. So, no rescue
8 medication; no augmentation with other antipsychotic drugs.
9 So, this is a rather pristine observational period. After
10 these assessments were captured, at two hours, if clinically
11 indicated by judgment of the clinician a second injection
12 could be given, again double-blind.

13 Then, in the two schizophrenia studies a third
14 injection could not be given for a minimum of four hours.
15 However, after the second injection in the two schizophrenia
16 studies one dose of a benzodiazepine, open-label rescue
17 could be given. After the third injection, if they got a
18 third injection, a second but single dose of a
19 benzodiazepine could be given in those two studies. That is
20 it for any kind of added medicine. So, up to three
21 injections of study medicines and maximum two
22 administrations of either IM or oral open-label
23 benzodiazepine for rescue if needed. So that ensures that a
24 placebo randomized patient has a relatively short window
25 upon which thereafter to go before they are actually

1 receiving active medicine. Short screening period
2 relatively speaking and then a study period that was not
3 excessively long, again, so that we could rationalize using
4 placebo and still study clinically meaningful agitation,
5 acutely agitated patients.

6 Because lorazepam was the comparator arm in the
7 two other studies, the bipolar study and the dementia, we
8 did not have benzodiazepine rescue. In those studies we
9 moved up the ability of having the next injection. So,
10 after the second injection one only had to wait one hour
11 before receiving their third injection, but no rescue
12 medicines. If you required a third injection and you were
13 on placebo, you were automatically randomized to double-
14 blinded olanzapine to give those placebo randomized patients
15 the opportunity to achieve an active treatment and not to go
16 an entire 24-hour period without the availability of any
17 active medication. So, again, trying to walk that delicate
18 balance between using placebo because of its scientific
19 usefulness and its informativeness but keeping the ethics
20 kind of very close in hand and trying to walk that balance
21 and also study very agitated patients at the same time.

22 [Slide.]

23 Important inclusion criteria, there were two and
24 both were important. First, there had to be a clinical
25 judgment that the patient was appropriate, that the patient

1 had clinically appropriate agitation and was an appropriate
2 candidate for the treatment with an IM. So, if you like, a
3 diagnosis was made, a categorical judgment by the
4 investigator was made, independent of any rating scale, that
5 that patient was an appropriate candidate for a parenteral,
6 an IM injection, that their clinical state warranted that.
7 So that clinical judgment I think is very important in
8 understanding the criteria.

9 In addition, they needed to have a PANSS Excited
10 component of at least 14 or greater, plus a score of at
11 least a 4, which is moderate, on at least one of the items
12 of the 5 items in the PANSS scoring system. So, that was
13 our key criteria for inclusion.

14 [Slide.]

15 These are just some noteworthy other entry
16 criteria. There are more obviously in the protocol but we
17 thought these would be of the most interest to you. DSM-IV
18 criteria for schizophrenia, bipolar. By the way, we used
19 the SCID for the bipolar diagnosis as well. DSM-IV or
20 NINCDS-ADRDA criteria for dementia was used for dementia.

21 The age range again, a minimum of 18 for
22 schizophrenia and bipolar; a minimum of 55 for the dementia
23 studies and no upper limit. So, patients could come in as
24 long as they were appropriate in other ways.

25 There was a determination made by the investigator

1 that the agitation was not caused by substance abuse but we
2 did not require confirmation by a tox screen. So, that
3 would be knowledge that the clinician had of the individual,
4 asking the patient or family if the agitation was related to
5 substance abuse but that was not confirmed by tox primarily,
6 again, because of the time parameters. We are screening
7 people; we are moving into studies quickly and to wait to
8 get the tox results back would have been prohibitive for
9 many of these patients in terms of coming in.

10 No benzodiazepines within four hours prior to
11 injections. No antipsychotic drugs within two hours or four
12 hours for the bipolar or dementia studies. So, they could
13 have had a dose of a benzodiazepine prior to. Many of these
14 patients came in through the ER. This is an inpatient
15 study, by the way, not conducted in the ER but patients
16 could have come in and many of them did come in through the
17 ER. It is possible they did receive a dose of an
18 antipsychotic drug, were transferred to the acute care floor
19 and at that point would have been evaluated for entry. By
20 the way, what I just described was rather typical in these
21 trials, patients coming in; acute care setting; oftentimes
22 coming in through the ER; oftentimes then being admitted to
23 a short-term unit and at that point being evaluated,
24 consented and entered into the study.

25 Well, how do you enroll these patients? Well, we

1 talked to our investigators quite thoroughly about this and
2 it was interesting that many of the investigators had prior
3 knowledge of the patients so that there had already been a
4 relationship developed and a knowledge base developed about
5 those patients. That relationship was actually important in
6 the patients deciding to trust the investigator to consent
7 and come into the trial. That is an important point in
8 understanding how you enroll these patients. You have all
9 heard of the revolving door, unfortunately, that in these
10 acute care settings many patients will come in. They will
11 be stabilized; they will go out, and they become known by
12 the clinical staff, the nursing staff, the docs that work in
13 these clinics, and many of the patients fit this kind of
14 scenario in terms of coming into the studies.

15 Then no clinically significant EKG abnormalities
16 at baseline that would preclude participation. That was
17 read on the spot in most instances by the site investigator
18 who, by the way, was not a cardiologist.

19 [Slide.]

20 Let's take a look at the profile of the samples.
21 First, we had good sample sizes. These were all powered to
22 separate from placebo at two hours. In the dose-ranging
23 study there were 270 patients; in the schizophrenia study
24 311 that, again, had a non-inferiority test associated to
25 it; the bipolar group had 201 and there are 272 patients

1 here. There was a very high rate of completion, over 90
2 percent, but, remember, we are talking about 24 hours. We
3 are generally accustomed to lower completion rates but that
4 is because we are accustomed to longer trials. These were
5 all inpatients, all being watched and monitored for 24 hours
6 so our completion rates were very high.

7 Our screening failures were very low -- a short
8 time interval before you enter the study. The lowest rate
9 in any of the studies, off the top of my head, was 82
10 percent and ranged up into the 90 percent in terms of people
11 who were screened and then entered the study with high
12 completion rates. That is important because our completer
13 analysis and our LOCF analysis is very, very similar
14 because, again, we had very, very few dropouts.

15 Let's look at their ages. The mean ages were
16 middle age for these three groups, 36, 38, 39. Note the
17 mean age for the dementia population, 77 going up to a
18 maximum of 97 years of age.

19 In terms of the gender distribution, there tended
20 to be more males in the younger patients and then, I think a
21 product of the demographics of the geriatric group, there
22 tended to be more females. No significant difference
23 between groups within each of the four studies on any of
24 these baseline measures.

25 [Slide.]

1 To give you a better feel for who were these
2 patients, these acutely agitated patients -- are these the
3 patients who would likely get the drug? I am going to come
4 back to that point periodically as we look at the data
5 because it is very important that we are studying
6 appropriate patients, the patients that would likely get
7 parenteral IM. By definition, the schizophrenia groups at
8 baseline had psychosis or history of psychosis. For the
9 bipolar patients, 52.3 percent had psychosis at baseline.
10 That was a categorical judgment that was determined by the
11 investigator as part of the assessment. In the dementia
12 study, 44.5 percent of patients had psychosis at baseline
13 and that was determined by the NPI.

14 This is very important again in understanding the
15 population, the length of current admission. If you look at
16 those in their current admission for less than five days,
17 you generally see the majority of patients, 84.5 percent of
18 bipolar patients had an admission of five days or less.
19 Even the dementia group, 51.3 percent. There was a
20 preponderance of general hospital settings in the dementia
21 population as opposed to nursing homes or long-term care
22 facilities, although there were some. That might explain
23 some of this number down here of 28.6 percent having a
24 greater than 30 days, but very low having greater than 30
25 days among the other groups. So, again, these tended to be

1 patients who had not been in the hospital very long, who
2 oftentimes came in because of their agitation, came in for
3 management of their agitation and then were enrolled in the
4 studies in that way.

5 In terms of other ways of just better clarifying
6 this group, their baseline BPRS total -- this is an 18-point
7 scale -- shows that they had moderate to severe levels of
8 general psychopathology across the board. The Young Mania
9 Rating Scale says the same thing about mania for the bipolar
10 group and 26 is clearly in that moderate to severe end of
11 the spectrum. Moderate to severe would be a good
12 characterization of the level of mania. Then the Mini
13 Mental State Exam for the dementia group is 11.8. Those of
14 you familiar with that scale would see that that is again
15 that sort of moderate to more moderately severe mean
16 representing their dementia, the cognitive impairment.

17 [Slide.]

18 Very important is getting at this level of
19 severity of agitation. Notice their baseline means are
20 relatively similar across the four groups. Again, this
21 issue of comparability in terms of is this agitation similar
22 across these different groups -- notice the upper limits go
23 quite high on the scale so that these individuals were, in
24 fact, going into higher levels of agitation. I think this
25 is better seen in the next slide.

1 [Slide.]

2 This looks at the distributions on the PANSS
3 total. First note there is not grouping around 14. If they
4 were barely making criteria you would tend to see grouping
5 around 14 and that is not the case. There is a distribution
6 that gets some skewing out towards this end of the spectrum.
7 By the way, a 34 is a very high level. The maximum score
8 that you can get is a 35. On the PANSS EC 5 items, top was
9 a 7. So, you are seeing some quite severely agitated groups
10 of patients. When we look at the need for second
11 injections, in time to second injection in the placebo
12 groups, you will see that this is a treatment needing group
13 of individuals.

14 Just through looking at these, I won't say that
15 these are transposable but I think one would agree that
16 these patterns have some similarity across the four groups.
17 So, again, is the agitation we are looking at across these
18 three very different populations, does it have some
19 similarity? I wouldn't go as far as to say they are
20 identical. I think that would be way too strong, but I
21 think to talk about comparability, at least on this
22 distribution severity, there is some similarity.

23 [Slide.]

24 That also gets to the core items. If you look at
25 the core items at baseline across these three groups, again

1 you tend to see some comparability across levels, less so
2 with uncooperativeness, particularly as it relates to
3 bipolar, but with the other items you tend to see some
4 similarity, some very good similarity between dementia and
5 schizophrenia in looking at the core features across
6 baseline and, again, thinking back to this morning's
7 discussion, we are noticing some comparability of the
8 phenomena, the characteristics of agitation.

9 [Slide.]

10 Let's get to the efficacy results. We will start
11 with primary.

12 [Slide.]

13 This is probably the most important analysis
14 because this was our primary analysis, LOCF two hours; PANSS
15 EC versus placebo -- grey is placebo in all of these. You
16 see the baseline measures here. These are changed scores
17 from baseline, the last observation carried forward. Then
18 you see the different doses. Here is the dose-ranging study
19 and here is 10 mg. Then also note that we have the active
20 comparator, Haldol; the active comparator lorazepam; the
21 active comparator lorazepam. The first important thing is
22 that all active doses of olanzapine separated statistically
23 significantly from placebo, every single one.

24 You also look at separation with haloperidol from
25 placebo. I think this supports this dose that we chose.

1 Also in the dementia study this appeared to be reasonable
2 comparability. That is also separating. No, we didn't
3 separate here lorazepam from placebo and I think the issue
4 of 2 mg and 4 mg is probably a reasonable discussion we
5 could have. I am going to show you that in the
6 preponderance of efficacy data lorazepam 2 mg did separate
7 from placebo but in this particular measure it did not
8 although it was trending in that direction.

9 [Slide.]

10 This is a useful measure. It looks at response
11 rates, 40 percent change. What is the meaningfulness of
12 these changes? Well, we have active comparator to get a
13 barometer, but a 40 percent criterion I think most people
14 would agree is a reasonable criterion. You often see 20
15 percent change in the schizophrenia literature. I think you
16 tend to see more 40 percent change in some of the affective
17 disorder but I think there is a general sense that 40
18 percent would be a reasonable criterion that would mirror a
19 clinically meaningful change. Here again you see all the
20 doses separating from placebo; active dose 10 mg separating.
21 Again, all active doses of olanzapine 2.5 to 10 separate
22 from placebo. Here you now see the active comparators
23 nicely separating from placebo as well on that measure.

24 [Slide.]

25 This is at 24 hours and you see again similar

1 patterns. I am going to point out that the 24-hour data is
2 maybe real world, but there is a lot of variability. It is
3 a more complex measure. Some patients got a third
4 injection; some patients didn't. Some patients got rescue;
5 some patients didn't. So, there is some usefulness from
6 what is it like in a clinic perspective but this was not our
7 primary and, indeed, there is variability from patient to
8 patient because of the design of the protocol.

9 [Slide.]

10 This is useful. It may be a little difficult to
11 see from the back but it is probably useful to look item by
12 item in all the studies. So, here are all five items across
13 all studies. I think the main point here is that there was
14 no single one item that contributed to the response. All
15 five items made a meaningful contribution to the PANSS EC.
16 So, it wasn't driven by one or two items. I think that is
17 important.

18 We get good separation, particularly in 5 mg to 10
19 mg, pretty much across the board. Again, if you just look
20 across studies you see the magnitude of treatment response
21 being in a reasonable ball park. I won't say precisely; I
22 won't say identical but reasonable, in the same ball park of
23 responses, getting to some of the issues we talked about
24 earlier in the morning.

25 [Slide.]

1 I will go quickly. This is the Agitation-Calmness
2 Scale. This is plotted slightly differently. This is the
3 mean value at endpoint. Here is the starting mean and this
4 shows the movement into that more sedated state. So, as
5 opposed to just the change, this is the mean endpoint just
6 indicating that the placebo group never really moved into
7 the normal or therapeutic range where you do see the active
8 treatment groups tending to move into this more therapeutic,
9 desirable state.

10 [Slide.]

11 Look at the Corrigan -- very robust separation
12 from placebo and, interestingly, the two higher doses of
13 olanzapine separated from haloperidol on the Corrigan as
14 well. In the bipolar study we see also separation.

15 Here we see separation with the Cohen-Mansfield on
16 5 mg and comparator, strengthening again that dose selection
17 of comparator, but we did not separate on the 2.5 from
18 placebo on the Cohen-Mansfield.

19 [Slide.]

20 Time to onset, raised earlier in the morning, is
21 an important issue. That is one of the important
22 characteristics. Safety -- you don't want acute dystonia
23 and EPS but you also want very fast onset otherwise the oral
24 and elixir formulation or something else could be a
25 reasonable substitute for many patients. We did see a very

1 rapid onset. This is the largest sample size. We can show
2 you similar figures for all four pivotal trials but they are
3 very similar to this. The earliest time point we measured
4 was 15 minutes. We had significant separation at 15
5 minutes. These are just pair-wise comparisons, by the way.
6 We also separated from haloperidol at 15 minutes. We see
7 that separation continuing here. Haloperidol catches up and
8 then at endpoint in two hours we see very similar endpoints.
9 All the doses separate from placebo but earlier separation
10 clearly with olanzapine 10 mg. On the other trials we had
11 30 minutes as the earliest time point and in every single
12 trial we had active doses of olanzapine separating from
13 placebo at the earliest time point. In those other studies
14 it was 30 minutes. So, we were able to demonstrate a
15 relatively rapid onset of action.

16 [Slide.]

17 An important point on severity -- were we
18 effective in that more severe end of the spectrum or were we
19 only effective in a more mildly or moderately ill group? We
20 have looked at this a number of different ways. We can show
21 you similar data that we are showing you here on all pivotal
22 trials. This shows a mean split of the data. This would be
23 the more moderate, this is the more severe group. We find
24 significant separation with the severe group as well.
25 Again, we have looked at this many different ways but the

1 severely ill patients, the highest levels of agitation, are
2 getting a good therapeutic response with the drug.

3 [Slide.]

4 This needs a little setup. This is the number of
5 IM injections during 24 hours. These are stat graphs. This
6 is 100 percent of placebo patients. This would indicate
7 that about 35 percent or so had one injection, in blue.
8 This would represent about 20 percent of the patients, and
9 this would represent the remaining 50 percent getting a
10 third injection. The first time you look at the graph it is
11 a little confusing. So, all of the blues are those who got
12 one injection. All of the yellows are those that got two,
13 and all of the reds are the ones that got one.

14 The take-home point here is that you see a dose
15 response of number of injections, significant separation on
16 all active arms versus placebo. This is in a dose-ranging
17 study. There were many, many more patients requiring a
18 third injection in placebo. A very small number of patients
19 randomized to olanzapine required a third -- very few third
20 injections needed. Patients were, by and large, well
21 controlled with the first injection, which again was a
22 criterion we put forth as an important milestone to meet.

23 Now, were these truly severely agitated patients?
24 I would argue if they were not, those investigators would
25 not have been giving them a second injection. Moreover,

1 they would not be giving them a third injection. This
2 suggests that those patients in this study were, indeed, in
3 our view, in need of a treatment for agitation, such that
4 those investigators were, in fact, giving them those
5 injections.

6 Another important point that is not on this slide
7 but I can give you the data is that when you look at time to
8 second injection -- remember, the minimum amount of time you
9 can go is two hours. Any time after that over 24, you could
10 give your second injection. The mean time to second
11 injection in all of the olanzapine treatment arms was
12 between 4 and 5 hours for those who got a second. The mean
13 time to second injection in placebo was 2.5 hours. So,
14 those patients, right at the point practically, when they
15 could get a second injection were given the second
16 injection, indicating that they were hanging on and getting
17 through that first 2-hour period but needed further
18 treatment. So, we think this is fairly powerful data to say
19 that we are studying agitated patients and confirmed by
20 other parameters.

21 [Slide.]

22 How about psychosis? With an antipsychotic drug
23 are we seeing a secondary effect of psychosis? We were able
24 to divide the bipolar patients and showed, in fact, that we
25 were able to see a significant effect in the non-psychotic

1 patients. We look at the dementia patients. Remember,
2 about half of them had psychosis at baseline. Again, very
3 similar effects. This happens to be significant but clearly
4 we are seeing a very similar pattern of effect in the non-
5 psychotic dementia patients. So, we do feel that we are
6 isolating agitation. I can show you this data if you would
7 like to see it but I am going to move rapidly because of
8 time.

9 Two other important parameters -- we took all
10 patients out of the analysis who had a 7, 8 or 9 on the ACES
11 scale. Those were the very, very calm, the sleeping and the
12 unarousable. We took sedation out of the picture, removed
13 everybody with a 7, 8 or 9, redid the analysis -- same
14 results, very powerful separation. We don't think we are
15 confounded with our efficacy on sedation with those
16 analyses. We can show you those numbers if you like.

17 Another one, what about mania? We had the YmRs.
18 We looked at the YmRs at endpoint -- absolutely no change in
19 the YmRs, a scale rating mania. You wouldn't predict you
20 would see a change in mania over 24 hours. We didn't
21 predict it and we didn't see it but we saw robust response
22 with agitation in the mania group. So, we feel we have
23 pretty good checks on psychosis, mania and sedation to
24 isolate the effect of agitation in the database and
25 demonstrate an effect on agitation.

1 [Slide.]

2 Let's move on to safety. It is traditional to
3 look at efficacy study by study. It tends to be a little
4 more traditional to look at safety with the largest sample
5 you can get so that if there is a signal you can see it.
6 That is why we have used integrated databases to look at the
7 safety of olanzapine. We have five different databases to
8 look at. You may want to be referring back to this in your
9 handout as we go through.

10 A placebo-controlled database for our three non-
11 geriatric groups, 415, these are clinical trial patients
12 versus placebo. In the haloperidol-controlled groups, the
13 two groups that had haloperidol double-blind, 316 and 166
14 integrated. It is useful to look at the geriatric group
15 alone because of their uniqueness and their unique
16 importance in being informative about safety in both the
17 placebo-controlled database and we have also a haloperidol-
18 controlled database. Then, there is an overall patient
19 database of all agitated patients, 722. Then, every single
20 individual ever, whoever got olanzapine IM, is 850. So, we
21 have the ability to look at questions across all of these
22 databases. I would argue that an exposure of 850
23 individuals is a healthy exposure rate to look at.

24 [Slide.]

25 Let's look at adverse events. I will go rapidly

1 but we can come back during Q&A. Discontinuations, only 0.7
2 percent; 5/722 olanzapine-treated patients discontinued due
3 to an adverse event. So, very low. Serious adverse events
4 were very low, 0.4 percent that were marked by the
5 investigator as serious. Here they are: One was anxiety
6 which was really a proxy for agitation. Another was
7 abnormal ECG. That ECG, by the way, was abnormal at
8 baseline and didn't change during the course of the study
9 but essentially that was not picked up at baseline, but
10 there was no effect or change on the ECG, but it was
11 flagged. Anemia -- there was a patient that was borderline,
12 a 33 hematocrit at baseline. That dropped a little bit in
13 the study and that was flagged. Then, tachycardia but this
14 patient discontinued because of agitation. They then
15 received open-label lorazepam and haloperidol and then they
16 developed the tachycardia. So, there was not a direct link
17 between the tachycardia and olanzapine.

18 [Slide.]

19 Looking at adverse events compared to placebo,
20 this is one percent of patients with them, with an incidence
21 greater than placebo. The bottom line is no significant
22 differences; very, very low rates. Again, we can come back
23 because I am moving quickly. They are in your handout. If
24 there are any questions we will certainly come back.

25 [Slide.]

1 Let's go on to the haloperidol -- the same
2 situation, no significant differences; very low rate of
3 adverse events with IM olanzapine.

4 [Slide.]

5 When we look at adverse events that were different
6 from haloperidol or lorazepam -- I am just summarizing. If
7 you would like to see the data we can look at it. Very
8 importantly with Haldol, acute dystonia. In all of our
9 cases, 850, not one case of acute dystonia, zero -- very
10 important part of the molecule. Zero cases of acute
11 dystonia in 850 exposures. I believe haloperidol was 7
12 percent. It was significantly different. Extrapyramidal
13 syndrome, as you would expect, dyspepsia, etc.

14 When we looked at lorazepam then olanzapine, at a
15 statistic level there were two. There was more nausea and
16 more vomiting with lorazepam, not so with olanzapine. No
17 adverse events significantly more frequently on IM
18 olanzapine versus IM haloperidol or IM lorazepam.

19 In terms of site reactions, there were no site
20 reactions, no allergic reactions. There was a small number
21 of reports that reported pain which you will get when you
22 are given an IM injection, but there was no erythema or any
23 evidence of a dermatitis or allergic reaction.

24 [Slide.]

25 Sedation -- this is very straightforward. We used

1 the ACES of 8s and 9s. In some clinical situations, deep
2 sleep as long as they are arousable, in some patients might
3 be a desirable outcome. Clearly, 9 is never a desirable
4 outcome -- an unarousable patient. No IM olanzapine patient
5 scored a 9 at any time throughout the study; 5.1 percent,
6 28/551 treated patients had an 8. So, low rates of 8, zero
7 9. No significant differences between IM olanzapine and
8 either comparator, haloperidol or lorazepam, in the
9 incidence of 8s or 9s.

10 [Slide.]

11 Looking at sedation from one other window, adverse
12 events using somnolence as the term. Somnolence was
13 reported 5.1 percent of IM olanzapine-treated patients. No
14 significant difference between IM olanzapine and any other
15 treatment group, including placebo, in the incidence of
16 somnolence. So, there was not, in our view, excessive
17 sedation.

18 [Slide.]

19 We did the full battery of laboratory tests.
20 There was one statistically significant difference between
21 olanzapine and placebo, that was in mean cell hemoglobin and
22 there actually was a decrease in the dementia placebo group.
23 So, the laboratory values were unremarkable. Remember, a
24 24-hour study, not the typical six weeks, etc. but over 24
25 hours no significant impact.

1 [Slide.]

2 Let's look at vital signs. We observed
3 bradycardia in some of the patients with olanzapine. We
4 felt that this warranted a closer look. Let me summarize
5 what we are going to be looking at. First we found that
6 there was a greater incidence of bradycardia in terms of
7 incidence and magnitude in healthy subjects versus patients,
8 usually associated with hypotensions. In three healthy
9 subjects, two IM and one oral, there were sinus pauses, and
10 the proposed mechanism is a vasovagal response.

11 After we have looked at this, we will then look at
12 vital signs in the IM clinical trial database so that we can
13 look at comparator issues, and we have two cardiologists who
14 have worked with us on the cardiovascular status of our
15 molecule, Arthur Moss and William Groh. Both are present at
16 the meeting and will be available for Q&A at that time.

17 [Slide.]

18 First the bradycardia -- in our healthy subjects
19 and there were 85, there were 28 of the 85 who met a priori
20 criteria for bradycardia, or 32.9. The bradycardia criteria
21 is in the book. It was 50 beats per minute or less by
22 palpation or 50 beats per minute or less by ECG. It is an a
23 priori standard that we have used for years and that flagged
24 them. If you had one you were flagged as a positive case.
25 Note that of these individuals there was a mean of 21 vitals

1 taken per subject, and only 2.4 vitals were positive for
2 meeting those criteria. So, it is very, very sensitive
3 criteria. This does not imply bradycardia with symptoms.
4 That was unusual. That was just meeting those criteria that
5 I just indicated.

6 In the patient database, of all patients, 765,
7 only 6 met the criteria, which was 4.7 percent. Of a total
8 of 850 total subjects there was 7.5 or 64 individuals that
9 met the criteria. Clearly, the lion's share was in the
10 healthy subjects, the subjects that really this drug is not
11 intended for and I will come back to that point.

12 Then, looking at the association of hypotension --
13 again, the criteria are in the book -- 19 of the 85 had
14 concomitant hypotension; 21 of the 765 had hypotension, with
15 total cases of 40. But I do want to underline the fact that
16 these cases were anybody who met it once at any time over 24
17 hours.

18 [Slide.]

19 There were three cases of sinus pause. We used
20 telemetry in a relatively small group of individuals, 60
21 normals. That is all. We do not have telemetry data on
22 anybody else. Of those healthy volunteers, there were three
23 individuals, a 26-year old male, a 55-year old male and a
24 47-year old male, all healthy, one was on 10 mg of oral, 5
25 mg IM, 5 mg IM. The sinus pause was up to 6 seconds. They

1 tended to be associated with hypotension. They also tended
2 to be associated with an event, if you like, a trigger like
3 standing for a blood pressure measurement. They were all
4 preceded by sinus bradycardia. They were all self-
5 terminating and followed by a return to sinus rhythm.

6 In terms of patients, we had no cases of sinus
7 pause. Note, however, we did not have telemetry. We had
8 rhythm strips. There was one baseline minimum and two post-
9 baseline EKGs on all 765 subjects but we did not have
10 telemetry. That is important to note.

11 I do want to note -- and this is getting a little
12 bit far afield -- that we have looked very carefully in our
13 toxicology data, in both different species of animals and we
14 have looked in the oral data set for the oral submission of
15 high doses, long-term exposures, and did not see sinus
16 pauses or asystole. If anything, we saw a mild bit of
17 tachycardia, not bradycardia.

18 Syncope in patients, total of two. There was one
19 in the clinical trials. That was in a bipolar patient.
20 There was none in dementia and there was one in a very early
21 PK trial. So, there are only two cases of syncope in all
22 the entire exposures in patients.

23 [Slide.]

24 Our understanding of what is happening, what we
25 think it is, we think that the bradycardia and the pauses

1 are consistent with a vasovagal response which also goes by
2 the term neurally-mediated reflex bradycardia. It is
3 important to note that olanzapine has alpha antagonism
4 properties. It has it. And, the alpha-1 antagonists will
5 have the propensity to decrease blood pressure and you will
6 see in the vital sign data in large clinical trials that can
7 happen as well with olanzapine but it is at very low levels.

8 The bradycardia tends to be associated with
9 hypotension and that is, again, supported by clinical and
10 animal data. Approximately ten percent of the general
11 population will have bradycardia in response to decrements
12 in blood pressure. That is a well-known, well-characterized
13 phenomenon. The most common response is tachycardia, an
14 increase in heart rate. About 90 percent of individuals do
15 that and most of our patients do that as well, as you will
16 see, but there is that ten percent where you can see this.

17 It is greater in healthy individuals. Possible
18 explanation, why is that the case? Well, healthy
19 individuals may have increased vagal tone. This would be a
20 predisposing factor to a vasovagal response. There was no
21 baseline agitation. Agitation would likely decrease vagal
22 tone. Maybe that is why we see such a low rate in patients
23 but in healthy volunteers who are not agitated, who have
24 lower heart rates, would be more likely to do so. Again,
25 these individuals were not taking any alpha-1 blocking

1 agents at baseline, particular antipsychotic drugs. Most
2 antipsychotic drugs have some alpha-1 antagonism properties.

3 The outcome? Self-terminating, transient; more
4 marked early versus later in treatment. Management, if
5 symptomatic, is recumbency and the outcome is generally
6 benign. Not to indicate that the risk of syncope is benign
7 but the overall outcome of this syndrome tends to be
8 relatively benign.

9 [Slide.]

10 Now let's get to the clinicians trial sets, I
11 will move quickly because I know we have a bit of a time
12 crunch. I think this is a critical data set to look at
13 vital signs. Now we are in the population the drug is
14 intended to be used for, the agitated patient. We have
15 randomization. We are able to look at comparator drugs
16 under very similar conditions. So, I think in terms of
17 getting a meaningful understanding of what is likely to
18 occur with this drug, if it is approved, we go to the vital
19 signs data.

20 What I am going to show you are vital sign data
21 where there would be a change at any time during 24 hours,
22 at any point. So, you might say it is worst case scenario.
23 Low supine -- this would be a drop in supine systolic, a
24 drop in diastolic, a drop in pulse. This would be a drop in
25 standing systolic, a drop in standing diastolic, a drop in

1 standing pulse and an orthostatic change. Note that there
2 is a drop in supine diastolic associated with IM olanzapine
3 compared to placebo, significantly so. Also, on standing
4 you see a significant difference from placebo; also on
5 standing diastolic. There is no significant orthostatic
6 change. You do see a rising heart rate which would be the
7 predicted response, as you see here. I will show you the
8 data if you like. These are outside predetermined reference
9 ranges.

10 If we look at 30 minutes peak PK, peak plasma
11 levels -- we will show you the data if you like -- no
12 significant differences. We see some of the similar trends
13 but no significant differences across the board. If you
14 look at endpoint at 24 hours when the patient is ready to go
15 home, no significant differences. This is the most
16 sensitive measure any time during 24 hours.

17 [Slide.]

18 This is haloperidol-controlled. Now you are
19 seeing more similarity with haloperidol, although we do see
20 a greater standing systolic demonstrated with haloperidol
21 here, but the differences between haloperidol become less
22 marked with that exception.

23 [Slide.]

24 The geriatric group are, again, a very important
25 group to look at in trying to understand the phenomena. The

1 bottom line, no significant differences. By the way, no
2 hypertension; no above reference range effects; and no above
3 reference range effects and no above reference ranges of
4 tachycardia in the supine position. I am not showing you
5 that data because there were no differences and that was not
6 terribly informative but we can show that to you if you
7 like.

8 [Slide.]

9 It is important to look at the oral data --
10 intramuscular data, olanzapine-placebo; olanzapine-
11 haloperidol, is there a signal? Does this translate into
12 something that there should be concern about? The two terms
13 that are probably most helpful are dizziness and syncope.
14 Then we look at the oral database and there are over 2000
15 olanzapine exposures here, 882 here, placebo, haloperidol,
16 and this is at any time. Most of these are six-week studies
17 so at any point, including day one of dosing, and basically
18 you see very low rates of syncope, a very comparable profile
19 of the oral and the IM in terms of these event terms with
20 these comparisons.

21 [Slide.]

22 Let's go to EKGs. Q-Tc is presented both as
23 change and as categorical, using Moss criteria, as you see
24 here. This is the placebo-controlled database. There is no
25 significant difference on any parameter in the non-geriatric

1 groups, if anything, a slight numerical difference with
2 placebo here but clearly no prolongation.

3 [Slide.]

4 When we look at haloperidol, again no significant
5 differences. Nobody above 500 msec. If you look at the
6 mean changes here, no significant mean effect on Q-Tc
7 prolongation.

8 [Slide.]

9 Remember the elderly, a unique population but a
10 very important one looking for safety signals. The vital
11 sign data in the elderly was remarkably strong and good. We
12 will look at EKGs and 45.2 percent were greater than 80
13 years of age; 8.8 were greater than 90 -- very substantial
14 co-morbid medical conditions in this group, as you would
15 expect with ages of that degree.

16 [Slide.]

17 When we looked at the data we saw something that
18 was a little surprising, and that was a baseline difference.
19 This baseline difference on the 5 mg was significantly lower
20 than the other three. That was perplexing to us. There
21 were no significant differences versus placebo in any of
22 these arms, although there was a 9 msec mean prolongation
23 here and we were a bit confused by that. We didn't
24 understand it.

25 [Slide.]

1 Because of this, we invited in external
2 consultants. They asked to actually look at the tracings,
3 which they did, in the dementia data set and found, in fact,
4 some discrepancies. Their determination on looking at the
5 Q-Tc was sometimes variant with what we had in the database.
6 The original guidelines for Q-Tc were common across all four
7 pivotal trials with one lab, and that was using lead two.
8 There was a suggestion by our external experts that with the
9 advanced age of this population and the significant co-
10 morbidity and the fact that there was a lot of noise in
11 these cardiograms, non-specific and non-specific low
12 amplitude T-wave, perhaps a different approach might be
13 indicated. They suggested a complete re-read of all the
14 dementia data.

15 That was done by two independent laboratories. A
16 protocol among these two labs was jointly agreed upon using
17 three leads, averaging these leads for the determination and
18 then having a clear hierarchical algorithm for alternative
19 leads if necessary. All of this was done double-blind,
20 unmarked EKGs. The first ten percent were done jointly for
21 reliability. The inter-rater reliability was very good.
22 The data came back. We looked at it individually site by
23 site. It was very, very consistent.

24 [Slide.]

25 We pooled the data. Now we are seeing data with

1 no difference at baseline, as you see here, with the 5 mg,
2 very consistent. We are seeing millisecond prolongations
3 that were no longer than placebo. There are some
4 significant differences but they were not with the 5 mg.
5 Here is placebo; there is the 5 mg but these were shorter
6 than placebo, significantly so. We thought that this data
7 was more valid.

8 [Slide.]

9 Here are the categoricals looking at what I just
10 showed you, the mean changes, the categoricals.

11 [Slide.]

12 Plasma levels -- we didn't take our EKGs at 30
13 minutes. That is peak. We did them at 2 hours and we did
14 them at 24 hours. One might wonder, well, what is the
15 effect of peak levels. They weren't done at 30 primarily
16 because of logistics. It is very difficult when a patient
17 is still agitated to get a second EKG in the middle of
18 getting vital signs, etc. So, we got them at 2 hours.
19 Remember, our plasma levels at 20 mg are relatively high at
20 steady state and relatively comparable to worst case
21 scenario. Remember, we had very few patients that ever got
22 three injections at 10 mg. Most were done in the 1 mg range
23 where we see these plasma levels.

24 [Slide.]

25 When we look at Q-Tc with 20 mg of oral at those

1 higher plasma levels, you find that, in fact, you do not see
2 Q-Tc prolongation as a product of blood level. You don't
3 see a dose-response relationship. You don't see categorical
4 effects suggesting that the higher plasma levels might be
5 implicated in Q-Tc prolongation.

6 [Slide.]

7 That just summarizes what I told you. Let's go to
8 the next slide.

9 [Slide.]

10 Let's close with extrapyramidal symptoms -- mean
11 change from baseline to 24 hours, this is a very
12 straightforward story. The EPS data is very good. We have
13 placebo level EPS in all of our studies. We were within
14 placebo ranges in all populations. This is a measure of
15 akathisia. This is a measure of Parkinsonism. Haloperidol
16 has significant effects as you would predict, and that is
17 demonstrated here. But the olanzapine doses, all of them,
18 were in the placebo range.

19 [Slide.]

20 If we look at the other schizophrenia study, the
21 same story.

22 [Slide.]

23 If we look at the bipolar group, no significant
24 differences here. We had lorazepam as a comparator. No
25 significant differences with placebo on either measure.

1 [Slide.]

2 If we look at the more vulnerable or sensitive
3 group to EPS -- you are only looking at the Simpson-Angus --
4 again, no dose dependency, no significant effects on EPS.

5 [Slide.]

6 Let's close with two slides, a summary of the
7 efficacy of olanzapine. The efficacy of olanzapine in the
8 treatment of agitation was established in all four pivotal
9 trials. IM olanzapine was superior to placebo in the
10 primary efficacy analysis of all doses studied, 2.5 to 10.

11 Secondary efficacy measures yielded similar
12 results. The majority of IM olanzapine-treated patients
13 required only one injection in 24 hours.

14 IM olanzapine, doses 5 to 10 mg, demonstrated
15 efficacy 15 to 30 minutes after the injection, always at the
16 earliest time point measured. IM olanzapine was effective
17 in patients with and without psychosis, was not confounded
18 by significant sedation or mania.

19 [Slide.]

20 In terms of our safety conclusions, IM olanzapine
21 was safe and well tolerated. Incidence of EPS was similar
22 to placebo. There were no cases of acute dystonia. There
23 were no clinically significant changes in laboratory
24 analytes or ECG data, including Q-Tc intervals. It was not
25 associated with adverse effects on vital signs, except for

1 the mild and transient decrements in blood pressure and
2 heart rate. It was not associated with excessive or
3 undesirable sedation. There is an overall favorable adverse
4 event profile.

5 So, I am going to close there with the formal
6 presentation. We are eager to engage in a discussion with
7 you on all aspects of the data and we look forward to that
8 interaction. Thank you very much.

9 DR. TAMMINGA: It may be that you will look
10 forward to some discussion with us after lunch rather than
11 before lunch, but I am going to hope that if anybody on the
12 committee has some pressing questions on either efficacy or
13 safety that Dr. Breier just presented we could ask those
14 pressing questions before lunch. But, if we have a
15 substantive discussion, we might do that after our break.
16 Dr. Katz?

17 DR. KATZ: I just have an informational question.
18 I wasn't clear on when the diagnosis of the underlying
19 condition was made. I know you said a number of patients
20 were known to the staff before, but in the other patients,
21 were these all patients who already carried their diagnoses
22 before they presented with the agitation episode or were
23 some of them diagnosed there?

24 DR. BRIER: All of them had to be diagnosed there
25 by protocol. They had to undergo a psychiatric assessment

1 by the site investigator. So, a diagnosis was made at
2 baseline for all patients. There were patients who were
3 known previously.

4 DR. KATZ: In other words, if a patient came to
5 the emergency room the investigator didn't know the patient
6 and at that moment diagnosed dementia, or at that moment
7 diagnosed schizophrenia? They were only seeing the patient
8 acutely. Right?

9 DR. BRIER: Well, the screening period was up to
10 24 hours. That patient may have been on the unit for five
11 days, 30 days in some instances. They would have access to
12 medical records and all the other sources that a clinician
13 would use in making a diagnosis, with the exception of
14 bipolar in which we used the SCID.

15 DR. KATZ: You said these were all inpatients.
16 Were these patients inpatients before this episode? They
17 were on a service in hospital for their other condition?

18 DR. BRIER: The majority of the patients were in a
19 general hospital setting. There are some exceptions in the
20 elderly although the majority of those were as well. Again,
21 the majority of the patients had relatively short stays and,
22 of those short stays, the majority of those were admitted
23 because of agitation. It is not true in every case. There
24 were patients in all groups that were in hospital longer,
25 and in those patients there will have been some who had a

1 flare-up of agitation, where there was some control and then
2 a flaring up, versus agitation that persisted as they came
3 in through the ER and were admitted to the hospital ward.
4 So, I can characterize the general complexion but there
5 would be an awful lot of exceptions to that generalization.

6 DR. TAMMINGA: I just want to make sure that I
7 understood your response, Dr. Brier. Before study entry all
8 of the subjects had a neuropsychiatric diagnosis made?

9 DR. BRIER: Yes.

10 DR. TAMMINGA: Would you clarify how much dystonia
11 you saw on haloperidol?

12 DR. BRIER: I believe it was 7 percent, and that
13 was in the clinical trials.

14 DR. FYER: So, all the patients were already
15 diagnosed with these neuropsychiatric disorders, and they
16 were mostly on units already?

17 DR. BRIER: Well, they were all inpatients. We
18 conducted no studies in the ER.

19 DR. FYER: And, the decision to enroll a
20 particular patient -- were the investigators people who were
21 on the units?

22 DR. BRIER: Yes.

23 DR. FYER: So, the investigators were the people
24 who ran the units and they approached the patients directly
25 about being in the study?

1 DR. BRIER: Typically, correct. They would
2 approach them. They would indicate that, you know, there
3 was a study available and that they looked like they might
4 qualify. Then, if the patient agreed, they would then enter
5 screening.

6 DR. FYER: So, the people who were doing the
7 research were the people who ran the units basically and
8 they approached the patients?

9 DR. BRIER: In most cases.

10 DR. FYER: Thank you.

11 DR. GRUNDMAN: Just to get a sense, who actually
12 consented to participate in the study, the patients who were
13 agitated themselves or some surrogate for them?

14 DR. BRIER: In 98.5 percent of the bipolar and the
15 schizophrenia studies, those individuals gave their own
16 consent. Can we pull up the consent slide?

17 [Slide.]

18 I actually got that right. In the schizophrenia,
19 bipolar studies patient consent only was 98.5 percent.
20 Legal representative only was zero. In some there was both
21 patient and legal representative.

22 The dementia study is a bit different, and 49
23 percent gave consent only; 41 percent had legal
24 representative only and 10 percent had both.

25 DR. GRUNDMAN: Despite the fact that these people

1 were agitated, the investigator still felt that they were
2 competent to give consent?

3 DR. BRIER: Yes. I think it is important to
4 remember that even severe agitation does not preclude the
5 ability to give informed consent, just like psychosis. In
6 some individuals it will and in some individuals severe
7 agitation will be such that the person is not able to hear
8 the protocol and not able to give an informed consent. But,
9 I think it would be erroneous to conclude that just because
10 a person has agitation, even high levels of agitation, they
11 are unable to give informed consent. We stress the
12 importance of informed consent. The training on how to get
13 informed consent is in the startups, in the training, and we
14 put a very high premium on that.

15 But to the point made earlier, there were
16 candidates for this study who could not give informed
17 consent, who would not likely agree, and those patients are
18 not in the study. There is that subgroup.

19 DR. TAMMINGA: If there are no more pressing
20 questions I think we will thank you for your presentation,
21 Dr. Brier, and we will take a break for lunch and please
22 return in 60 minutes. Thank you very much.

23 [Whereupon, the proceedings were recessed at 12:25
24 p.m., to reconvene at 1:45 p.m.]

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AFTERNOON PROCEEDINGS

[1:45 p.m.]

DR. TAMMINGA: We have one public comment from Dr. Rex Cowdry.

Open Public Hearing

DR. COWDRY: Carol, thank you very much. It is a pleasure to be here with you all again. I am Rex Cowdry. I am the medical director of NAMI, the National Alliance for the Mentally Ill, and I have just a few brief comments I would like to make, starting with a disclaimer, of course, of conflict of interest since I think that is often asked for. NAMI does have an anti-stigma foundation that receives educational grants that are unrestricted from pharmaceutical companies and from managed care organizations, but it is a separate 501(c)3 and we have structured it that way specifically to try to maintain a kind of independent voice, and I hope that is part of what you hear today in these brief comments.

We believe there is a vital need from the perspective of family members and consumers for an intramuscular form of an atypical antipsychotic to control acute agitation in severe mental illness. Why? Well, there are a couple of reasons.

One of them was touched on in the presentation this morning, and that is the occurrence of adverse

1 reactions to IM conventional antipsychotics which is a
2 deterrent to continued treatment with the medication for the
3 individual who experiences it.

4 The second reason is what I had best call
5 therapeutic inertia. We know there is inertia of rest and
6 inertia of motion. This is inertia of motion, that is, once
7 you start on a medication the tendency is to continue that
8 medication. So, to the extent that a person is started for
9 a psychotic episode on a conventional neuroleptic there is
10 some tendency to continue into long-term treatment with that
11 neuroleptic, and we strongly believe that that is not in the
12 best interest of the great majority of our members.
13 Avoiding tardive dyskinesia is, needless to say, highly
14 valued by our members because if there is any situation that
15 interferes with social and occupational functioning or love
16 and life than having severe and persistent mental illness,
17 it is having severe and persistent mental illness with a
18 movement disorder.

19 Beyond that, it is clear that for a substantial
20 number of our members, actually, access to neural
21 medications can be life transforming. So, I think this
22 issue of inertia is one reason that we feel that
23 particularly there is a great need.

24 We talked about indications and I would suggest,
25 from a consumer perspective, that you want to treat in acute

1 situations in which, number one, continued agitation may
2 pose a medical risk to the patient or a behavioral risk to
3 the patient or others. Urgent intervention is needed and,
4 as part of it, behavioral interventions or oral formulations
5 are not reasonable options.

6 The complex issue of consent comes up in
7 involuntary administration of medications, and we know that
8 is a very complicated, politicized issue. It is simply not
9 a controversy that can or should be addressed by labeling.
10 But the problems with full informed consent and capacity to
11 consent in severely agitated individuals do play a role in
12 weighing risks and benefits in emergency situations. I
13 think they do have some implications for the warning
14 sections because in these situations consumers are
15 especially dependent on the clinical judgment of clinicians.
16 And, I think the issue that you will face is whether these
17 limitations in consent and the limitations in clinical
18 assessment, and particularly assessment of other medications
19 that the person may be taking when they present in an
20 emergency room with sometimes impaired capacity to give a
21 history, whether that then influences the kind of warning
22 that you provide in the labeling about the use of
23 medications or drug interactions, in fact, may be an issue.

24 Finally a brief comment about ethical issues in
25 these studies, this is somewhat of the topic but it came up

1 during the discussions and I thought it was worth a brief
2 comment. This is a major problem and we believe that there
3 is a substantial need for industry standards in this area.
4 It is well illustrated by this kind of situation where you
5 have a severe situation. The most extreme ends of it verge
6 on the kind of issues that came up in developing regulations
7 for emergency treatment, that is research in emergency
8 interventions where consent is not possible. Here, I think
9 it has been dealt with in a very thoughtful way but one
10 still has to raise the underlying question of how full an
11 informed consent, and how full the understanding is in
12 patients with excitable scores of 30 out of 35. I think
13 that is an issue.

14 Having said that, I think that informed consent is
15 only a part of that issue and the major protection really
16 lies in the design. At least from the description this
17 morning, the use of short time periods for measuring
18 response; the use of rescue medications relatively early as
19 an option; the very favorable randomization ratios; the
20 exclusion of the most agitated and, therefore, probably the
21 least capable to consent are all very positive aspects to
22 this design that I think make it very responsible.

23 This type of research is absolutely crucial, but
24 there is that problematic crux with informed consent and I
25 think it would be better if we could find a way to forge

1 industry-wide standards, voluntary guidelines that would
2 produce some greater consistency and consensus compared with
3 the current wide-ranging kinds of responses that you would
4 get if you took protocols like this to different IRBs. I
5 think that is a tremendous problem and, actually in a
6 disturbing way, it inhibits the research not to have greater
7 agreement and consensus about the kinds of procedures and
8 protections that are appropriate to enable this research to
9 move forward. Thank you very much. I appreciate the
10 opportunity.

11 DR. TAMMINGA: Thank you, Dr. Cowdry, for your
12 comments in the open public hearing. I would like to ask if
13 there are any additional comments that people would like to
14 make in the open public hearing.

15 [No response.]

16 Committee Discussion

17 If not, the committee will move ahead with its
18 discussions of the presentation of the product that was
19 presented this morning by Lilly. The questions that the
20 committee has to consider this afternoon are two questions.
21 One is the question of efficacy and the other is the
22 question of safety. I think that it might be reasonable to
23 proceed with the two questions in that order. Are the data
24 that we saw this morning convincing in terms of
25 effectiveness in the treatment of agitation? I would like

1 to open that question to the committee for its discussion.

2 Dr. Pritchett?

3 DR. PRITCHETT: I know that I am here to discuss
4 safety but there was something very provocative that showed
5 up in the efficacy presentation, and I would like to ask Dr.
6 Brier. In the dose-ranging study, I was intrigued that
7 every dose tested was significantly better than placebo,
8 including the 2.5 mg dose. I wondered whether you
9 considered the 2.5 mg dose to be a clinically useful dose
10 and, if not, why not? And, if it is a clinically useful
11 dose, can you tell me what the dose would be that would be
12 too low to be clinically useful? If Dr. Lipicky, from
13 Cardiorenal were here, he would be jumping up and down,
14 wanting to know the answer to these questions.

15 DR. TAMMINGA: Dr. Brier, if you have a slide of
16 the range of responses in each of those groups, it might add
17 to what Dr. Pritchett is asking.

18 DR. BRIER: Let's look at the primary outcome
19 measure, the PANSS EC at two hours, which shows the 2.5
20 effect.

21 [Slide.]

22 I think those are good questions. What would be
23 the recommended, for example, starting dose for most
24 patients? Why not recommend the 2.5, for example? I think
25 there are a couple of important points. One is that we

1 tested, and it was part of the protocol in the dose-finding
2 study, a dose-response relationship. That was formally
3 tested and, indeed, we have a significant dose-response
4 relationship suggesting better efficacy with higher doses.

5 I just want to take you back to a comment I made
6 at the beginning of my presentation, and that is the
7 usefulness of that first dose being effective and when we
8 looked at the stat graph, the 2.5 group required more second
9 and third injections -- not as many as placebo but more than
10 the other injections. So, there is a higher likelihood,
11 because of the dose-response relationship, that a 2.5 may
12 not be as efficacious as one of the higher doses. So, I
13 think that is part of it.

14 On some of the other measures the 2.5 did not
15 separate. So, it was not clearly as robust in terms of
16 efficacy as the higher dose. So, we would recommend a
17 starting dose of 10 for the non-geriatric patients, for most
18 patients, not every patient -- some clinical judgment is
19 obviously needed depending on the individual -- because it
20 consistently demonstrated a very high level of efficacy.
21 There were not significant side effect differences between
22 the next lowest dose, 7.5, and 10. So, again, in the spirit
23 of a dose that appeared not to carry additional safety
24 issues, it appeared to deliver the highest level of
25 efficacy, most likely with the fewest number of injections.

1 DR. PRITCHETT: Thank you. Can I just pursue that
2 one step further? It looks like the 2.5 is associated with
3 a decrease of minus 6 in the PANSS score. I would just ask
4 the committee members who deal with PANSS scores, and I
5 don't, if somebody came forward with a new drug and said it
6 produces a minus 6, is that a clinically important effect?
7 What does anybody think? I am trying to learn something.

8 DR. BRIER: I think that is a good question, and
9 we will ask the panel, but I think you might also, in
10 addition to looking at this change, you may also consider
11 this change -- subtract the placebo change --

12 DR. PRITCHETT: It is twice as good as placebo.
13 Placebo got about a minus 3 and 2.5 got about a minus 6. I
14 just wondered if anybody thinks that is good.

15 DR. BRIER: It is a five-item scale scored so that
16 the top score would be a 35.

17 DR. PRITCHETT: Right.

18 DR. BRIER: So, it may be significant. I wouldn't
19 call that robust --

20 DR. PRITCHETT: Oh, it is significant. I am just
21 asking whether it is important.

22 DR. TAMMINGA: Well, I think that you can look at
23 it in relationship to the active comparator, which is
24 Haldol, which shows about a minus 8, I guess. So, it is an
25 effect that is clearly less than the active comparator and

1 if you are a clinician you might choose to use the
2 haloperidol instead of the 2.5 mg dose if that is all there
3 was.

4 Do you have any variability data with the 2.5
5 versus the 5 or versus the 10?

6 DR. BRIER: We can pull up a table that shows the
7 means and the standard deviations for the PANSS EC at two
8 hours. Let's look at the standard deviations. That would
9 be a table, a numeric table that has the baseline means and
10 then the change with the standard deviations for PANSS EC at
11 two hours.

12 DR. FYER: I just wanted to ask if they could do
13 it for 5 also while they are doing that, not just for 2.5
14 but for 5 also.

15 DR. BRIER: We will look at the entire study.

16 [Slide.]

17 Here is the PANSS and there are the change scores
18 and the standard deviations.

19 DR. TAMMINGA: Additional comments?

20 DR. HAMER: I just want to remark that for the
21 PANSS EC the standard deviations remain relatively constant
22 across the doses, and even at the 2.5 mg dose that is a
23 standard deviation which is not bad.

24 DR. FYER: Could I just ask Dr. Brier about the 5
25 and the 7.5 from the same point of view that you discussed?

1 Because it looks like 5 is not bad.

2 DR. BRIER: Yes, the 5 did separate and the 5
3 separated on more items. It was more robust but, again, I
4 would take us back, and we didn't present those analyses but
5 they were part of the protocol, that is, we did a formal
6 dose-response relationship in that study, which was strongly
7 significant, again indicating that the higher the dose the
8 more efficacy. So, although you are getting a significant
9 effect from placebo, you are likely to get a larger
10 magnitude of response from 10 versus 5.

11 DR. FYER: I guess the issue is instead of one of
12 these change scores, you know, maybe we could see some data
13 about how many people didn't do well on 5 and 7.5.

14 DR. BRIER: Shall we look at the 40 percent
15 responder figure? Could we have that from the CORE, the 40
16 percent at two hours, PANSS EC?

17 [Slide.]

18 Clearly significant but that is rather steep. So,
19 you are getting more responders as you go up in dose.

20 DR. TAMMINGA: You don't have that at 20, 30 and
21 40 percent, do you?

22 DR. BRIER: No, we have it at 24 but, again, there
23 is a lot more going on and it is a little more complex.

24 DR. HAMER: To stick with the dose-response issue,
25 did you fit a linear term to that? As a statistician, I

1 should be ashamed to admit that I can never pronounce this
2 right -- a Jonckheree test of order to facts on those?

3 DR. BRIER: I am going to turn it over to our
4 statistician, Dr. David.

5 DR. DAVID: My name is Stacy David. I am the
6 statistician working on this for Lilly. What we identified
7 in the protocol was using Tukey's stepdown contrast to
8 control for the type-1 error.

9 DR. HAMER: And what did you show?

10 DR. DAVID: A significant dose response with the
11 minimally effective dose of 2.5, which was still effective
12 versus placebo.

13 DR. HAMER: Okay, thanks.

14 DR. TAMMINGA: Dr. Temple?

15 DR. TEMPLE: Of course, you knew that without
16 elaborate fitting procedures because the 2.5 dose beat the
17 placebo by standard pair-wise comparison.

18 Usually when you are worried about what dose to
19 use you ask what the cost of the higher dose is. I didn't
20 see any dose-response relationship for side effects. Now,
21 you only have one study that would allow you to look at
22 that, but did it appear that the higher response rates at
23 7.5 and 10 cost anything that you could discern?

24 DR. BRIER: We did not have any dose-response
25 relationship regarding side effects. We looked at Q-Tc and

1 we looked at vital sign changes, and those were not dose
2 response. Would you like to see some of that data?

3 DR. TEMPLE: It is really up to the actual
4 committee.

5 DR. BRIER: I think we can pull that up if you
6 would like to see it.

7 [Slide.]

8 It was by dose. So, here is the variety of
9 different indices. Here are the statistics. No linear
10 quadratic relationships between the doses of olanzapine. I
11 did show you earlier some Q-Tc data roughly by dose. I can
12 show you that again but there was not a dose-response
13 relationship.

14 DR. TAMMINGA: Dr. Fyer?

15 DR. FYER: Yes, I was just trying to clarify what
16 exactly that was. Do you have any data about this question
17 that came up before as to how -- I don't know -- I will use
18 the word sedated. It is not a very good term but people
19 sort of agree that we would like patients to be calm and
20 able to talk and, you know, deal with this situation. Do
21 you have any data about the doses with respect to that kind
22 of outcome?

23 DR. BRIER: Yes. We can look at -- let's see, I
24 am thinking of what would be the best way to approach that.
25 Somnolence as a term is not going to help us. The ACES by

1 dose -- let's take a look at that.

2 [Slide.]

3 That is the scale that started in the agitated
4 area. These are one of the stack bars. They are a little
5 bit hard to get your arms around. We will need to remember
6 the qualifiers here. This is unarousable, and 1 is very,
7 very agitated. Then this is sort of the categorical so this
8 would be 100 percent of the 2.5, 100 percent of the 0.5.
9 And, 4 we define as normal levels of verbal and motor
10 activity, to give you a sense of where you are. That is the
11 grey. We essentially have no 9s on this one; 8 would be
12 sleeping but arousable, where you could arouse someone from
13 sleep either verbally or with tactile stimulation.
14 Unfortunately, this isn't helping us a whole lot because 7
15 is probably a fairly desirable endpoint.

16 DR. GRUNDMAN: One question about the ACES, I
17 notice it goes from calm to deep sleep. I was wondering
18 whether there was anything in between.

19 DR. BRIER: Yes, let's pull up one that is more
20 detailed. There is normal, mild calmness, moderate calmness
21 would be 6. We have descriptions for each of these. Marked
22 calmness, deep sleep and unarousable. Going in the other
23 direction, it is mild agitation, moderate agitation and
24 marked agitation.

25 DR. GRUNDMAN: That is much better. So,

1 basically, the people who were 7 were still sleeping?

2 Right?

3 DR. BRIER: Seven is marked calmness, sleeping
4 lightly, aroused by mild to moderate verbal or physical
5 stimulation -- it would be a slight dozing, not a true
6 sleep.

7 DR. GRUNDMAN: So, we could look at the 7 to sort
8 of see whether or not they had a decreased level of
9 consciousness.

10 DR. BRIER: Yes. So, let's do that. Here are the
11 7s, in blue. It is a little bit different to eye ball it.
12 We could look at that statistically.

13 DR. GRUNDMAN: I am not sure this is really the
14 best way to present those data because what you really want
15 is sort of 7, 8 and 9 lumped together to look at the
16 relationship between that and dose. If you have a slide
17 that does this conversely, that shows each of the scores on
18 the ACES and then what doses, what the average dose was for
19 people who had that score. For example, on slide 65 you
20 said that you had 28 people who had a score of 8. It would
21 be interesting to see what dose those people were on.

22 DR. BRIER: That is something we could do. I
23 think you are right, it is going to be difficult to do it
24 here. Unfortunately, this is the only study with the range
25 of doses. The other studies had 10 mg. So we are not able

1 to test the question of 2 versus 5 versus 7.5 in other
2 studies. We have no 9s and such a small number of 8s, we
3 would really only be able to look at the 7s I think. But it
4 is something that we could do.

5 DR. FYER: Maybe you could lump the 7s, 8s and 9s.

6 DR. BRIER: We could do that but we have no 9s.

7 DR. FYER: Well, the 7s and 8s by dose. I think
8 that would answer the question.

9 DR. BRIER: We can do that.

10 DR. GRUNDMAN: To answer the question that you
11 raised before, if you look at the 2.5 dose you can see that
12 about 10 percent or 8 percent had mild sleeping whereas with
13 the higher doses, 5, 7.5 and 10, it looks like it is closer
14 to 20 percent. So, there does seem to be some sort of dose
15 response with respect to somnolence.

16 DR. BRIER: We can commit to doing a thorough look
17 at that.

18 DR. TAMMINGA: Somnolence in this case is not a
19 completely undesirable side effect. It is not like blood
20 pressure as a side effect. So, it wouldn't necessarily be
21 the cost that Dr. Temple was referring to. Dr. Laughren?

22 DR. LAUGHREN: Just to follow-up on that, I mean,
23 if you have a patient who has been awake for 48 hours and is
24 now sleeping lightly, that might not be a bad thing.

25 DR. TAMMINGA: Could you just review with us

1 again, Dr. Brier, why you recommended the 10 mg dose instead
2 of something lower?

3 DR. BRIER: Again, we would suggest that the
4 labeling include a range but for many patients a starting
5 dose of 10 might be appropriate. We base that on the fact
6 that we demonstrated the dose-response relationship,
7 suggesting that as you go up in dose you get more responders
8 and a better response. We do think that getting a maximally
9 efficacious response on the first dose is desirable in this
10 patient population. We have not been able to confirm a
11 dose-response relationship to side effects. We have not
12 seen any significant differences between 7.5 and 10
13 regarding side effects. So, if the side effect profile is
14 not different and you are getting better efficacy and you
15 are less likely to have to go to a second injection, for
16 example, then that is why we came to 10. So, 7.5 was very
17 effective as well.

18 DR. TAMMINGA: Dr. Laughren?

19 DR. LAUGHREN: Could you show the data on the need
20 for a second dose?

21 DR. BRIER: Yes.

22 DR. LAUGHREN: It doesn't look as though there is
23 much difference between 5 and 10 really.

24 DR. BRIER: Yes, I am sure that that is not going
25 to be a significant difference. You are right.

1 [Slide.]

2 Obviously we didn't power this question and the
3 sample sizes are probably not adequate to truly test that.
4 We are kind of using some extrapolation from the dose-
5 response efficacy data. If you have a significant dose
6 response you are just likely to see better efficacy as you
7 move up in dose. But those are good points.

8 DR. TAMMINGA: Any additional discussion on the
9 dose-response issue? There is one other issue that we
10 should discuss, and that is what Dr. Brier himself brought
11 up, which is that people with the most severe agitation were
12 screened out of this study. So, the data that we are
13 looking at right now are the data of moderately agitated
14 people with a neuropsychiatric diagnosis. So, we would have
15 to make the assumption, I guess, that the agitation in the
16 severely agitated is of the same nature as the moderately
17 agitated and that the response picture would look somewhat
18 similar. Dr. Katz?

19 DR. KATZ: Well, there is certainly precedent for
20 limiting in a claim the severity of the condition for which
21 the drug is approved. If you look generally at the
22 Alzheimer's examples, they are approved for mild to moderate
23 dementia. So, you don't have to include everybody in the
24 indication. You don't necessarily have to assume that very
25 severe patients will respond the same. They can be

1 excluded, at least by indication.

2 But, there was some discussion earlier and I
3 thought that some people were making the point that the
4 critical part of a definition of agitation ought to be
5 violent behavior or clearly manifestly hostile behavior.
6 Those probably are the more severe ones which, presumably,
7 haven't been excluded from these studies. So, the question
8 is does the committee think that that is critical towards
9 the approval? If they don't, I think we could work out in
10 labeling what it ought to say but I would be interested to
11 hear what people think about that.

12 DR. TAMMINGA: Clearly, I think that clinicians
13 would not want the most severely agitated people left out of
14 the labeling since that is really the group that most people
15 would want to treat. Dr. Temple?

16 DR. TEMPLE: Another thing we have done, and it is
17 a matter of judgment, is to describe without qualification
18 that it is for people who are agitated and then take note of
19 who was in the trials. That is done a lot, actually,
20 because we don't usually see the most severely ill people in
21 trials.

22 DR. HAMER: It is also not unusual, and perhaps
23 even the rule in many psychiatry trials, to exclude from
24 your trials a significant portion of the population to whom
25 you are eventually going to wind up giving the medication.

1 We exclude suicidal people from depression trials. We
2 exclude drug abusers from antipsychotic trials. So, the
3 fact that we have excluded the most agitated patients from
4 this trial isn't necessarily a whole lot different.

5 DR. KATZ: Absolutely. Clinical trials are always
6 artificial and the attempt is to identify usually a very
7 homogeneous population and often you exclude both ends, the
8 very severe and the very mild. So, I think if the committee
9 decides that it is not critical to have studied the severe
10 patients because those people really are the ones with sort
11 of important agitation, then we can deal with it in
12 labeling. But I would still like to hear the committee sort
13 of follow up on its earlier discussion about whether or not
14 it is critical that we study patients who are the most
15 severe or violent or risk of hurting themselves or others in
16 order to actually approve treatment for agitation.

17 DR. MALONE: Didn't they show data looking at the
18 most severe scores and what happened to them? I thought I
19 recalled a slide on that.

20 DR. KATZ: They broke it down by severity but it
21 doesn't necessarily imply that the most severe in this
22 dichotomy were actually the most severe patients that they
23 could get.

24 DR. TAMMINGA: In fact, I think Dr. Brier said
25 that they had been excluded.

1 DR. BRIER: Yes, we did look at this question in
2 our data a number of different ways including this; we
3 thought this was the most powerful. But we have mapped all
4 scores on an axis and looked at their response so that you
5 could look across every level of the PANSS Excited, and it
6 essentially shows what you are seeing here. You see strong
7 effects in the more severely ill. They have more symptoms
8 to improve. But I think that is right, although we had a
9 wide range of agitation in terms of severity, there is a
10 subgroup out there that we did not study, and that would be
11 the subtype that you would likely see in restraints who
12 would not be in a position, or would be ethically
13 prohibited, to participate in a study of this nature.

14 DR. GRUNDMAN: I wonder if you have any of the
15 items analysis of the CMAI, because the CMAI actually give
16 you fairly specific behaviors and, as Dr. Laughren mentioned
17 earlier, it would be nice to get a handle on what these
18 types of behaviors those patients were actually
19 experiencing.

20 DR. BRIER: We can do that. We don't have it item
21 by item. You know, it was a secondary measure. We did do,
22 as you note, the item by item by the PANSS.

23 DR. GRUNDMAN: Not just at the baseline, just to
24 sort of see what types of behaviors were present versus
25 absent.

1 DR. BRIER: We can do that as well. I don't have
2 that data but we can look at that. Also with the Corrigan
3 as well, as another approach because there are those kinds
4 of descriptors. I think the hostile item on the PANSS may
5 come close to some of what we are talking about, and those
6 scores were comparable to the other items on the PANSS.

7 DR. TAMMINGA: Dr. Laughren?

8 DR. LAUGHREN: Just to follow up on that, you
9 know, one thing that is missing here for most development
10 programs is the definition of the entity. Just as an
11 example, if you do a study of schizophrenia you have
12 diagnostic criteria for schizophrenia and clinicians make a
13 judgment about whether or not patients meet those criteria
14 to enter into the trial. Here, it sounds as if you left it
15 up to clinicians to make the judgment about whether or not a
16 patient was agitated, basically using the clinician's own
17 personal definition of what agitation is because nowhere is
18 it defined. Now, maybe it is obvious and you said yourself
19 earlier that agitation is the kind of thing -- I think you
20 used the words "you'll know it when you see it." Maybe that
21 is true but it is hard to write labeling based on that
22 definition. So, we will have to define it in some way in
23 labeling.

24 DR. BRIER: You recall our inclusion criteria was
25 in two parts; there was an "and" and the first was a

1 categorical clinical judgment that, indeed, in this patient
2 was agitation was such that an IM would be clinically
3 appropriate. The other was the PANSS criteria that was a 14
4 or above for a total score and at least one item with a 4.
5 So, in some ways perhaps that PANSS definition is our
6 operationalized definition.

7 DR. LAUGHREN: Yes, that comes about as close as
8 anything we have here to a definition and we will probably
9 have to rely on something like that, but it is not quite the
10 same as having laid out in advance diagnostic criteria, as
11 difficult as it is to come up with them here.

12 DR. KATZ: Do you know how many people met the
13 PANSS criteria for entry who met it on the hostility item?
14 It could have been any time, right?

15 DR. BRIER: It has to be a total of 14 --

16 DR. KATZ: Right.

17 DR. BRIER: -- and a 4 --

18 DR. KATZ: On any item. Do you know what the
19 distribution was of patients who entered with regard to
20 which item they made the criterion on? Probably many people
21 made it on many items.

22 DR. BRIER: Yes, you always had to have the first
23 one of the categorical judgment. I don't know that we have
24 the data cut that way because we would have the 14 plus 4.
25 Dr. Katz, we can look at that but we don't have that.

1 DR. TAMMINGA: What seems to be the strength of
2 the data set is that when you looked at your response you
3 saw a rather even response across all of the five items of
4 the PANSS EC, which would suggest that no matter where they
5 started at baseline their response to this medication was
6 rather similar across the five characteristics.

7 DR. RUDORFER: I have a slightly different
8 question about the inclusion criteria. Alan, you mentioned
9 that substance abuse was an exclusion criterion but that
10 toxicology screening was not routinely done. Do you have
11 the information after the fact for any of these people?
12 Did, in fact, a tox screen prove positive?

13 DR. BRIER: We were just talking about that. We
14 don't have that data. We could actually obtain that data
15 but we do not have it. In other words, we have urine
16 samples but we do not have that data, but that would be an
17 interesting sort of post hoc analysis in terms of
18 contaminated urines but we have not looked at that. Again,
19 the rationale there was that many patients were moving
20 fairly quickly into the study and in some centers it would
21 take quite some time to get those results back.

22 DR. RUDORFER: In the course of a patient's
23 routine clinical care a tox screen might have been obtained
24 on admission and later analyzed.

25 DR. BRIER: Yes. We don't have that data. It is

1 a good question and I think that we could probably get some
2 of those urines run and look at some of that data, but we do
3 not have that at this time.

4 DR. GRUNDMAN: I was wondering if you have a list
5 of the concomitant medications that the patients were on at
6 baseline, since a lot of these people were in the hospital
7 at the time and I am sure you collected that.

8 DR. BRIER: Yes, we have nice tables of
9 exclusionary medicine. Would that work?

10 DR. GRUNDMAN: I was thinking more in terms of
11 what antipsychotics or sedatives they might have been taken
12 before.

13 DR. BRIER: Let just review some of the criteria
14 with you. There were no benzodiazepines unless it was in
15 one of the two arms where rescue was allowed four hours
16 prior to baseline. Antipsychotic drugs were not allowed
17 four hours before baseline in the two non-schizophrenia
18 studies. In the bipolar study, if they were on a mood
19 stabilizer, they were allowed to continue it but not to
20 start a mood stabilizer during the study period or change
21 the dose. In terms of antipsychotic drugs at baseline, the
22 information is such that we have a record of what the
23 patient was on 24 hours before entering but not lengthy past
24 history information. The numbers were approximately this,
25 very, very low levels in the dementia study. It was greater

1 than 90 percent were not on an antipsychotic drugs at a 24-
2 hour time point before randomization. The bipolar group was
3 approximately 50 percent, and the two schizophrenia studies
4 were in the neighborhood of 50-60 percent. I would have to
5 check the schizophrenia number on that.

6 DR. HAMER: Does this mean that someone could
7 conceivably had had a depo injection of an antipsychotic
8 three days before?

9 DR. BRIER: We had criteria specifically on the
10 time before depo and it was one dosing interval. So, if it
11 was a four-week depo it would have been four weeks before; a
12 two-week depo, two weeks before but not more proximal than
13 that.

14 DR. HAMER: I don't know if you did this analysis,
15 but was there any difference in efficacy between patients
16 that were naive to antipsychotics versus patients who
17 weren't?

18 DR. BRIER: No, we did not do that and, quite
19 frankly, the data capture on past medicines, to really
20 isolate that group of naives was really not sound enough to
21 make a clear determination that an individual was, indeed,
22 naive to antipsychotic drug therapy. We can look at the
23 demographics, and the treatment setting, and the symptom
24 scores and make some inferences, and I think that the
25 profile here is really more chronic individuals with

1 schizophrenia and bipolar. The mean ages were in the late
2 30s, this type of thing.

3 DR. GRUNDMAN: In the dementia study, what was the
4 breakdown of the Alzheimer's patients?

5 DR. BRIER: Could we have that slide up?

6 [Slide.]

7 It was 60 percent for Alzheimer's disease, 59.9
8 percent. Vascular was 22.4, mixed was 17.6.

9 DR. GRUNDMAN: An obvious follow-up question is
10 whether or not you saw -- I am not sure if you did any sort
11 of subgroup analysis but whether or not there were any
12 particular groups that might have benefited.

13 DR. BRIER: We did not subgroup according to this.
14 The only subgrouping we did was the psychosis/non-psychosis;
15 the severity; the mean split, we did that in the dementia
16 study as well as the others; and we looked at the effects of
17 sedation by removing the 7s, 8s and 9s, and still
18 demonstrated the same kinds of effects.

19 DR. GRUNDMAN: On the subject of the psychosis, it
20 looked to me as if the patients who had the non-psychosis
21 related agitation seemed to have a more robust effect than
22 the patients who had a psychotic-related --

23 DR. BRIER: Let's put that up.

24 [Slide.]

25 There was a significant difference. I wouldn't

1 make too much out of this, in part because of the power.
2 That is bipolar. The next study is the dementia. You see
3 significant effects here. The change is similar across the
4 studies. There is a bigger placebo response over here. So,
5 I don't think I would make too much out of those
6 significance, other than to say that the magnitude of
7 response was comparable.

8 DR. HAMER: So, in this study the psychotic group
9 at baseline did not respond significantly better to drug
10 than placebo.

11 DR. BRIER: It did not reach significance,
12 correct. But I would just suggest again that we have cut
13 our power quite substantially in terms of looking at those
14 effects.

15 DR. GRUNDMAN: On that subject, how did you define
16 psychosis here?

17 DR. BRIER: It was on the MPI. So, if they had
18 anything other than a zero on delusions or hallucinations
19 within the week before, then that was considered psychosis.

20 DR. GRADY-WELIKY: I have a different question,
21 and it relates to the demographic breakdown of your
22 patients. I believe in the slide that you showed there was
23 white African descent and my question there is how you are
24 defining African descent. How many of those subjects were
25 actually African-American or black as opposed to African

1 from Africa.

2 [Slide.]

3 DR. BRIER: Good question. The reasons these are
4 a bit higher is because in these two studies we did have
5 sites in Africa.

6 DR. GRADY-WELIKY: I know. Do you have any sense
7 of the numbers of folks that were studied here just in terms
8 of potential differences?

9 DR. BRIER: In general? Yes, the majority of
10 patients were in North America. In fact, the dementia study
11 was almost exclusively North America. The bipolar was
12 predominantly in North America. About a third of this group
13 was in North American, and none of these patients were
14 studied in the U.S.

15 DR. GRADY-WELIKY: So, in fact, for the
16 schizophrenia studies there were very few African-Americans
17 from America.

18 DR. BRIER: From the U.S.

19 DR. GRADY-WELIKY: Right.

20 DR. BRIER: We could look at that. We don't have
21 it broken out that way but that would not be difficult to
22 do.

23 DR. GRADY-WELIKY: My only concern is that there
24 is growing data to show that African-Americans who are
25 diagnosed as schizophrenic may be more likely to get

1 antipsychotic medications, perhaps more likely to get
2 intramuscular injections.

3 DR. BRIER: That is interesting.

4 DR. GRADY-WELIKY: So, the question would be would
5 there be a similar response or a different response, and we
6 don't know.

7 DR. BRIER: We have a portion of patients here and
8 we can actually take a look at that but we have not looked
9 at it. That is a good point.

10 DR. TAMMINGA: Are there additional efficacy
11 comments? Dr. Fyer?

12 DR. FYER: I don't know where we appropriately
13 discuss this issue about agitation as an indication in the
14 labeling. Under this area or at the end?

15 DR. TAMMINGA: Any questions about efficacy I
16 think we ought to address to Dr. Brier or consider amongst
17 ourselves now, not necessarily the labeling considerations
18 which we could interact on after. Just state your issue.

19 DR. FYER: I just want to return to this issue
20 about whether agitation in these three disorders can be
21 considered agitation in other things. I will just say very
22 clearly that I don't agree with the approach to labeling
23 whereby you say that this is a drug for agitation, and then
24 afterwards that the data comes from these three disorders.
25 I think that what you have demonstrated is that it is

1 effective in agitation in patients in these three disorders
2 and that there needs to be qualification as to the fact that
3 we don't really know empirically what happens in other kinds
4 of agitated patients.

5 I guess I was a little concerned about the idea
6 that by showing that you could ask, you know, ten questions
7 across people with different disorders and get people who
8 responded in each of these disorders and that, yes, one then
9 concludes that there is something common about these things
10 on an etiologic basis. You know, if you look back to the
11 whole idea of, say, cough and fever, we could ask a group of
12 patients who had cough and fever and we would find people
13 with colds, lung cancer, pneumonia, etc., and nobody would
14 presume to think at this point in time that the best
15 treatment is something that suppresses cough. In fact, you
16 get into all kinds of dangerous situations that way. I
17 would sort of urge a conservative approach to this.

18 DR. BRIER: It is good to share some thoughts. I
19 think those are good comments. Just on one point, I think
20 we are all going to concede that etiology and
21 pathophysiology is going to be something that is going to be
22 very difficult to kind of address in this model. I think
23 that there is a natural reflex perhaps for me as a
24 scientist, as a researcher to say, well, if you haven't
25 studied it, how can you know it really works? And, I must

1 say that I brought that into the project initially and then
2 had to really sort of wrestle with that. I don't know if
3 there is a simple or easy answer. I kind of think back to
4 some of the earlier comments today of, well, how many
5 indications are enough? Would one ever consider that one
6 could then extrapolate from enough studies to say that
7 treatment A is efficacious for agitation?

8 But I understand where you are coming from. I
9 think the way we have the label and the diversity of the
10 population would allow a clinician to look at that and,
11 without having to do too much stretching, make some
12 reasonable decisions on what they might think is appropriate
13 and what they might not based on the samples that were
14 studied, the robustness of the effect, etc.

15 I am not an expert on the pain labeling, but I
16 understand that when you get approval for analgesia it is
17 worded that these are the populations that were looked at,
18 but that doesn't mean carte blanche that any kind of pain is
19 now thought to be a suitable target, nor would we conclude
20 from our studies that any kind of agitation is going to have
21 an identical treatment response to what we saw here.

22 DR. FYER: I think those are good points. I guess
23 my sense is it is interesting what people have done in other
24 areas, but the criterion for me in terms of medicine is
25 whether or not something has a potential to hurt people. I

1 feel that you have not demonstrated this in non-psychiatric
2 disorders and among people who don't have psychiatric
3 disorders there seems to be some potential for difficulties,
4 and because of that, I would have a concern about people
5 reading that this drug has demonstrated efficacy for
6 agitation would think it is for agitation. And, we don't
7 have very clear operational criteria. We don't have data
8 from non-psychiatric disorder groups, and we have some
9 suggestion that there may be some difficulties in patients
10 outside of these diagnostic categories. I think at this
11 stage of the game I would feel much more comfortable with a
12 more conservative approach given the absence of those.

13 DR. BRIER: A couple of comments. I understand
14 where you are coming from. I think that it is really
15 important to appreciate the data in our geriatric
16 population. We studied a group of patients there that are
17 kind of pushing the limits in clinical trials in terms of
18 age. The safety profile in that group was very, very good.
19 You are right though, it really does come down to safety.
20 If I put my clinician's hat on, do I doubt that the
21 agitation that would occur in major depression, or some
22 other state would likely decrease with IM olanzapine? My
23 hunch is that it probably would, that agitation probably
24 really is this non-specific syndrome. But it is the safety
25 that I think maybe gives people some pause in terms of,

1 well, we haven't looked at safety in this patient group or
2 that patient group.

3 DR. FYER: I think why could the sponsor not do
4 some studies in other kinds of agitation before you have
5 that kind of blanket indication? I mean, it wouldn't hurt
6 the people with schizophrenia/bipolar that Dr. Cowdry was
7 talking about and you could then proceed.

8 DR. BRIER: One point, and I don't mean to kind of
9 keep saying this, but how many populations is enough, or it
10 is going to be per population? So, perhaps if you all
11 approved it for these three populations, if we studied one
12 more would that then be added to the label?

13 DR. FYER: I don't think that is the issue. I
14 think the issue is you would like to extend it to being used
15 in general agitation in non-psychiatric disorder patients,
16 and in most settings the distinction between those groups is
17 reasonably clear. There is a small number of substance
18 abuse, psychiatric dual diagnosis patients where both of
19 those issues are, and what I am saying is I don't feel
20 comfortable with that extension without your doing at least
21 some patients in these other groups where they don't have
22 major psychiatric disorders. I am not saying you should go
23 on endlessly. It is a fairly specific sort of issue. I
24 mean, you don't have anybody in the other sort of major ER
25 presenting categories, like Dr. Malone was talking about or

1 substance abuse or mixed substance abuse populations.

2 DR. BRIER: Fair enough.

3 DR. MALONE: I too continue to have these
4 concerns. It seems that most of the subjects in these
5 studies really were psychotic. The schizophrenics were all
6 psychotic. The bipolars were half psychotic. Half the
7 population was psychotic. I think even in the dementia
8 population you had half of the population labeled as
9 psychotic. So, actually, I would be fairly convinced that
10 it was effective in the treatment of agitation in psychosis
11 but I would not be that convinced that it was just generally
12 a good idea to label it as effective in agitation.

13 There are two main reasons that come to my mind.
14 One is that when you looked at the normal, healthy
15 population that is where you had some of your more serious
16 side effects, as I recall, with sinus pauses and with
17 changes in blood pressure and I think with bradycardia and
18 hypotension.

19 Secondly, I think once you label a medication for
20 the use of agitation, then it becomes advertised for use in
21 agitation and promoted by various people for that usage.
22 They don't go around saying, by the way, we only looked at
23 schizophrenia and bipolar and patients with dementia, half
24 of whom were psychotic. So, those are really safety
25 concerns that I have.

1 DR. BRIER: I wonder if there is an in between
2 place in labeling where, on the one end it is unlimitedly
3 broad and then, at the other end there is something that
4 would be not -- I don't exactly know how to frame this, that
5 would be something that sort of is maybe well represented by
6 the study so that an extrapolation from the study base that
7 we looked at would have a high level of comfort for people
8 from the safety and efficacy perspective.

9 DR. TAMMINGA: Dr. Laughren?

10 DR. LAUGHREN: Obviously, we have a lot of
11 flexibility in how we write labeling but I think the
12 feedback we have gotten from the two members is very useful
13 from my standpoint. I would like to hear a broader array of
14 opinions from the rest of the committee to see where people
15 stand on this. This is the issue that is critical to us,
16 you know, whether you tie this to specific diagnoses or you
17 give a broad claim. So, I would like to hear more
18 discussion.

19 DR. TAMMINGA: I think that this morning when we
20 were talking about agitation, although there is agitation in
21 lots of different medical and psychiatric diagnoses, at
22 least two general categories fell out which was agitation in
23 psychiatric diagnoses and agitation in non-psychiatric or
24 medical conditions.

25 I would feel, from my point of view, that it is

1 not only a safety issue but an efficacy issue. There may
2 well be a difference in efficacy of these kind of compounds
3 or this particular drug on agitation in non-psychiatric
4 compared to psychiatric indications. So, it would really be
5 an assumption to say that it would only be in the area of
6 side effects and not efficacy, and I would really weigh in
7 on Dr. Fyer's side that it would be very difficult to just
8 say this was a treatment for agitation of all categories,
9 all general categories, non-psychiatric as well as
10 psychiatric. It seems to me that the data that we have
11 looked at so far demonstrates a rather broad testing of this
12 in psychiatric diagnoses, although the diagnoses are rather
13 weighted toward the psychotic diagnoses.

14 DR. LAUGHREN: Right. Just to broaden it a bit,
15 there has been a lot of interest in using this class of
16 drugs in children with conduct disorder. One wonders
17 whether or not you can extrapolate from these to that
18 population.

19 DR. TAMMINGA: Even in efficacy, let alone in
20 safety.

21 DR. GRUNDMAN: On the other hand -- correct me if
22 I am wrong, but I haven't seen any data to show that, if
23 anything, it is more effective for psychotic agitation than
24 for non-psychotic agitation. In fact, in the dementia study
25 it was in the other direction. So, it seems like the non-

1 specific agitation was equally, at least from the data I
2 have seen, as diminished as the agitation associated with
3 psychosis.

4 On the other side, just trying to get a handle on
5 what the symptoms of these patients were, you referred me
6 back to the PANSS before for some of those symptoms of
7 hostility, and tension, and poor impulse control, and if you
8 look at the numbers and how they relate to the excited
9 component, how they are rated, it looks like most of the
10 patients that were actually included in the study would be
11 characterized as mild in terms of symptoms and the effect
12 was to reduce it to more or less minimal or absent. So, it
13 sounds to me like we are not dealing with the severe
14 agitated patients, at least on a mean level.

15 DR. BRIER: I think that there was a spectrum.
16 Again, when we took the most severe end of the spectrum
17 where those means were greater --

18 DR. GRUNDMAN: You might even make the argument
19 that had you included more of the severe you would have had
20 a more robust effect because you had some limitation on how
21 much patients could improve because, if they start off at a
22 2 or a 3 they can only go down to a zero, whereas if they
23 started off at a higher level on that score they might have
24 had a more robust effect. So, there is some sort of a floor
25 effect that you may be bouncing into.

1 DR. BRIER: So, we would suggest that the most
2 severely agitated groups or patients in the study were
3 getting an efficacious response. I think, again, going back
4 to the placebo group and the increased number of injections,
5 again thinking as a clinician, that is fairly powerful.
6 There was a large number getting 3 injections over a 24-hour
7 period, and if it was very mild agitation I think it is
8 unlikely that those centers would have given those
9 injections. That is my guess. So, I think that it again
10 gets back to the point that there was that certain subgroup
11 that is not in the study. Within the study there is quite a
12 range of agitation and we think that we have demonstrated
13 that in that sicker end of the range we were efficacious.

14 DR. HAMER: There are sort of both efficacy and
15 safety issues with respect to other populations. One
16 important population which really was left out of this was
17 the substance users and abusers. I think one of the reasons
18 why it is important to think about that, that they were left
19 out, is that although if you look at the hepatic enzymes and
20 the pharmacokinetics and pharmacodynamics of this, it is
21 unlikely that it will interact with most drugs. You know, I
22 am not at all sure that there may not be some substances out
23 there that people might use, like cocaine or PCP or drugs I
24 have never heard of, for which there might be some potential
25 for an interaction. In some sense, it sort of troubles me

1 that in a population which this is likely to be used, people
2 who roll into ERs high on something and belligerent, angry
3 and hostile, that we really don't know how it might interact
4 with whatever they have rolled in on. So, that does kind of
5 trouble me.

6 The other issue, vaguely related I think to what
7 Dr. Fyer also was talking about, is the more general safety
8 issue. Even though it is labored perhaps, I would go back
9 to the analogy with pain. We have medications which are
10 approved non-specifically for pain but we have educated
11 clinicians or we trust clinicians to know that before they
12 treat someone with pain they need to do, as best they can,
13 appropriate diagnostic workups so that they know they are
14 not giving someone medication that will then mask whatever
15 the problem is, thus leaving the problem unrevealed. We
16 want to be careful that whatever way the labeling is written
17 here that clinicians are not encouraged to give this for
18 agitation of utterly and completely unknown reason, thus
19 potentially masking the information that you would need in
20 order to do a diagnosis.

21 DR. GRADY-WELIKY: Just to weigh in with Dr.
22 Laughren on the question of what committee members think, I
23 would agree with what has been said already, not leaving the
24 labeling too broad. Another group that I have concern about
25 would be related to the conduct disorder question with the

1 prison population, some of whom might have a psychiatric
2 illness but many of whom might have more of a character
3 disorder and my guess would be that these agents will be
4 used in that population as well and we don't know if it
5 would be effective or safe in that setting.

6 DR. RUDORFER: Yes, I would add to that. If I can
7 go back a step, the data we have seen related to two severe
8 Axis 1 mental disorders, schizophrenia and bipolar manic
9 type. Going back to our non-specificity rubric, I am
10 willing to accept that in another severe Axis 1 mental
11 disorder agitation would be an appropriate indication, for
12 instance, unipolar depression -- let's say a psychotic
13 depression that is neither schizophrenia nor bipolar mania.
14 But I think what we are all saying, which I would agree
15 with, is that once you go beyond those Axis 1 disorders,
16 either to Axis 2, to no mental disorder, or to an acute
17 organic insult, whether that relates to substance use,
18 substance withdrawal or a metabolic insult related to a non-
19 central nervous system disease, the fact is we have no data
20 upon which to judge even just looking at efficacy. Dr.
21 Hamer pointed out the various forms of substance abuse. I
22 am not an expert in that but my clinical recollection is
23 that even there a typical antipsychotic might be very
24 helpful in agitation related to cocaine use but be
25 counterproductive for PCP use.

1 DR. TAMMINGA: Yes, Dr. Ortiz?

2 DR. ORTIZ: In regard to the question, my concern
3 with the elderly is two-fold. Again, what Dr. Grundman
4 pointed out, that there seems to be some question of
5 efficacy in an agitated psychotic patient. I am also
6 concerned that if we approve agitation and imply usefulness
7 in dementia it is going to be misused clinically because I
8 think most of what is going to hit emergency rooms with
9 elderly folks is going to be delirious elderly and it is
10 easily confused with dementia in that kind of a clinical
11 setting. So, I also would like to see a little bit more
12 clarity or specificity rather than just giving it blanket
13 use for agitation.

14 DR. TAMMINGA: In the discussions this morning,
15 plus in our continued discussion now, it would seem like
16 surely acute agitation is what we mean and not chronic forms
17 of agitation. I haven't really heard Dr. Breier, in his
18 presentation of this, or any of us around the table, suggest
19 that something like this IM preparation would be useful in
20 chronic agitation.

21 DR. ORTIZ: Again, my concern would be that even
22 if you said chronic agitation in a demented patient, how it
23 would be used clinically may be totally different.

24 DR. HAMER: To also expand on Dr. Ortiz's point,
25 many of the elderly are already on five, or seven, or ten

1 medications prescribed by five, or seven, or ten different
2 doctors, and it is not uncommon for the combination of
3 medications ultimately to overwhelm and confuse the elderly
4 person. So, you then may have someone rolling into an ER
5 who looks delirious and/or demented, and the issue is that
6 the person is already on too many medications and, if we are
7 not careful, we could wind up encouraging the ER staff to
8 put that person on another medication.

9 DR. TAMMINGA: I have a suggestion that we might
10 broaden our discussions to include whatever additional
11 questions on safety we have so we can let Dr. Breier sit
12 down.

13 DR. BRIER: Can I just ask one question on one
14 point that is a little bit unclear from just listening to
15 the comments, and that is, is there discomfort with applying
16 the pain model in any form to this target? In other words,
17 getting back to your comment, if there were one more study
18 or two more studies in different populations, would there
19 then be comfort with it or would there always be a bit of
20 residual discomfort with the group that wasn't studied? So,
21 I am not sure if there is concern about studying the right
22 populations or the right number of populations or if there
23 is just discomfort with extrapolating into groups that no
24 one has ever studied because of the lack of understanding of
25 the pathophysiology, etc.

1 DR. TAMMINGA: It seemed to me that it was clear
2 that there was discomfort with extrapolating to children and
3 adolescents, number one, and to non-medical agitation,
4 number two.

5 DR. BRIER: I thought Mat's point was good about
6 PCP and then cocaine abuse, and I think there are several
7 different permutations around that in that agitation is
8 quite common and occurs in so many different states. So,
9 again it is where those limits are.

10 DR. KATZ: I think in part what I am hearing is
11 that it sounds like there are some settings in which
12 agitation occurs in which people think it would be
13 inappropriate to treat the agitation specifically as a
14 symptom because there is an underlying cause, that really
15 the treatment is correcting the underlying -- whether it is
16 a metabolic disorder or hypoxia, whatever it is. So, it
17 sounds like there are some clinical settings in which even
18 studying it probably is not worthwhile. I don't think
19 people are entertaining the fact that it might ultimately be
20 approved for the agitation of hypoglycemia or something.
21 That wouldn't be an appropriate treatment. So, there may be
22 other models in which it would be appropriate to study it
23 and ultimately to grant a claim, but it sounds like there
24 are some where it just wouldn't be appropriate at all. At
25 least, that is what I think I am hearing.

1 DR. TAMMINGA: Dr. Temple?

2 DR. TEMPLE: That is not entirely different from
3 the analgesic situation. Although many of them are labeled
4 non-specifically, nobody would think that just any old
5 analgesic would automatically be assumed to be effective in
6 migraine. It is possible they are but that hasn't been
7 assumed in things like neuropathic pain which are generally
8 treated differently. So, it is partly a matter of how much
9 experience you end up with. What I hear is a lot of
10 reservations about things that aren't psychiatrically or at
11 least brain oriented or initiated because there is not much
12 data on them.

13 But a fruitful area for study certainly seems to
14 be to look into agitation resulting from intoxication or
15 withdrawal and things like that. More of those might help
16 people get more comfortable with the general idea of
17 agitation, although still not for hypoglycemia.

18 DR. FYER: To respond to Dr. Breier's question,
19 about a year or two ago the committee met about an
20 indication for PNDD and that was a new indication. In
21 thinking about this issue of agitation in that particular
22 session, I think what is striking to me is I couldn't say to
23 you, well, I have the feeling that I could never approve
24 something for an indication for agitation or not because I
25 think in that case a lot of people, not necessarily the

1 sponsor but a lot of people had done a lot of careful,
2 extensive and costly work to look into the validity of that
3 diagnosis and its impact, etc. Here, it doesn't seem to me
4 that we have that kind of a data set to look at and maybe
5 that is really the issue. You know, when you want to pick
6 up a new indication you have to have an empirical data set
7 upon which to base the existence of that entity and justify
8 that particular therapeutic approach.

9 DR. HAMER: I don't want to keep going back to the
10 pain analogy but you wouldn't apply for general approval for
11 a medication for pain and say, yes, we have shown that it
12 works in several different models. We have shown it in a
13 root canal model and a molar extraction model and a cavity
14 model. To some extent, that is an exaggeration of what we
15 have done here. That is, we have three psychiatric
16 indications, all of which have psychosis heavily involved as
17 a major piece of them and it is perhaps somewhat of a leap
18 to then go beyond that to a virtually infinite number of
19 very different areas.

20 DR. TAMMINGA: Physicians may well take that leap
21 since they have done it with other drugs like IM
22 haloperidol. But at least for labeling to not be
23 misleading, we would be making recommendations for labeling,
24 for sure.

25 Additional discussion about efficacy? I am not

1 meaning to curtail the efficacy discussion but mostly
2 letting us ask whatever additional questions on safety we
3 have for Dr. Brier. Dr. Grundman?

4 DR. GRUNDMAN: Just along the lines of efficacy,
5 thinking about what alternatives there are for treating
6 agitation, you know, we can give people lorazepam, which was
7 done in these trials, or we can give them haloperidol, which
8 was done in these trials. I guess the question is whether
9 or not we decide that it is legitimate to expand the
10 indication to other areas or not. If we approve it for
11 psychiatric conditions it may be used similarly to those
12 agents. I guess really the critical question for us to
13 grapple with is whether or not we think this is any worse
14 than what clinicians are already doing with haloperidol and
15 lorazepam.

16 DR. TAMMINGA: Part of that would really depend on
17 the safety data and we did see the safety data presented
18 this morning. What else would we like to see from Dr.
19 Breier in order to extend our discussions to include safety?
20 Dr. Fyer?

21 DR. FYER: I disagree with Dr. Grundman. I don't
22 think the issue is whether we think people will do something
23 worse because it is not going to say in the labeling we are
24 letting you do this because we think what you might do is
25 worse. I think the FDA has an educational responsibility.

1 I have said this before to this committee and I know some of
2 the FDA people disagree with me about that, but I think that
3 what comes out of this committee has behind it the force of
4 an organization that is supposed to be responsible for the
5 health of the people in this country and I think we have to
6 take that reasonably seriously. The fact is we don't have
7 the empirical data upon which to base that indication at
8 present and I think we ought not to do it.

9 DR. GRUNDMAN: I actually don't disagree on that.
10 I am just saying that even if we approved it for agitation
11 in psychiatric illnesses and dementia, or at least approved
12 it for agitation in situations where those illnesses have
13 been studied, there is a good likelihood that people are
14 going to use it in other situations where they can't find
15 and underlying cause of the agitation. I think we just may
16 have to live with that.

17 DR. FYER: I think we may have to live with it but
18 I think it is our responsibility to make people as aware as
19 possible of what the possible risks are, known and unknown.
20 I think that by labeling it without those qualifications we
21 are obscuring the issue.

22 DR. GRUNDMAN: I think we actually agree with each
23 other.

24 DR. TAMMINGA: It sounds to me like you do. Dr.
25 Katz?

1 DR. KATZ: Again, the labeling can address some of
2 these issues. It can say, you know, don't use this in
3 anybody in whom you don't really have a definitive cause.
4 Check for metabolic derangements. You know, that can go
5 into labeling. We all know that labeling isn't followed 100
6 percent or 10 percent, whatever the number is --

7 [Laughter.]

8 -- but at least we can get into labeling what
9 would think is the appropriate thing to do without really
10 completely encroaching on the practice of medicine.

11 DR. TEMPLE: It is also worth answering the
12 question that was put, which is what additional data, if
13 any, could make one think that this is more like a pain
14 pill, that is, doing something about agitation whatever the
15 cause. You may not have those data yet but it is worth
16 thinking about whether anything would be convincing on that
17 score. Probably, I would guess, not with respect to
18 specific interactions with toxic drugs but there might be
19 studies in other arenas that would be of sufficient breadth
20 that would be convincing on that point. It is worth
21 thinking about sometime, maybe not now.

22 DR. PRITCHETT: I will think about it. I mean, I
23 like that idea and I think it involves setting up a study
24 that says we are testing this drug in agitation; all comers
25 welcome, and you let into the study whoever they think has

1 agitation and then keep track of what they have and you
2 might identify subgroups where it doesn't work. But I can
3 imagine a study that is sort of wide open. I don't know
4 whether it would make sense to do that with this drug or
5 not, but I can certainly imagine very broad entry criteria
6 for a clinical trial that might give you some comfort in
7 that direction. I could be perfectly comfortable with
8 labeling for this drug that said it is useful for the
9 agitation that occurs in association with dementia of the
10 Alzheimer's type, schizophrenia and bipolar disorder,
11 period.

12 DR. TEMPLE: So, we are talking about a large,
13 simple agitation study.

14 DR. PRITCHETT: Plus N equals lots.

15 DR. TAMMINGA: I would even broaden Dr.
16 Pritchett's recommendation slightly in that in the
17 discussions this morning it was clear that these kinds of
18 compounds are used in emergency rooms and in ICUs. And, to
19 base studies in agitation in those kinds of environments
20 would be more likely to catch those kinds of patients than
21 locating these studies in psychiatric hospitals and
22 psychiatric emergency rooms.

23 DR. LAUGHREN: The one problem with a large study
24 like that is that, you know, there is so much diversity that
25 you may end up with cells that are so small that you reach

1 the wrong conclusion because the numbers are too small for
2 various subsets. I think they are great for hypothesis
3 generating but maybe not so great for hypothesis testing.

4 DR. PRITCHETT: Again, if the numbers of patients
5 who wind up in the cells of these studies are very small,
6 then that would tend to tell me that population is very
7 small and that, therefore, the overall risk in that
8 population would be very small. If the study is
9 unsuccessful because it recruits a bunch of patients who
10 don't respond to the drug, that is the sponsor's problem;
11 that is not your problem. And, if they want to spend fifty
12 million dollars working up a drug for an indication and get
13 a negative study, I think that is an acceptable risk. I
14 don't think that you have to do a study like that and say,
15 well, two percent of the patients were patients who were
16 rolling in on Ecstasy and, therefore, we now have to do a
17 prospective Ecstasy study.

18 DR. TAMMINGA: Safety questions, Dr. Rudorfer?

19 DR. RUDORFER: I am going to bridge efficacy and
20 safety. I have a question about drug-drug interactions.
21 Dr. Breier, I understand that you observed no drug-drug
22 interactions in terms of medications that people were on at
23 baseline.

24 DR. BRIER: Designed to specifically look at drug-
25 drug interactions, we did do a drug interaction study with

1 lorazepam and we have done it with the oral with other
2 drugs. So, we have a rather full database on that and there
3 tends not to be significant drug-drug interactions and a lot
4 of that has to do with metabolic pathways of the drug.

5 DR. RUDORFER: Right, because one thought that
6 came to mind in treating bipolar disorder a medication of
7 concern is carbamazepine which can induce metabolism of many
8 drugs, including, if I am not mistaken, oral olanzapine but
9 I gather that you didn't see anything like lower plasma
10 levels.

11 DR. BRIER: Yes, we have done a drug-drug
12 interaction study with carbamazepine.

13 DR. RUDORFER: So, in other words, based on your
14 data we have no reason to consider that any given medication
15 that a patient is on at baseline would be a contraindication
16 to use of IM olanzapine.

17 DR. BRIER: I can't say that we have studied every
18 drug but I think the main ones that one would be concerned
19 about in these disorders we have.

20 DR. TAMMINGA: There will certainly be medical
21 drugs that wouldn't even have been tapped into in these
22 extensive studies that we have already seen because we would
23 see mostly the psychiatric concomitant medication studies,
24 not the myriad of drugs that one might see in emergency
25 rooms or in ICUs. Dr. Temple?

1 DR. TEMPLE: You don't have to study everything.
2 Remind me, I should know, but how is it metabolized? Is it
3 a 3A4 drug? What do we have here?

4 DR. BERGSTROM: I am Rich Bergstrom,
5 pharmacokineticist at Lilly. Yes, it is glucuronated and it
6 is metabolized by cyp 1A2. We know we have drug
7 interactions with carbamazepine. Carbamazepine induces the
8 metabolism of olanzapine.

9 DR. TEMPLE: So you get decreased blood levels?

10 DR. BERGSTROM: Decreased blood levels, and with
11 cyp 1A2 inhibitors there is an increase in blood levels.
12 But we showed in our data, for example on the slide for the
13 20 mg oral daily dose that there is a wide range of
14 concentrations that result from olanzapine. There is a
15 natural four-fold variability among the population. So,
16 drug interactions in general for olanzapine are not a
17 problem.

18 DR. TEMPLE: And it doesn't inhibit anything?

19 DR. BERGSTROM: It does inhibit --

20 DR. TEMPLE: 3A4?

21 DR. BERGSTROM: No, it doesn't inhibit 3A4. We
22 have tested 2D6 and it does not inhibit 2D6.

23 DR. TAMMINGA: Since we are talking about 24-hour
24 data here, one might be more interested in what the acute
25 drug-drug interactions would be than the drug interactions

1 that alter metabolism, or certainly in addition to the drug
2 interactions that alter metabolism.

3 DR. BERGSTROM: Right. Well, most of the drug
4 interaction studies that we have conducted actually are
5 acute experiments where we have done single dose, and some
6 of the studies have involved administration of maybe eight
7 days of olanzapine or eight days of the other agent before
8 we gave single doses of the interacting drug. But, again,
9 what we would anticipate for the use of the short-acting IM
10 is that our extensive database on the oral drug would be
11 applicable. So, the labeling that is already in place for
12 the oral would also be applicable to short-acting IM.

13 DR. TAMMINGA: Getting into other issues of
14 safety, Dr. Breier presented data on cardiovascular safety
15 and, among other side effects, predominantly motor side
16 effects, and we do have cardiovascular issues to discuss.
17 Are we interested in asking any additional questions and
18 seeing more data?

19 DR. PRITCHETT: I would just like to know in the
20 normal volunteer studies where all the action was with
21 respect to adverse effects, did you have any placebo
22 patients in those studies?

23 DR. BRIER: No, those were open-labeled.

24 DR. PRITCHETT: Do you wish you did?

25 [Laughter.]

1 DR. BRIER: Yes.

2 DR. GRUNDMAN: I mean, this is a really
3 interesting situation because I, like you, have come to
4 believe that if you want to demonstrate adverse events in
5 patients you go to your most vulnerable populations, which
6 would be the sickest and, indeed, you did that population,
7 your geriatric group, and they did fine. In fact, the most
8 dramatic side effects you had occurred in normal volunteers,
9 presumably very early on in the development program. One
10 can only speculate about the conversations that took place
11 in Indianapolis when those first couple of cases of sinus
12 arrest showed up.

13 So, it is kind of troubling to try to understand,
14 and I think you have put forward a plausible explanation for
15 what went on and why normal volunteers might be more subject
16 to this finding than the patients in your studies, and you
17 certainly monitored them better than you monitored the
18 patients in the studies. Indeed, I think that is
19 appropriate. I don't think you could have monitored these
20 agitated patients with ECG telemetry. I mean, agitated
21 patients won't tolerate having the recording electrodes on
22 and that sort of thing. You know, you just wound up getting
23 something you wish you hadn't seen and it is a little bit
24 hard to know exactly what to do with that. I mean, if you
25 look at the pharmacodynamic effects of the drug, you

1 wouldn't necessarily expect to see those kind of sinus
2 pauses. So, I think your explanation is, as I said,
3 plausible. It is just a little unsettling.

4 DR. BARBEY: If time allows, I would like to make
5 a couple of remarks. One question, how drug naive was your
6 elderly, demented population?

7 DR. BRIER: The data capture was on the 24-hour
8 period prior to entering in the study and, again, over 90
9 percent were not on antipsychotic drugs. But in terms of
10 long-term history and total drug naivety, meaning never
11 having had an antipsychotic drug, unfortunately, we didn't
12 capture that but we can surmise that at least coming into
13 the study the lion share of those patients were not being
14 treated with antipsychotic drugs.

15 DR. BARBEY: So, they were not acutely, you
16 explained that, but it is not inconceivable that quite a few
17 of them had been in the weeks preceding --

18 DR. BRIER: At some point. That is certainly
19 possible. Again, remember that the majority of those
20 patients had only been in the hospital five days so that
21 they were unlikely to have had an antipsychotic drug in the
22 recent time frame, but to suggest that they had not had
23 antipsychotic drugs at any point in their past is data we
24 don't have.

25 DR. TAMMINGA: Questions? Additional safety

1 questions? I know you have more comments. Why don't we see
2 if we can ask all the additional questions of Dr. Breier and
3 then we can let him sit down?

4 DR. GRUNDMAN: Just a clarification, among the
5 elderly demented patients, how many of them did not receive
6 antipsychotics previously? Was it 90 percent or 50
7 percent?

8 DR. BRIER: Over 90 percent were not taking
9 antipsychotic drugs 24 hours before coming in.

10 DR. MALONE: What about other kinds of
11 medications? I forget what the rule-out criteria were.
12 Were they on other medical medications?

13 DR. BRIER: We have exclusionary information that
14 I can show you. If you are particularly interested in the
15 geriatric study, we can take a look at that. Again, there
16 were no benzodiazepines allowed four hours before
17 randomization; no antipsychotic drugs in that population
18 four hours before randomization. The likelihood of any mood
19 stabilizers would be very low in that particular population.
20 Do we want to take a look at the exclusionary medications?

21 [Slide.]

22 These were the con meds that were not allowed. Do
23 we have those cataloged? We can get that but we don't have
24 it with us. I mean, these were individuals who had
25 extensive medical problems and 40 percent had hypertension;

1 30 percent had some significant cardiac abnormalities in the
2 past. Their advanced age and the fact that they were in an
3 institutional setting at least for the period of this study
4 would support the fact that they would likely be on
5 substantial medicines for their medical conditions.

6 DR. TAMMINGA: I think we can let you sit down,
7 Dr. Breier, not that we promise not to ask you to come back
8 up but at least you deserve a break. I think that we could
9 easily continue our conversation about the cardiovascular
10 effect.

11 DR. BARBEY: If you can spare me indulgence of a
12 few minutes, when I received Sandra Titus' call I feared
13 that we would be having long discussions about the QT
14 interval again, which many of us here have had to
15 participate in. Although when I received my material, I
16 realized, thankfully, that it was not that. Indeed, as an
17 aside, and I don't want to speak for my other colleagues --
18 based on data from other discussions and studies, the QT
19 data for olanzapine is very reassuring. Even if in this
20 study the time was not optimal in terms of relating to Cmax,
21 I don't believe there is any ambiguity in terms of any
22 unexpected electrophysiologic property of this drug, and we
23 agree, or I agree that we are looking at autonomically-
24 mediated processes that account for the sinus pauses,
25 hypotensions and sporadic bradycardias and that, indeed, the

1 dichotomy that this is observed much more in normal
2 volunteers than in the relevant psychiatric population is
3 not unique to this drug.

4 I will share a little experience with clozapine.
5 As a matter of just general background for people who don't
6 do this every day, vasovagal syncope was a clinical syndrome
7 described many years ago, and when there is a noxious
8 stimulus that triggers an event where there is both
9 manifestation of high vagal activities or diaphoresis,
10 nausea, as well as hypotension, vasodilation so there is
11 vagal hyperactivation and this is a frightening but benign
12 entity that self-corrects with the patient passing out,
13 being horizontal, and it is not an uncommon occurrence and
14 there is really no way to screen for this and probably no
15 need to. Subsequently, however, when people had similar
16 kind of episodes without the occurrence of a clear trigger,
17 that generated some anxiety in physicians and that is where
18 the technique of tilt testing became popular in the late
19 '80s. Indeed, some of us several times a week will bring
20 and deliberately put someone on a tilt table and have them
21 stand there long enough until eventually some of them have
22 symptoms and have bradycardia, hypotension or both and
23 occasionally even quite impressive bradycardia. In that
24 controlled setting, however, this is still not -- well, it
25 is a serious but not life-threatening situation; nothing to

1 do with QT prolongation and Torsade de pointes, and often
2 there is no need for pharmacologic treatment of this entity.

3 Interestingly though, while some drugs are that
4 are peripherally acting have been advocated to treat this,
5 centrally acting drugs have been advocated as well and
6 manipulation, particularly of the serotonin sort of pathway,
7 is sometimes advocated. Several of the SRRIs and peroxetine
8 in participant have come close to satisfying a double-blind,
9 placebo-controlled demonstration of efficacy. On the
10 opposite, interestingly, one group has reported injecting
11 intravenous clomipramine to enhance the likelihood of
12 syncope, and there are various models where either treating,
13 pretreating or adding serotonin to the brain can cause this.
14 I think the ancillary properties of this drug, beyond its
15 alpha-blocking properties, may be relevant in that area
16 although I don't claim, unfortunately, to understand it.

17 If I can share briefly what happened with
18 clozapine, and it would perhaps be similar to that, when
19 clozapine became available for generic use, a generic
20 company in California chose to begin testing in normal
21 volunteers with a dose of 25 mg as opposed to the hundreds
22 of milligrams that are sometimes used in patients. After a
23 dozen patients or so had three or four of these instances,
24 just like you describe in your volunteers -- pauses, perhaps
25 syncope, and I met with the generic branch at that time and

1 pointed out that this was a benign entity that one should
2 not be worried about, and the fact that the drug was given
3 in a profoundly fasting state at 6:00 a.m. to sort of semi-
4 somnolent patients who then for the first time would get up
5 three hours later to go to the bathroom and faint was not so
6 surprising. Since this was not a relevant problem in
7 chronically treated patients, one could come up with a
8 guidance so the testing could be done safely. So, my
9 suggestion was that the subjects be brought in the night
10 before, hydrated copiously, made to get up and walk around,
11 and exclude patients with a history of vasovagal syncope,
12 and have them dosed at 9:00 a.m. with the 12.5 mg dose, as
13 low as possible, with intravenous access and somebody
14 watching, even cardiac telemetry, to put 30 or 40 subjects
15 through this without difficulty.

16 That was approved and, sure enough, I ate sort of
17 the soup I had cooked for myself in the sense that a few
18 weeks later another generic company said, well, why don't
19 you do that yourself since you are so smart and set this
20 guideline? So, I had this sort of disconcerting experience
21 and, indeed, two subjects in this study who disobeyed these
22 guidelines -- one gentleman felt he could not urinate when
23 he was supine so he sat on the edge of the bed to urinate.
24 By the time we ran down and said, you know, "lie down' lie
25 down, you silly boy" sure enough, he had one minute of

1 asystole post micturition syncope. Another subject, when
2 his food tray arrived, he sat up.

3 So, I sort of witnessed and was convinced there
4 was sort of qualitatively something that was quite
5 spectacular, however, of no relevance in the way the drug
6 was being used. So, if you want, I am quite willing to
7 believe this dichotomy. And, to the extent that the
8 intended prescription of this drug is for either pretreated
9 or chemically different sort of patients, I have no concern
10 at all. If the broader indication is the one that is
11 accepted and people who come close to being healthy, normal,
12 young volunteers receive this drug perhaps in the setting of
13 dehydration, alcoholic indulgence etc., it wouldn't surprise
14 me that there would be a propensity for vasovagal syncope
15 the first time these people get up and go to the bathroom or
16 something like that. While this does not have the dramatic
17 connotation or seriousness of a QT arrhythmia, it is not an
18 entirely benign, innocuous process. Again, should this use
19 be contemplated, you know, whether it should be discouraged
20 or whether there should be strategies and guidelines to sort
21 of minimize the problems in that context which, again, is
22 intrinsically a non-life-threatening problem particular when
23 it is well controlled.

24 DR. TAMMINGA: Could you go a little further and
25 say what might be the serious consequences of sinus pauses,

1 number one, and because none of the patients had telemetry
2 are we to assume since they saw very little syncope, very
3 little other kinds of those kinds of side effects that none
4 of these sinus pauses occurred in the patients? Would you
5 be satisfied enough?

6 DR. BARBEY: Well, I think we would all agree that
7 asymptomatic sinus pauses are of no clinical consequence.
8 So, I don't have a concern for that. The fact that there
9 were few clinical events that could have been ascribed to
10 arrhythmia or hypotension among the patients, you know, that
11 is quite satisfactory to me. So, in fact, I don't disagree
12 that this is normally a self-correcting process and normally
13 a benign entity. It is particularly so when the
14 circumstances are a little bit more controlled. I think it
15 was said by the other speakers that, of course, one could
16 injure oneself falling; one could aspirate; one could
17 unnecessarily be coded, intubated and find oneself in
18 intensive care when there might not have been a need to do
19 that. So, the consequences would be unlikely to be directly
20 life-threatening but some morbidity and concern could arise
21 from that.

22 DR. TEMPLE: Well, the difference between the
23 dramatic and frequent adverse effects seen in normal
24 volunteers in clozapine studies and the lack of a similar
25 history after considerable length of treatment -- you know,

1 you couldn't do generics right away -- was very striking and
2 doesn't seem entirely explained because a lot of
3 schizophrenics aren't very old. They might be
4 cardiovascularly normal volunteers and, yet, it certainly
5 was not conspicuous in the history prior to the
6 bioavailability studies.

7 DR. TAMMINGA: I would like to say that
8 schizophrenics who are treated with clozapine are not put on
9 their final treatment dose in the first day. Very commonly
10 they even start on 12.5 mg and gradually work up to their
11 top doses.

12 DR. TEMPLE: But these were relatively low doses,
13 25 mg.

14 DR. BARBEY: We actually used 12.5. I think some
15 cases were elicited way back from the drug development phase
16 in Europe, and the answer for clozapine was that because of
17 its hematologic liability it was hardly ever used first.
18 So, drug-naive patients were very rarely exposed so they
19 were perhaps desensitized. I would have to say that it
20 seems inconceivable to me -- and that is sort of beside the
21 point -- that some of your patients take hundreds of
22 milligrams of clozapine because when you give 12.5 to normal
23 volunteers they basically conk out for 12 hours easily.
24 They are extraordinarily sedated.

25 DR. TEMPLE: But these are all peripheral alpha

1 blockers, right, and you get used to that.

2 DR. BARBEY: Right. No, no, absolutely. But an
3 interesting study would be if these same subjects received a
4 pure peripheral alpha blocker versus these drugs that have
5 these more complex CNS effects.

6 DR. TEMPLE: With the pure alpha blockers you
7 overcome the substantial tendency for syncope by starting at
8 a low dose. You can essentially eliminate it.

9 DR. BARBEY: Right, right. So, perhaps the fact
10 that clozapine -- I don't know that a comparison with
11 olanzapine is entirely fair. I am not suggesting that
12 either, but I think that its effect on the serotonin and
13 perhaps dopamine central mechanism makes the same trigger
14 have much more marked consequence --

15 DR. TEMPLE: That could be. I don't think that
16 pedisine-like drugs keep you having inappropriate
17 tachycardia as a rule.

18 DR. BARBEY: Yes.

19 DR. TAMMINGA: It is not only with dopamine
20 antagonists that schizophrenics and normals have a different
21 response but also with dopamine agonists for those of us who
22 try to treat schizophrenia with agonists. The emetic
23 response of normals is very, very much more severe to the
24 same dose of agonists than schizophrenics.

25 The cardiologists have suggested that this isn't

1 anything to worry about, although it is an interesting and
2 puzzling situation. Is this the take-home message non-
3 cardiologists should take home?

4 DR. BARBEY: Again, it is sort of a fine line
5 between worrying unnecessarily and not being cautious
6 enough. I don't think it is an entirely trivial occurrence
7 in a population where as a matter of fact, not to be too
8 purist, the benefit has not fully been defined. So, I think
9 the normal volunteer who could become agitated by having
10 drunk alcohol may well respond equally but maybe is more
11 susceptible to a form of morbidity, not mortality, that is
12 not entirely trivial.

13 DR. PRITCHETT: As I said, this is something that
14 I wish hadn't happened. I wish that we hadn't seen this in
15 the normal volunteers, but I think the preponderance of
16 safety data on the compound really comes from the clinical
17 trials, and I am pretty impressed by the safety database
18 there. I am impressed that a plausible explanation has been
19 put forward as to why this might have shown up in the Phase
20 I studies and not have a clinical counterpart in the
21 clinical trials.

22 Also, I think in general I kind of like this
23 development program. If the people sitting around the table
24 tell me that they believe that this is a real indication and
25 that the demonstration of efficacy was meaningful efficacy,

1 I am not terribly troubled, assuming that the labeling sort
2 of specifies who the patient population was that was studied
3 and that the drug was safe in them. Whether you put some
4 words about in case you happen to use this drug in normal
5 volunteers, you might get in trouble but I think that is an
6 unlikely indication.

7 DR. TAMMINGA: Are there things that doctors
8 should watch out or special things to measure?

9 DR. PRITCHETT: See, I think it is very easy for a
10 cardiologist to recommend things like ECG monitoring and
11 stuff like that, but you just have to carefully monitor the
12 patient. But I think it has serious consequences when you
13 say that you have to monitor somebody and you raise the
14 question of whether you need to do continuous ECG telemetry,
15 and where do you have to do that, and how best to look at
16 it, and what is your response to that. You know, that
17 wasn't done during the clinical trials and I don't think it
18 is necessary to use that during the routine administration
19 of the drug.

20 I think that the fact that this happened probably
21 is going to wind up in labeling somewhere but I am not sure
22 where, what section of labeling this winds up in, this
23 description of this adverse event, but in terms of the
24 clinical use in the target population, I don't think it has
25 much of a role.

1 DR. LAUGHREN: Given that if we approve this
2 product it is likely to be used in relatively
3 physiologically normal people who have not had prior
4 exposure to antipsychotics, I think we are going to have to
5 label this in some fairly prominent way. What would your
6 thoughts be about what that labeling statement should say?

7 DR. PRITCHETT: See, I don't know that an agitated
8 18- or 20-year old, for whatever reason they are agitated,
9 is physiologically the same as a normal volunteer, wherever
10 you did these things, is the same person. I have done
11 normal volunteer studies myself. I have also dealt with
12 patients who passed out when you did supine and standing
13 blood pressures, and I have some great slides that I show to
14 medical students of asystole and that sort of thing. So, I
15 don't know whether an agitated young, otherwise healthy,
16 person is really the same as that. So, as I said, I am open
17 to suggestion. Where do you think it needs to go in the
18 labeling? If you are going to put it in the labeling
19 someplace, where would you put it?

20 DR. LAUGHREN: Well, I think for something like
21 this generally we would probably think about precautions.
22 But as another possibility, given the likelihood that this
23 drug will be used in agitated young people who haven't had a
24 prior history of antipsychotic exposure, do you think it
25 would be useful studying that population? That is not a

1 population that was studied here to see what the risk is in
2 that relatively naive population who don't have the
3 histories that schizophrenics and bipolar patients have.

4 DR. PRITCHETT: Well, I would certainly want to
5 include that population in my study that said, the agitated
6 population, all comers welcome. I think it would be good to
7 include that. Whether you set that up as a totally separate
8 group -- it is an interesting idea. Again, in general I
9 like this development program and I would like to see a
10 broader, less selected population studied and include some
11 of these things that we have talked about, including taking
12 this drug onto the medical wards. I like the idea of
13 getting it out of the hands of psychiatrists and getting it
14 into the medical wards and seeing what happens because I
15 think it is going to be used there. So, I think if you
16 mounted a study that looked at agitated patients on medical
17 wards, people in emergency departments and things like that,
18 you know, I would be in favor of that. I hope the sponsor
19 will do that.

20 DR. BRIER: Although we haven't specifically
21 looked at IM in neuroleptic naive individuals, we are now
22 having a fair amount of experience with the oral in that
23 population without titration, with starting doses of 10 mg
24 and 15 mg, etc. So, we are getting that neuroleptic naive
25 exposure in patient populations, bipolars and schizophrenia.

1 We are not seeing a signal in that group of syncope or these
2 kinds of events.

3 DR. TAMMINGA: Dr. Katz?

4 DR. KATZ: Yes, we have sort of assumed, I think,
5 that there has been a demonstration of safety, or at least
6 this particular event doesn't seem to occur in the elderly,
7 but I am just wondering how many elderly patients actually
8 were part of this development program at, let's say, a dose
9 that you believe is the appropriate dose in the elderly?
10 Beyond that, what do we know about the experience with oral
11 olanzapine in the elderly?

12 DR. BRIER: That is a good point, and I think that
13 with so many of the PK parameters being similar, with the
14 exception of Cmax, but particularly AUC, no new metabolites,
15 I think we can kind of bridge to our oral experience. So,
16 in terms of elderly individuals with the IM we are talking
17 about -- let's see, how many did we have altogether -- 137.
18 We have a rather large program under way currently looking
19 at the oral in dementia populations, particularly targeting
20 the psychosis of dementia, and those numbers range up to 450
21 patient exposures with studies going on currently. So, I
22 think in terms of the availability of safety data from a
23 larger pool of individuals with very significant dementia we
24 have that safety data and, again, we are not seeing that
25 signal at this point.

1 DR. KATZ: I think you said 137 in the controlled
2 trial, but there were two doses in that trial.

3 DR. BRIER: Yes, 2.5 and 5.

4 DR. KATZ: And, you would recommend which dose in
5 labeling, 5?

6 DR. BRIER: We are recommending 2.5 as a starting
7 dose.

8 DR. KATZ: But, as you said, the kinetics are
9 pretty much the same except for Cmax. Cmax and Tmax may be
10 critical for this particular phenomenon or perhaps other
11 phenomena. Presumably the oral experience wouldn't
12 necessarily speak directly to that risk, if there is any. I
13 am just trying to get a sense of how robust the experience
14 is with this product in the elderly, and whether or not the
15 committee is comfortable with that amount of safety data.

16 DR. TAMMINGA: I don't recall, Dr. Breier, that
17 with the oral drug there ever occurred anything like sinus
18 pauses in the entire database, and you have a large database
19 that goes to relatively high doses --

20 DR. BRIER: Yes.

21 DR. TAMMINGA: -- and up to relatively high doses
22 I don't recall this happening. So, I would assume that
23 these kind of sinus pauses may be dependent on the plasma
24 level spike that you see at the beginning.

25 DR. BRIER: And, I think that is also consistent

1 with vasovagal where you tend to see this more in younger
2 individuals with high vagal tone, while the elderly tend not
3 to have that in terms of the pauses and the bradycardia.
4 But just to reinforce Dr. Tamminga's point, our original
5 development program included doses up to 15 mg oral in
6 dementia. So, we were actually seeing fairly high blood
7 levels in those oral studies. We have two very large global
8 trials under way currently with significant numbers of
9 patients, and those doses range, I think, up to 10 mg. So,
10 we are seeing significant blood levels and, again, have not
11 seen a signal that would suggest pauses, bradycardia, excess
12 cases of syncope and that sort of thing.

13 DR. GRUNDMAN: Excuse me, Dr. Breier, along the
14 same lines of how robust the experience is in the elderly, I
15 noticed in the FDA briefing document that although there
16 were no deaths during the trial there were two patients, one
17 who was 90 and one who was 77, who died about eight or nine
18 days after the study was completed. There isn't really any
19 indication as to what may have caused their death in the
20 briefing document. I was wondering if you had any more
21 information about that.

22 DR. BRIER: Yes, I don't have specific information
23 on that case. They were very closely examined to determine
24 if there could be a linkage between their exposure to the
25 drug, and there was a decision that that was not the case in

1 terms of cause of death but I don't, at my fingertips, have
2 the actual cause of death but we can get that. Again, just
3 to remind you that the age of the population that we are
4 talking about was fairly substantial.

5 DR. GRADY-WELIKY: I just wanted to clarify with
6 our cardiology colleagues, to get back to a point Dr.
7 Laughren made, how comfortable would you be if this drug
8 were released in a broad manner, with the broad indication
9 of agitation and with the understanding that maybe conduct
10 disorder adolescents or young adults with non-psychiatric
11 illness might be exposed to it. Does that shift your
12 thinking around this sinus pause question?

13 DR. BARBEY: Well, you obviously have two slightly
14 different consultant opinions. My thought would be that I
15 have no qualms and no difficulty in saying that there were
16 no autonomic processes in the target population presented to
17 us. Should the drug be used more liberally to sort of
18 sedate an inebriated student who shows up in the emergency
19 room, it remains to be proven to me that not 20 percent of
20 them or 10 percent of them will have fairly substantial
21 syncope when they get up the first time to go to the
22 bathroom, which is not necessarily intolerable but that
23 evidence does not exist. Perhaps I am over-extrapolating
24 from what I saw with clozapine and perhaps that is not a
25 fair comparison, but I think this discrepancy is noticeable

1 and, again, when they present acutely agitated they are not
2 like your sleepy, normal volunteer but four hours later,
3 when they are not drunk anymore and they are dehydrated and
4 want to get up, and they feel embarrassed and want to go
5 home, then they are. So, in that regard I don't think
6 telemetry is necessary. I mean, you know, telemetry gives
7 you the five second before they faint notice and clarifies
8 that it is not a respiratory arrest but a sinus pause. But
9 in terms of a nurse in a clinic or somebody there, they
10 could immediately understand what is happening, lay them
11 down and raise their legs and make sure they don't bang
12 their head when they fall. So, I think that is my concern.

13 DR. PRITCHETT: I don't think that we have seen
14 efficacy data in that patient population and I don't think I
15 am hearing the sponsor asking for labeling in that
16 population, or anyone proposing labeling in that population.
17 This goes to the age-old question of once the drug is out
18 there, what do you do about this halo around it of related
19 illnesses where the drug may be used. I don't know that we
20 are going to solve that here today, but I would hope that if
21 we get to the point where we are talking about labeling the
22 drug in that population that we will have a lot more
23 experience using it in that population.

24 DR. LAUGHREN: Even in the population for which
25 the drug would be indicated there may be some patients who

1 would face that risk. You may have a first break
2 schizophrenic who has had no prior history of drug exposure,
3 a young patient who, it seems to me, might be in that
4 situation after having the initial sedative effect of the
5 drug.

6 DR. PRITCHETT: Possibly, although I guess I am
7 more inclined to think that one of the distinguishing
8 features of the patient population is not so much the
9 demographics of the population but the agitated state, and
10 it is the agitated state and the sympathetic tone that goes
11 with that rather than the fact that they are, you know, 18
12 to 20 and in good health and don't have coronary-artery
13 disease that is the protective effect, and an agitated young
14 adult probably has that similar kind of sympathetic drive.

15 DR. BARBEY: The company probably has some data
16 regarding initiating therapy in young, first-time psychotic
17 episodes as opposed to the setting of IM injection in the
18 emergency room of a drunk student. So, there you have some
19 data at least to talk about.

20 DR. TAMMINGA: Not IM data though. They would
21 probably have oral administration data. Do you think that
22 this phenomenon of sinus pause is related to the initial
23 spike in plasma levels because of the IM injection, or do
24 you view it as unrelated to the plasma levels?

25 DR. BARBEY: Well, it was certainly not so

1 obvious. I think what is also interesting is people are
2 talking in terms of susceptibility to this process and
3 saying, well, young males with vagal tone are more likely to
4 have this but I think the susceptibility is more complex in
5 terms of brain chemistry as well, and I don't know that we
6 have disproven that being acutely schizophrenic -- you know,
7 you don't start off with an altered serotonin and dopamine
8 situation, that you are perhaps more protected from this
9 situation than not. I don't know.

10 DR. PRITCHETT: I think you dodged the question.
11 You didn't answer Carol's question. I don't think this is
12 an acute Cmax issue. The data that you gave us or the
13 numbers that you tossed out said that peak plasma
14 concentration occurred 15 to 45 minutes after the injection.
15 Even if you add in half an hour of historrhesis, I think
16 that the time course is not quite right.

17 DR. TEMPLE: Well, there is a lot of reason from
18 the cardiovascular drugs to think that it is related both to
19 Cmax and to the rate at which you reach it. We had one
20 experience, for example, in which a more bioavailable form
21 of prazosin had a more rapid rise time and induced syncope
22 at doses that never induce syncope when you just have the
23 same old -- actually, people from Pfizer can probably tell
24 us all about it. So, the rate of rise was important because
25 this is something to which the body becomes accustomed very

1 rapidly. You rapidly become resistant to the first dose of
2 effective alpha blockers. So, I think there is a lot of
3 reason to think it is a combination of how quickly you
4 approach it, which you obviously do more in the IM form, and
5 how high it goes. I mean, that is certainly the experience
6 from the peripheral alpha blockers.

7 DR. BARBEY: However, the confounding factor would
8 be that, of course, the stimulus that could cause the
9 episode could occur at different times. So, the critical
10 timing there was when the subject got up to go to the
11 bathroom rather than how close he was to Cmax.

12 DR. TEMPLE: It is all of those at the same time.
13 I mean, after four, five or eight hours you probably could
14 get up and go to the bathroom lots and nothing would happen.

15 DR. PRITCHETT: But what I was looking at was if
16 we looked at these episodes of sinus pauses, when they
17 occurred, and here is one that occurred four and a half
18 hours following the dose. So, you know, we are long past --
19 I mean, I do believe that there is something going on with
20 rapid rate of rise. I think it is an under-studied
21 phenomenon. I think the rate of rise probably is important,
22 probably more important than peak plasma concentration, but
23 all the action took place substantially outside the window.
24 As I said, even if you add in 30 or 40 minutes for delayed
25 effects, which we certainly saw with the calcium channel

1 blockers, then these events are still happening outside that
2 acute window.

3 DR. TEMPLE: It is probably all of the above. The
4 other thing you see with peripheral blockers is that people
5 are okay after an increase in dose until they run for a bus
6 or do something else. So, it doesn't have to be immediate.
7 But there was the dosage form of prazosin phenomenon which
8 was a more rapid rise time, and then the very striking
9 ability to reduce the rate of syncope from 1/100, which is
10 what the 2 mg prazosin dose used to give, to less than
11 1/1000, which is what happens when you start with 1. So, it
12 must have something to do with dose and, therefore, peak.

13 DR. BARBEY: This is why we argued that the
14 strategy of lowering the clozapine dose was not clearly
15 effective. So, again, whether the psychiatric drugs are
16 more complex than the simple peripheral alpha blockers I
17 think is a component to consider as well.

18 DR. TEMPLE: It may be that the malleability of
19 the autonomic system has something to do with it too. It is
20 obviously complicated.

21 DR. LAUGHREN: This is a question for Dr. Breier.
22 I think we asked you this before and I don't remember
23 whether you sent us the data or not, did you see this
24 phenomenon in normal volunteers given the oral form?

25 DR. BRIER: We are now collecting all of our

1 clinical trials data sets. I think we communicated to you
2 that the readily available data was the Phase II/III data
3 which we now have and have submitted to you. We showed you
4 the syncope and the dizziness rates. Today we also can show
5 you the vital sign data from those large samples. We are
6 gathering the healthy volunteer Phase I. Charles, do we
7 have it all at this point?

8 DR. BEASLEY: Charles Beasley, with Lilly. I have
9 actually been around since the early Phase I data with the
10 oral were done. A couple of comments on that. First of
11 all, telemetry was not done in those early oral studies. My
12 sense is that we will have a higher incidence of cases of
13 syncope within that normal volunteer population than we had
14 in either the oral patient population or the IM patient
15 population, probably somewhat comparable to what we have
16 seen with regard to syncope in our normal volunteers.

17 An interesting point is that, in fact, one of
18 these individuals, one of these three, was an individual who
19 had the sinus pause on oral, not on IM. That is the
20 interesting patient who was delayed at 4.5 hours at about
21 where you would see peak. So, I think we will see a higher
22 incidence of syncope. It will not be as high as we have
23 seen likely with the oral, but we are still bringing the
24 data in for you.

25 DR. TAMMINGA: And when will you have those data

1 done?

2 DR. BEASLEY: I am hoping, with the exception of
3 Japan where we have to go over and translate data for 80
4 individuals, probably within about three weeks.

5 DR. TAMMINGA: Additional discussion or comments
6 about the cardiology? I do want to say one thing about the
7 motor side effect profile. I don't think we should ignore
8 the difference between the active comparator and the drug
9 that is used widely now, which is haloperidol, and this
10 particular compound. The motor side effect profile of
11 olanzapine was significantly better than haloperidol and
12 would surely be a strength of this compound over the active
13 comparator, haloperidol.

14 DR. BEASLEY: There is probably one more comment
15 worth making about the Phase I data, particularly since
16 clozapine has come up. We were very surprised that we could
17 give full oral antipsychotic dose. In fact, we had given 15
18 mg a day from start to normal volunteers. This is in marked
19 contrast to what apparently has to be done with clozapine
20 not only in normal volunteers especially but also patients.
21 There wasn't a tremendous amount of dysphoria or
22 unacceptability of normal volunteers, walking away from
23 those studies when they were started at 15 mg a day from day
24 one.

25 DR. TAMMINGA: Additional discussion about the

1 safety? Questions? Points to make?

2 [No response.]

3 I think we might be ready to move on to a final
4 discussion, if you will, of efficacy and safety. Dr.
5 Laughren, if you could help the committee with this, I
6 suspect, just having listened to the committee, that the
7 answer to the question is this safe and effective in anybody
8 who is agitated would be different than is this safe and
9 effective in agitation associated with neuropsychiatric
10 diagnoses. Do you want an answer to each one of those
11 questions or the more broad one or the more limited one?

12 DR. LAUGHREN: I think we have gotten pretty much
13 of a consensus from the committee on that issue, that you
14 would prefer a more narrow indication rather than a broad
15 indication. So, I think your vote can be on the narrow
16 question. I think we have already gotten past that issue.

17 DR. TAMMINGA: I would propose then a final
18 discussion on the question of efficacy in the use of
19 olanzapine intramuscular form in the situation of agitation
20 in persons with neuropsychiatric diagnoses. Dr. Fyer?

21 DR. FYER: Being someone who studies anxiety
22 disorders, I would object to the broad term neuropsychiatric
23 disorders and limit it to either the disorders that were
24 studied in this NDA or possibly something like psychotic
25 disorders and some definition of dementia that Dr. Grundman

1 might offer from his expertise.

2 DR. TAMMINGA: There were both bipolar and
3 demented patients without psychosis.

4 DR. FYER: Yes, I am sorry, I was being not so
5 specific. You know, what I would prefer would be actually
6 the disorders that were studied. If somebody wanted to
7 broaden the type of psychotic disorders, I would be
8 comfortable with that but I wouldn't be comfortable with
9 just any neuropsychiatric disorder.

10 DR. TAMMINGA: Additional discussion? Dr. Malone?

11 DR. MALONE: I would generally agree too because
12 neuropsychiatric disorder could include Axis 2 diagnoses and
13 a lot of other diagnoses that I wouldn't want to include.

14 DR. TAMMINGA: Could we say Axis 1 diagnoses?
15 Would that be limited enough?

16 DR. MALONE: Conduct disorder is an Axis 1
17 diagnosis, but I don't have them all memorized.

18 DR. FYER: Why can't we just say the disorders
19 that were studied, and if somebody wants to extend it -- for
20 instance, someone gave the example of major depression with
21 psychosis, something like that, but I think anything that
22 extends to psychiatric or neuropsychiatric is going to be
23 including a variety of things that the committee has already
24 expressed the opinion that they shouldn't be included.

25 DR. HAMER: I agree. I think the range of data

1 that we have is relatively narrow and I don't think we
2 should go much beyond that.

3 DR. TAMMINGA: So, then we would be considering
4 the efficacy of this compound in its intramuscular form in
5 schizophrenia, bipolar disorder and dementia and related
6 conditions, closely related conditions. Any additional
7 comments?

8 [No response.]

9 It might be time for us just to go around the
10 table and for people to express their opinion on the
11 efficacy question in this particular group of psychiatric
12 diagnoses. I hate to start with you, Dr. Barbey, but you
13 are at the end of the table so we will start with you.

14 DR. BARBEY: Well, to the extent that my expertise
15 is more with the toxicity, I am reasonably convinced that
16 there was proof of efficacy for the indications in the
17 groups studied. I am not quite as convinced about the
18 choice of doses but I guess we don't want to quibble about
19 that. So, again, I feel comfortable that efficacy has been
20 demonstrated.

21 DR. TAMMINGA: And you could say perhaps
22 specifically what you think about the doses.

23 DR. BARBEY: Well, depending on the studies, I
24 thought the difference between 5, 7.5 and 10 was not always
25 as striking as the lower dose but, as Dr. Temple asked, what

1 was the cost or what was the increased toxicity, I
2 appreciate the fact that there didn't seem to be any and
3 that perhaps we had kept off the study population below the
4 sort of peak people. So, I might be willing to consider 10
5 mg as the dose for some of these indications but I just
6 wasn't struck that the difference was as marked as that.

7 DR. PRITCHETT: Are we voting here? I am an SGE;
8 I don't vote but my opinion is that I believe the efficacy.

9 DR. GRUNDMAN: I think that in all the conditions
10 that were studied the drug was shown to be efficacious, and
11 I think it also compared favorably with haloperidol and
12 lorazepam with respect to side effects, which brings me back
13 to another question, not necessarily that I would disagree
14 to broaden this to other forms of agitation since we don't
15 really have data, but it just makes one think about the
16 situation that we are going to be treating people who have
17 other types of agitation, and if we think as a group that
18 this drug actually, in terms of its side effects, may be
19 preferable that might be worthwhile noting. I don't know if
20 we agree with that or not based on the data that we have
21 seen, but as you mentioned before, with respect to
22 haloperidol, for example, it seemed to have less
23 Parkinsonism, akathisia, dystonia, and with respect to
24 somnolence it seemed like it compared favorably with
25 lorazepam.

1 So, I don't know what the group thinks about that.
2 Obviously, we don't want to go over the edge and say, yes,
3 go ahead and give this medication for conditions we don't
4 know anything about. On the other hand, the other drugs are
5 going to be used for that purpose and are they as safe as
6 this drug?

7 DR. BANISTER: I very much support Dr. Fyer's
8 comments and very much believe that the efficacy has been
9 demonstrated for what they have studied, but I have grave
10 concerns about it being generalized more broadly.
11 Certainly, when I think about the conditions in ICU or ER,
12 some places like that, that would be very troubling to me.

13 DR. HAMER: I think this drug is effective in the
14 type of patients for which it was studied and should be
15 contraindicated in normal volunteers.

16 [Laughter.]

17 DR. GRADY-WELIKY: I would agree that for the
18 conditions studied the company has shown efficacy data.

19 DR. MALONE: I think it has been shown effective
20 for the conditions they studied.

21 DR. FYER: I will say two things. I agree with
22 everyone that it has been shown effective in the conditions
23 that it has been studied in. I share Dr. Grundman's
24 curiosity about the usefulness of this drug in other
25 populations, and I would like to say that the concern I have

1 really is why should we be in the position of having to
2 approve something without data when it is possible for
3 people, with some expense and effort, to get the data, and I
4 think that is really the point I would reiterate, that I
5 would encourage the sponsor to get the data rather than put
6 us in a position of approving it without that.

7 DR. ORTIZ: I guess I concur with the general
8 feeling that efficacy has certainly been demonstrated, as
9 well as possible superiority to EPS with haloperidol and
10 sedation issues maybe with lorazepam.

11 My concerns are still with the elderly. You know,
12 there is this question of psychosis versus non-psychosis
13 that is unclear to me. There was also a question in the FDA
14 background paper about QTc prolongation in the elderly, and
15 I would hope that there would be some cautions about the
16 sinus pause and the bradycardia issues in the warning.

17 DR. RUDORFER: Yes, I would agree that the drug is
18 efficacious in the conditions studied. As I mentioned in my
19 example of unipolar depression with agitation, I would find
20 acceptable the use of a phrase such as closely related
21 disorders. I think also what we are saying is -- and I
22 don't know if this is appropriate in the labeling -- but we
23 are talking about adults and the elderly because I think we
24 have not heard data on adolescents or younger people and I
25 think, especially given the diagnostic confusion that often

1 arises in younger individuals, it would seem that they might
2 be the people who are closest to the healthy volunteers that
3 we are trying to avoid.

4 DR. TAMMINGA: My opinion is that the efficacy has
5 been rather reasonably demonstrated in the groups which the
6 company studied. I hear a lot of support for what we could
7 call "the Pritchett study" for getting this drug out of the
8 hands of psychiatrists and into the hands of internists and
9 see what, in fact, this drug might look like in emergency
10 rooms and ICUs. But also I would add I am really in support
11 of Dr. Rudorfer's point of studying this drug in adolescents
12 and children where, if it were misused, its misuse could be
13 really quite significant and quite important.

14 I would think that we could do this with a hand
15 vote, and only people should vote who are allowed to vote
16 and we would be voting only on efficacy -- we haven't yet
17 considered safety -- in those populations in which we saw
18 data. For everyone who answers yes to the question, please
19 raise your hand.

20 [Show of hands.]

21 And everybody who says no, please raise your hand.

22 [No response.]

23 Terrific.

24 DR. TITUS: So, for the record, we have nine yes
25 and zero no.

1 DR. TAMMINGA: Now we will talk about safety. The
2 question we have to answer about safety is has the sponsor
3 provided evidence that olanzapine IM is safe when used in
4 the treatment of agitation? So, what we are voting on is
5 not the use of this drug in normal volunteers or in people
6 without agitation, but only in people with agitation with
7 the conditions on which we have seen data.

8 Why don't we go around quickly and just get an
9 opinion from everybody first, and we will start with you,
10 Dr. Barbey.

11 DR. BARBEY: With the proviso that you gave, I
12 think the evidence for safety is good.

13 DR. PRITCHETT: I agree.

14 DR. GRUNDMAN: I just want to make sure that the
15 dose that is being recommended for the elderly is 2.5 mg.
16 Is that right?

17 DR. TAMMINGA: As I understood, the dose
18 recommended for adults would be 5 to 10 and the dose for
19 elderly would be 2.5 to 5.

20 DR. BRIER: The suggested starting dose is 2.5 in
21 the elderly.

22 DR. TAMMINGA: With the suggested dose of 5 or 10
23 in the non-geriatrics.

24 DR. GRUNDMAN: I believe it would be safe at those
25 doses.

1 DR. BANISTER: I agree.

2 DR. HAMER: Yes.

3 DR. GRADY-WELIKY: I also agree.

4 DR. MALONE: I agree.

5 DR. FYER: I agree. I also just want to say that
6 I would support Dr. Laughren's statements from before about
7 some sort of labeling issues about the normal population.

8 DR. ORTIZ: I agree.

9 DR. RUDORFER: I agree.

10 DR. TAMMINGA: This was faster than I thought it
11 would be. Let's just have a quick show of hands so Sandy
12 can count up again the voting members of the committee who
13 would agree this is safe in the conditions in which it has
14 been studied.

15 [Show of hands.]

16 Anybody in disagreement?

17 [No response.]

18 DR. TITUS: So, we have nine yes and zero no.

19 DR. TAMMINGA: I think this concludes the job of
20 the committee for the day. I wonder if Dr. Laughren or Dr.
21 Katz or Dr. Temple have anything else to add.

22 DR. KATZ: No, I think you are right. Thank you
23 very much. It has been very interesting, very useful to us,
24 needless to say, and not easy. We appreciate your efforts.
25 Thank you. See you tomorrow. And, we would all like to work

1 on the "Pritchett study" too.

2 DR. TAMMINGA: Tomorrow morning we will reconvene
3 at eight o'clock, and we will hear about another drug.

4 Thank you all very much.

5 [Whereupon, at 4:04 p.m. the proceedings were
6 recessed, to be resumed on Thursday, February 15, 2001 at
7 8:00 a.m.]