

1 to that after lunch. Dr. Potter's been
2 patiently waiting.

3 DR. POTTER: Yes. I have a couple
4 questions. The first is relatively
5 straightforward.

6 In Dr. McDonnell's presentation, in
7 the voiceover, he mentioned on the acute
8 study that the mixed model suggested that the
9 higher dose might be somewhat more
10 efficacious. That's the 300 milligrams every
11 two weeks. And I just do that as a lead-in
12 to another comment that was made in looking
13 at the longer term study, that's slide 32, in
14 which was commented -- of course, with the
15 150 milligrams every two weeks, you had
16 actually intermediate protection.

17 The design as I understand it was
18 you were optimizing the dose during the
19 open-label for the eight-week period on oral
20 olanzapine. Therefore, people could be on
21 oral following that, on 10, 15, or 20
22 milligrams stably for the next 24 weeks. Do

1 I understand that properly?

2 DR. CORYA: Yes.

3 DR. POTTER: Okay. So what does the
4 analysis look like if you look at the rate of
5 exacerbation -- times exacerbation, proportion
6 of patients times exacerbation, as a function of
7 the optimal -- their maintenance dose on oral,
8 their stabilization dose on oral, versus which
9 dose of OP Depot to which they were randomized?
10 Now, you may or may not have that to display,
11 but I think that would be interesting to see if
12 you don't have that summarized on a slide.

13 DR. McDONNELL: Yes, and that relates
14 to a question about why we have the table about
15 the higher doses in the first two months.

16 DR. POTTER: No, no, I understand
17 that. Do you have that displayed? That's all
18 I'm asking here.

19 DR. McDONNELL: This is how we further
20 looked at data from the study HGKA. One of the
21 advantages of that study is it did give us very
22 good switching information. And what it did

1 show is that patients who switched from 10
2 milligrams to the equivalent dose of depot, 150
3 milligrams, did slightly worse in the first two
4 months. There were more relapses in the first
5 two months. And that was also true of the
6 15-milligram dose if they switched to 405
7 milligrams.

8 So we came up with a recommendation
9 that is reflected in the briefing document
10 that for the first two months, for patients
11 on equivalent of 10 or 15 milligrams, they
12 should go up a dose. So they should either
13 be -- for patients for 10 milligrams, they
14 should be treated with 210 milligrams every
15 two weeks or 405 milligrams every four weeks,
16 and patients on 15 milligrams should go up to
17 300 milligrams every two weeks, at least for
18 the first two months of treatment.

19 DR. POTTER: Yes, okay. Actually,
20 it's quite -- I'm just noticing that. I just
21 noticed your hazard ratio -- if you go from 20
22 milligrams to 45, what's that, an eightfold

1 hazard ratio? So it is sort of interesting,
2 that's all.

3 The other question has to do with
4 the -- I guess your plans for the future
5 should this be introduced on the market, your
6 risk management plan.

7 And whether or not anything beyond
8 an observational study was considered, and
9 with appreciation for how difficult it might
10 be to get at this. Is there any idea of a
11 design which would actually help you to learn
12 beyond the anecdotal sort of cases how many
13 people -- this is complicated -- how many
14 people do you need to look at to convince
15 yourself that there are people who really,
16 really need this particular depot medication
17 versus an alternative one or an oral
18 medication?

19 So I'll just go to the anecdotal
20 case of the individual who was taken off of
21 the depot and then relapsed when he or she
22 went to oral.

1 What we didn't hear was whether or
2 not that individual would have done all right
3 on another depot.

4 I mean, it's just a question
5 of -- I mean, this is setting a very high
6 hurdle. You know, it's not to set the
7 hurdle, it's just to ask the question. Is
8 there any design that would allow you to
9 understand -- without studying tens of
10 thousands of people -- that would allow you
11 to understand is there a population of people
12 who really, really, really need this
13 particular drug? That's what I'm trying to
14 get at.

15 DR. RUDORFER: May I make a
16 suggestion? I think that's a good topic for our
17 discussion this afternoon.

18 DR. POTTER: Matt, what I was asking
19 was whether they had specifically considered
20 such a design, because they didn't present it.
21 I mean, that's all. It's not to debate whether
22 there should be. This is to ask, in fact, was

1 such a design considered and then rejected?

2 That's what I was asking, maybe because it was
3 not feasible.

4 DR. RUDORFER: We have three people in
5 the queue: Drs. Leon, Caplan, and Geller. If
6 you could each ask a brief clarifying question,
7 then we'll wrap up the morning program.

8 Dr. Leon?

9 DR. LEON: Can I ask two brief
10 clarifying questions? Two very brief. Okay.
11 Dr. Anderson referred to a study of the risk
12 among people who've had at least 35 injections.
13 Right? I just want to know, when I glance at
14 the cases who had injections, I see at least
15 6 of the 24 were discontinued before Week 35.
16 So I would think -- to what extent are you
17 underestimating the risk when you dilute the
18 pool? Those most at risk are removed from the
19 study. I just counted them up quickly since you
20 talked, but there might be more that I didn't
21 see there.

22 DR. ANDERSON: And the expected number

1 calculation looked at all patients; you know, it
2 didn't focus on those who had an event. So I
3 see your point that you don't know because they
4 stopped early, so you don't know what --

5 DR. LEON: You've removed the most
6 vulnerable from the group that you're
7 studying --

8 DR. ANDERSON: Right, right.

9 DR. LEON: My other question relates
10 to that risk about penicillin injections, the
11 .08 percent. I mean, is that the generally
12 accepted standard number that's well-known in
13 the medical field? Is it based on a study?
14 What's the sample size? I mean, what's the
15 source? It was just parenthetically shown to us
16 in the slide.

17 DR. CORYA: That is a very specific
18 number that was studied I believe by the company
19 who makes the penicillin G procaine when they
20 started having these events and they wanted to
21 know what the incidence rate was. We have just
22 one data slide on it, which when they did study

1 it -- and I do not know the exact Annanet (?)
2 study; I'll see if we've got it back behind
3 me -- but their rate of inadvertent
4 intravascular injection was .08 percent, which
5 is very similar to the rate of excessive
6 sedation events that we've seen in our clinical
7 trials.

8 Unfortunately, we could not find
9 very much information, really any more
10 information than that, about any of the other
11 IM-administered products, even though many of
12 them have label language that says be sure
13 not to inject intravascularly. But there
14 just hasn't been a lot of work either in
15 humans or animals, I think for a multitude of
16 reasons, to explain that.

17 DR. RUDORFER: Dr. Caplan?

18 DR. CAPLAN: Okay, I have two brief
19 questions and one comment.

20 The data that we got on the
21 background really indicates that these
22 studies were done primarily on Caucasian

1 males. And my question is, what is the
2 company doing to look at both what's
3 happening in terms of safety and efficacy in
4 females and also in different ethnic groups?
5 Because we know that they metabolize these
6 drugs very, very differently. And then I'll
7 ask you the other questions.

8 DR. CORYA: That's a very good
9 question, and we have been concerned about that
10 as a company, that research in general is
11 conducted primarily in certain populations and
12 not others. And we think that that's a very
13 important problem that needs to be corrected.

14 So we're actually making efforts
15 within our company in our clinical trials to
16 make sure that we are doing studies,
17 including the study -- the 5,000-patient
18 study that I described, and any other studies
19 that we're conducting in different countries,
20 also within the United States, to try to
21 increase our population of minorities and
22 women there, but also in different countries,

1 so that we can really better understand this
2 across a wider population. But that's what
3 we have right now.

4 DR. CAPLAN: So the current data we
5 have in terms of the safety and these events are
6 really primarily on Caucasian males, right?

7 DR. CORYA: I'm looking at --

8 DR. CAPLAN: Can we can conclude that?
9 In other words --

10 DR. CORYA: Yeah.

11 DR. CAPLAN: All these events occurred
12 primarily in Caucasian males; is that correct?

13 DR. CORYA: No, not the excessive
14 sedation events. They did not all.

15 DR. CAPLAN: Okay.

16 DR. CORYA: But you can see here is
17 the actual breakdown of males versus females in
18 the clinical trials, so there were more males.
19 About two-thirds of the patients were males and
20 one-third were females. And then the breakdown,
21 also, with origin.

22 DR. CAPLAN: Right, but for the

1 events, the sedation events?

2 DR. CORYA: The events were not
3 primarily -- they were both men and women, and
4 they were also minorities who experienced
5 excessive sedation events as well.

6 DR. CAPLAN: Okay. And then the
7 second thing is, is Lilly doing anything in
8 terms of following up the people who had events
9 to look at their more long-term cognitive and
10 other functioning? Because really the duration
11 of some of the events was very long, and one can
12 anticipate that there might be some additional
13 damage that's caused by that.

14 DR. CORYA: We are following the
15 patients who have remained in the clinical
16 trial, so the 16 patients who continued to stay
17 in the clinical trial. We have not
18 specifically -- nor do I know that we
19 could -- follow the patients after they've left
20 the clinical trial. We have not followed them
21 with the specific question in mind of asking the
22 investigators have they had changes in cognitive

1 functioning since that event. We certainly have
2 had conversations with the investigators about
3 how the patients are doing. That's an
4 interesting, very specific question that I think
5 we might ask in the future.

6 DR. CAPLAN: Yes, I think it's quite
7 relevant to schizophrenic patients, given that
8 this is one of the areas of deficits, and
9 additional compromise wouldn't be helpful to
10 their functioning.

11 And one last thing, you had
12 mentioned that the term "sedation" was
13 introduced, and you actually welcomed
14 discussion on that, whether this should be
15 called -- you know, the event should be
16 called "sedation." And I really want to
17 second that, because I think the CNS
18 involvement of this event is really quite
19 significant and includes several different
20 systems.

21 And I think one really needs to
22 consider this is just a simple sedation

1 rather than something much more important.

2 DR. CORYA: Yes, that was our concern,
3 that it overlooked things like delirium, ataxia,
4 and so on and so forth.

5 DR. RUDORFER: And finally, since it
6 is still morning in St. Louis, Dr. Geller gets
7 the last question for the morning session.

8 DR. GELLER: I just wanted to go back
9 to what I was trying to say before but obviously
10 didn't say well enough. It was said very well
11 by the gentleman from the company, that at the
12 lower dose, you actually want to load with a
13 higher dose initially. And since in my
14 experience anyway, that's unusual with the depot
15 medications, I wonder if the company's going to
16 have some educational material that will make
17 that clearer to clinicians.

18 DR. CORYA: Yes, we absolutely will.
19 And I'm sorry that I did not understand your
20 question when you asked it before. I believe
21 that Haldol is actually -- if you look at the
22 Haldol product label, one of the most commonly

1 used antipsychotic depot medications, they
2 actually have a recommendation for a very
3 similar loading dose that we're recommending.

4 But absolutely, our product label
5 will contain that information. All of the
6 educational processes which I described
7 previously will definitely put appropriate
8 emphasis on the importance of that dose.

9 DR. GELLER: The importance of doing
10 that is you don't want a patient who might do
11 well staying on the higher dose longer than they
12 should and starting to get side effects.

13 DR. CORYA: Absolutely.

14 DR. RUDORFER: Okay, thank you. We
15 will now break for lunch. We will reconvene
16 again in this room in one hour from now, at 1:10
17 p.m. Please take any personal belongings you
18 may want with you at this time.

19 The ballroom will be secured by FDA
20 staff during the lunch break, and you will
21 not be allowed back into this room until we
22 reconvene.

1 Panel members, please remember that
2 there should be no discussion of the meeting
3 during lunch amongst yourselves or with any
4 member of the audience.

5 Thank you.

6 (Whereupon, at approximately
7 12:10 p.m., a luncheon recess was
8 taken.)

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1 For example, this financial
2 information may include the sponsor's payment
3 of your travel, lodging, or other expenses in
4 connection with your attendance at this
5 meeting. Likewise, FDA encourages you at the
6 beginning of your statement to advise the
7 Committee if you do not have any such
8 financial relationships.

9 If you choose not to address this
10 issue of financial relationships at the
11 beginning of your statement, it will not
12 preclude you from speaking.

13 The FDA and this committee place
14 great importance in the open public hearing
15 process. The insights and comments provided
16 can help the agency and this committee in
17 their consideration of the issues before
18 them. That said, in many instances and for
19 many topics, there will be a variety of
20 opinions. One of our goals today is for this
21 open public hearing to be conducted in a fair
22 and open way, where every participant is

1 listened to carefully, and treated with
2 dignity, courtesy, and respect. Therefore,
3 please speak only when recognized by the
4 chair. Thank you for your cooperation.

5 And now I believe we're ready for
6 our first open public hearing speaker.

7 MR. BOEHM: Good afternoon. My name
8 is Vince Boehm and I operate an Internet mail
9 listserv.

10 It goes out to mental health
11 professionals and other people interested in
12 the thing. I have nothing to declare. I
13 don't get paid for this or anything.

14 I want to enter into the record
15 here three responses from my people on my
16 listserv, and the first one is Stephen P.
17 Kryzinski (?), M.D. Stephen is a
18 psychiatrist who lives in Harrisburg,
19 Pennsylvania.

20 "Re: Zyprexa Adhera, olanzapine
21 pamoate, depot preparation, safety concern,
22 identified severe somnolence. To the

1 Psychopharmaceutical Drug Advisory Committee
2 formed to examine issues of certain side
3 effects, especially somnolence related to IM
4 injection of olanzapine pamoate.

5 Dear Colleagues, I am not able to
6 attend the forum today, but I respectfully
7 ask you to consider certain collateral issues
8 in regard to the safety of olanzapine during
9 your deliberations. As a point of reference,
10 I am a board-certified psychiatrist in
11 general adolescent addiction and geriatric
12 psychiatry and addiction medicine. I trained
13 at Harvard Medical School, UMD&J, Robert Wood
14 Johnson Foundation at Duke University.

15 Currently I practice clinical
16 research and educational psychiatry in
17 Harrisburg, Pennsylvania. I am actively
18 licensed without restriction in Pennsylvania,
19 Texas, California, New Jersey, Indiana,
20 Nebraska, and Delaware. I'm a long-time
21 member of the American Psychiatric
22 Association and other subspecialty groups.

1 "My primary concern is that this
2 advisory committee has been asked to come
3 together to examine the negative effects of
4 sedation due to Zyprexa pamoate without or in
5 lieu of examination of other current and
6 significant adverse effects associated with
7 Zyprexa. Allow me to briefly articulate my
8 concerns.

9 "This meeting has been called to
10 discuss somnolence as an untoward side effect
11 of injectable Zyprexa. While this side
12 effect has important negative consequences,
13 and some benefit perhaps for a highly
14 agitated patient, Zyprexa pamoate is not
15 alone in induction of this effect in the
16 world of psychopharmaceuticals. In other
17 words, significant and problematic somnolence
18 occurs with other antipsychotics, both oral
19 and injectable form.

20 Somnolence is also problematic for
21 other atypical antipsychotics, including
22 quetiapine/Seroquel from AstraZeneca. The

1 same problem occurs with typical
2 antipsychotics, such as intramuscular
3 fluphenazine decanoate/Prolixin.

4 "Zyprexa pamoate obviously deserves
5 the full, careful scrutiny of its predecessor
6 neuroleptics. Caution with operating
7 machinery, vehicles, awareness for
8 potentiation of falls, awareness of
9 synergistic benefits, effects with alcohol
10 and other sedating compound, including any
11 other compounds with alpha-1 and enterogenic,
12 hysterogetic, and musculogenic side effects.

13 However, importantly, I'm not aware
14 of any advisory committee having been formed
15 to discuss the somnolence in these or similar
16 psychoactive drugs, or to discuss the
17 somnolence as a separate adverse effect with
18 other classes of drugs widely used in current
19 psychiatric practice, such as Depakote and
20 Paxil.

21 "That being said, I would ask this
22 convened forum why it is not focusing on

1 addressing the issues of potentially greater
2 magnitude in terms of morbidity and mortality
3 in regard to Zyprexa? These issues, as
4 briefly highlighted in the (inaudible) below,
5 include but are not limited to weight gain,
6 hyperlipodemia, hyperglycemia, insulin
7 resistance exasperation -- or initiation of
8 Diabetes Type II, (inaudible) metabolic
9 syndrome, increased prolactin levels, risk of
10 extrapyramidal side effects, infection, and
11 others. Those issues appear to be
12 particularly troublesome for young people.

13 "Despite these findings and because
14 Eli Lilly, makers of Zyprexa, requested the
15 FDA approval of Zyprexa specifically for
16 teenagers, I question the Committee to ask
17 themselves and the FDA moderators why no
18 similar committee has been convened to
19 examine the clinical data or the FDA MedWatch
20 reports that underscore metabolic and similar
21 concerns. Risk assessment would demand that
22 adverse events like the aggravation of

1 obesity, diabetes, and other hypolipidemia
2 deserve as much or more attention than the
3 potentiation of sleepiness.

4 "I appreciate your listening to my
5 comments. I am perplexed that somnolence is
6 the reason for this advisory committee
7 meeting, while equally more pressing medical
8 and social concerns, especially the use of
9 Zyprexa in children and adolescents, are
10 being simultaneously ignored. Respectfully,
11 Stephen P. Kryzinski, M.D."

12 The other two comments here are
13 very brief, but they express the anguish of
14 two mothers who had lost children to Zyprexa.
15 The first case, Kay Sexton (?). She lives in
16 Midland, Texas.

17 "My son, Scott William Sexton, who
18 was an honor graduate with a B.A. and M.B.A.
19 from Rice University, was diagnosed with
20 bipolar disorder in June of 2005. He was put
21 on Zyprexa and other drugs by the end of June
22 and the first part of July. He started his

1 new jobs with a multinational consulting
2 company in September, at a six-figure salary.
3 He died on December 7, 2006, at the age of 28
4 from complications of pancreatitis brought
5 on, I believe, by faithfully ingesting
6 Zyprexa, a drug prescribed so that he could
7 lead a normal life. It took him 13 horrible
8 days at St. Luke's ICU in Houston to die.

9 "Sometime before his death, the
10 Zyprexa had I believe stopped working to
11 stabilize his moods. He was not going to
12 work. He was smoking too much and keeping
13 odd hours. His mind was racing and he was
14 depressed.

15 "If the committee does its
16 homework, I believe it will uncover studies
17 that show that Zyprexa is often no more
18 effective than traditional medications for
19 treating bipolar disorder. Older medications
20 have fewer life-threatening side effects and
21 cost a great deal less.

22 "It is my belief that Eli Lilly

1 Company has been less than straightforward
2 and forthcoming in the matter of the dangers
3 of Zyprexa. There was no black box warning
4 during the time my son took Zyprexa.

5 "My son's death has completely
6 (inaudible) my life. I was suicidal for
7 months. I still teach, and find some solace
8 in my work, but I will never be the same.
9 Simple, straightforward warnings would have
10 kept Zyprexa from killing my son.

11 "If I were a member of the
12 committee, I would think long and hard before
13 I believed anything from Eli Lilly concerning
14 Zyprexa. N.S.K. Sexton."

15 The second letter is another
16 bereaved mom. "My name is Ellen Libositch
17 (?) from Silver Spring, Maryland. After 13
18 years on lithium for manic depression, my son
19 made the mistake of going on a Maryland
20 Medicaid program. He was pressured into
21 taking Zyprexa. The reason being -- given
22 the longer one has this condition, the more

1 severe it becomes, so a stronger medication
2 was necessary.

3 "This was a lie. There is no
4 warning from the doctor nor on the label that
5 we should be on guard. Lithium is a cheap
6 generic pill, never caused any problems with
7 thirst. After two years, a great weight gain
8 on Zyprexa, my son felt funny. I learned
9 later that this is one of the symptoms of
10 hyperglycemia. He fell into a coma and died
11 four days later at the age of 39. He had a
12 master's degree in city and regional planning
13 from Cornell and was about to go back to work
14 at the National Capital Council and Planning.

15 "This drug should be taken off the
16 market, not approved for yet another lethal
17 use. The Justice Department is now in
18 discussion with Lilly to get a billion
19 dollars back for off-label marketing and
20 hiding side effects. These are civil
21 charges. Where are the civil charges for the
22 deaths of our sons? Why are these despicable

1 men not going to prison? Where is the
2 justice for all of the bodies lying all over
3 the battlefield from this drug?

4 "FDA did not approve it, another
5 murder weapon, on this two-week shot. It
6 represents to me (inaudible) and will cause
7 deaths."

8 And it's signed Ellen Libositch.
9 That concludes my presentation. I've got my
10 notes if anybody needs them. I'll be briefly
11 out in the lobby or out in the hallway out
12 here. So I've got contact information and so
13 forth.

14 Thank you so much for listening to
15 me.

16 DR. RUDORFER: Thank you, Mr. Boehm.
17 We appreciate your comments.

18 There is a second gentleman
19 registered to make comments, but I'm not sure
20 that he's in the room.

21 That being said, the open public
22 hearing portion of the meeting has now

1 concluded, and we will no longer take
2 comments from the audience. The Committee
3 will now turn its attention to address the
4 task at hand: The careful consideration of
5 the data before the Committee as well as the
6 public comments.

7 Now, I've been asked by the
8 representatives of the sponsor to -- if they
9 could be able to address some of the concerns
10 we had left hanging at the end of the morning
11 session, so perhaps we'll turn to them first.

12 DR. CORYA: Thank you for that
13 opportunity. Yes, there were a couple of
14 discussion points that came up prior to lunch
15 that we wanted to be able to perhaps provide a
16 little bit better explanation around for you.
17 There are three of us who will do that. I'll
18 just say a few things and then pass it on to our
19 statistician and to our PK expert.

20 First of all, with regard to your
21 question about whether or not there is a
22 difference in risk per injection per dose,

1 that was one of the questions. The answer to
2 that is yes. Let me show you the data for
3 that.

4 Here, we have the breakdown for the
5 dose strengths on the left, and then the
6 number of injections that they got and the
7 number of excessive sedation events that they
8 had. So you can see what percentage of their
9 injections at that dose resulted in an
10 excessive sedation event. And as we've been
11 discussing, that rate is higher with the
12 405-milligram dose. It appears to be equal
13 with the 300 and the 210.

14 I will reiterate one thing that I
15 said earlier, which is that if you just look
16 at dose in a single injection and compare two
17 doses, you do see that difference. If you
18 look over time, at the cumulative risk over
19 time, because of the fact that 405-milligram
20 strength is given every four weeks and the
21 210 and the 300 are given every two weeks,
22 that frequency difference ends up so that the

1 actual rate of risk in a patient who's on the
2 medication over time is about the same. It's
3 still 1.1 odds ratio for more risk on the 405
4 than, say, on the 210. But that does tend to
5 equal out over time. But for a single
6 injection, the higher dose is a higher risk.

7 Now, does the risk per injection
8 change over time? Which I would believe was
9 your question, Dr. Temple. The answer to
10 that is no, it does not.

11 Again, the cumulative risk does for
12 each patient. So at this point, I'm going to
13 call Scott Anderson up to maybe provide a
14 little bit more detail about the statistical
15 analyses that reached that conclusion.

16 DR. ANDERSON: First of all, I need to
17 clarify why the beta-binomial is the model that
18 we think is appropriate. And again, the data
19 from that, the data because of the patient with
20 two events, makes the binomial model -- doesn't
21 approximate the data as well as the
22 beta-binomial. We've done goodness-of-fit tests

1 as well that also support that. In addition,
2 the risk factor analysis that identifies
3 different risks for different patients also
4 contribute to the beta-binomial not fitting as
5 well.

6 In terms of Dr. Laughren, I think,
7 who mentioned is the hazard over time
8 constant -- based on the number of injections
9 as a risk factor not being significant, we
10 believe then that supports the fact that the
11 risk is constant over time.

12 DR. WINOKUR: So that's 17 of the
13 events, or the other ones are just various doses
14 in the middle?

15 DR. CORYA: Oh, I'm sorry. Yes, I
16 meant to mention that. So the others were not
17 any of these exact doses, so there were seven
18 other events.

19 And the dose range for those events
20 was between 100 and 300 milligrams, but we
21 didn't have time at our break to calculate
22 out the exact rates for those in-between

1 doses.

2 One of the other questions that had
3 come up prior to the break was around the
4 mechanism of action, the proposed mechanism
5 of action. And I'm going to ask
6 Dr. Berkstrom to come up and perhaps
7 elaborate a little bit further on, again, the
8 reasons we believe this is the mechanism, and
9 perhaps other things that we have considered
10 around that.

11 DR. BERKSTROM: So the event, when it
12 occurs, is obviously something that was very
13 concerning to Lilly, and we spent many, many
14 hours of discussion around the possible
15 mechanism of this event. And clearly, I think
16 as we've examined this, we don't come down to
17 any single mechanism that we believe is the
18 absolute cause of this event. But we have
19 considered a lot of the evidence around this
20 event, and we think we have certainly some very
21 important facts that contribute to why this
22 event occurs.

1 So I'm going to go back to the core
2 slide that was presented during the
3 presentation that Dr. Corya presented, and
4 reiterate a few things from that slide for
5 you, but also just to give a few perspectives
6 on this. So clearly, although we don't have
7 plasma concentration data from every single
8 event, in all the events where we have
9 collected plasma concentrations during the
10 event, they are elevated. So I think we can
11 agree and I think the FDA agrees, you saw in
12 their presentation, that this event is indeed
13 related to excessively high concentrations of
14 olanzapine in the bloodstream.

15 So the fundamental question is,
16 well, how does that happen? And so the
17 clinical presentation of this certainly is
18 consistent with a rise in concentration. The
19 progression of symptoms and so on is
20 consistent with the presence of OP Depot or
21 olanzapine really in the bloodstream.

22 We have conducted solubility

1 experiments in plasma. And this perhaps for
2 us was one of the key findings that we had
3 relative to this event, because it was really
4 quite surprising to us that olanzapine
5 pamoate would be more soluble in plasma.

6 But plasma, and of course blood are
7 very complex biologic matrices, containing
8 lipids and proteins and counter-ions and all
9 other sorts of things.

10 We did test the solubility of OP
11 Depot across a wide variety of conditions, in
12 solvents and pH ranges and other things, and
13 it is, under a variety of different
14 conditions, a poorly soluble or an insoluble
15 salt, very low solubility salt. But placing
16 it in blood, we saw how fast or how high the
17 solubility had gone up. I think the FDA
18 document, again, said 167 times more soluble
19 in blood than in an aqueous system, so
20 clearly more soluble in plasma.

21 So again, how does OP Depot get
22 into the bloodstream? Please go back to the

1 prior slide. So we have certainly indicated
2 that there may be more than one way for OP
3 Depot to get into the bloodstream. And it
4 was raised why isn't training a part -- you
5 know, helping this? Well, first of all, we
6 do not necessarily believe that the needle
7 needs to be inside the vein. In other words,
8 there does not need to be necessarily a
9 direct intravascular injection of the drug
10 with the end of the needle being inside the
11 vessel.

12 But as this cartoon kind of helps
13 us understand, in a normal injection, you
14 would expect the material to end up in the
15 muscle and be distributed. That's the top
16 portion of the slide. And so in this
17 portion, you would expect that distribution
18 of the substance in blood. But if there was
19 either damage to the vessel by nicking the
20 vessel with a needle or completely passing
21 through the vessel with the needle such that
22 the needle was still in muscle, the end of

1 the needle was still in muscle, when you'd
2 aspirate in this situation, you would not
3 obtain a blood drawback on the aspiration.
4 But upon completion of that injection, then
5 either nicking or completely penetrating
6 through the vessel, there could be slow
7 leakage from the site of injection back into
8 the vasculature because there's a
9 direct-access route.

10 The slide that we presented and
11 Dr. Corya talked about during her
12 presentation was that there was a third
13 mechanism postulated, and that would be what
14 about substantial extravascular bleeding and
15 blood being pooled around the vessel and
16 around the site of injection? And certainly
17 that's a possibility as well. However,
18 considering the solubility of olanzapine
19 pamoate in blood, it would take a very large
20 amount of olanzapine -- excuse me, a very
21 large amount of blood to dissolve even
22 20 percent of a dose of olanzapine pamoate.

1 And so the size of a hematoma that would have
2 to be present there would have to be
3 substantially large, and there's no evidence
4 in any of our cases that there were visible
5 signs of hematoma.

6 So that's our belief. We don't
7 think we have absolute proof of any
8 mechanism. I think what we have is evidence
9 that olanzapine does enter the -- it is
10 released too rapidly and appears to enter the
11 bloodstream in some manner.

12 DR. RUDORFER: Dr. Potter?

13 DR. POTTER: Yes. I don't know if
14 Dr. Berkstrom can answer this. I just was
15 curious, independent of the mechanism issue,
16 just noticing in the experience, in the Phase 1
17 and the Phase 1-B studies, I don't know if they
18 were single dose, but there were at least 457
19 injections. So in none of those instances was
20 this problem observed? Obviously that would be
21 across all doses and everything.

22 DR. BERKSTROM: We had several Phase 1

1 studies where most of the Phase 1 studies were
2 single dose and we had no IAIV events or
3 excessive sedation events in those clinical
4 trials. We did have one event in what we
5 considered a Phase 2 clinical trial, which was
6 our Study LLBE. And that was a six-month
7 duration trial, and it was actually the Case
8 No. 1 that you saw during the presentation that
9 occurred in Study LLBE.

10 DR. RUDORFER: Dr. Laughren?

11 DR. LAUGHREN: Given that the
12 mechanism appears not to be direct entry of the
13 needle into the vein, and of course none of the
14 clinical experience fits with that, it doesn't
15 occur right away, how confident are you about
16 this time interval of risk of one to three
17 hours? And I understand that that's your
18 experience based on the injections that you've
19 had, and you've had a lot of injections,
20 something like 27,000 and about 24 events or 25
21 events. But that's a fairly limited experience
22 compared to what one would anticipate if this

1 drug were to be marketed. And I guess given the
2 uncertainty about the mechanism, one might
3 wonder if there is some possibility of the event
4 happening beyond three hours.

5 DR. CORYA: I think I'll actually ask
6 Dr. Berkstrom to come up again, because I think
7 that that does relate to the formulation and
8 what happens after it enters the body.

9 DR. BERKSTROM: Yes, Dr. Corya, feel
10 free to add to my answer if you care to. But
11 yes, so you saw the video this morning of the
12 reconstitution of the product, and it is a solid
13 in suspension. So the material does need to
14 be -- you know, we're really by that vehicle
15 providing a means of getting it in the body, to
16 make it into essentially a fluid-like liquid
17 that gets into the body. But that vehicle
18 really won't stay at the injection site very
19 long once it's in there because it's just water
20 essentially, a little bit of CMNC with that to
21 make it a little bit more viscous.

22 So the material, once it's in the

1 muscle, after a short period of time, that
2 vehicle is going to be absorbed. And so it's
3 going to end up sort of integrating itself
4 into the muscle tissue. So there is a period
5 of time, I believe, close to the
6 injection -- again, this is all theoretical,
7 so I think you understand that -- where there
8 would be an increased risk, where the
9 material could leave the site of injection
10 because it still is contained in vehicle.
11 But once the vehicle has left the injection
12 site and the solid materials' left behind,
13 it's less likely that that material will be
14 as free-flowing.

15 DR. CORYA: And just to add to that I
16 guess from a clinical perspective is -- what you
17 said is correct. What we have that assures that
18 it's going to happen within three hours is the
19 data that we do have. But it is possible that
20 an event could occur outside of that time
21 period. And that's what we're going to be
22 watching for incredibly closely, not only the

1 time of onset of any events that do occur once
2 it's out in the general population, but also the
3 outcome of those events. Is the clinical
4 picture any different when it happens later or
5 not, and how have those patients done?

6 And of course, as I described, not
7 only is our pharmacovigilance plan and how we
8 intend to capture that information and
9 understand it important there, but so is that
10 observational study, so that we can again
11 better understand that and characterize that.

12 Again, that's where the risk
13 management plan comes in and the training of
14 the sites, and making sure that everyone, all
15 physicians and nurses, and everyone who's
16 using this product understands the
17 conversations that they need to have with
18 their patients about benefit and risk, about
19 the observational period. And if information
20 comes to light that suggests that any events
21 have occurred outside of the three-hour
22 period, we would be immediately forthcoming

1 about that and would have to decide based on
2 all the circumstances around that event, is
3 that something that would have an impact on
4 what we are recommending for management in
5 clinical practice?

6 DR. RUDORFER: Dr. Shaffer?

7 DR. SHAFFER: I just wanted to get
8 back to the basis for the rate information. As
9 I understand it, these somnolent events were
10 derived from serious adverse event reports; is
11 that right?

12 DR. CORYA: Not all of them.
13 Sometimes -- many of them were, sometimes they
14 were not.

15 DR. SHAFFER: But the PANSS, which is
16 the routine thing, really deals with the present
17 state at the time of examination. Did you use
18 any kind of retrospective inquiry about whether
19 there'd been a period of somnolence following
20 the treatment? And do we really know what the
21 numerator is? Might there have been people who
22 were discharged home who then slept for a day,

1 and do we know what the edge of the -- do we
2 really know what the frequency is?

3 DR. CORYA: We are reliant on the
4 reporting of the events; that is absolutely
5 true. I think with the amount of attention that
6 we have given to these events and to this
7 possibility and the extra training that we've
8 done and the communications we've had with the
9 investigative sites, that that would have been
10 much more likely the case, that we might have
11 missed things that happened prior to that
12 training about a little over a year and a half
13 ago now, I think. Since that time, we can feel
14 very confident that any events that occurred, as
15 long as they were reported to the investigator,
16 were reported to us.

17 We did go back retrospectively and
18 look at all of the adverse events of sedation
19 and delirium, whether they were serious or
20 not, that were reported by patients to the
21 clinicians in the clinical trials, all the
22 clinical trials, to determine were there

1 potentially some events of excessive sedation
2 that were missed because they were not
3 reported as serious. And we were not able to
4 identify beyond the 25 events that I've
5 already described any more events of
6 excessive sedation.

7 DR. RUDORFER: Dr. Mann and then
8 Dr. Winokur.

9 DR. MANN: Do you think that the fact
10 that you didn't observe any events at all on the
11 150-milligram dose suggests something, such
12 as -- especially since only partial absorption
13 of the bigger doses produced quite measurable
14 effects, that perhaps either Dr. Shaffer's
15 right, that once you get below a certain dose,
16 you're no longer clinically detecting by the
17 system events that are taking place, or the
18 volume that you're injecting is below a certain
19 threshold, which has reduced the odds of this
20 happening?

21 DR. CORYA: I think it's potentially
22 both of those. And I might ask Dr. Berkstrom to

1 elaborate. One other point I do want to clarify
2 is that there were a lot fewer of the
3 150-milligram injections given, so the
4 denominator there is a lot smaller. So it's a
5 little bit difficult to say, but I would say
6 also the fact that it's a smaller volume that's
7 being injected could make it lower risk. And
8 then, Dr. Berkstrom, I think I would need you to
9 comment about the olanzapine concentrations and
10 if they were high enough and we just weren't
11 picking up events.

12 DR. BERKSTROM: Yes. Could you
13 clarify your question on the concentration
14 relationship?

15 DR. MANN: Just the thought if you
16 absorb most of the 150 milligrams, perhaps you'd
17 get a blood level that's somewhere in the range
18 where you're seeing marked sedation.

19 DR. BERKSTROM: Can I have slide 184
20 please? So to clarify for the Committee, we
21 have had various events across all different
22 doses. And so we showed you some data earlier

1 relative to the different doses. But I think,
2 Sara, I'm going to have to ask you to move so I
3 can point at the slide.

4 Thank you. Not the right one. I
5 want the one with the dose that they got in
6 the events. I think it's 184, isn't it? I'm
7 sorry, it's 185. Excuse me.

8 So this is the slide of all the 25
9 events. And you can see that some
10 patients -- here, a patient was receiving 100
11 milligrams every two weeks, and he had the
12 event -- he or she, I'm not sure -- as well
13 as patients all the way up to 405. And then
14 there's all kinds of doses in between, 210.
15 So I don't think there's a dose that really
16 is not possible to have this event.

17 I believe from a pharmacokinetic
18 perspective and in the way we hypothesize the
19 mechanism, it could even occur I believe with
20 perhaps even the 45 milligram injection,
21 although that's a fairly low dose of
22 olanzapine, so it would take a larger of

1 that.

2 Does that answer your question?

3 DR. CORYA: Dr. Berkstrom, could you
4 maybe clarify what sort of an olanzapine
5 concentration we would expect to see if a full
6 dose of 150 milligrams were injected
7 intravascularly?

8 DR. BERKSTROM: Yes. Obviously, if an
9 entire dose goes intravascularly, the
10 concentrations would be way above what we've
11 seen in any of these events. So even for 100-
12 or 150-milligram dose, if that was to be
13 entirely delivered intravenously, within a few
14 minutes, we'd see concentrations greatly
15 exceeding.

16 DR. CORYA: Okay.

17 DR. RUDORFER: Dr. Winokur?

18 DR. WINOKUR: I wanted to ask a
19 question or a couple of questions about the risk
20 management program strategy, which seems crucial
21 to our comfort and the FDA's comfort with the
22 idea of this going forward. So to preface this,

1 Dr. Laughren in his comments this morning
2 mentioned that you introduced some training of
3 sites involved in the study, but there were 10
4 of these events after that. So that suggests
5 that even with training and tuning up on the
6 technique of injection, they're still going to
7 happen.

8 So then the other part of the
9 equation is being able to identify them and
10 have patients in safe circumstances, not kind
11 of slumped over in the bus stop -- I mean,
12 things that are very concerning to us in
13 terms of imagining outcomes.

14 So Dr. Lauriello presented I think
15 a beautiful example of how in his clinic they
16 would gear up to handle this whole
17 administration.

18 I'm going to be a devil's advocate,
19 or just maybe grounded in some reality, and
20 imagine that in many clinical settings, I
21 would say probably including our own, that
22 many sites that are seeing a lot of patients

1 would be very hard-pressed to reliably
2 provide the kind of oversight and management
3 post-injection that ideally we'd like to see.
4 I'm interested in what kind of feedback and
5 information you've received from your
6 clinical consultants, and how you see this
7 playing out in terms of really having
8 confidence that the idealized version of the
9 risk management is realistically feasible.

10 DR. CORYA: Certainly. One piece of
11 data that we have to address that -- and again,
12 the clinical trial setting is not necessarily
13 the real-world setting either, but they're not
14 all necessarily like Dr. Lauriello's clinics,
15 but that's the data that we have so far. And in
16 the clinical trial setting, we actually found
17 that the investigators and the patients were
18 very cooperative with the recommendations that
19 we made with regard to the three-hour
20 observational period, which we had implemented
21 partway through the trials to try to collect
22 additional information. They were very

1 cooperative with that.

2 And what we found is that those
3 investigators as well as other external
4 advisors and psychiatrists that we worked
5 with, as soon as they understood this event,
6 they started helping us think of ways that
7 this could work in clinical practice, and
8 how, from a practical standpoint like what
9 you're talking about, this could actually be
10 done. And we're trying to take that
11 information and put it into the training so
12 that we can help them do that.

13 Because it is more steps, and it's
14 going to be more difficult for them to
15 manage.

16 Again, remember that depots are
17 prescribed just by a limited number of
18 prescribers, not -- you know, most
19 psychiatrists are not even prescribing
20 depots, especially the newer, only approved
21 atypical depot. That's limited to about 6-
22 or 8,000 psychiatrists. And the system that

1 they have in most of those cases is very
2 different than a general psychiatric
3 practice, so they already have a lot of the
4 systems in place, depot clinics and in
5 hospital settings and whole teams of people
6 who do this. So we want to work with those
7 systems to ensure that we're doing that
8 education, and sort of use the benefit of
9 those sort of systems, and then also take the
10 learnings from those to other clinics.

11 Again, we do not think people
12 should be using this medication without the
13 training. And we intend to ensure that all
14 people who do use it and intend to use it are
15 trained. You know, as I mentioned, we've got
16 the live in-person training that's going to
17 go on. This, of course, will be information
18 that is in the label extensively.

19 We also do intend to send out a
20 Dear Health Care Professional letter out
21 prior to the time that it's even on the
22 market, before they can even prescribe it.

1 Again, making a lot of noise about this,
2 frankly, out there so that people understand
3 it and they understand what they need to do
4 to manage this risk appropriately.

5 DR. WINOKUR: I'm just going to
6 make -- we have a clinical research site and a
7 clinic actually on the same floor, and our
8 staffing for the clinical research is totally
9 different than what our basic outpatient
10 department/clinic has. So I'd be very concerned
11 about the realistic aspect of extrapolating
12 what's worked pretty well from the kind of
13 adequate amount of attention per patient in a
14 clinical research setting to what may be
15 feasible.

16 Other people may have other
17 opinions about that, but that's just
18 something that I would raise to think about.

19 DR. CORYA: I think just one thing I
20 do want to interject there is that we aren't
21 really asking people to do special things that
22 they aren't going to understand how to do. So

1 they're going to understand that there's a risk
2 of this event occurring, and I think they'll be
3 very able to understand what that is, and then
4 it's going to involve observation and knowing if
5 and when a patient needs to have other medical
6 care, and having that nearby. So it's not
7 special blood tests or special medical training.
8 You know, they are health care professionals.

9 So your point is well-taken, but I
10 also think that without necessarily the
11 special facilities -- and what we've seen in
12 our clinical trials is that the investigators
13 and nurses and practitioners have been able
14 to actually cope very well with these events,
15 and the patients have gotten the care they
16 needed and have done well.

17 DR. RUDORFER: Before we move on to
18 the specific questions to the Advisory
19 Committee, Dr. Corya, could I ask you a
20 hypothetical question just based on our
21 discussion to this point? If there is
22 potentially more of a concern with the higher

1 doses, given that the incidence of pain and
2 discomfort seemed relatively minimal in the data
3 you showed, is there any merit to giving a
4 higher dose as two separate smaller injections
5 at different sites, so that the volume issue
6 might be contained?

7 DR. CORYA: I think I'm going to turn
8 that over to Dr. Lauriello to maybe comment on
9 what -- I mean, yes, scientifically, there's
10 merit to that, of course, but as to what impact
11 that might have on your patients or your
12 practice to give two injections at the same time
13 instead of one per visit.

14 DR. LAURIELLO: Yes. First of all, my
15 understanding of the data is it's not clear to
16 me that the volume is really one of the driving
17 issues.

18 I mean, your question posits that
19 there is a volume issue. But I will say we
20 do have experience with approaching patients
21 for two injections, and it is not a good
22 approach. Patients do not like to get two

1 injections. So I think we would not
2 recommend that.

3 DR. CORYA: I guess the only thing I
4 would add to that is with every injection there
5 is a risk of an event. So you would be giving
6 them twice as many injections. And we know from
7 the analyses that we've done that that then
8 would end up incurring the same amount of risk
9 over time for a patient as the larger single
10 injection at a time.

11 DR. RUDORFER: Okay, thanks.

12 Dr. Wells?

13 DR. WELLS: I have a question about
14 the training that was provided to those that
15 prepared and administered the medication. I
16 understand that there apparently was no impact
17 on the frequency of occurrence of the excessive
18 sedation event. Do you have any data to show
19 that your training actually had any impact on
20 the administration -- the preparation and
21 administration technique that was used by those
22 that were administering the medication?

1 DR. CORYA: Well, it's definitely a
2 difficult thing to measure because we're not
3 there at the different sites where they're
4 actually doing the injections. So we don't, we
5 don't really know. We hope and do presume that
6 the extra training and also the extra attention
7 in making sure that they understood what was at
8 risk if they didn't do the injection technique
9 properly, we hope that that would have an
10 impact, and believe it probably did. But the
11 truth is we believe these events will occur with
12 perfect injection technique.

13 One point I didn't make earlier in
14 the penicillin G studies, which just for your
15 reference, since I didn't have that before,
16 it was a study conducted in 1978 by Downum et
17 al. It was actually 10,000 patients that
18 they studied where they found that
19 .08 percent risk. They did the same thing
20 where they did training like we have, and
21 they also did not see a decrease in the event
22 frequency after that training. So I think

1 it's actually more likely that the nurses all
2 along were doing a good job and yet these
3 events were still occurring, which is why the
4 I think most important part of our risk
5 management plan is not around the injection
6 technique. While that's part of it and we
7 certainly intend to focus on that, it's
8 around what to do after the injection and
9 what to do in the event that an event occurs.

10 DR. WELLS: I ask simply because I
11 think we all know that all training is not
12 effective. And in many cases, even when
13 training is effective, it has to be repeated at
14 periodic intervals to be sure that the effects
15 of the training were maintained.

16 I have one other question as well,
17 and that relates to the quality of life
18 measurements. Can you provide any
19 information on quality of life data on
20 patients on OP Depot overall? And also, in
21 particular, is there any separation? That is
22 to say, is there any differences in these

1 quality of life data between the various
2 dosing groups?

3 DR. CORYA: I'm going to have
4 Dr. McDonnell address that.

5 DR. McDONNELL: We did have quality of
6 life measures in both of the Phase 3 studies,
7 but because of the design of those studies, they
8 were double-blind, patients were getting dummy
9 injections and taking tablets. We really didn't
10 see any benefits. And unfortunately, really,
11 that's our best comparative study that we have.

12 I don't have the result. Our
13 open-label study is not complete, so we
14 haven't got a complete set of results -- we
15 concentrated on the safety analysis from that
16 study. But we do have from one of our
17 interim sites, we included a patient
18 satisfaction measure. And just -- the
19 purpose of this really was because there's a
20 perception that even the patients who take
21 depots don't like taking depots. And really
22 what we were trying to do is trying to

1 address that question, to see when patients
2 were on depots, did they mind taking them.

3 And what you can see from this
4 study is that really overall -- and it's got
5 floors in the way we measure it -- but
6 overall, patients were satisfied with the
7 depot compared to what they'd previously been
8 treated with. And I mean, this is not rocket
9 science. It's usually the response you get
10 to the current medication any patient's on.
11 But that really just specifically for depot
12 patients is actually encouraging data, but I
13 don't have any of the other data with me.

14 DR. RUDORFER: We're going to have to
15 take two final questions for the sponsor.

16 Drs. Follmann, then Potter, and
17 then we'll need to move on.

18 DR. FOLLMANN: Thanks. I was
19 interested in the 5,000-person observational
20 study, which you briefly alluded to and which is
21 described in a little more detail in the packet.
22 So that's a pretty big study, and it seems like

1 you could do a lot with it in a way. And I
2 guess I'd like a description of sort of why
3 you're doing it and sort of what you hope to
4 learn from that study that would help us today
5 and I guess in future.

6 DR. CORYA: Certainly. What this is
7 is it's a non-interventional prospective
8 post-marketing study designed to -- the main
9 reason we will be conducting it is to assess the
10 incidence of these events in clinical practice.
11 Because as we've already discussed, clinical
12 trials are not real-world, and we want to look
13 at that over two years. But we also then want
14 to use the information collected from that study
15 to see if can better characterize these events.
16 We haven't had that many of them and we want to,
17 as we get more of them, really understand are
18 there other risk factors that we have missed?
19 Do the risk factor -- not that we've missed, but
20 because we don't have enough patients to tell.
21 Are there other things about the clinical
22 presentation that we can learn? Do all the

1 events always occur within three hours or not?

2 So again, just really better
3 characterize the incidence rate in the real
4 world, and also the clinical presentation and
5 outcomes and so on and so forth.

6 The study was powered specifically
7 based on the incidence rate that we know of,
8 to hopefully confirm the incidence rate that
9 we have. And we do anticipate that we should
10 see it. And again, it's a global study, so
11 it's worldwide. So even though we only
12 anticipate about 30 to 40 events in the
13 United States in the first year after it's
14 approved, if it's approved, we do anticipate
15 67 events occurring in this clinical trial,
16 which would provide us obviously a lot more
17 information than we have even now about the
18 events themselves.

19 DR. FOLLMANN: I'd just like to follow
20 up on that. So it seems to me a real key thing
21 to capture in this would be estimate the
22 incidence of people who have the events after

1 the three hours or after they're out of the
2 clinic. And it might be 1 out of 1,000 have the
3 event in the clinic and then 0 out of 1,000
4 outside. And that would be, I think, very
5 important.

6 The other thing is, this is a big
7 study and you want to investigate risk
8 factors.

9 Maybe you could consider a
10 randomized aspect to this. For example, you
11 could consider different needle sizes. You
12 know, it was brought up before the idea of
13 cutting the dose in half and doubling the
14 shots, maybe in both buttocks if that's where
15 it goes. You'd have a good power to detect a
16 doubling of the risks, or equivalently the
17 halving of the risks. And if you're
18 interested, is it the shot itself or the
19 dose? You know, the doubling of the
20 injections and halving the dose would be kind
21 of a good way to look at it within the
22 context of the study.

1 DR. POTTER: So 50,000 injections is
2 how many patients? I mean, what's the average
3 number of injections per patient per year?

4 DR. CORYA: Well, it depends. It'd be
5 12 if they're getting it once every month and 24
6 if they're getting it twice.

7 DR. POTTER: So 4- or 5,000 patients.
8 It's not that many patients.

9 DR. CORYA: Not that many patients.
10 You know, as I mentioned, and I guess I should
11 reiterate that out of all the antipsychotics
12 that are prescribed, only 3 percent of them are
13 in depot formulations. It's actually a quite
14 limited patient population.

15 DR. WINOKUR: So just to highlight the
16 point, to get to the point, so the observational
17 study could actually be bigger than the actual
18 experience in one year is what you're telling
19 us.

20 DR. CORYA: Well, yes, because
21 remember, it's a worldwide -- it's a global
22 study, and the other numbers that I was just now

1 talking about are just in the United States.

2 DR. RUDORFER: Thank you very much.

3 Before we look at Question No. 1, does any
4 member of the panel have a question for the FDA
5 team?

6 DR. POTTER: I guess a little
7 clarification, because the way the questions are
8 worded, I'm not quite sure I understood the
9 risk-benefit question, and I wonder how -- if
10 our colleague, if they could help educate us a
11 little bit more, or is it just a very open
12 question?

13 DR. LAUGHREN: Which questions? You
14 mean Questions 3 through 6 or the first two?

15 DR. POTTER: It's really the second
16 one. It's a funny -- because basically it seems
17 to me at a high level one is being asked to
18 assess risk-benefit, and you're almost saying
19 something about what risk management procedures
20 would be necessary.

21 I guess we're trying to look at
22 some guidance on how you, the FDA, view the

1 standards for risk-benefit to be sensitive to
2 actually the patient, and whether the letters
3 that were read into the record -- it was
4 interesting about the perception of
5 individuals who wrote those letters about
6 what risk-benefit should be. And I guess is
7 there any sort of reference standard -- and
8 that's what I was trying to get in my earlier
9 questions -- about the need to show benefit
10 when there is a very apparently defined risk.

11 Let's just say we accept the point,
12 the estimates that the FDA and the sponsor
13 have made, that there is a 1 percent or a
14 little more risk per patient if they continue
15 on the drug of getting one of these events,
16 which can be pretty dramatic, and to get to
17 Dr. Winokur's point, might not be caught as
18 well out there in the real world as it would
19 be in a very carefully managed clinic.

20 So let's say all those concerns are
21 real. Then is that a different level of
22 benefit than you would expect, for instance,

1 with a normal antipsychotic? I mean, there's
2 a history to this, as you know. I mean, like
3 what we went through with clozapine.

4 So that's what I'm trying to get
5 at. Is there any reference point that the
6 FDA has in mind?

7 DR. LAUGHREN: Questions 1 and
8 2 -- and they're really not questions, they're
9 topics for discussion. You know, our hope was
10 that you would fully discuss all the pertinent
11 issues that would go into a risk-benefit
12 decision -- judgment, which is inherent in
13 Questions 3 through 6. And what we wanted to do
14 was to lay out what the range of options are in
15 terms of special risk management -- things one
16 can do with labeling going all the way to the
17 extreme of having a black box warning, having
18 second-line status, all those kinds of things.

19 If one were to make a decision that
20 the benefits -- and you've heard the benefits
21 such as they are.

22 I mean, these are fairly standard

1 trials: An acute efficacy trial and a
2 maintenance trial. We don't -- you know, you
3 mentioned earlier, you raised the issue of
4 whether or not there should be some special
5 benefit beyond that to justify this, and
6 that's what we want the Committee to discuss.
7 So it's really that the first two questions
8 serve as a stimulus to get you thinking about
9 all the issues that we want you to consider
10 before you actually vote on the risk-benefit
11 questions.

12 DR. RUDORFER: Dr. Temple.

13 DR. TEMPLE: But in a more general
14 way, what you have to show depends on how bad
15 the risk is. So we approve clozapine because it
16 clearly worked in a population of people who
17 didn't respond to other drugs. So that made it
18 worthwhile to accept, we thought, 1-1/2 or so
19 percent risk of agranulocytosis, which is
20 sometimes lethal.

21 But when certain nonsteroidal
22 anti-inflammatory drugs turn out to have a

1 risk of Stevens-Johnson syndrome in the
2 neighborhood of 1 in 1,000, nobody could
3 think of a reason to have the drug available
4 anymore, because it didn't seem to offer an
5 advantage. So it's always that kind of
6 thing, and you obviously are bringing to bear
7 what you know about the drug in all of its
8 dosage forms.

9 And you probably presume some of
10 those features are still true, including the
11 good things and the bad things. But there's
12 no good formula.

13 DR. RUDORFER: Ms. Lawrence?

14 MS. LAWRENCE: Yes, I have a question.
15 I know that some of the other injectables, such
16 as Risperdal, which I am more familiar with than
17 anything else, there's always side effects, as
18 you just said. And I wonder if the labeling on
19 that when it was developed and made injectable
20 would be any different as far as the risk
21 management than what would be on this drug. I'm
22 not that familiar with what the labeling was

1 when it was approved by the FDA.

2 DR. LAUGHREN: I think the concern we
3 have here, as I pointed out, we haven't seen
4 this event with the other depots. We didn't see
5 it either during the development of risperidone
6 depot or post-marketing. This event appears to
7 be unique. And I think there's general
8 acceptance of that, that this is unique to this
9 formulation. And that's why -- I mean, from a
10 public health standpoint, 1 out of 100 patients
11 in a relatively short observation period having
12 this event is of concern.

13 MS. LAWRENCE: Thank you.

14 DR. RUDORFER: If I could direct the
15 Committee's attention to Question 1, which I'll
16 read for the record, and it's on the screen:
17 What are the public health consequences of a
18 depot antipsychotic that leads unpredictably to
19 profound sedation in 1 percent or more of
20 patients exposed to this product?

21 Would anyone like to start a
22 discussion on that question?

1 Ms. Griffith.

2 MS. GRIFFITH: Could I ask
3 Dr. Laughren to articulate "a concern"? I mean,
4 when you say that this particular event raises
5 concern, I take it you're talking about -- you
6 know, what does it mean, a public health
7 consequence? But in your opening presentation,
8 in your remarks, you also said that you hadn't
9 made a final determination. You hadn't done the
10 final risk-benefit analysis.

11 I guess I'm just puzzled as to how
12 do you define "concern." Is 1 percent a
13 concern? Is it an extraordinary concern if
14 it goes to 2 percent? What does it mean?

15 DR. LAUGHREN: Well, we're obviously
16 concerned because we brought it to this
17 committee. We haven't reached a final judgment.
18 I mean, we have reviewed this application.
19 We've looked at the efficacy. We've looked at
20 the full range of safety, and I want to be clear
21 about that. You know, we haven't limited our
22 review to this one event. We've looked at

1 everything. And we've compared it with the
2 existing formulations of olanzapine.

3 We have paused in making a final
4 decision because this event is unique in our
5 experience. And we're worried obviously,
6 because 1 in 100 patients having a very
7 severe and profound sedation to the point of
8 losing consciousness in this population which
9 is already vulnerable is something we worry
10 about. We want to understand how worried you
11 are about this. I mean, you're the committee
12 of experts from various standpoints, consumer
13 perspective, investigator and clinician
14 perspective. And so we want to share this
15 knowledge with the community of experts and
16 get your views on it and your advice before
17 we make the final decision.

18 DR. RUDORFER: Drs. Follmann and
19 Winokur.

20 DR. FOLLMANN: The first question
21 talks about the public health consequences.

22 And for me, that means I want to

1 think about the other depot antipsychotics
2 that are out there. And so to me, the
3 question really has to be answered in that
4 context. And I don't know a lot about the
5 other depot antipsychotics actually. So what
6 I would -- I was impressed by Dr. Kane's
7 discussion of the consequences of patients
8 with schizophrenia who can't stay on their
9 medication. And I appreciate the need for a
10 depot antipsychotic.

11 And so I would think, even without
12 thinking about it too deeply, that this is
13 probably good for patients who can't take the
14 other depot antipsychotics for whatever
15 reason. I would rather have this available
16 than this not available for that select
17 population group. And whether it's better
18 than the other depot antipsychotics is a
19 question I can't really answer, and we don't
20 really have data on, because there wasn't a
21 head-to-head comparison.

22 So I think at least as a

1 second-line or last possibility drug, to me
2 it would have appeal. So that's my quick
3 read on this, and I would just like to hear
4 if that sounds reasonable to other people.

5 DR. RUDORFER: It seems to me that a
6 key first step is for us to agree whether we see
7 that there is a need for this product or there
8 is value to this product. And then the flipside
9 of that is, is there a way that it could be made
10 available with enough of a safety margin that
11 we're comfortable? Of course, going back to
12 what Dr. Temple was describing before, if we
13 don't see that there's a particular need for
14 this product, then almost any degree of
15 additional safety concern would be particularly
16 problematic.

17 DR. WINOKUR: So to try to start
18 discussion of this first point, I think to
19 follow up on the initial point, that it does
20 need to be viewed in a risk-benefit ratio
21 context. The question is asking us simply to
22 focus on the consequences. But just to take

1 that for a minute, I see a couple of aspects to
2 this that strike me.

3 One is whether or not we anticipate
4 that what happens when the drug is out on the
5 market in the "real world" with this
6 excessive sedation will mimic and replicate
7 what's been seen in the clinical trials, or
8 it might go beyond. And I think Lilly has
9 acknowledged that there are possible factors
10 in the real world that are hard to predict or
11 extrapolate from the clinical trial. And
12 certainly the observational study, if that
13 happens, sounds like an immensely important
14 next step to build on this. I think none of
15 us have enough information to feel completely
16 comfortable.

17 I'm mindful, and I'm not sure this
18 is an exactly apt analogy of some of the QTC
19 issues that came up actually before the
20 ziprasidone review with a couple of other
21 medications not in the psychiatric area that
22 had modest QTC effects until they got out

1 there in the use -- in the context with other
2 medications that affected their metabolism.
3 That's why I raised that one question.

4 And that's just one example of a
5 number of things that can happen to
6 complicate the picture in the translation
7 from the more controlled clinical trial. So
8 that's one issue that we're going to have to
9 toss around, is what we've seen so far what
10 we're going to see or not? And then the
11 other, assuming that what we've seen in the
12 clinical trial data basically is what the
13 story is.

14 And so the good news is that so
15 far, all of the subjects who had this have
16 recovered.

17 So unlike the clozapine, which I
18 think is another apt analogy, we haven't had
19 fatalities. We've had very serious
20 concerning incidents, but people have
21 recovered, apparently without any lasting
22 impact. And that raises the issue of if it

1 is in fact possible to carry off the
2 observational program to minimize the impact
3 of these events that seem unavoidable, but
4 may be manageable, then the consequences may
5 be within a realm of being acceptable as long
6 as we think the benefits are there.

7 And I think we've heard some
8 convincing presentations. We'll talk about
9 how convincing we think the efficacy data
10 are, but I think we heard two excellent
11 clinical presentations this morning that
12 argue for the need for more options in the
13 long-term depot preparation, which I agree
14 with.

15 DR. RUDORFER: Thank you.

16 Dr. Shaffer and then Dr. Potter.

17 DR. SHAFFER: It seems to me that
18 Dr. Kane made a wonderfully articulate case for
19 depot medication and depot use in the management
20 of this terrible disease. I guess that if you
21 project from the CATIE study, then maybe there
22 are no particular advantages therapeutically

1 from the atypicals. I'm not sure that one could
2 conclude that -- that we do know, and we heard
3 from the audience and we know from other
4 sources, that olanzapine carries with it many
5 other unwanted effects. And I think that, as
6 Dr. Laughren said, the concern, or maybe you
7 said, the concern about a patient who may not be
8 in full control of their resources and of the
9 ability to respond to stresses and so on in a
10 useful and productive way is very much there.

11 And we don't really know what the
12 tail-end of the incidence is because we
13 haven't systematically obtained information
14 about the frequency of passing out. And I
15 think that as Andy said earlier on, the
16 design of this study actually precluded
17 continued collection of events in proportion
18 of people who'd already had one. So we don't
19 know the full -- we don't know what the
20 potential for multiple events or series
21 events is from these data.

22 So all in all, I would have to say

1 that my conclusion is that the public health
2 consequences are significant, and I would say
3 that there is a concern.

4 DR. RUDORFER: Dr. Potter, and then
5 Dr. Geller.

6 DR. POTTER: So I guess there's one
7 question of fact perhaps we -- I'm not sure, but
8 maybe the whole Committee -- I mean, we could
9 clarify and perhaps even you could,
10 Dr. Rudorfer. Did the CATIE study show what was
11 implied by the slide presented by the sponsor?
12 There was something about olanzapine looking
13 positive in that. I mean, is there some
14 evidence of in some cut of the data, that there
15 might be evidence for olanzapine doing some
16 better in some overall sense? I mean, or is
17 that an argument of debate from the CATIE study?
18 Just specifically what do people think the CATIE
19 study did or did not show? I'm hearing
20 different things.

21 DR. RUDORFER: Well, my understanding
22 is that the main outcome measure was all-cause

1 discontinuation. So over a period I believe of
2 18 months, several antipsychotics were compared
3 to one another on that measure. And on that
4 score, olanzapine came out on top in terms of
5 having the least discontinuation. It was still
6 greater than 50 percent, but it was superior to
7 the other drugs.

8 DR. POTTER: So the implication by the
9 sponsor, I suppose, or of the people who say it
10 might be important to have -- there might be a
11 benefit in some patients to this is at least
12 supported by that kind of data. Is that true?
13 I mean, I'm really asking you as -- the CATIE
14 study and all. I'm not trying to give my
15 opinion.

16 DR. LEON: Is there any chance that
17 Lilly has a CATIE slide on the primary outcome,
18 please? The primary outcome, not what we've
19 seen so far.

20 DR. TEMPLE: We know what Lilly
21 believes about this, and we also think we know
22 what the CATIE study shows, which is that for

1 effectiveness, there were fewer discontinuations
2 on olanzapine than on other drugs, and for
3 intolerability, there were more. But that goes
4 with their view that it may -- and they have
5 some trials that they think supports this idea,
6 too, that at least in some settings it seems to
7 work a little better.

8 DR. POTTER: So okay.

9 DR. TEMPLE: Is that a fair summary of
10 what you think?

11 DR. POTTER: Yes. So I think, and
12 we've already addressed the point, that in this
13 instance, once does not have the comparator data
14 to in a scientific way establish that for some
15 patients, this really is superior to anything
16 else out there on the market. So it has to be
17 an inferential belief argument that perhaps it
18 is true that this is the case.

19 And then just thinking -- now, even
20 though I am an industry representative, I
21 want to make it very clear to people that I
22 worked for 25 years at the NIMH and also have

1 been someone who treated very, very sick
2 patients. So as a scientist, as a clinical
3 scientist and research scientist, making this
4 equation, I have to ask if a limited number
5 of patients are going to be exposed to this
6 after a great deal of thought and highly
7 educated to the risk, and I as a clinician
8 think there might be inferentially a
9 marginal -- a real benefit for certain
10 patients, a response that I could not get
11 with risperidone, and I probably -- my bias,
12 and maybe it's a bias, is that the tardive
13 dyskinesia findings do look encouraging with
14 this more recent class of drugs, so I might
15 not want to do some of the old-fashioned
16 long-acting drugs and put people for years on
17 those, I'd say, gosh, one would have a hard
18 time saying I would not want this option for
19 those patients, recognizing that there is a
20 very real risk of this dramatic, very
21 dramatic, deep sedative property.

22 But that's a personal statement,

1 and I guess we're being asked to do that as
2 well.

3 So again, I'm trying to separate.
4 That's why I sort of asked. I'm trying to
5 respond beyond as an industry representative
6 and just say as a research psychiatrist.

7 DR. RUDORFER: Thank you. Dr. Geller?

8 DR. GELLER: I think there's no
9 question, especially given the very excellent
10 minds in this room, that any of us could argue
11 cogently either way. But what holds the day for
12 me are the comments by Dr. Kane and the others
13 of what we face clinically. What CATIE showed
14 more than anything is we don't have the drugs we
15 need, which means what we wind up doing
16 clinically is the best we can with any one
17 patient, and very frequently going from option
18 to option until we get the combination that
19 allows the patient to be an electrician's
20 helper, to use the example given this morning.

21 So I am very reluctant to say that
22 we would not take advantage of a new type of

1 drug. And I would consider most of the
2 things I've heard that would say maybe there
3 are some very serious concerns are things
4 that perhaps we can address in Question 2 in
5 terms of labeling and second-line and black
6 box and questions like that.

7 DR. RUDORFER: I recommend two
8 additional comments on Question 1, and then I
9 think you're right, Dr. Geller, that will lead
10 us into the next question.

11 Dr. Wells and Ms. Griffith have the
12 last two words.

13 DR. WELLS: Thank you. I would agree
14 that it seems to me that there are significant
15 public health consequences associated with the
16 drug, both negative and positive. Certainly
17 when these events occur of excess sedation,
18 certainly when they do occur, it is a profoundly
19 disabling event. And of course, many of these
20 patients do not have good family support,
21 certainly some do, many of them don't. If they
22 went home after one hour and began to manifest

1 this clinical presentation, there may or may not
2 be someone there that could help them. So I
3 think these are matters of concern. And also,
4 in my own mind, just because no deaths have
5 occurred to date doesn't necessarily mean that
6 no deaths will occur at some point in time.

7 On the other hand, I agree with
8 Dr. Geller and others that it seems to me
9 that this dosage form does have quite a bit
10 to offer. I do believe that there are large
11 numbers of patients who would significantly
12 benefit from having this drug available to
13 them. So I think we need to give a lot of
14 thought to managing the risks, and what needs
15 to be done to be sure that the risks are
16 minimized.

17 DR. RUDORFER: Thank you.

18 Ms. Griffith?

19 MS. GRIFFITH: It occurred to me as I
20 was sitting here that the last time the
21 Psychopharmacological Committee met, it was
22 about SSRIs and we were looking at suicidality

1 and suicide risk. And I have to say that if
2 you're talking about an adverse event that
3 causes excessive sedation for a period of one to
4 three hours, it may be cynical, but I have to
5 say that it's not as consequential as the
6 suicide risk for this particular population.

7 And I'm moved by something that
8 Dr. Winokur said, just quoting it, he said
9 this may pose a number of adverse event
10 risks, which may be unavoidable, but it also
11 seems that it may be manageable. And that's
12 sort of what I took from this morning's
13 presentation with regard to the public health
14 consequences.

15 DR. RUDORFER: I'd like to take a stab
16 at summarizing the sense of the Committee. I
17 just wrote out something. If you'll forgive me,
18 this I believe is the longest sentence that will
19 be said in Silver Spring today.

20 Given the value of having an
21 additional depot preparation of an atypical
22 antipsychotic for some patients with

1 schizophrenia, the Committee believes there
2 is value to seeking to better understand,
3 manage, and if possible, prevent the greater
4 than 1 percent risk of the severe sedation
5 episodes.

6 And if people are okay with that,
7 we're not asked to vote on Question 1, just
8 have the discussion, which I believe leads us
9 nicely into Question 2, which gets at what
10 we're all approaching, which is how does one
11 safely work with a medication like that
12 should it appear in the real world?

13 So for the record,
14 Question 2 -- again, this is a discussion
15 question, not a vote: If OP Depot were to be
16 approved and marketed, what risk management
17 procedures would be necessary, including
18 labeling advice, to ensure the safe use of
19 this product? For example, would the
20 labeling changes include a second-line status
21 and a black box warning?

22 And if I could just start by

1 following up on Gail's comment a minute ago,
2 I was thinking also about the comparison with
3 discussions the committee has had around
4 SSRIs. And I would like to remind us that as
5 we were hearing from the sponsor, one issue
6 with medication such as SSRIs is that they're
7 very widely available and easily prescribed.

8 In fact, that was always one of
9 their apparent advantages, that many family
10 physicians would be very quick to prescribe
11 them, sometimes without enough in the way of
12 forethought or management after prescribing.
13 And here, in a sense, there is something of a
14 built-in control system. As we were hearing,
15 there are only so many psychiatrists who
16 actually use depot preparations, and
17 especially if we're talking about a period of
18 observation, I would think that the odds that
19 this would wind up being a general office
20 practice would be pretty remote.

21 I would second the concerns that
22 have been expressed about the real-world

1 situation. I think the video was very
2 informative, and I realize that was kind of
3 slow motion to emphasize the point, but then
4 again, I was trying to visualize a busy
5 public clinic, and with trying to make sure
6 that the solution was adequate and the powder
7 wasn't stuck to the sides. And I fear that
8 there are opportunities for real-world
9 shortcuts that might pose a problem.

10 Dr. Geller?

11 DR. GELLER: I want to go back to a
12 comment that Dr. Caplan made this morning about
13 calling this a sedation event. When I read the
14 material that came and saw "a sedation event,"
15 what I imagined in my mind was people were
16 sleeping 24 hours. I didn't imagine they were
17 having coma, convulsions, hypertension, slurred
18 speech, and not recovering for several days.
19 I'm wondering if other people have had this
20 reaction, and if it might not help address the
21 problem if we gave it a name that was more
22 fitting for the phenomena.

1 DR. POTTER: Didn't we hear someone
2 use the word "delirium?" I mean, I don't know
3 who suggested that, but that doesn't really seem
4 to fit, either.

5 DR. CAPLAN: I think the emphasis on
6 significant change in state of consciousness
7 really needs to be there. This is not just a
8 delirium. This is a really significant change
9 in state of consciousness.

10 DR. RUDORFER: Dr. Mann?

11 DR. MANN: I'd like to have a go at
12 the comment on the potential labeling type of
13 language.

14 It seems to me that if the
15 clinician is being given some guidance in the
16 labeling language as to where this medication
17 fits in, that we'll probably start by some
18 kind of description of what type of patients
19 should be treated with the depot neuroleptic
20 in the first place. And then the discussion
21 between the doctor and the patient is about
22 would you -- something like would you like to

1 trade off the possibility that 1 in 1,000
2 injections is going to do all the things that
3 my colleagues on the left are trying to
4 describe versus the risks of the metabolic
5 syndrome, hyperlipidemia, all those sorts of
6 things, diabetes, and versus lower risk for
7 akathisia?

8 So it seems to me that there's a
9 very specific and relatively narrow clinical
10 target that one is directing the use of this
11 medication to, but I think that there is
12 probably an additional labeling requirement
13 for these kinds of medications given the
14 dialogue that has gone on in the greater
15 community. And that is, I think there should
16 be some language trying to address potential
17 off-label uses that come to mind readily.

18 For example, one could see the
19 convenience of this sort of medication in
20 nursing homes, where there is already a
21 concern about the use of atypical
22 antipsychotics to keep people calm and out of

1 trouble, and make life easier on the staff
2 and a lot of things like that. So giving a
3 shot once every two weeks to somebody who's a
4 bit out of line could be tempting. And I
5 think that in trying to guide the clinician a
6 little more so the medication's use does
7 target the real population that's being
8 expected to be receiving this medication,
9 some additional language like that should
10 also be introduced or considered.

11 DR. RUDORFER: Yes. And in fact,
12 Dr. Mann, I'm glad you said that. That was part
13 of what I had in mind this morning when I made
14 reference to the inclusion of people with
15 schizoaffective disorder. I was concerned about
16 that kind of diagnosis creep. And I think that
17 that is the kind of specific language that
18 certainly could be -- we certainly could
19 recommend for labeling.

20 Yes, Ms. Lawrence?

21 MS. LAWRENCE: I was wondering if,
22 aside from specific wording directed to the

1 doctor, if there's any -- and I'm assuming this
2 was done in the study, any pretreatment to make
3 sure that somebody doesn't have any cardiology
4 problems. I mean, is there a physical that's
5 done before someone starts on this type of a
6 drug? You know, medically to make sure that
7 someone is not predisposed to diabetes. I mean,
8 I know a lot of these antipsychotics all with
9 the weight gain can cause and have all those
10 side effects. But if this one has even more of
11 a risk, is there any type of a physical that's
12 given before someone's even considered to go on
13 the injectable?

14 DR. RUDORFER: Dr. Temple.

15 DR. TEMPLE: Well, Tom may want to
16 address this, but this drug is already labeled
17 as distinct from other drugs in terms of
18 metabolic syndrome for its oral dosage format.
19 It's relatively recently been changed to include
20 that.

21 It also has a big, black box that
22 says don't use in elderly people who are

1 demented because they'll die. And that's
2 part of current labeling already. Does that
3 stop it? Probably not, but it's quite loud
4 at the moment.

5 Can I also just mention one other
6 thing? This is actually a great discussion,
7 I think. We have a wide range of ways in
8 which we've told people to watch out in
9 varying degrees. The most extreme is to say
10 you have to fail on the other therapy first.
11 That's what clozapine says. Whether that's
12 always honored or not, I doubt, but that's
13 what it says.

14 For ziprasidone, where there was a
15 modest but real increased QT interval, it
16 said you might want to think about there
17 being drugs that don't have this problem when
18 you're choosing your therapy. On the other
19 hand, it doesn't have -- oh, I don't know, it
20 may not have as much metabolic things. So
21 there are a bunch of things to bring into
22 consideration.

1 So labeling like that is something
2 to think about. And it varies from don't you
3 dare until you failed on the other things,
4 you might want to think about this problem
5 before you do it, et cetera, et cetera. And
6 I think you're heading in that direction in
7 many ways. But we have a wide range of
8 things we can suggest or demand.

9 DR. RUDORFER: What I'm starting to
10 think, Dr. Temple, is there a glass half full
11 approach of labeling, such that this is a depot
12 preparation that should only be used in patients
13 who are demonstrated responders to the oral form
14 of this drug?

15 DR. TEMPLE: Well, that's certainly a
16 possibility, too. A more extreme version would
17 be to say even in responders, you should try
18 them on something else. But there's a wide
19 range. I'm not advocating any one of them, I'm
20 just pointing out that there's a lot of
21 flexibility, in an attempt to make sense.

22 DR. RUDORFER: Dr. Caplan.

1 DR. CAPLAN: Well, I didn't realize
2 mine is one. I mean, in terms of the public
3 health safety, just to get back to that issue, I
4 recognize the issue of nonadherence of
5 schizophrenic patients in terms of their oral
6 medication, and that that is a significant
7 issue. However, if Lilly does its study which
8 it's suggesting to do for another two years, and
9 we get much more information in terms of
10 predictors, who are the patients at risk, what
11 is the more long-term outcome of this, we will
12 have a much better sense of sort of what this
13 really is and how we could define it. If we
14 could call it whatever change in state of
15 consciousness, plus-plus, or whatever, and what
16 it really means in terms of underlying
17 mechanisms and in terms of the results for these
18 patients.

19 So my concern is, if we're going to
20 be explaining to schizophrenic patients about
21 all these side effects, many of them are not
22 going to be able to understand the long-term

1 implications of this. It's not like the
2 SSRIs, where there's all these advocates and
3 big groups. I mean, look, we didn't have
4 lots of public presenting here today. It's a
5 very, very different story.

6 So I really think it behooves us to
7 think of getting additional information from
8 the sponsor over the next two years and then
9 revisiting this.

10 DR. RUDORFER: Your point is
11 well-taken, Dr. Caplan. I'm thinking two
12 related ideas. One is, as I understand the FDA
13 team, labeling is not static as we're just
14 hearing about the black box warning on oral
15 olanzapine. So that I'm assuming that whatever
16 conclusions we may reach today will not be set
17 in stone as further information becomes
18 available. So I think one issue before us is,
19 based on what we know today, would we want to
20 see the drug labeled for marketing in some way
21 or other, or is the answer that we don't want to
22 see it on the market until the further

1 information is gathered?

2 Dr. Laughren?

3 DR. LAUGHREN: Yes. I mean, that's
4 inherent in Questions 3 through 6. I mean, we
5 wanted you to -- and you've having a very good
6 discussion, by the way, and I think you're
7 touching on all the important issues. But you
8 have to each of you individually decide whether
9 or not you think, based on the information
10 available at this point in time, you think this
11 drug could be approved -- whether or not. And
12 if you thought it could be approved, we're
13 asking you for advice on what the labeling
14 should look like and what risk management
15 programs should look like to make it possible to
16 use it safely.

17 DR. RUDORFER: Before I turn to
18 Dr. Potter, I just want to respond to
19 Dr. Caplan's other point, what I think is maybe
20 under the heading of "informed consent." You
21 were using the comparison of SSRIs. And part of
22 my thinking in terms of putting on the table an

1 idea such as thinking about oral olanzapine
2 responders is to not even have that discussion
3 with the patient until the patient is clinically
4 stable. For example, clinically stable on oral
5 olanzapine, and then have the discussion of
6 potential benefits versus risks, as opposed to a
7 patient who's acutely psychotic.

8 Dr. Potter?

9 DR. POTTER: I wanted to follow up on
10 Dr. Caplan's comment about what one would
11 additionally learn from the proposed
12 5,000-patient observational study that would
13 help one make a better judgment about the
14 risk-benefit. As I understand it, and perhaps
15 some of my other colleagues on the panel can
16 address this -- as I understand it, the
17 observational study will provide more
18 information about the event, the cluster of
19 events related to this change of consciousness.
20 I was not hearing that there was anything in
21 that study that would inform us in any
22 meaningful way on the relative benefit to

1 existing treatments.

2 Now, I'm not suggesting that that
3 be a criteria, but again -- and just putting
4 something very out on the table because I
5 suspect the real-world issues that have
6 already been referred to, somebody referred
7 to a lawsuit or something -- I mean, a
8 settlement of the particular sponsor -- in
9 the real world, the question always is if you
10 are a company -- and I know this may not
11 sound believable, but sometimes companies
12 actually do studies and introduce drugs way
13 beyond what the finances would dictate. So
14 not every -- companies are not always making
15 money when they introduce drugs. I do not
16 know from these projections whether this
17 particular form of drug would or would not
18 make money for Lilly.

19 But the point is at a certain point
20 in time, and this is one of the histories in
21 the field and perhaps Dr. Temple can comment
22 on this, the requirement to do what we as