

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS  
ADVISORY COMMITTEE MEETING

Silver Spring, Maryland  
Wednesday, February 6, 2008

1 PARTICIPANTS:

2 Committee Members:

3 MATTHEW V. RUDORFER, M.D., Acting Chair  
National Institute of Mental Health

4 ROCHELLE CAPLAN, M.D.  
5 University of California, Los Angeles

6 BARBARA G. WELLS  
University of Mississippi

7 Temporary Voting Members:

8 DEAN A. FOLLMANN  
9 Institute of Allergy and Infectious Diseases  
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10 BARBARA GELLER, M.D.  
11 Washington University in St. Louis

12 ANDREW LEON  
Medical College of Cornell University

13 J. JOHN MANN, M.D.  
14 New York State Psychiatric Institute

15 DAVID SHAFFER  
Columbia University/NYS Psychiatric Institute

16 ANDREW WINOKUR, M.D.  
17 University of Connecticut Health Center

18 Food and Drug Administration (Non-Voting):

19 THOMAS P. LAUGHREN, M.D.  
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21 Center for Drug Evaluation and Research

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- 1 PARTICIPANTS (CONT'D):
- 2       ROBERT TEMPLE, M.D.
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- 7       WILLIAM Z. POTTER, M.D.
- 8       Merck & Co., Inc.
- 9 Designated Federal Official:
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- 12 Consumer Representative:
- 13       GAIL W. GRIFFITH
- 14       Washington, D.C.
- 15 Patient Representative:
- 16       MARGY LAWRENCE
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- 18 FDA Presenters:
- 19       ANDRE JACKSON
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2 Industry Presenters:

3 GREGORY BROPHY  
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4 SARA CORYA, M.D.  
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6 JOHN KANE, M.D.  
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7 JOHN LAURIELLO, M.D.  
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1 P R O C E E D I N G S

2 (8:05 a.m.)

3 DR. RUDORFER: We're going to go ahead  
4 and get started. I'd like to welcome everyone  
5 to this meeting of the FDA Psychopharmacologic  
6 Drugs Advisory Committee. I'm Dr. Matt Rudorfer  
7 from the National Institute of Mental Health.  
8 I'm serving as acting chair today.

9 Some of you may recall that earlier  
10 this decade, I served as a regular member and  
11 chair of this committee, and I'm honored to  
12 be invited back today, especially to work  
13 with this distinguished panel. I can assure  
14 everyone that we have represented here both  
15 scientific and clinical expertise as well as  
16 a lot of compassionate concern for people  
17 with serious mental disorders, who will, we  
18 trust, be the beneficiaries of our work today  
19 as we discuss a particular new, long-acting,  
20 depot atypical antipsychotic, a new  
21 olanzapine formulation.

22 I have a little bit of housekeeping

1 I'm supposed to do. First, I want to tell  
2 you I myself only have two simple ground  
3 rules. I suggest that everyone here today  
4 keep an open mind and a closed cell phone. I  
5 also want to remind everyone, both on the  
6 committee and in the audience, if you're  
7 going to make a comment, please state your  
8 name for the record before your comment, so  
9 we'll keep that accurate.

10           And now I'm required to read the  
11 following: For topics such as those being  
12 discussed at today's meeting, there are often  
13 a variety of opinions, some of which are  
14 quite strongly held. Our goal is that  
15 today's meeting will be a fair and open forum  
16 for discussion of these issues, and that  
17 individuals can express their views without  
18 interruption. Thus, as a gentle reminder,  
19 individuals will be allowed to speak into the  
20 record only if recognized by the chair. We  
21 look forward to a productive meeting.

22           In the spirit of the Federal

1 Advisory Committee Act and the Government in  
2 the Sunshine Act, we ask that the advisory  
3 committee members take care that their  
4 conversations about the topic at hand take  
5 place in the open forum of the meeting. We  
6 are aware that members of the media are  
7 anxious to speak with the FDA about these  
8 proceedings. However, FDA will refrain from  
9 discussing the details of this meeting with  
10 the media until its conclusion. Also, the  
11 committee is reminded to please refrain from  
12 discussing the meeting topic during breaks or  
13 lunch.

14 Thank you.

15 And now perhaps we should introduce  
16 the members of the committee. Shall we go  
17 around the table?

18 Perhaps we'll start with  
19 Dr. Potter.

20 DR. POTTER: I'm Dr. Bill Potter. I'm  
21 actually with Merck Research Laboratories. And  
22 I am the non-voting industry representative to

1 the committee.

2 DR. GELLER: I'm Barbara Geller. I'm  
3 professor of psychiatry, Washington University  
4 in St. Louis.

5 DR. MANN: I'm John Mann. I'm from  
6 the Department of Psychiatry at Columbia  
7 University and New York State Psychiatric  
8 Institute.

9 DR. SHAFFER: David Shaffer from New  
10 York State Psychiatric Institute, Columbia  
11 University, a psychiatrist.

12 DR. WELLS: I'm Barbara Wells. I'm  
13 dean of the School of Pharmacy at the University  
14 of Mississippi, and executive director of our  
15 Research Institute of Pharmaceutical Sciences.

16 MS. LAWRENCE: I'm Margy Lawrence,  
17 patient representative from Potomac, Maryland.  
18 I serve on our NOMY (?) Montgomery County Board  
19 of Directors, and I'm also on the Citizens  
20 Advisory Committee for Springfield Hospital  
21 Center in Sykesville, Maryland.

22 MS. GRIFFITH: I'm Gail Griffith. I'm

1 a writer and mental health advocate and I live  
2 here in Washington, D.C.

3 DR. RUDORFER: Again, I'm Matt  
4 Rudorfer from NIMH, serving as acting chair.

5 DR. NGO: LCDR Diem Ngo, designated  
6 federal official.

7 DR. FOLLMANN: I'm Dean Follmann, head  
8 of statistics at the National Institute of  
9 Allergy and Infectious Diseases.

10 DR. LEON: I'm Andrew Leon, professor  
11 of biostatistics at Weill Cornell Medical  
12 College.

13 DR. WINOKUR: Andy Winokur. I'm  
14 director of psychopharmacology at the University  
15 of Connecticut Health Center.

16 DR. CAPLAN: I'm Rochelle Caplan,  
17 child psychiatry at UCLA.

18 DR. ZORNBERG: I'm Gwen Zornberg,  
19 medical team leader, Division of Psychiatry  
20 Products at the FDA.

21 DR. MATHIS: Mitchell Mathis, deputy  
22 division director, Division of Psychiatry

1 Products at FDA.

2 DR. LAUGHREN: Tom Laughren. I'm the  
3 director of the Psychiatry Products Division at  
4 FDA.

5 DR. TEMPLE: Bob Temple. I'm director  
6 of the Office of Drug Evaluation I that  
7 Psychiatry resides in.

8 DR. RUDORFER: Thank you. Now I'd  
9 like to turn this over to Dr. Diem Ngo to  
10 conclude our housekeeping activities.

11 DR. NGO: Good morning, everybody.  
12 First, I would like to identify the FDA press  
13 contact, Ms. Sandy Walsh. If you're in the  
14 room, please stand up. Okay, I think she may be  
15 running a little bit late this morning.

16 Now I'd like to read the --

17 DR. RUDORFER: There she is.

18 DR. NGO: There you go.

19 I'd like to read the Meeting  
20 Statement into the record.

21 The Food and Drug Administration is  
22 convening today's meeting of the

1 Psychopharmacologic Drugs Advisory Committee  
2 under the authority of the Federal Advisory  
3 Committee Act of 1972. With the exception of  
4 the industry representative, all members and  
5 consultants are special government employees  
6 or regular federal employees from other  
7 agencies and are subject to federal conflict  
8 of interest laws and regulations.

9           The following information on the  
10 status of the Committee's compliance with  
11 federal ethics and conflict of interest laws  
12 covered by, but not limited to, those found  
13 at 18 U.S.C. 208 and 712 of the Federal Food,  
14 Drug, and Cosmetic Act is being provided to  
15 participants in today's meeting and to the  
16 public.

17           FDA has determined that members and  
18 consultants of this committee are in  
19 compliance with federal ethics and conflict  
20 of interest laws. Under 18 U.S.C. 208,  
21 Congress has authorized FDA to grant waivers  
22 to special government employees who have

1 potential financial conflicts when it is  
2 determined that the agency's need for a  
3 particular individual's services outweighs  
4 his or her potential financial conflict of  
5 interest. Under 712 of the FD&C Act,  
6 Congress has authorized FDA to grant waivers  
7 to special government employees and regular  
8 government employees with potential financial  
9 conflicts when necessary to afford the  
10 committee essential expertise.

11 Related to the discussions of  
12 today's meeting, members and consultants of  
13 this committee who are special government  
14 employees have been screened for potential  
15 financial conflicts of interest of their own  
16 as well as those imputed to them, including  
17 those of their spouses or minor children, and  
18 for purposes of 18 U.S.C. 208, their  
19 employers. These interests may include  
20 investments, consulting, expert witness  
21 testimony, contracts/grants/CRADAs,  
22 teaching/speaking/writing patents and

1 royalties, and primary employment.

2 Today's agenda involves discussions  
3 of a new drug application 22-173 Zyprexa  
4 Adhera -- olanzapine pamoate depot -- a  
5 long-acting intramuscular injection  
6 210-milligram, 300-milligram, and  
7 405-milligram per vial, sponsored by Eli  
8 Lilly and Company, for treatment of  
9 schizophrenia. A particular safety concern  
10 for discussion is the occurrence of severe  
11 somnolence in some patients who are  
12 administered this depot formulation of  
13 olanzapine.

14 Based on the agenda for today's  
15 meeting and all financial interests reported  
16 by the Committee members and consultants,  
17 conflict of interest waivers have been issued  
18 in accordance with 18 U.S.C. 208(b)(3) to  
19 Drs. Andrew Winokur, Andrew Leon, and David  
20 Shaffer, and a waiver has been issued in  
21 accordance with 712 of the FD&C Act for  
22 Dr. Leon.

1           Dr. Winokur's waiver involves his  
2           employer's study of a competing product for  
3           an unrelated indication of which he received  
4           no personal remuneration. His institute  
5           received less than \$100,000 in funding.

6           Dr. Leon's waiver covers his  
7           service on data safety monitoring boards for  
8           two competing products for which he receives  
9           between \$10,000 and \$50,000 per year, and  
10          another DSMB for a competing product for  
11          which he receives less than \$10,000 per year.

12          Dr. Shaffer's waiver entails his  
13          employer's studies of competing products.  
14          His institute received less than \$100,000 in  
15          funding for each study. Dr. David Shaffer is  
16          the chief of the Division of Child and  
17          Adolescent Psychiatry at Columbia University  
18          Medical Research Center, and has no direct  
19          involvement in these trials.

20          The waivers allow these individuals  
21          to participate fully in today's  
22          deliberations. FDA's reasons for issuing the



1 noted for the record.

2 FDA encourages all other  
3 participants to advise the Committee of any  
4 financial relationships that they may have  
5 with any firms at issue.

6 Thank you.

7 DR. RUDORFER: I've been asked to  
8 remind everybody at the table, after you finish  
9 speaking, please remember to turn your  
10 microphone off. And we are going to try to have  
11 the two main presentations, by the sponsor and  
12 by FDA, fairly uninterrupted. If there is a  
13 pressing clarifying question, feel free to call  
14 that to my attention. But otherwise, we're  
15 going to have plenty of time for discussion  
16 during the day, so in the interest of time and  
17 efficiency, we'll try to get the presentations  
18 going smoothly.

19 We will now proceed to the FDA  
20 presentation. Before Dr. Laughren's  
21 presentation I'd like to remind public  
22 observers at this meeting that while this

1 meeting is open for public observation,  
2 public attendees may not participate except  
3 at the specific request of the panel.

4 And again, I want to remind the  
5 members of the Committee to please not  
6 discuss the issues at hand among yourselves.

7 It's now my pleasure to introduce  
8 Dr. Tom Laughren, who's the director of the  
9 Division of Psychiatry Products at the FDA.

10 DR. LAUGHREN: Thank you, Matt. And  
11 I'd like to welcome everyone to the meeting this  
12 morning.

13 Today's meeting is going to focus  
14 on a depot formulation of olanzapine, an  
15 antipsychotic, that is intended for  
16 administration every two to four weeks in the  
17 treatment of schizophrenia. It's a pamoate  
18 formulation, and the company will be  
19 referring to this, and we will as well, as  
20 "OP Depot" for olanzapine pamoate depot.

21 Now, we've reviewed this  
22 application from the standpoint of both

1 safety and efficacy, and we've reached some  
2 tentative conclusions about it. However, we  
3 have not made a final risk-benefit judgment  
4 about the product. And our primary concern,  
5 as you know, is this event of excessive  
6 sedation that has been observed. We want to  
7 get your views on this event and its  
8 implications for clinical use of this product  
9 before we reach a final conclusion.

10 Now, the questions that we're going  
11 to ask you to vote on are the usual broad  
12 questions of safety and efficacy. And you've  
13 received our reviews, both the clinical and  
14 the statistical reviews, on the overall  
15 application. You've also received a  
16 background package from the sponsor that  
17 provides a broad overview of the efficacy and  
18 safety of this product. And you're going to  
19 hear from us today, both FDA and from the  
20 sponsor, about these same matters -- again,  
21 the safety and the efficacy more broadly.

22 And so when we make a final

1 decision about this, we're going to be taking  
2 into consideration all of these issues, all  
3 the safety issues and all the efficacy  
4 issues. But this one adverse event is what  
5 we would like the committee's advice on in  
6 particular.

7           Now, from the standpoint of  
8 efficacy, Lilly has conducted two trials:  
9 One a short-term trial and one a maintenance  
10 trial. The short-term trial was conducted in  
11 patients with acutely exacerbated  
12 schizophrenia. This was an eight-week study,  
13 again involving acutely ill patients. It was  
14 a double-blind, randomized trial. There were  
15 three fixed doses of the depot formulation  
16 and a placebo group. No oral antipsychotic  
17 supplementation was provided.

18           The primary endpoint was changed  
19 from baseline to endpoint on the PANSS total  
20 score. And the bottom line was that all  
21 three active drug groups were superior to  
22 placebo, with no clear indication of a dose

1 response. So that was the short-term  
2 trial/acute study.

3 As I mentioned, the other trial was  
4 a maintenance study. This was 24 weeks.  
5 This began with patients who were  
6 stable -- schizophrenic patients who were  
7 stable, on some antipsychotic. They were  
8 switched to oral olanzapine for continued  
9 observation for stability for at least four  
10 weeks. At that point, they were randomized  
11 to one of five treatment groups: There were  
12 four doses of oral olanzapine, three doses  
13 intended to have efficacy, and one dose which  
14 was admittedly a suboptimal dose for  
15 comparative purposes; and the fifth group was  
16 oral olanzapine.

17 Now, there were two goals for the  
18 study. One was to show non-inferiority of  
19 the depot formulation to oral olanzapine, and  
20 the other was to show superiority of  
21 hopefully effective depot doses to the  
22 suboptimal dose. Now, at FDA, we have not

1 yet accepted a non-inferiority approach, and  
2 so our focus was on the superiority part of  
3 this trial.

4 And again, the bottom line, as you  
5 will see later, is that all three of the  
6 higher depot doses were superior to the  
7 suboptimal dose, and again, without any  
8 strong indication of dose response.

9 Now, the efficacy question that  
10 we're asking you to vote on is actually  
11 divided into two questions. This was at Matt  
12 Rudorfer's suggestion.

13 He felt it would be important to  
14 distinguish between acute efficacy and  
15 maintenance efficacy.

16 Now, it's true that if this product  
17 were to be approved, its use would probably  
18 primarily be in maintenance treatment. But  
19 one can imagine situations where a patient  
20 with acutely exacerbated schizophrenia  
21 might -- or a clinician might want to start  
22 that patient on the depot formulation. For

1 example, a patient who has been unable to be  
2 compliant with another antipsychotic, that  
3 patient might be treated with a few doses of  
4 oral olanzapine to establish tolerability and  
5 then immediately switch to the depot. That,  
6 in essence, was the short-term trial.

7           However it would be used, whether  
8 in acute treatment or maintenance treatment,  
9 it would be standard practice to always give  
10 patients oral olanzapine initially to  
11 establish tolerability. This is a standard  
12 practice for all depots, and it would be  
13 standard practice in this case as well.

14           In any case, you're going to hear a  
15 lot more about efficacy today. But I can say  
16 that based on our review of the data, we've  
17 concluded that the sponsor has shown that  
18 olanzapine depot is effective both in acutely  
19 exacerbated schizophrenia and in maintenance,  
20 but we would appreciate your advice on this  
21 as well.

22           Turning to safety, we've reviewed

1 data for over 1,900 patients who have been  
2 exposed to the depot formulation. Our  
3 review, again, has covered the full spectrum  
4 of safety findings, so we're not just  
5 focusing on the safety event. We've looked  
6 at all the safety data. And you have  
7 received, again, our review, as well as the  
8 sponsor's background package, and you will  
9 hear from both of us in much detail today.

10 But I can say again in summary,  
11 that based on our review of safety, we have  
12 found that the safety profile overall for the  
13 depot formulation appears to be quite  
14 comparable to what you see with oral  
15 olanzapine, with the exception of this  
16 excessive sedation event, and of course, with  
17 the exception of injection site reactions and  
18 particular pain.

19 As for efficacy, we've split the  
20 safety questions into two: One focusing on  
21 its use in acutely exacerbated schizophrenia,  
22 and a second one in maintenance treatment.

1 Again, as I've indicated, the focus of  
2 today's meeting is primarily on this event of  
3 excessive sedation. The sponsor has referred  
4 to this as "inadvertent intravascular  
5 injection events." These are instances of  
6 profound sedation occurring shortly after an  
7 injection, generally in the range of one to  
8 three hours after the injection. They are  
9 believed to have resulted from rapid release  
10 of olanzapine into the systemic circulation.  
11 And this view is supported by what limited  
12 plasma level data we have, where these  
13 patients for whom we have plasma level data  
14 have had very excessive levels compared to  
15 what you would expect to see with the depot.  
16 These events occurred in 24 out of 1,915  
17 patients, giving a crude risk of roughly  
18 1 percent of patients.

19 So we'd like you to fully discuss  
20 this event, its public health consequences,  
21 as well as possible strategies for mitigating  
22 the risk if this product were to be approved,

1 and to factor this into your thinking when  
2 you vote on these broader questions of safety  
3 and efficacy.

4 I want to make a few points finally  
5 for you to consider during the proceedings  
6 today. Again, I want to emphasize that these  
7 are not instances of a little bit of  
8 sleepiness, but rather very profound  
9 sedation. Most of these patients had to be  
10 hospitalized. These events did occur mostly  
11 within a short period of time of the  
12 injection. However, it's still not clear to  
13 us that we have fully characterized the risk  
14 interval.

15 These events appear to be entirely  
16 unpredictable. They could happen in any  
17 patient with any injection. It could be the  
18 first injection. It could be the hundredth  
19 injection. It's very difficult to know.

20 Now, the sponsor, as I indicated,  
21 feels that they understand the mechanism.  
22 And in fact, it's implied in the name, IAIV.

1 Again, we're not entirely convinced that that  
2 is the case. If this were simply a matter of  
3 the needle being placed in a vessel, one  
4 would think that retraining of staff would  
5 solve the problem. That has not been the  
6 case. The events have continued to occur  
7 despite retraining of staff.

8 Another concern that I want you to  
9 think about is how the risk of this event  
10 might change as you move from the fairly  
11 controlled setting of clinical trials to a  
12 real-world environment where things are not  
13 as controlled.

14 And finally, I want you to think  
15 about another possibility that occurred to  
16 us. The events that we've seen, as I  
17 indicated, occurred very shortly after  
18 injection. But what would happen, what could  
19 happen to a patient who has an injection, and  
20 several days later, is injured at that site?  
21 Would that put the patient at risk of having  
22 one of these events? We've not seen that.

1 I'm just raising it as one other possibility.

2 Finally, I want to mention that  
3 although intravascular injection is obviously  
4 a concern for any intramuscular formulation,  
5 we have not seen similar events to this for  
6 the other depot antipsychotics that are  
7 available. We've not seen events that are  
8 similar in character to these events.

9 So I'm going to stop there and  
10 introduce Dr. Jing Zhang, who's going to  
11 present FDA's review.

12 DR. ZHANG: Hi. Good morning. I'm  
13 Jing Zhang. I'm a medical reviewer from the  
14 Division of Psychiatry Products at FDA. I will  
15 discuss FDA's clinical review of olanzapine  
16 pamoate depot in the treatment of schizophrenia.

17 Can you hear me?

18 So I will give you a very brief  
19 overview of the clinical program, and a  
20 summary of the efficacy and the general  
21 safety. Then my presentation will focus on  
22 the excessive sedation events, which is

1 today's primary safety concern for this  
2 formulation.

3 I would like to give you some basic  
4 information about olanzapine pamoate depot.  
5 We'll refer to it as OP Depot from now on.  
6 As a monohydrate crystalline salt, OP Depot  
7 is practically insoluble in aqueous medium,  
8 but it is much more soluble in plasma. I  
9 will get to here later.

10 So, OP Depot is administered by  
11 deep gluteal muscular injection for the  
12 indication of schizophrenia. The clinical  
13 data, where it came from, eight clinical  
14 data -- clinical trials, which include two  
15 controlled clinical trials. The efficacy  
16 evaluation was based on these two controlled  
17 trials. The safety evaluation was based on  
18 data from all eight OP Depot clinical trials,  
19 which include the two controlled trials I  
20 just mentioned plus six open-label studies.

21 The acute efficacy evaluation was  
22 based on the data from Study HGJZ, which is

1 an eight-week inpatient and outpatient,  
2 multicenter, double-blind, randomized,  
3 placebo-controlled trial. This trial  
4 contained four treatment arms, and they were  
5 randomized equally. So here you can see here  
6 listed all those treatment arms. They are OP  
7 Depot arm fixed-dose. Here is the injection  
8 frequency.

9 406 patients were enrolled, 404  
10 patients were randomized, including about 100  
11 patients in each treatment arm. The overall  
12 completion rate was 66 percent. Here, you  
13 can see the breakdown by treatment arms.

14 The primary analysis for this study  
15 is mean change from baseline to eight-week  
16 endpoint on PANSS total score. The results  
17 showed all OP Depot treatment groups were  
18 superior to the placebo and now cleared  
19 dose-response relationship.

20 The long-term efficacy evaluation  
21 was based on Study HGKA, which is a 24-week,  
22 multicenter, double-blind, controlled,

1 parallel group study of clinically stable  
2 schizophrenia patients. This study contained  
3 five treatment arms, which are listed here.  
4 The OP Depot dose ranged from 45 milligrams  
5 to 405 milligrams. Here is the injection  
6 frequency. It is noteworthy that 45  
7 milligrams/4-week dose is not efficacious  
8 (inaudible) low-dose control in this study.  
9 The oral olanzapine arm is flexible dose.

10 So 1,065 patients were randomized.  
11 The overall completion rate is about  
12 71 percent. Here is a breakdown by the  
13 treatment arms. So as you can see, the oral  
14 olanzapine arm had the highest completion  
15 rate.

16 The longer term efficacy  
17 evaluation -- oh, that's right. Okay, the  
18 primary analysis is time to exacerbation of  
19 symptoms or relapse. The results showed all  
20 higher OP Depot groups, which they are listed  
21 here, were superior to the low OP Depot dose.

22 Now I will switch gears to the

1 safety evaluation. The safety evaluation was  
2 based on the data from eight clinical trials.  
3 In the placebo-controlled database, the data  
4 came from Study HGJZ; 306 patients were  
5 exposed to OP Depot for up to eight weeks.  
6 In the olanzapine-controlled database, the  
7 data came from Study HGKA, the long-term  
8 study; 599 patients were exposed to OP Depot  
9 for up to 24 weeks. The overall integrated  
10 database includes all patients treated with  
11 OP Depot in the two controlled trials I just  
12 mentioned and the six open-label studies.

13 In terms of patient exposure, by  
14 June 2006, 936 patients were exposed for at  
15 least 24 weeks, 445 patients were exposed for  
16 at least 48 weeks, a total of 1,778 patients  
17 were exposed to OP Depot for at least one  
18 dose, which equals about 1,039 patients a  
19 year exposure.

20 The discontinuation due to adverse  
21 events was lower than 6 percent in all three  
22 databases. The common reasons for

1 discontinuation were worsening of the  
2 underlying psychiatric diagnosis, and other  
3 events which were similar to observed in oral  
4 olanzapine treatment, such as weight gain,  
5 sedation, and increased hepatic enzymes.  
6 Three deaths were reported in OP  
7 Depot-treated patients, and one death was  
8 reported in oral olanzapine-treated patients.  
9 All these deaths came from the open-label  
10 clinical trials, and none of these deaths  
11 were considered as study drug-related.

12 In terms of other serious adverse  
13 events, 14 out of 19 patients who reported at  
14 least one serious adverse event were from OP  
15 Depot-treated patients. The most commonly  
16 reported severe adverse events were  
17 consistent with underlying psychiatric  
18 diagnoses, which is the case in all three  
19 databases.

20 In terms of common adverse events,  
21 in the placebo-controlled database, the  
22 common treatment emergent adverse events,

1 defined as a report for at least 5 percent in  
2 at least one of the OP Depot arms and at  
3 least twice that of placebo, were headache,  
4 sedation, nausea, dry mouth, increased  
5 appetite, nasopharyngitis, and vomiting. In  
6 the olanzapine-controlled database, the  
7 common adverse event profile is similar to  
8 that of oral olanzapine.

9 In terms of injection site-related  
10 adverse events, the overall reporting rate is  
11 about 8.5 percent. The injection site pain  
12 was the most commonly reported injection  
13 site-related adverse event. Four patients  
14 discontinued the study due to injection  
15 site-related adverse events.

16 Now I will briefly discuss the  
17 metabolic syndrome-related safety data. This  
18 table summarizes the percentage of patients  
19 who gained at least 7 percent of their  
20 baseline weight to the end of this eight-week  
21 study. This data is from Study HGJZ. As you  
22 can see, the left column is the treatment

1 arms, the right column is the percentage of  
2 patients who gained at least 7 percent of  
3 their baseline weight.

4 So in the OP Depot treatment  
5 groups, the percentage of patients gained  
6 more than -- at least 7 percent of their  
7 baseline weight is bigger compared to the  
8 placebo group.

9 This is the triglyceride data from  
10 this eight-week study. Here, the left column  
11 is the treatment group; again, the right  
12 column is the percentage of patients who had  
13 triglyceride change from normal to high,  
14 which is defined here at the bottom of the  
15 table. As you can see, the percentage of  
16 patients on the OP Depot treatment is higher  
17 compared with the placebo treatment.

18 The previous two slides I did from  
19 the eight-week study. Now I will present  
20 data from the 24-week study.

21 This table summarizes the mean  
22 change from baseline to endpoint in weight.

1 So you can see the same pattern. More  
2 patients on OP Depot treatment gained a large  
3 amount of weight compared with the low-dose  
4 control. And here, you also can see a dose  
5 relationship. The higher dose OP Depot  
6 treatment is associated with a large amount  
7 of weight gain.

8 This table summarizes the mean  
9 change from baseline in fasting glucose  
10 levels. You can see the same pattern again.  
11 This column is the mean change in fasting  
12 glucose in millimole per liter. Patients on  
13 the study drug had highest fasting glucose  
14 level at the end of the study as compared to  
15 the patients on low-dose placebo.

16 This table summarizes the  
17 percentage of patients who had fasting  
18 triglycerides change from normal to  
19 high -- they have the same  
20 definition -- during the 24-week study. More  
21 patients on the OP Depot treatment had the  
22 shift from normal to high during the study

1 compared with those patients on a low-dose  
2 control.

3 In summary, OP Depot is associated  
4 with weight gain, lipid and glucose  
5 dysregulation, but the profile is similar to  
6 oral olanzapine. In general, the overall  
7 safety profile of OP Depot is similar to that  
8 of oral olanzapine, except as an injection  
9 site-related adverse events and the excessive  
10 sedation events.

11 Now I will focus on the primary  
12 safety issue of this formulation, the  
13 excessive sedation events. The ES events are  
14 characterized by severe sedation and  
15 temporally associated with OP Depot  
16 injection. The clinical signs and symptoms  
17 were consistent with those observed in oral  
18 olanzapine overdose, such as profound  
19 sedation, seizure, dizziness, confusion,  
20 disorientation, slurred speech, altered gait,  
21 and weakness. I will present to you a few  
22 cases first to help you understand how this

1 event presents clinically.

2 And by the way, I also wanted to  
3 mention, the case number here, I kept the  
4 same case number Lilly assigned to this  
5 patient to be consistent.

6 Case No. 1, 31-year-old man had his  
7 second injection of 300 milligrams/4 weeks.  
8 Forty-five minutes after injection, he  
9 experienced severe sedation, moderate  
10 akathisia, dizziness, and feelings of  
11 weakness. After about six hours, the patient  
12 was still sedated, but he was reported to  
13 feel better. He recovered approximately 48  
14 hours, and continued in the study.

15 This is the olanzapine plasma  
16 concentration data collected from this  
17 patient. So you can see the small peaks.  
18 This relative lower olanzapine plasma  
19 concentrations were corresponding to the  
20 injection without ES events. You can see a  
21 big spike right after the second injection.  
22 This high olanzapine plasma level was

1 corresponding to the ES event the patient  
2 experienced.

3 Case No. 2, a 32-year-old man  
4 received his first injection of 405  
5 milligram/4 weeks. Ten minutes after the  
6 injection, he experienced dizziness. His  
7 speech progressively altered and somnolence  
8 appeared. After about one hour and a half,  
9 there was no response to verbal stimuli.  
10 After about two hours, he had profound  
11 sedation, bilateral miosis with no photomotor  
12 reflex, automatic movements, Babinski sign on  
13 left side, and no response to pain. He was  
14 hospitalized. A brain CT was negative. He  
15 was able to speak with difficulty the next  
16 morning. He recovered in approximately 60  
17 hours. He was discontinued from the study.

18 Case No. 3, a 63-year-old man  
19 received a second injection of 405  
20 milligram/4-weeks. About 15 to 20 minutes  
21 post-injection, he appeared pale, with  
22 unsteady gait and confusion. Thirty minutes

1 post-injection, he became disoriented, with  
2 seizures in hands and legs. He walked into a  
3 wall, suffered from superficial injuries. He  
4 was hospitalized with the diagnosis of  
5 tonic-clonic convulsions and partial  
6 consciousness. He was intubated. The ECG,  
7 brain CT, and lumbar puncture were normal.  
8 He recovered in about 60 hours and he was  
9 discontinued from the study.

10 Case No. 6, a 51-year-old man had  
11 his 24th injection of 300 milligrams/2 weeks.  
12 Ten minutes post-injection, he left the study  
13 site without any complaint. Fifteen minutes  
14 post-injection, he was found unconscious at a  
15 bus stop. He was hospitalized and remained  
16 in a coma for 12 hours. Vital signs and ECG  
17 were reported to be normal. He was recovered  
18 in approximately 24 hours. He continued in  
19 the study.

20 Case No. 17, a 59-year-old woman  
21 received her 27th injection of 300  
22 milligrams/2 weeks. Two hour and 45 minutes

1 post-injection, she experienced significant  
2 somnolence. Twenty minutes later, she  
3 experienced difficulty with speech, motor  
4 restlessness, and anxiety. Six hours 15  
5 minutes post-injection, she progressed to  
6 profound sedation.

7 She was unarousable for eight  
8 hours, but she was responsive to pain. Okay,  
9 the vital signs were reported as normal. She  
10 was hospitalized. She recovered in about 12  
11 hours and she continued in the study.

12 This is olanzapine plasma  
13 concentrations data collected from a patient  
14 who had two separate events. Those low  
15 olanzapine plasma levels were corresponding  
16 to the injection without ES events. These  
17 two sides of high olanzapine plasma levels  
18 were temporally corresponding to the two  
19 separate events, even though the patient  
20 received the same doses, but as you can see,  
21 the olanzapine plasma level was very  
22 different in those two separate event.

1                   Summary of ES events. As of  
2   30 September 2007, 25 ES events have been  
3   reported in 24 patients; 34,825 injections  
4   have been given to 2,054 patients, which  
5   transfers to an ES event in about 1.2 percent  
6   of patients and .07 percent of injections.  
7   The clinical symptoms of this event were  
8   consistent with those reported in the cases  
9   of oral olanzapine overdose. Here, I studied  
10  two additional cases, but I just heard Lilly  
11  just received one report, so one additional  
12  case. That means three additional cases have  
13  been reported after September 30, 2007.  
14  Because these three cases were reported  
15  recently, they are not included in my review.

16                   Summary of severity of ES events.  
17  The severity of sedation has ranged from  
18  drowsiness to deep coma. Twenty out of 24  
19  patients were hospitalized. Two cases were  
20  in coma, two patients were intubated.  
21  Delirium symptoms were reported in two cases,  
22  and tonic-clonic convulsions were reported in

1 two cases. High blood pressure was observed  
2 in one case.

3 In terms of time from injection to  
4 onset of initial symptoms, the majority of  
5 cases occurred within one hour of injection,  
6 which is about 84 percent. But it has ranged  
7 from immediately post-injection to up to  
8 three hours after injection.

9 With regard to number of  
10 injections, most events occurred after  
11 patient had received several months of  
12 injection. It has ranged from the 1st  
13 injection to the 40th injection. One patient  
14 experienced two events.

15 All patients who experienced ES  
16 events were reported to have recovered within  
17 about 3 to 72 hours. The majority of these  
18 patients remained in the study.

19 The causality of these events  
20 remains unknown, but the evidence suggests an  
21 excessive amount of olanzapine into the  
22 systemic circulation more rapidly than

1 intended. The large bore needle, which is 19  
2 gauge used for regular injections, may play  
3 some role in causing local tissue or vascular  
4 injury. The opacity and thickness of the  
5 product may make it difficult to detect  
6 aspirated blood in the needle.

7 To address the accidental  
8 intravascular injection, Lilly retrained  
9 their study personnel in proper injection  
10 technique in July 2006. However, the  
11 incidence and pattern of the events remained  
12 unchanged after the training. Ten additional  
13 cases were reported following the training.

14 To understand this mechanism, Lilly  
15 conducted some solubility investigations. In  
16 the in-vitro solubility experiment they found  
17 about 35 to 68 percent of OP monohydrate  
18 dissolved in human blood within roughly a  
19 half-hour, which is much higher than  
20 anticipated for an insoluble OP monohydrate  
21 salt. In the equilibrium solubility  
22 experiment, the solubility of OP monohydrate

1 in plasma is about 167 times higher than that  
2 in an aqueous medium, which is similar to the  
3 actual cellular fluid in the muscle tissue.

4 In conclusion, the incidence of ES  
5 events is relatively common, occurring in  
6 1.2 percent of patients and .07 percent of  
7 injections. The pattern of this event is  
8 unpredictable, and remained unchanged by  
9 systematic retraining of their nursing staff.  
10 The sedation symptoms tend to be severe,  
11 which included 2 cases in coma, 2 patients  
12 were intubated, and 20 out of 24 patients  
13 were hospitalized.

14 Thanks for your attention. This  
15 concludes my presentation. So now I will  
16 hand over the podium to Dr. Andre Jackson,  
17 who came from our Division of Clinical  
18 Pharmacology.

19 DR. JACKSON: Good morning, everyone,  
20 and welcome. My presentation will be on  
21 exposure-safety assessment. Essentially what I  
22 will be doing is giving you some feel for what

1 the relationships that we've been able to see  
2 from our review related to the types of doses  
3 that seem to be more prevalent in these  
4 occurrences, and also what relationship this has  
5 to blood level.

6           Okay, the key review questions for  
7 us at the agency were: Are the symptoms of  
8 sedation, dizziness, confusion, and coma,  
9 which we're calling "excessive sedation," are  
10 they in fact related to olanzapine  
11 concentrations? And in a very global sense,  
12 we can say yes, there is some relationship.  
13 We're not saying it's the entire cause, but  
14 there is some relationship. More patients  
15 receiving the 405-milligram every 4 weeks  
16 dose seem to exhibit the excessive sedation,  
17 and patients with higher olanzapine  
18 concentrations -- and we're saying 150, but  
19 we're not saying that once you reach 150 it's  
20 going to happen because I'll show you the  
21 graphs that don't totally support that -- but  
22 somewhere in that region seem to exhibit a

1 higher risk for this adverse effect.

2 More patients receiving the  
3 405-milligram every 4 weeks dose exhibit  
4 excessive sedation. Out of 2,054 subjects  
5 that were dosed with the OP Depot olanzapine  
6 as of September 30, 2007, there were 25  
7 documented events of this excessive sedation.  
8 Of these 25 events, 32 percent of the  
9 excessive sedation events occurred in  
10 subjects dosed with the 405-milligram every  
11 4 week dose, 24 percent of the excessive  
12 sedation events occurred in subjects dosed  
13 with 300 to 390-milligrams every 4 weeks.

14 Second point: patients with higher  
15 olanzapine concentrations, greater than 150  
16 nanograms per milliliter, exhibit higher risk  
17 of this AE. Now, the slide may look a little  
18 busy, but I'll walk you through it. We have  
19 four categories here. We have the OP Depot  
20 given the ranges from the studies that you've  
21 already been introduced to; we then have our  
22 oral, which are the 10, 15, and 20 milligrams

1 per day; and then you have the OP Depot,  
2 which is the blue, from excessive sedation  
3 patients not during an event; and then in red  
4 you have the OP Depot data from excessive  
5 sedation patients at the time of the event.  
6 Now let's go through this.

7           If you look first at the oral, what  
8 you see is that by and large, the oral, which  
9 is the white, do not go above roughly 150  
10 nanograms per mil. If you then look at the  
11 OP Depot, 45 every 4 weeks to 405 milligrams  
12 every 2 weeks, you notice that the levels are  
13 quite widely distributed. But most  
14 noteworthy, you'll notice that there is a  
15 level up around 2,000 and there's a level at  
16 around 150, if you look at time and months  
17 around nine months. So these are just normal  
18 subjects that are getting the OP Depot, but  
19 are not showing an excessive sedation.

20           Okay, let's then look at the blue.  
21 We see the OP Depot data from excessive  
22 sedation patients not during the event, and

1 you notice those levels are very similar to  
2 what you see in oral. And when you then look  
3 at the final group, which is in the red, you  
4 see that there's a proclivity of those  
5 subjects to have much higher levels. But  
6 also keep in mind that during the event, some  
7 of them also have lower levels. So again,  
8 this speaks to the question of -- there's not  
9 really a causative factor here.

10           And we want to also point out that  
11 it may be something related to getting the  
12 higher dose. It could be related to the fact  
13 that the volume associated with the dose. It  
14 could be that it was the most prevalent dose  
15 that was given during this particular study.  
16 And also, it's the largest amount of drug  
17 that was administered at one time. So you  
18 can't really pinpoint it. It's something  
19 that's occurring when you give the larger  
20 dose.

21           So the key review question, as I  
22 initially posed, was are the symptoms of

1 sedation, dizziness, confusion, and coma,  
2 which we're calling "excessive sedation,"  
3 related to olanzapine concentrations? And  
4 again, our response would be yes. Why?  
5 Because more patients receiving the  
6 405-milligram every 4 weeks dose exhibit  
7 excessive sedation. And patients with higher  
8 olanzapine concentrations of greater than 150  
9 exhibit a higher likelihood or risk of this  
10 particular adverse event.

11 Thank you for your time.

12 DR. RUDORFER: We have time for  
13 clarifying questions from the Committee.

14 Dr. Mann?

15 DR. MANN: It wasn't entirely clear to  
16 me in the last presentation whether you were  
17 saying that the frequency of the excessive  
18 sedation was different across the doses, or  
19 whether the 405-milligram dose was just given  
20 more often and the rate was about the same.

21 DR. JACKSON: Well, I think it's the  
22 latter. It seems to be related to the events

1 surrounding the 405-milligram dose. That would  
2 be our conclusion.

3 DR. TEMPLE: That's not what he asked.  
4 He asked about the rate. Was the rate higher in  
5 the people who got the higher dose, the  
6 likelihood of having this event?

7 DR. JACKSON: Yes, I think it would be  
8 higher. Yes, I think so.

9 DR. RUDORFER: What was that?

10 DR. JACKSON: Yes, the likelihood  
11 would be higher for the people receiving the  
12 higher dose, yes.

13 DR. RUDORFER: Dr. Potter?

14 DR. POTTER: I have a question for the  
15 previous presenter. To understand the design of  
16 the maintenance phase study, the statement was  
17 made that the oral dosing was flexible. Does  
18 that mean, for instance, that if an individual  
19 was showing some clinical signs, there was a way  
20 in the protocol that the investigator could  
21 increase the dose of the oral in that study? I  
22 mean, you made the statement it was a flexible

1 dose, and I had not understood that.

2 DR. ZHANG: Yes, there are 3 doses:  
3 10, 15, and 20. Generally they pick these three  
4 different doses, make sure the patient have good  
5 control for their symptoms, it's effective for  
6 those patients.

7 DR. POTTER: No, no, my question was,  
8 during the course of the study, during the blind  
9 phase after the lead-in, was it still a flexible  
10 dose? In other words, could the investigator  
11 adjust the dose up or down based on clinical  
12 signs in some way?

13 DR. LAUGHREN: That was my  
14 understanding. I think the flexible dose was  
15 the run-in phase and then they were assigned  
16 to -- but Lilly can answer, but I believe that's  
17 the way it was.

18 DR. RUDORFER: Dr. Follmann?

19 DR. FOLLMANN: I had a question for  
20 the last speaker. It refers to that slide you  
21 referred to as the "busy slide," with all the  
22 dots on it and so forth. One thing that -- I

1 hadn't seen that before, and one thing that  
2 struck me was how most of the events seem to  
3 cluster later in time. I was wondering -- so if  
4 you look after nine months, the lion's share of  
5 the excessive sedation events have occurred, and  
6 yet it seems like most of the data is to the  
7 left of nine. You know, I guess that just is  
8 the way the studies would happen, where you'd  
9 have more injections early, then they would  
10 dissipate as the studies closed.

11                   Anyway, have you looked at that?  
12 Did you, like, do a statistical test for that  
13 or do you think it's real?

14                   DR. JACKSON: No, I didn't do any  
15 statistical analysis. I think Lilly may have  
16 done some. I think the reason for the  
17 clustering there is that -- realize there were  
18 only seven subjects that they actually collected  
19 blood samples for. And I think in some cases,  
20 this was done sort of later on.

21                   I have some backup slides that  
22 could tell you exactly when it was done, but

1 I think it may be an artifact of when the  
2 samples were actually collected.

3 DR. FOLLMANN: Thank you.

4 DR. RUDORFER: Dr. Leon?

5 DR. LEON: Could you clarify that? So  
6 only seven of those red dots were from what,  
7 from the date of the event?

8 DR. JACKSON: The data that I'm  
9 showing there for the subjects that had  
10 excessive sedation were only 7 subjects out of  
11 the 25 events that occurred. Most of the  
12 subjects did not have plasma samples taken.

13 DR. LEON: From that plot, can we tell  
14 which seven?

15 DR. JACKSON: No, you -- well, no, you  
16 couldn't do it from there, no. I have a backup  
17 slide that lists that, if you'd like to see  
18 which subjects they are.

19 DR. LEON: Sure.

20 DR. JACKSON: Okay. These are the  
21 actual subjects that had an event with the  
22 plasma levels actually measured, so there were

1 seven. And actually for Event 5 and Event 8,  
2 they occurred in the same subject about 200  
3 study days apart. But these were the only  
4 subjects that actually had blood levels  
5 measured, and the other two are here. So that  
6 what you're seeing on that slide is really a  
7 composite of these levels here. And as you see,  
8 some of these were collected late in time.

9 DR. LEON: Is there some target plasma  
10 level you're shooting here for?

11 DR. JACKSON: I don't think so, no,  
12 not to my knowledge.

13 DR. TEMPLE: But those levels are like  
14 times or seven or eight times higher than the  
15 typical level after injection.

16 DR. JACKSON: Right.

17 DR. TEMPLE: Which is shown in  
18 Dr. Zhang's review for some of these people.

19 DR. JACKSON: Well, if you go back to  
20 the -- when you look at what you see for normal  
21 oral as well as for some of the OP Depot, you  
22 can see that those levels are much, much higher.

1 DR. RUDORFER: Dr. Mann?

2 DR. MANN: Yes. I note that slide, by  
3 the way, is not very helpful in the sense that  
4 you've got an irregular Y axis there, so you've  
5 truncated the highest range, which is actually  
6 the one that may be of most interest. But I was  
7 wondering whether you could actually give us the  
8 actual rates of this event per injection dose  
9 rather than just give us generalities.

10 DR. JACKSON: I don't have that  
11 information. Lilly will have to present that  
12 information for you.

13 DR. MANN: And was the rate  
14 statistically different between the doses?

15 DR. JACKSON: Again, I'll have to  
16 defer to Lilly to answer that question.

17 DR. RUDORFER: Dr. Leon?

18 DR. LEON: This is a 24-week study,  
19 but the X axis, does that say months? Is that  
20 meant to be weeks?

21 DR. JACKSON: No, it should be months.  
22 So the open-label studies went out.

1 DR. LEON: Oh, the open-label -- oh,  
2 okay.

3 DR. RUDORFER: And speaking of which,  
4 I have a question about the open-label studies.  
5 I notice that in contrast to the two controlled  
6 studies we reviewed, the open-label studies  
7 included some patients who had schizoaffective  
8 disorder and not just schizophrenia. And I  
9 wonder if we know the numbers and whether there  
10 was any diagnostic difference in the findings in  
11 those six studies.

12 DR. LAUGHREN: Matt, are you asking if  
13 there's a difference in the distribution of  
14 events across diagnostic groupings?

15 DR. RUDORFER: Yes.

16 DR. ZHANG: Is the question it's only  
17 24 weeks or you were asking for --

18 DR. RUDORFER: It was just the --

19 DR. ZHANG: So is your question is for  
20 a 24-week controlled study, it's also for the  
21 open-label study.

22 DR. RUDORFER: My understanding was

1 that the 24-week-only had patients with DSM-IV  
2 schizophrenia.

3 DR. ZHANG: Yes, that's true.

4 DR. RUDORFER: And it was just the  
5 open-label were included schizoaffective  
6 patients.

7 DR. ZHANG: No, no. For the two  
8 controlled studies, they only included patients  
9 with diagnosis of schizophrenia. But for the  
10 open-label studies, it does include patients  
11 with diagnosis of schizoaffective disorder.

12 DR. RUDORFER: Right. And I'm  
13 wondering if the findings were analyzed  
14 separately.

15 DR. ZHANG: No, some are still  
16 ongoing, so -- and also, it's not our review  
17 focus. We are more focused on the controlled  
18 trials. We only look at those open-label  
19 studies for safety purposes.

20 DR. RUDORFER: Right.

21 DR. LAUGHREN: I don't think we have  
22 the answer, but maybe Lilly could tell us what

1 the diagnostic distribution was for the 24  
2 events.

3 DR. RUDORFER: Right. I mean, it's  
4 just the -- as I've said on other occasions, I  
5 have a particular concern about that because  
6 this product is not labeled for the treatment of  
7 schizoaffective disorder. And so I'm concerned  
8 that some of the data we're reviewing included  
9 some of those patients, and we don't have the  
10 specifics about them. I realize that the  
11 open-label were for safety purposes. On the  
12 other hand, as was in some of the documents we  
13 saw from the sponsor, those were included under  
14 their discussion of efficacy. So I just wanted  
15 to call that to the agency's attention.

16 DR. LAUGHREN: But we should be able  
17 to easily get an answer to that.

18 DR. RUDORFER: Dr. Temple?

19 DR. TEMPLE: With reference to some  
20 previous discussion, in Dr. Zhang's review on  
21 page 42, there's a nice figure that shows blood  
22 levels after seven injections reaching a peak of

1 about 40, 45 in most cases, and going to about  
2 200 in the one instance of severe sedation,  
3 which gives some of the flavor for this. It  
4 always rises after the injection course, but  
5 then it drifts off, and only once was it up  
6 through the roof. I guess we don't have that  
7 data on all of them.

8 DR. ZHANG: Yes, we do have this slide  
9 as a backup slide if you want to show that.

10 DR. TEMPLE: I don't know if that  
11 would -- but it just sort of gives the flavor of  
12 what's happening. It's an intermittent thing.  
13 And it would be interesting to know what the  
14 rate per injection was, which Dr. Mann keeps  
15 trying to get. Right. I don't know. Lilly may  
16 have that, too.

17 Can I ask Dr. Zhang one other  
18 thing? The data that you showed seems to  
19 show that the higher BID dose of 300 confers  
20 no advantage on effectiveness, but gives you  
21 considerably more intolerance. Does that  
22 lead to a conclusion that it doesn't make

1 sense to use that dose? You didn't  
2 specifically say that, so I wondered.

3 DR. ZHANG: Yes, a higher dose does  
4 have a better response, but it's not  
5 statistically significant, but still better.  
6 The higher dose is still better, but it's not  
7 reached statistical significance. But the side  
8 effect profile was slightly worse.

9 DR. LAUGHREN: We haven't obviously  
10 gotten around to labeling on this product, but  
11 clearly that would be an issue in recommending  
12 dose, the finding, as I pointed out in my  
13 comments, that there appears to be no dose  
14 response either in the acute study or in the  
15 maintenance study for efficacy, whereas there is  
16 clearly dose response on a variety of safety  
17 outcomes.

18 DR. RUDORFER: Dr. Potter?

19 DR. POTTER: But as a corollary to  
20 Dr. Temple's question, I would wonder if you  
21 actually -- instead of the categorical as you  
22 did with the triglycerides, but was the weight

1 where, you actually have a measured variable,  
2 and so not in the fraction of people who show  
3 X-percent, but if you simply look at the change  
4 in triglycerides or the change in weight as a  
5 function of response, would you observe a  
6 meaningful positive correlation? You might want  
7 to look at that as relevant to this discussion.

8 DR. RUDORFER: Are there other  
9 questions from the Committee?

10 DR. CAPLAN: Yes, I have one more  
11 question.

12 DR. RUDORFER: Please.

13 DR. CAPLAN: What was the rate of the  
14 sedation events in patients who were on the  
15 150-milligram dose?

16 DR. ZHANG: So do you want to know the  
17 dose distribution in those ES events? So how  
18 many people on 150, how many people on a higher  
19 dose, is that the question? Yes, I think we  
20 have a backup slide.

21 I guess we don't have it, the  
22 injection numbers. Yes, maybe Lilly can

1 answer the questions.

2 DR. RUDORFER: Is there someone from  
3 the sponsor who would like to address that?

4 DR. CORYA: Hi. I'm Sara Corya. I'm  
5 the medical director for Zyprexa and for OP  
6 Depot at Lilly. We did not have any of the  
7 excessive sedation events on the 150-milligram  
8 dose. We did have several events in the 200  
9 range in the open-label study where we allowed  
10 different dosing.

11 DR. RUDORFER: Thank you. Dr. Leon?

12 DR. LEON: Just back to Dr. Mann's  
13 question as a point of clarification. The  
14 randomization, remember, was twice as many were  
15 randomized to that highest dose. And I don't  
16 think we even saw twice as many events in that  
17 higher dose. So it was 2-to-1-to-1-to-1, the  
18 "2" being the 400 and the oral.

19 DR. LAUGHREN: But most of the events  
20 occurred in the open-label rather than the  
21 controlled phase. And I guess the question that  
22 I have for Lilly, because I don't know the

1 answer, in the open-label extensions, were  
2 patients who started that open-label always  
3 maintained on the same dose or was there  
4 switching around from dose to dose? And do you  
5 have an answer to the question of what's the  
6 rate per dose?

7 DR. TEMPLE: Yes. Sedation events  
8 divided by the number of doses of a given size.  
9 That's what Dr. Mann's been trying to get at for  
10 a long time. We don't seem to be able to quite  
11 tell.

12 DR. CORYA: On the questions that you  
13 asked earlier, the actual injection rate, so  
14 rate per injection is .07 percent. We're  
15 actually gathering the information and we'll  
16 have that for you right after the break for the  
17 exact number, and we have a slide that shows the  
18 exact number of events that occurred at exactly  
19 what dose, so we can share that with you. And  
20 we have a lot more information in our  
21 presentation about these questions that you're  
22 asking.

1 DR. RUDORFER: Thank you. Okay. I  
2 think we can go ahead and let the record reflect  
3 we're ahead of schedule.

4 Suppose we take a 15-minute break,  
5 and then we'll resume with the presentation  
6 by the sponsor. So we'll resume at, say,  
7 9:35.

8 (Recess)

9 DR. RUDORFER: Welcome back. As we  
10 continue our morning program, we'll now hear  
11 from the sponsor. Again, there'll be several  
12 speakers, so unless there is something very  
13 pressing to clarify en route, let's save our  
14 discussion until the end, because I know there's  
15 a lot of data to get out on the table that we  
16 can then talk about.

17 So I will now turn it over to the  
18 Eli Lilly Company.

19 DR. BROPHY: Thank you very much.  
20 Members of the Advisory Committee, FDA  
21 representatives, ladies and gentlemen, today,  
22 we're here to discuss the application for

1     olanzapine pamoate depot, or "OP Depot," as  
2     it'll be referred to by us during the  
3     presentation, for the treatment of schizophrenia  
4     in adults. OP Depot is the long-acting  
5     injectable formulation of olanzapine.

6             My name is Greg Brophy. I'm the  
7     director of U.S. Regulatory Affairs at Lilly.  
8     I just wanted to provide a brief overview of  
9     how we will be spending our time during the  
10    formal presentation this morning.

11            After my introductory remarks,  
12    Dr. John Kane will provide an overview of the  
13    disease state of schizophrenia as well as the  
14    need for additional depot antipsychotics.  
15    He'll be followed by Dr. David McDonnell of  
16    Lilly who will review OP Depot's development,  
17    including pharmacokinetics and dosing, as  
18    well as summarizing the efficacy as  
19    demonstrated in multiple Phase 3 clinical  
20    trials.

21            Dr. Sara Corya, also of Lilly, will  
22    review the safety of OP Depot, including

1 general safety topics as they compare to oral  
2 formulation of olanzapine, as well as the new  
3 risk that was identified with OP Depot termed  
4 "excessive sedation events."

5 And as Dr. Laughren previously  
6 referred in some of the Lilly briefing  
7 material, this was also referred to as IAIV  
8 or inadvertent intravascular injection, but  
9 we will also be referring to it as excessive  
10 sedation during the presentation.

11 Dr. John Lauriello will then  
12 provide overall conclusions. And finally, at  
13 the request of FDA, we will also be providing  
14 a video demonstration of the reconstitution  
15 of OP Depot.

16 We have three external consultants  
17 with us today, including our speakers,  
18 Drs. Kane and Lauriello. Dr. John Kane is  
19 the chairman of the Department of Psychiatry  
20 at Zucker Hillside in New York. Dr. John  
21 Lauriello is professor and vice chair of the  
22 Department of Psychiatry at the University of

1 New Mexico, and also the executive medical  
2 director of the University of New Mexico's  
3 Psychiatry Center. He was also one of the OP  
4 Depot clinical trial investigators. And  
5 finally, Tracy Schmelling, who's a nurse from  
6 Synergy Clinical Research Center in San  
7 Diego, who also was an OP Depot clinical  
8 trial nurse.

9           From an historical perspective,  
10 oral olanzapine has been extensively  
11 researched. The oral formulation was first  
12 approved by the FDA in 1996. And since that  
13 time, over 24 million patients worldwide have  
14 been treated with olanzapine. Its safety and  
15 efficacy have been demonstrated in numerous  
16 Lilly-sponsored trials as well as numerous  
17 externally sponsored trials, including the  
18 landmark NIMH study termed "CATIE." The  
19 clinical development of OP Depot was  
20 therefore based on the overall safety and  
21 efficacy profile of olanzapine.

22           Our presentation today will focus

1 on three objectives. The first is to  
2 describe the efficacy and safety data for OP  
3 Depot as it relates to oral olanzapine.  
4 Secondly, we'll discuss these additional  
5 risks, that is excessive sedation, and what  
6 has been done to better understand this risk  
7 and how it can be appropriately managed.  
8 Thirdly, we'll discuss the benefit-to-risk  
9 profile of OP Depot, and demonstrate that for  
10 a substantial population of schizophrenia  
11 patients, the benefit-to-risk profile is  
12 positive.

13 With that, let me now turn it over  
14 to Dr. John Kane, who'll provide an overview  
15 of schizophrenia and the need for additional  
16 depot antipsychotics.

17 Dr. Kane.

18 DR. KANE: Thanks very much. It's a  
19 pleasure to be here. I just wanted to share  
20 with you for a few minutes my perspective on why  
21 it's so important that we have depot  
22 antipsychotic drugs available, and why it would

1 be so important to have another alternative to  
2 the ones that are currently available.

3 I've been doing research in the  
4 treatment of schizophrenia for the past 30  
5 years, and have conducted a number of studies  
6 with long-acting injectable antipsychotics  
7 going back to fluphenazine enanthate and  
8 fluphenazine decanoate in the mid-1970s.  
9 Many of our studies were actually funded by  
10 NIMH.

11 And the reason that we often chose  
12 to use depot antipsychotics in these studies  
13 was that in a situation where we were trying  
14 to identify minimum effective dose  
15 requirements for relapse prevention in  
16 schizophrenia, it was very important that we  
17 knew our patients were getting exactly the  
18 doses that we intended. Because if someone  
19 was on a very low dose and they missed a few  
20 doses, that could easily confound any  
21 attribution of cause and effect.

22 In another NIMH-funded study, we

1 were interested in looking at the effects of  
2 family therapy on relapse prevention in  
3 schizophrenia. But we were concerned that  
4 potentially the effects of family therapy  
5 might be mediated by increases in adherence,  
6 so we decided that the only way we could  
7 truly study the additive effects of family  
8 therapy was to use long-acting injectable  
9 medications. So it's the idea of having a  
10 certainty that the patients are getting the  
11 medication intended in the dose prescribed.  
12 I've always found it ironic that in routine  
13 clinical practice, we don't seem to be as  
14 concerned about having that degree of  
15 certainty.

16 Now, clearly schizophrenia is a  
17 challenging illness. It affects about  
18 1 percent of the population. It tends to  
19 begin in late adolescence or early adulthood.  
20 It's often described as a chronic relapsing  
21 illness, which I think is unfortunate,  
22 because that almost assumes that patients

1 will relapse. I think we could do much  
2 better in preventing relapse. I think it's  
3 one of the major public health problems in  
4 the treatment of schizophrenia. The  
5 consequences of relapses are enormous, and  
6 we'll come back to that in a moment.

7           This disease affects the  
8 way -- judgment, insight. It can cause  
9 delusions, hallucinations, loss of pleasure  
10 capacity, loss of motivation, and cognitive  
11 dysfunction. And many of these things also  
12 can have an impact on adherence.

13           It's a disease with considerable  
14 morbidity and mortality. The age-adjusted  
15 mortality rates in schizophrenia are  
16 significantly higher than in the general  
17 population. Current estimates are that  
18 people with this illness have an expected  
19 lifespan of 20 years shorter than the general  
20 population. The suicide rate, successful  
21 suicide rate, is between 5 and 10 percent.  
22 So enormous costs to society, health care

1 resources, tremendous individual suffering,  
2 and family burden.

3           The reason I said that I think  
4 relapse is the major public health problem is  
5 that this is what often fuels the progression  
6 of the illness, that each time someone  
7 relapses, the recovery can be more difficult.  
8 There are admissions to the hospital. The  
9 illness can become more resistant. There's  
10 the risk of self-harm, harm to others,  
11 homelessness, and so forth. It gets harder  
12 and harder to get back to where you were  
13 before each time you relapse. And let me  
14 just give you an example.

15           If we think about a 20-year-old  
16 university student who has a first episode of  
17 schizophrenia, is admitted to hospital, does  
18 well, goes back to school, what happens if  
19 that person has another psychotic episode?  
20 What are the chances that they'll be able to  
21 go back to school? Or if it's their first  
22 job and they're doing well on the job until

1 they get sick, the boss is understanding. He  
2 or she takes them back to work, but then they  
3 get sick again. What are the chances of  
4 getting that job back? Or friends. You're  
5 20 years old, you have some close friends,  
6 intimate relationships. They see you  
7 becoming psychotic. They stick by you. It  
8 happens again, happens again.

9           They begin to perhaps distance  
10 themselves. And my point is that with each  
11 relapse, we begin to see some of life's  
12 opportunities eroding. And so that's why I  
13 feel so strongly that we have to do  
14 everything we can to prevent each and every  
15 relapse.

16           And nonadherence is really the big  
17 challenge. This is a big challenge in all of  
18 medicine, but it's a particular challenge in  
19 schizophrenia because of the cognitive  
20 dysfunction, the frequent lack of insight,  
21 poor judgment, the stigma associated with the  
22 illness, et cetera, et cetera. So if we look

1 at the data, over 40 percent of patients with  
2 schizophrenia have significant problems with  
3 adherence. Many will cycle in and out of  
4 adherence. At my own hospital, we've  
5 surveyed -- it's a 230-bed hospital, we've  
6 surveyed the reasons for readmission to the  
7 hospital. Half the time, it's nonadherence,  
8 poor or partial adherence.

9           And it's not typically a conscious  
10 decision. Most of these patients are not  
11 saying I refuse to take my medicine. Most of  
12 the time it's just they're unable to take it  
13 on a consistent and regular basis, and unable  
14 to take full advantage of the beneficial  
15 effects of the drug. And again, that can be  
16 because of cognitive dysfunction and a  
17 variety of other things.

18           Another challenge is that  
19 clinicians often overestimate the degree of  
20 adherence in their own patients. It's a  
21 little bit of cognitive dissonance. We're  
22 hesitant to conclude that our patients are

1 not following our recommendations. Patients  
2 also overestimate the degree to which they're  
3 adhering. When we do studies asking patients  
4 about adherence and then do pill counts or  
5 microelectronic monitoring systems, we see a  
6 difference between the patient's perception  
7 and what we can document.

8 Another concern I have is that  
9 often physicians may think that, well, it  
10 takes a great deal of nonadherence to lead to  
11 a relapse. And the reality is if you look  
12 at -- this is a large data set from  
13 California Medicaid, over 4,000 patients,  
14 looking at gaps in prescription refill in  
15 relation to the risk of rehospitalization.  
16 And what we see is that gaps as short as 1 to  
17 10 days are associated with a significant  
18 increase in the risk of hospitalization. And  
19 we see that risk increasing as the patient  
20 experiences more and more days in not having  
21 medication to take.

22 So this is a very, very important

1 phenomenon, and I don't think we've done as  
2 good a job as we could in terms of really  
3 addressing this.

4 Another example in terms of  
5 potential morbidity and mortality, these are  
6 data from the Netherlands, over 600 patients,  
7 again prescription refill data. Among those  
8 patients who had more than a 30-day  
9 interruption in medication, the risk of  
10 suicide attempts increased more than  
11 threefold.

12 So the potential benefits of depot  
13 antipsychotics: preventing or delaying  
14 relapse, early identification of  
15 nonadherence. And this is something I want  
16 to emphasize especially, because as we  
17 mentioned earlier, physicians and patients  
18 often overestimate the degree of adherence.  
19 And we as clinicians may not know that our  
20 patient is missing medication until we get a  
21 call from the family or the emergency room.  
22 If someone is receiving long-acting

1 injectable medication and they miss an  
2 injection, we know immediately that they're  
3 not nonadherent. We can do a family visit.  
4 We can do whatever's necessary to re-engage  
5 that person in treatment. And in fact, we  
6 have a little time to do that because there's  
7 still medication in the patient's system.

8 Another challenge, particularly for  
9 those people working in acute care hospitals,  
10 is often when someone is readmitted to the  
11 hospital, we're not sure whether the relapse  
12 was due to nonadherence or perhaps the  
13 nonadherence occurred after the person  
14 started to become psychotic. When someone is  
15 on a depot drug, we know that they were  
16 getting the medication, and we can make an  
17 assumption that they broke through the  
18 medication due to environmental stress or  
19 substance abuse or what have you. We can  
20 deal with that. If not, we're really not  
21 sure what exactly happened.

22 Controlled administration, improved

1 global functioning, and I want to emphasize  
2 also improved interaction with the family.  
3 One of the most difficult situations that we  
4 as clinicians have to deal with is when we  
5 get a call from a family member saying my  
6 loved one has schizophrenia. They've had an  
7 exacerbation. They're experiencing psychotic  
8 symptoms and they don't want to go back to  
9 the hospital. I can't get them to go back to  
10 the doctor. What should I do?

11           And the only thing we can say at  
12 that point is, well, you have to call the  
13 police and they'll have to take the person to  
14 the hospital. That's a horrible situation  
15 for families to be in. They don't soon  
16 forget that. And as a result, when that  
17 patient is treated and returns home, there's  
18 going to be a constant degree of tension  
19 between the patient and the family. Are you  
20 taking your medicine? Are you not taking  
21 your medicine? Leave me alone, I'm a  
22 grownup. If someone's on long-acting

1 injectable drugs, it eliminates that kind of  
2 family tension and family burden, and I can't  
3 emphasize that enough.

4 We currently have three approved  
5 depot antipsychotic drugs in the U.S., two of  
6 them are conventional, one of them is  
7 atypical. I would argue that we need more  
8 alternatives. Clearly, olanzapine is a very  
9 efficacious drug. I think as we saw in CATIE  
10 and other -- and some of the meta-analyses,  
11 CATIE's one of the most efficacious drugs  
12 that we have to treat schizophrenia.

13 Why do I think it's important to  
14 have another atypical drug? Well, we've done  
15 a lot of research in tardive dyskinesia over  
16 the years. This is from a paper we published  
17 in the American Journal of Psychiatry four  
18 years ago. And our impression from the data  
19 that are available is that the risk of  
20 tardive dyskinesia is significantly lower  
21 with the second generation or atypical  
22 antipsychotic drugs, and that applies to

1 adults and also elderly patients. The  
2 contrast here is between adults on an  
3 atypical drug and adults on haloperidol. The  
4 contrast here would be with other data in the  
5 elderly suggesting a risk of tardive  
6 dyskinesia of 25 percent within the first  
7 year. So we believe there's a substantial  
8 reduction in that risk.

9           This is actually the only published  
10 study with long-acting injectable drugs,  
11 which followed patients out for two years. I  
12 just want to emphasize that the benefits, the  
13 potential benefits, of a long-acting  
14 injectable drug actually may accrue over  
15 time. And in this study that Gerry Hogarty  
16 published, no difference in the first year;  
17 we begin to see considerable separation the  
18 second year. This was not statistically  
19 significant because of the small sample size,  
20 but I point to this just to demonstrate that  
21 we also need a long-term perspective when we  
22 think about relapse prevention.

1           So in summary, I think there are  
2 enormous unmet medical needs in the treatment  
3 of schizophrenia. Depot antipsychotic  
4 medications can improve outcome in the long  
5 term. Nonadherence is an enormous problem in  
6 the treatment of schizophrenia. It's  
7 significant, it's often underrecognized, and  
8 I don't think we are doing everything that we  
9 can to address it. The consequences of  
10 nonadherence are severe, so obviously as you  
11 consider the benefit-to-risk ratio in your  
12 deliberations, we have to keep in mind the  
13 potential benefits of having drugs like this  
14 available.

15           There are few depot antipsychotics  
16 currently on the market. I think we need  
17 more alternatives. Not each patient is going  
18 to respond to any particular drug. And  
19 having additional treatment options and  
20 having more depots I hope will help  
21 facilitate the increase in utilization that  
22 we should see with these medications.

1                   Thanks very much. And now I'd like  
2 to introduce Dr. David McDonnell.

3                   DR. McDONNELL: Hi. My name is David  
4 McDonnell. I'm a research physician with Eli  
5 Lilly.

6                   I'm a psychiatrist by training, and  
7 practiced in Ireland prior to joining Lilly,  
8 and have treated patients with schizophrenia.  
9 I've worked on the development of a depot  
10 formulation of olanzapine since 2001. And in  
11 my presentation, I will briefly review the  
12 properties of the formulation, the  
13 pharmacokinetics of OP Depot, and the  
14 clinical efficacy.

15                   This is the molecular structure of  
16 olanzapine pamoate monohydrate. It has a  
17 molecular weight that's approximately double  
18 that of olanzapine alone. It's virtually  
19 insoluble in water, and its properties give  
20 it the potential to be used as a  
21 once-every-two-week or a once-every-four-week  
22 injection.

1 Pamoic acid has no known  
2 pharmacological activity and the pamoate salt  
3 has been used for many years in other  
4 approved products. And one example is the  
5 oral drug hydroxyzine pamoate, which is  
6 Vistaril, which is indicated for the  
7 treatment of anxiety in the U.S. since around  
8 the 1970s. Thus, the olanzapine pamoate salt  
9 has the properties that make it an ideal  
10 candidate to develop a long-acting  
11 formulation.

12 OP Depot has been extensively  
13 studied in toxicological animal and human  
14 studies. These are the clinical studies that  
15 have been performed on OP Depot to date, all  
16 of the clinical studies. There were five  
17 early phase clinical studies which confirmed  
18 a range of doses of OP Depot that could be  
19 administered as a once-every-two-week or a  
20 once-every-four-week injection. They also  
21 demonstrated that OP Depot was  
22 well-tolerated, both systemically and at the

1 site of the injection.

2           There are three Phase 3 studies; I  
3 will talk a little bit about them later. And  
4 there are two ongoing studies. Study HGKB,  
5 which I will describe later, this is a  
6 long-term safety study and we are doing a  
7 two-year comparison study looking at  
8 treatment effectiveness of oral olanzapine  
9 versus OP Depot. The doses in the Phase 3  
10 studies were based upon extensive clinical  
11 and pharmacokinetic data, and I know it's not  
12 always easy to convert doses delivered by a  
13 depot to the known oral equivalents.

14           This table aids the understanding  
15 of what a dose of OP Depot approximately  
16 corresponds to at steady-state, and these  
17 recommendations are based upon both clinical  
18 and pharmacokinetic data. As you can see  
19 from the table, the highest dose of OP Depot  
20 is the 300 milligrams given every two weeks,  
21 which is approximately equivalent to 20  
22 milligrams of oral olanzapine a day.



1 site of the injection. This slow dissolution  
2 allows a once-every-two-week or a  
3 once-every-four-week injection. The systemic  
4 exposure to olanzapine from therapeutic doses  
5 of OP Depot is similar to that seen with  
6 doses of 5 to 20 milligrams of oral  
7 olanzapine. The metabolism of OP Depot is  
8 also comparable to oral olanzapine. And  
9 there is dose proportionality across the OP  
10 Depot strengths.

11           Important clinically is that there  
12 is immediate systemic availability of  
13 olanzapine after each injection. And this  
14 may allow a transition to OP Depot without  
15 the need to supplement with oral  
16 antipsychotic medication. The olanzapine  
17 concentration profile of OP Depot reflects  
18 these findings.

19           This is looking at the olanzapine  
20 concentration profile -- after a single dose  
21 of OP Depot of 405 milligrams, patients were  
22 stable on oral olanzapine prior to receiving

1 this dose. The bars on the graph represent  
2 the standard deviations of concentrations  
3 seen in this study. And as you can see,  
4 there are some variability in the  
5 concentrations. This variability in  
6 concentrations is also seen with oral  
7 olanzapine dosing.

8           The highest concentration of OP  
9 Depot occurs within the first week after the  
10 injection, and there's a slow decrease in  
11 concentrations to the end of four weeks.  
12 Plasma concentrations are sustained for the  
13 full duration of the four weeks.

14           The PK profile of OP Depot is very  
15 different to the profile of risperidone  
16 long-acting injection, the only other  
17 atypical depot medication available in the  
18 U.S. This is the published data on the  
19 pharmacokinetic profile of risperidone  
20 long-acting injection after a single  
21 injection of 25 milligrams. This medication  
22 is a very different formulation. It's a

1     microsphere formulation, designed to be given  
2     once every two weeks. And the most obvious  
3     difference in the pharmacokinetic profile is  
4     that there is virtually no release of  
5     risperidone for three weeks after the initial  
6     injection. After this period, there is a  
7     typical profile of the release of the drug  
8     over two weeks. This profile is unique  
9     compared to other depot antipsychotic  
10    medications, which have a PK profile which is  
11    more similar to the OP Depot.

12                 This is the published data on the  
13    plasma concentration profiles of three  
14    typical depot antipsychotic medications.  
15    Only fluphenazine decanoate is available in  
16    the U.S. Similar to the concentration  
17    profiles seen with OP Depot, medication is  
18    released immediately after the injection.  
19    Maximum concentrations are reached around the  
20    first week after the injection. And there is  
21    a slow decrease, with concentrations  
22    sustained for the full duration of the month.

1 As you can see from the pharmacokinetic data,  
2 OP Depot has a profile that makes it a very  
3 suitable depot medication.

4 The efficacy of olanzapine pamoate  
5 depot was assessed in two double-blind,  
6 randomized control studies, and the first  
7 study was mainly performed in the U.S. Study  
8 HGJZ is an eight-week, double-blind OP Depot  
9 versus placebo study in patients who are  
10 acutely ill with schizophrenia. There were  
11 approximately 100 patients in each group and  
12 there were three doses of OP Depot in the  
13 study: 210 every two weeks, 405 every four  
14 weeks, and 300 every two weeks. Patients  
15 were switched to OP Depot with no taper or  
16 supplementation of oral antipsychotic  
17 medication. There was an option for patients  
18 to stay as inpatients for the full duration  
19 of the study. Patients who completed the  
20 study were allowed to move into the  
21 open-label safety study, HGKB.

22 As I said previously, patients were

1 acutely ill at baseline. The primary  
2 efficacy was measured using the Positive and  
3 Negative Syndrome Scale, otherwise known as  
4 the PANSS. The PANSS is a universally  
5 accepted scale to measure the symptoms of  
6 schizophrenia. There are 30 items, with a  
7 maximum score of 210. Patients with a score  
8 of approximately 116 are considered severely  
9 ill, and a score of 58 represents mild  
10 illness. As you can see from the scores,  
11 patients were markedly ill when they entered  
12 the study HGJZ, with PANSS scores of 101,  
13 confirmed by CGI-Severity scores of nearly 5.

14           The scores in the PANSS, BPRS,  
15 and -- sorry, these patients clearly had a  
16 history of not doing well on their current  
17 oral medication. Over 70 percent of the  
18 patients had experienced two exacerbations in  
19 the previous two years. Patients with two or  
20 more exacerbations in two years are known to  
21 be at risk for nonadherence to their  
22 treatment regime. Almost a quarter of the

1 patients in this study had had five or more  
2 exacerbations in the past two years.

3           Clearly, patients were currently  
4 not doing well on whatever current treatment  
5 regime they were on. And despite the fact  
6 that the patients did have a history of poor  
7 control of their illness and being extremely  
8 well when they entered the study, 60 percent  
9 of the patients did manage to complete the  
10 study. And this was probably due to the fact  
11 that we allowed them to stay inpatients. Over  
12 80 percent of the patients remained as  
13 inpatients for the full duration of the  
14 study. However, there was a clear difference  
15 in the control of symptoms between the  
16 groups.

17           This is looking at the visit-wise  
18 PANSS total score and change. The primary  
19 objective of the study was met, with all  
20 three doses of OP Depot being superior to  
21 placebo at the end of eight weeks.

22           What was surprising from the study,

1 and something that would not necessarily be  
2 expected from a depot medication, was that at  
3 three days after receiving the first  
4 injection, with no oral supplementation, two  
5 of the doses of OP Depot, the 405 and the 300  
6 every two weeks, separated from placebo by  
7 one week -- all three doses were  
8 statistically superior to placebo.

9           These findings were confirmed on a  
10 mixed model analysis. As you can see, there  
11 was some dose effect. This was not  
12 statistically superior in this analysis, in  
13 the LOCF analysis. In the mixed modeling  
14 analysis that was done, the 300-milligram  
15 dose was superior to the other two doses.

16           This treatment effect is very  
17 similar to the treatment effect seen in very  
18 similar oral olanzapine studies in acutely  
19 ill patients. And it's mirrored in the PANSS  
20 positive, negative, and general  
21 psychopathology scores, and also in the  
22 clinical global impression scores of severity

1 and improvement.

2 Thus, Study HGJZ demonstrated  
3 short-term efficacy in acutely ill patients  
4 with schizophrenia.

5 To examine the effects of OP Depot  
6 over the longer term, we performed Study  
7 HGKA. Study HGKA is a 24-week, double-blind,  
8 randomized control study which had two  
9 questions. The first question was, was three  
10 of the therapeutic doses of depot, which is  
11 150 every two weeks, 300 every two weeks, and  
12 the 400 every four weeks -- were those doses  
13 superior to a very low dose of OP Depot? To  
14 give you a grounding on what 45 milligrams  
15 given every four weeks equates to, it's about  
16 1-1/2 milligrams of oral olanzapine a day.

17 The second question that was asked  
18 in the study, and it was mainly for European  
19 regulatory requirements, was, were the three  
20 doses of OP Depot non-inferior to oral  
21 olanzapine in terms of maintenance of  
22 treatment?

1           Patients entered the study stable.  
2           And once they entered the study, they were  
3           converted to treatment with oral olanzapine  
4           alone and they were stabilized on either 10,  
5           15, or 20 milligrams of oral olanzapine.  
6           Once they proved that they could maintain  
7           stability for at least four weeks in this  
8           period, they were randomized to the  
9           treatments. Once again, it's important to  
10          emphasize there was no supplementation with  
11          oral antipsychotic medication allowed at any  
12          time, and there was no treatment with mood  
13          stabilizers or antidepressants allowed in  
14          this study.

15                 One of the questions I get asked  
16          about the study is whether we expected depot  
17          to beat oral olanzapine in the study. And  
18          what we would not have expected is that depot  
19          would have been superior to oral olanzapine.  
20          First of all, because of what Dr. Kane said,  
21          the study duration is too short. Generally  
22          speaking, studies that want to show a

1 difference between depot and oral medications  
2 need to be at least one year in duration,  
3 preferably 18 months in duration, before you  
4 start to see an effect.

5           The other part was that the  
6 patients who were stable on oral olanzapine,  
7 who were randomized to treatment with oral  
8 olanzapine, remained on the same dose of oral  
9 olanzapine. Patients who were randomized to  
10 depot were not stratified. So patients who  
11 were -- for instance, stabilized on 20  
12 milligrams of oral olanzapine a day could  
13 have been randomized to a much lower  
14 equivalent dose. So clearly there was going  
15 to be some effect of that, so patients maybe  
16 on the 150-milligram dose might not have done  
17 as well as other patients, and you'll see  
18 that from the results.

19           Over 70 percent of the patients who  
20 entered the double-blind period completed the  
21 24 weeks of treatment. The primary efficacy  
22 measure was exacerbation or early relapse of

1 schizophrenia, and exacerbation was defined  
2 by measures used in previous oral olanzapine  
3 studies of a similar nature. This was a set  
4 change of BPRS positive scores or  
5 hospitalization for positive symptoms of  
6 schizophrenia.

7           In the superiority primary  
8 analysis, which is shown here, the three  
9 doses of OP Depot were superior to the  
10 45-milligram low dose of OP Depot. However,  
11 the 45-milligram dose -- the 150-milligram  
12 dose given every two weeks was statistically  
13 inferior to the oral olanzapine dose and the  
14 300-milligram dose.

15           The other primary, as I said, was a  
16 non-inferiority analysis, performed mainly  
17 for regulatory requirements in Europe. And  
18 this did show that the three therapeutic  
19 doses were non-inferior to oral olanzapine.

20           In addition to exacerbation, we  
21 also monitored overall psychopathology for  
22 stable patients who were directly

1 transitioned from oral to depot medication,  
2 with no tapering or supplementation with oral  
3 antipsychotic medication. This is looking at  
4 PANSS total score by visit, and it shows the  
5 PANSS total scores throughout the study. As  
6 you would expect from the study design, all  
7 of the patients were relatively stable, with  
8 total PANSS scores of less than 60 entering  
9 the study. This score range indicates that  
10 the patients were mildly ill at the time of  
11 study entry.

12 Patients who were randomized to the  
13 very low dose of OP Depot did experience a  
14 significant worsening in their total PANSS  
15 scores. Patients who were transferred to  
16 therapeutic doses of OP Depot remained  
17 relatively stable for the full duration of  
18 the study. However, the dose of 150  
19 milligrams every two weeks did experience a  
20 significant disimprovement in their scores,  
21 although the score did remain below 60 on the  
22 total PANSS.



1 be treated in as a real-world fashion as  
2 possible in this study.

3 Patients were initially given a  
4 dose of 210 milligrams of OP Depot. But from  
5 that point onwards, we left the treatment of  
6 the patients to the clinical discretion of  
7 the investigators. And one of the questions  
8 that came up was about the dosing. Some of  
9 the funny doses that you're seeing in some of  
10 the cases are because in the study, we  
11 allowed flexible dosing in partial doses. So  
12 out of the 405-milligram vial, you can  
13 partially dose depot in 15-milligram  
14 increments. So all of the doses are  
15 multiples of 15 from the doses. So that's  
16 why you see those other doses there.

17 Physicians were also allowed to  
18 treat the patients with a once-every-two-week  
19 or once-every-three-week or  
20 once-every-four-week injection. In order to  
21 mimic clinical practice, physicians were also  
22 allowed to supplement patients with oral