FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE (PDAC) AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Virtual Meeting

Friday, October 9, 2020

10:00 a.m. to 3:39 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

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Division of Advisory Committee and

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C O N T E N T S

P R O C E E D I N G S

(10:02 a.m.)

Call to Order

DR. NARENDRAN: Good morning and welcome. First, I would like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Lindsey O'Keefe. Her email and phone number are currently displayed. We'll wait for it to be displayed. There it is.

My name is Dr. Raj Narendran. I will be chairing today's meeting. I will now call the October 9, 2020 Joint Meeting of the Psychopharmacological Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee meeting to order. Dr. LaToya Bonner is the designated federal officer for today's meeting and will begin with the introductions. I will pass it on to Dr. Bonner.

Introduction of Committee

DR. BONNER: Good morning. My name is LaToya Bonner. I am the designated federal officer

for today's meeting. For the record, all voting members have confirmed via email that they have used the prerecorded presentation for today's meeting in their entirety.

I will now proceed forward with the introductions. When I call your name, please introduce yourself by stating your name and affiliation. Please also state for the record that you have viewed the FDA and Alkermes, Incorporated prerecorded presentation in their entirety. We will start with Dr. Dunn. Please introduce yourself into the record.

DR. W. DUNN: This is Dr. Walter Dunn. I am an assistant clinical professor at UCLA. I confirm that I have viewed the presentations.

DR. BONNER: Next is Dr. Fiedorowicz

DR. FIEDOROWICZ: Yes. This is Jess Fiedorowicz. I'm professor of psychiatry at the University of Ottawa with an adjunct appointment at the University of Iowa. I have reviewed the presentations.

DR. BONNER: Thank you, sir.

Dr. Iyengar?

DR. IYENGAR: My name is Satish Iyengar. I'm from the statistics department at the University of Pittsburgh, and I also confirm that I have viewed everything.

DR. BONNER: Dr. Jain?

DR. JAIN: Good morning. This is Dr. Felipe Jain. I'm a psychiatrist at Massachusetts General Hospital and assistant professor at Harvard Medical School. I confirm I have reviewed the presentations.

DR. BONNER: Thank you, sir.

Dr. Jeffrey?

DR. JEFFREY: Good morning. This is Dr. Jessica Jeffrey. I'm an assistant professor of child and adolescent psychiatry at UCLA. I confirm that I viewed all presentations in their entirety.

DR. BONNER: Thank you.

Dr. Krishna?

DR. KRISHNA: Hello. This is Dr. Sonia Krishna. I'm a child adolescent and adult psychiatrist and affiliate faculty at Dell Medical

School at the University of Texas, Austin. I confirm I have viewed the presentations in their entirety. Thank you.

DR. BONNER: Thanks.

Dr. Narendran?

DR. NARENDRAN: This is Dr. Raj Narendran. I'm a psychiatrist at UPMC. I'm also a professor in the Department of Radiology and Psychiatry at the University of Pittsburgh. I confirm for the record that I've viewed the presentations provided by the agency, as well as Alkermes.

DR. BONNER: Thank you, sir.

Dr. Thomas?

DR. THOMAS: Hello. This is Dr. Patrick Thomas. I'm a psychiatrist at the Menninger Clinic and assistant professor at Baylor College of Medicine, and I confirm I have reviewed the presentations.

DR. BONNER: Thank you, sir.

Ms. Kim Witczak?

MS. WITCZAK: Good morning. Kim Witczak from Woodymatters. I'm the consumer representative

on the committee, and I confirm that I have reviewed all the materials provided by the FDA and the sponsor.

DR. BONNER: Thank you, ma'am.

Next we'll have Dr. Boudreau.

DR. BOUDREAU: Good morning. Denise Boudreau, scientific investigator at Kaiser Permanente Washington and also affiliate professor at the University of Washington, and I confirm that I've reviewed the FDA and sponsor material.

DR. BONNER: Thank you.

Dr. Calis?

DR. CALIS: Good morning. This is Karim Calis. I'm director of clinical research and compliance with the National Institute of Child Health and Human Development at NIH, and I'm also chair of the NIH Intramural IRP. I affirm that I reviewed all of the material and the presentations.

DR. BONNER: Thank you.

Dr. Meisel?

DR. MEISEL: Good morning. Steve Meisel. I am the director of medication safety for M Health

Fairview, an integrated health system based in Minneapolis, and I confirm I've reviewed the materials.

DR. BONNER: Thank you, sir.

Dr. Mehta?

DR. MEHTA: Hi --

DR. BONNER: I can hear you.

DR. MEHTA: Hi. This is Reema Mehta. I am head of risk management and safety surveillance research at Pfizer, a nonvoting industry rep, and I confirm as well.

DR. BONNER: Thank you, ma'am.

Next is Dr. Amirshahi.

DR. AMIRSHAHI: Good morning. Maryann Amirshahi. I'm an emergency medicine physician, medical toxicologist, and clinical pharmacologist. I'm associate professor of emergency medicine at Georgetown University School of Medicine and I practice at Washington Hospital Center and the National Capital Poison Center. I confirm that I have reviewed the presentations in their entirety.

DR. BONNER: Thank you, ma'am.

Dr. Bohnert?

DR. BOHNERT: Hi. I'm Amy Bohnert. I'm an investigator with the Department of Veterans Affairs Health Services, Research and Development. I'm also an associate professor with the Department of Anesthesiology and Psychiatry at the University of Michigan, epidemiologist by training, and I have read all of the materials. Sorry. I have reviewed all of the videos in their entirety.

DR. BONNER: Thank you, ma'am.

Dr. Krebs?

DR. KREBS: Good morning. Erin Krebs. I'm chief of general internal medicine and a health services researcher at the Minneapolis VA Health Care System, and professor of medicine at the University of Minnesota. My research focuses on chronic pain and opioid management. I confirm that I have viewed the presentations in their entirety.

DR. BONNER: Thank you.

Mr. Racher?

MR. RACHER: Good morning. This is Matthew Racher, certified recovery peer specialist and

patient representative. I confirm that I have viewed the presentations in their entirety.

DR. BONNER: Thank you, sir.

Dr. Zacharoff?

DR. ZACHAROFF: Hi. Good morning. My name is Kevin Zacharoff. My areas of expertise are anesthesiology, pain, and substance-use disorders. I am the course director of pain and addiction, faculty and clinical instructor at the Renaissance School of Medicine at Stony Brook University, and I confirm that I have viewed all the materials provided.

DR. BONNER: Thank you, sir.

We will now move to our FDA participants. Dr. Dunn?

DR. B. DUNN: Yes. Good morning. This is Dr. Billy Dunn. I direct the Office of Neuroscience at the FDA.

DR. BONNER: Thank you, sir.

Dr. Bastings?

DR. BASTINGS: Good morning. This is Dr. Eric Bastings. I am acting deputy director of

the Office of Neuroscience, FDA.

DR. BONNER: Thank you, sir.

Dr. Farchione?

DR. FARCHIONE: Hi. This is Tiffany Farchione. I'm the acting director of the Division of Psychiatry here at FDA.

DR. BONNER: Next is Dr. Fischer.

DR. FISCHER: Hi. I'm Bernie Fisher, acting deputy for Division of Psychiatry at FDA.

DR. BONNER: Thank you.

Dr. Staffa?

DR. STAFFA: Good morning. Judy Staffa, associate director for Public Health Initiatives in the Office of Surveillance and Epidemiology at FDA.

DR. BONNER: Thank you, ma'am.

DR. BONNER: Next is Dr. Southammakosane.

DR. SOUTHAMMAKOSANE: Hi. Cathy Southammakosane. I'm a medical officer in the Division of Psychiatry.

DR. BONNER: Thank you.

And last will be Dr. McAninch.

DR. McANINCH: Hi. Jana McAninch. I'm the

senior medical epidemiologist for the nonmedical use teams in the Division of Epidemiology in OSE, CDER, FDA. Thanks.

DR. BONNER: Thank you.

I will now turn the meeting back to our chair, Dr. Narendran.

DR. NARENDRAN: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the

meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of the meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I will now transfer it to Dr. Bonner, who will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. BONNER: Thank you, sir.

The Food and Drug Administration is convening today's joint meeting of the Psychopharmacologic Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to

federal conflict of interest laws and regulations.

The following information on the status of the committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of the committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's

meeting, members and temporary voting members of the committees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of the efficacy, safety, and benefit-risk profile of new drug application 213378, olanzapine/samidorphan oral tablets, submitted by Alkermes, Incorporated, for the proposed indications of schizophrenia and bipolar I disorder. This is a particular matters meeting during which specific matters related to Alkermes' NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection

with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Reema Mehta is participating in today's meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Mehta's role in this meeting is to represent industry in general and not any particular company. Dr. Mehta is employed by Pfizer

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial

relationships that they may have with the firm at issue.

Thank you. I will now turn the meeting back over to the chair.

DR. NARENDRAN: Thank you. We will now proceed with FDA's opening remarks from Dr. Bernie Fischer.

FDA Opening Remarks - Bernard Fischer

DR. FISCHER: Good morning, and welcome to this joint meeting of the Psychopharmacologic Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The purpose of this meeting is to discuss a new drug application submitted by Alkermes, Incorporated for ALKS 3831, a fixed-dose combination product of the antipsychotic olanzapine and samidorphan, an opioid receptor antagonist that is a new molecular entity. The samidorphan in this combination product is intended to mitigate olanzapine-associated weight gain.

The application for ALKS 3831 was submitted under the 505(b)(2) pathway. Under this pathway,

an applicant is able to rely on FDA's previous findings of safety and effectiveness for an approved product to support their own application. In this case, the applicant has conducted a relative bioavailability study comparing ALKS 3831 to an approved form of olanzapine. The relative bioavailability study allowed the applicant to propose ALKS 3831 for the same schizophrenia and bipolar indications as olanzapine.

During development, FDA advised the applicant to provide evidence that the addition of samidorphan does not interfere with the efficacy of olanzapine and to demonstrate their product's weight mitigation effect in a dedicated study. We recommended that the weight mitigation study be at least 6 months long.

We also recommended two co-primary endpoints, the percent change from baseline and body weight and the proportion of subjects with at least 10 percent weight gain from baseline. We also indicated to the applicant that in addition to the effect on weight gain, FDA would consider

changes in metabolic laboratory parameters in the review of their application.

The applicant's development program included a phase 2 proof-of-concept study, Study A302; a 6-month weight mitigation study, Study A303, which was conducted according to FDA recommendations; and a 4-week antipsychotic efficacy study, Study A305. The program also included two 12-month open-label extension studies, one each for studies A303 and A305. The details of these studies are provided in the background document and were reviewed in the agency's presentation.

As discussed in our background document and presentation, Study A305 supports the conclusion that samidorphan does not meaningfully impair olanzapine's efficacy. Although this study only enrolled people with schizophrenia, we have no reason to believe the samidorphan component would uniquely interfere with olanzapine's efficacy for bipolar disorder. Therefore, in conjunction with the relative bioavailability data mentioned previously, we believe the applicant has

demonstrated that ALKS 3831 would be effective in treating schizophrenia and bipolar disorder.

Regarding Study A303, the pivotal weight mitigation study, both co-primary endpoints were statistically significant. The mean change from baseline and weight between the ALKS 3831 and the olanzapine groups at week 24 was negative 2.38 percent. The proportion of subjects with a weight gain of 10 percent or more from baseline at week 24 was approximately 18 percent in the ALKS 3831 group and 30 percent in the olanzapine group.

Waist circumference, a prespecified secondary endpoint, was significantly different between the two groups and favored ALKS 3831. There was also a nominal difference in systolic blood pressure favoring ALKS 3831. However, there were no meaningful differences in metabolic laboratory values between ALKS 3831 and olanzapine, and there is a suggestion, as detailed in our background document, that blood glucose parameters may be less favorable with ALKS 3831. Finally,

there were no differences in measures of quality of life between the two groups.

FDA requested long-term, follow-up studies to ensure that any weight mitigation observed during Study A303 was not merely a delay of weight gain; that is that the initial weight mitigation effect continued beyond the acute trials. We did not ask the applicant to include an olanzapine arm in these studies, so comparisons can only be made via cross-study looks at historical data, which is inherently limited. Nevertheless, we did not see a late excess of weight gain in either of the long-term studies.

In general, the adverse event profiles of ALKS 3831 and olanzapine were very similar, however, the samidorphan component does confer additional risk. Because samidorphan is an opioid antagonist, it can precipitate withdrawal in patients who are physically dependent on opioids. A patient taking samidorphan was hospitalized for precipitated withdrawal during ALKS 3831 development.

Samidorphan may block opioid-related analgesia when medically necessary or prevent a high in people with an opioid-use disorder. In these latter situations, there's a hypothetical risk of overdose if the patient tries to overcome this blockade. A patient taking ALKS 3831 was hospitalized for opioid overdose during product development, although it's unclear if this event was actually connected to the samidorphan.

As detailed in our background document, epidemiologic data support the potential risk of samidorphan. Some of what would be the indicated populations have a higher rate of opioid use compared to the general population, and despite contraindications in labeling, opioids and products containing the opioid antagonist naltrexone are frequently co-prescribed.

FDA agrees with the applicant and many public comments that addressing medication-induced weight gain is important. However, FDA would like to remind today's audience that ALKS 3831 is not intended as a weight-loss treatment. In other

words, ALKS 3831 is not intended to treat people who have already gained weight on olanzapine, and neither would ALKS 3831 prevent all of the weight gain associated with olanzapine.

Most people taking ALKS 383 also gained weight, albeit less than with olanzapine. What the applicant has demonstrated is that in people who are not currently taking olanzapine, starting ALKS 3831 instead of olanzapine may prevent some of the weight gain that a person might have otherwise experienced with olanzapine alone.

In reviewing this application, FDA is considering several issues. One is whether the degree of this statistically significant weight mitigation was robust enough to be clinically meaningful. We are also considering why olanzapine mediated weight gain is an important safety issue and whether mitigation of weight gain in the absence of a clear effect on metabolic parameters addresses the safety issue. We are also considering the apparent benefits of the product, taking into account the opioid antagonist risks of

the samidorphan component.

After viewing presentations by the applicant and the agency, as well as considering comments from the public, the committees will address these questions and points of discussion. Number 1, has the applicant presented adequate evidence that samidorphan meaningfully mitigates olanzapine-associated weight gain?

Number 2, has the applicant adequately characterized the safety profile of ALKS 3831? Number 3, is the labeling sufficient to mitigate the risks related to the opioid antagonist action of samidorphan? And number 4, what, if any additional data, are needed to address outstanding issues?

Finally, on a practical note, we have a large group of multidisciplinary scientists and FDA leadership involved in this meeting. There may be slight delays in our responses to the committees as we confer virtually to make sure that we identify the optimal respondent to any questions asked, so thank you in advance for your patience. With that,

I will turn it back over to the meeting chair.

DR. NARENDRAN: Thank you, Dr. Fischer.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including Alkermes' non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interest, and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning

of your presentation, it will not preclude you from speaking.

We will now proceed with Alkermes' summary presentation. I'll hand it over to Alkermes.

Applicant Presentation - Sarah Akerman

DR. AKERMAN: Good morning to the chair, members of the advisory committees, the agency, and other attendees. My name is Sarah Akerman, and I'm a senior medical director at Alkermes and a psychiatrist with board certification in psychiatry and addiction.

We're pleased to be speaking with you today about olanzapine/samidorphan, also referred to by the abbreviation OLZ/SAM, for which we are seeking indication for schizophrenia and bipolar I disorder. I will be presenting today a summary of the video presentation and briefing document. No new data will be presented in this summary.

The basis for the development of OLZ/SAM is grounded in the fact that olanzapine is a highly effective antipsychotic. FDA approved since 1996 under the brand name Zyprexa, the field has

extensive clinical experience with olanzapine. And while it's highly effective, it has the very concerning side effect of weight gain, which is limited [inaudible – audio fades].

The majority of patients do gain weight on olanzapine, and this is -- for some individuals, approximately 60 percent -- clinically significant weight gain, which not only impacts their quality of life but leads over time [inaudible], as well as increased morbidity and mortality.

There are currently no FDA-approved pharmacological treatments to suspend [indiscernible] or treat antipsychotic associated weight gain, and as you heard from Dr. Rene Kahn and Dr. Ginger Nicol in the recorded presentation, prescribers are at times faced with the difficult decision of switching [inaudible] -- antipsychotic efficacy, which carries inherent risks for the patient.

Samidorphan is an opioid receptor antagonist or blocker. The opioid system has been shown to play a role in food reward and metabolism, so our

approach adds samidorphan to olanzapine, and as you've seen in our clinical data, samidorphan mitigates or prevents olanzapine-associated weight gain while maintaining its known and antipsychotic efficacy.

The proposed indications and therapeutic range for OLZ/SAM would be consistent with the Zyprexa prescribing information, with the addition of a fixed dose of 10 milligrams of samidorphan to mitigate weight gain. We are not seeking an indication for weight mitigation.

At the end of our phase 2 program, we aligned with the agency on the phase 3 registration package and included two studies, both in schizophrenia. The first was an antipsychotic efficacy study comparing OLZ/SAM to placebo with an olanzapine active control, and the second was a weight mitigation, also referred to as a weight efficacy study, comparing OLZ/SAM and olanzapine with endpoints that were specifically chosen to demonstrate clinically meaningful changes in weight.

The data that we'll be focusing on today is in patients with schizophrenia. We are also seeking an indication for bipolar I disorder both as a monotherapy and as an adjunct to lithium and valproate, consistent with the current indications [inaudible].

To support this bipolar indication, we align with the FDA on a bridging strategy. The strategy relies in part on the established efficacy of olanzapine in bipolar I disorder, as well as two necessary components, which we accomplished; first, establishing that the olanzapine exposure within OLZ/SAM is bioequivalent to Zyprexa, and second, demonstrating similar antipsychotic efficacy to olanzapine in the schizophrenia program. We also established that there were no drug-drug interactions with lithium or valproate.

In addition to the phase 3 studies, we've conducted an extensive safety and efficacy evaluation with 27 clinical studies, including three long-term, open-label studies evaluating up to three and a half years of OLZ/SAM treatment.

I'll describe the phase 3 studies in more detail, the first of which is the antipsychotic efficacy, or 305 study, which met its primary and key secondary endpoints.

The efficacy of olanzapine alone is well known to the field. The antipsychotic efficacy of OLZ/SAM was established in a 4-week, double-blind, randomized, placebo-controlled study in acutely ill patients with schizophrenia, comparing OLZ/SAM to placebo with olanzapine added as an active control. The primary endpoint was the change from baseline and positive and negative syndrome scale total score at week 4 for OLZ/SAM compared to placebo.

This figure represents the primary outcome measure of PANSS total score with change from baseline on the Y-axis and visits and weeks on the X-axis. OLZ/SAM Sam is in blue, olanzapine in orange, and placebo in gray. A decrease in PANSS score indicates symptom improvement, and at the end of 4 weeks, we saw a significantly greater improvement in PANSS total score for patients treated with OLZ/SAM compared to placebo.

A similar improvement is seen in the olanzapine treatment arm as expected. The key secondary endpoint of change from baseline in CGI-S score demonstrated similar findings to the primary endpoint. Long-term improvements in PANSS and CGI-S scores were also observed in open-label studies with over 76 weeks of treatment with OLZ/SAM.

In this study, we demonstrated the antipsychotic efficacy of OLZ/SAM compared to placebo. This efficacy was similar to what is known for olanzapine and was also demonstrated across multiple phase 2 and phase 3 studies, as well as in long-term safety studies. This leads to the conclusion that OLZ/SAM has retained the known antipsychotic efficacy of olanzapine, supporting the indications of both schizophrenia and bipolar I disorder.

The second phase 3 study is the weight efficacy study, which also met is co-primary and key secondary endpoint. The effects of OLZ/SAM on weight were examined in a 24-week, double-blind, randomized controlled study in stable outpatients

with schizophrenia. 561 patients with body mass index between 18 and 30 were randomized to treatment with OLZ/SAM or olanzapine. One co-primary endpoint examined the percent change from baseline and body weight at week 24.

The other co-primary endpoint examined the proportion of patients gaining greater than or equal to 10 percent of their body weight. This 10 percent cutoff was chosen, as this signifies a clinically meaningful amount of weight gain for a patient. For instance, in a person weighing 170 pounds, this represents 17 pounds in weight gain over just 24 weeks. The key secondary endpoint examined the 7 percent cutoff, as this is widely used in psychiatry studies and antipsychotic labeling.

The co-primary and key secondary endpoints were met in the study with p-values listed here in the right-hand most column. The difference in percent change in weight reflects the mean change in the whole population of the study, and this difference is 2.38 percent, which was significantly

different from olanzapine. For patients gaining greater than or equal to 10 percent of their body weight, the risk difference between OLZ/SAM and olanzapine was 13.7 percent, and for the 7 percent cutoff, it was 15.9 percent, both values, again, being significantly different from olanzapine.

This figure represents the co-primary endpoint of percent change from baseline and body weight by week with study weeks on the X-axis and the percent change from baseline and weight on the Y-axis. At the end of the 24 weeks, the percent change in body weight with OLZ/SAM is significantly lower than olanzapine. There was some initial weight gain with OLZ/SAM, which stabilized from 4 weeks on and was stable for the remainder of the study.

The weight gain with olanzapine alone continued throughout the 24 weeks, and the difference between the treatment groups continued to grow, resulting in a very different trajectory for OLZ/SAM than what is known to occur with olanzapine. The long-term stability of weight with

OLZ/SAM is seen in patients continuing treatment for 76 weeks in the extension study.

Next are the categorical co-primary and key secondary endpoints. First to the table on the left, OLZ/SAM led to a 50 percent reduction in the risk of gaining clinically meaningful weight, defined as gaining either greater than or equal to 10 or 7 percent of body weight.

The figure on the right is the cumulative responder plot with the cumulative percentage of patients on the Y-axis and the percent change from baseline and body weight at week 24 for all patients. You can see that the OLZ/SAM curve in blue is consistently shifted to the left of the olanzapine curve in orange. This shows us that OLZ/SAM reduced the risk of weight gain compared to olanzapine no matter how clinically meaningful is defined along this curve.

The widest separation points between these curves is at the important cutoff points of 10 and 7 percent, and this indicates that the risk reduction with OLZ/SAM treatment is more pronounced

in those patients who are most susceptible to the greatest weight gain associated with olanzapine.

This 50 percent reduction in risk is not only seen in the weight data, again shown here on the left, but also seen in waist circumference and systolic blood pressure. The figure in the center is showing the exploratory endpoint of change from baseline and waist circumference for OLZ/SAM in blue and olanzapine in orange over 24 weeks.

Waist circumference is an accepted proxy for central adiposity, and central fat is a major driver of downstream metabolic impairment. Similar to the changes in weight at 24 weeks, there were lower increases in waist circumference for OLZ/SAM.

The differences in waist circumference occurred earlier than the changes in weight, suggesting that changes in the distribution of weight may occur earlier than changes in actual weight. OLZ/SAM also reduced the risk of gaining 5 centimeters in waist circumference by 50 percent compared to olanzapine, and the changes in waist circumference were stable in patients on OLZ/SAM,

continuing for 76 weeks.

The figure on the right shows the post hoc finding of systolic blood pressure. Systolic blood pressure on olanzapine treatment increased by greater than 2 millimeters of mercury, where it was unchanged with OLZ/SAM. Systolic blood pressure is an independent risk factor and established biomarker. Every 2 millimeters of mercury increase in systolic blood pressure is associated with an approximately 7 percent higher long-term risk of death due to cardiovascular disease.

The benefits of blood pressure were further reflected by a 50 percent reduction in the risk of shifting from normal to hypertensive blood pressure levels. Stability of blood pressure was demonstrated in patients remaining on OLZ/SAM treatment for 76 weeks. Taken together, these data indicate a reduction in three important cardiometabolic risk factors.

Unlike the changes in weight, waist circumference, and blood pressure, we did not see differences in metabolic laboratory parameters

between OLZ/SAM and olanzapine in 24 weeks. This plot shows the change from baseline in lipid and glycemic parameters at week 24 with olanzapine in orange and OLZ/SAM in blue. Changes were generally small and similar for both treatment groups.

We included these parameters as exploratory endpoints, understanding that observing weight-related differences in these parameters may be confounded by several factors, including weight independent effects of olanzapine, inconsistencies in fasting status, and importantly, study duration. While we were confident that 6 months was sufficient to see differences in weight, it was not clear that this timeframe was sufficient to observe weight-driven changes in metabolic parameters.

Also, since this is a weight-prevention and not a weight-loss study, patients were non-obese and generally metabolically healthy entering this study. And as Dr. Evan Stein noted in his presentation, 24 weeks was likely not sufficient time to see a difference between the treatment groups in a population with this profile. What we

do know is that over time, weight gain is a major driver of glucose and lipid abnormalities, with prevalence of diabetes and dyslipidemia increasing progressively with increasing BMI. With long-term OLZ/SAM treatment and the open-label studies, lipid and glycemic parameters remained stable through 76 weeks.

When we look at a composite view, we see benefits for OLZ/SAM versus olanzapine across multiple cardiometabolic risk factors. In this forest plot, each row denotes a clinically meaningful change for that risk category. The circles denote the absolute risk difference for OLZ/SAM versus olanzapine, along with the confidence intervals.

You can see that in the 24-week study, treatment with OLZ/SAM was associated with a significant reduction in the risk of weight gain, obesity, central adiposity, and hypertension. Lipid and glycemic parameters cross zero, and therefore showed no difference between OLZ/SAM and olanzapine, and as we saw in the previous slide,

changes were generally small for both treatment groups at 24 weeks. The stability of these parameters were seen in the long-term studies through 76 weeks.

To summarize the weight effects, OLZ/SAM reduced the mean percent change in weight versus olanzapine and resulted in a 50 percent reduction in the risk of clinically meaningful weight gain. We also saw improvements in waist circumference and systolic blood pressure. The stability of weight, waist circumference, blood pressure, and metabolic parameters was also seen in long-term studies.

The next section of data I'll show you is the safety data, which demonstrated an overall safety profile consistent with olanzapine with less weight gain. Our understanding of the safety profile of OLZ/SAM is informed by an extensive safety data accumulated for Zyprexa. Effects of samidorphan have been studied in over 600 patients and healthy volunteers.

Supportive to this is well-established clinical experience with the class of opioid

antagonists, which are used in the field of addiction as a treatment for opioid- or alcohol-use disorder, including in patients with comorbid schizophrenia or bipolar disorder. As we monitored our clinical studies, we focused on the known safety profiles of both components while being vigilant to new unexpected adverse events or amplification of known signals that might have emerged from the combined use of olanzapine and samidorphan.

The overall safety profile of OLZ/SAM is informed by a total of 1601 unique exposures to OLZ/SAM with 1262 of those in patients with schizophrenia, providing a total of 910 person-years of exposure in this population. Close to 400 patients were on OLZ/SAM treatment for more than a year in the studies going up to three and a half years.

Now I'll review the adverse events or AEs. The colored columns here represent the studies. Adverse events were generally mild to moderate in severity and similar between the OLZ/SAM and

olanzapine treatment groups. There were few treatment discontinuations due to AEs across treatments. Most were related to the exacerbation of underlying schizophrenia.

Serious AEs were infrequent and again were largely related to the exacerbation of underlying psychiatric disease. Neither olanzapine nor samidorphan have demonstrated any evidence of abuse potential. Our overall experience to date suggests that the safety profile of OLZ/SAM is generally consistent with that of olanzapine, with the exception of less weight gain.

I'll next describe what is known historically about olanzapine and opioid antagonists. As a second-generation antipsychotic, olanzapine is known to cause effects such as weight gain and metabolic changes, as well as effects such as extrapyramidal and anticholinergic effects.

For opioid antagonists, important risks that were not commonly seen across our clinical program in an evaluation of 1600 patients that are known class risks include precipitated opioid withdrawal

in patients who are physically dependent on opioid agonists; attempts to overcome the opioid blockade with opioids, which could lead to fatal opioid overdose; reduced or inadequate opioid analgesia when taking an opioid analgesic concurrently with an opioid antagonist.

To address these risks, we have proposed a contraindication for patients dependent on or chronically using opioids, as well as warnings and precautions describing these risks. We know that opioid use an opioid-use disorder do occur more frequently in patients with schizophrenia or bipolar disorder than in the general population. The FDA has raised the point that these risks could be mitigated through labeling, and we agree.

In addition, because patients' safety comes first, we have leveraged our experience in patients with serious mental illness and proactively propose a robust educational plan to ensure that potential prescribers and patients understand the contraindications and warnings and precautions. Our pharmacovigilance plan ensures safety data

collection, signal detection, and regulatory reporting in accordance with the current regulations.

To summarize the phase 3 for OLZ/SAM, we demonstrated antipsychotic efficacy compared to placebo and mitigation of olanzapine-associated weight gain while maintaining the known efficacy of olanzapine. The durability of the antipsychotic and weight mitigation efficacy was also seen in longer term data and replicated across the program in nonclinical species, healthy human volunteers, and in patients with schizophrenia.

The safety profile is consistent with what is known for olanzapine with the benefit of less weight gain. Class risks associated with opioid antagonists are well characterized and can be managed through labeling, pharmacovigilance activities, and education.

I'd like to turn now to four points for consideration raised by the FDA and would like to give our findings on these important points. First, the changes in weight seen with OLZ/SAM are

both statistically and clinically meaningful. The endpoints that we aligned with the FDA on were carefully selected for clinical meaningfulness [inaudible – audio fades], and we met those co-primary and key secondary endpoints.

The mean difference in weight gain between OLZ/SAM and olanzapine is in line with what we anticipated for a 24-week study in a non-obese and generally metabolically healthy population. This mean difference also increases over time, altering the known trajectory of weight gain associated with olanzapine.

Not only did we show significant difference in the population mean weight gain, OLZ/SAM also shifted the overall weight distribution curve toward less weight gain. This resulted in a 50 percent decrease in the risk of gaining greater than or equal to 10 or 7 percent. We also saw this 50 percent reduction in risk across several cardiometabolic risk factors, including weight gain, waist circumference, the measure of central adiposity, and systolic blood pressure.

Second, the safety of OLZ/SAM is well characterized. Greater than 900 person-years of exposure data demonstrated a safety profile for OLZ/SAM and was consistent with olanzapine with the benefit of less weight gain.

Third, the class risks associated with opioid antagonist can be managed through labeling. Labeling and education will provide an appropriate balance of communicating these well-characterized risks while avoiding barriers for patients who are often challenged with access to medications.

Fourth, ongoing studies will provide additional supportive data. We are committed to future research on OLZ/SAM. In addition to our ongoing open-label extension study, we're evaluating the efficacy of OLZ/SAM in patients most vulnerable to weight gain and have an ongoing study in early illness enrolling schizophrenia, schizophreniform, and bipolar I disorder patients.

We've also developed a comprehensive pediatric study plan to evaluate OLZ/SAM in pediatric patients with schizophrenia or bipolar I

disorder. Our current data package, however, is complete to support approval of OLZ/SAM, and the totality of data demonstrate a favorable benefit-risk profile for OLZ/SAM, a potential new treatment option that addresses an important unmet need for patients with schizophrenia or bipolar I disorder.

We are fortunate to be joined today by four clinicians, scientists, and experts in the fields of psychiatry, addiction, and lipid disorders and metabolism. We also have a number of Alkermes attendees available to answer any questions you may have. Thank you for your time.

Clarifying Questions to Applicant

DR. NARENDRAN: Thank you for the summary presentation. We will now take clarifying questions for Alkermes. Please use the raised-hand icon to indicate that you have a question and remember to put your hand down after you ask you a question.

Please remember to state your name for the record before you speak and direct your question to

a specific presenter if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible. Finally, it will be helpful to acknowledge the end of your question with a thank you and end your follow-up question with "That is all my questions," so we can move on to the next panel member.

The first question is from Dr. Zacharoff.

DR. ZACHAROFF: Yes. Hi. Good morning. This is Kevin Zacharoff from Renaissance School of Medicine at Stony Brook University. My questions are for Dr. Akerman, and the first question is with respect to slide CS-20. I don't know if you're going to bring that up.

Dr. Akerman, my question on this slide really focuses around, when we say educate the healthcare professionals, are we talking about educating the healthcare professionals who would likely prescribe this medication or are we talking about a more general, broad healthcare education activity?

DR. AKERMAN: If I could have slide up,

please? We have proposed a comprehensive educational plan -- this is some of the components here -- that would be directed both to healthcare professionals and patients. We'd like to propose an initial communication to all potential prescribers and then ongoing education as appropriate. This will include information about the contraindication warnings and precautions.

We also have a number of patient-directed materials, such as a doctor discussion guide and wallet card that could be helpful for patients as they discuss this potential medication with their providers.

DR. ZACHAROFF: Okay. So then it seems to me the education will be directed towards the prescribers, so we might consider that that might be a psychiatrist, for example, or some other healthcare provider.

My question to you is, is there any plan to provide educational materials to clinicians that might find themselves in a situation of needing to give opioid analgesics to patients who are on this

medication, such as emergency department physicians, or orthopedists, or even anesthesiologist like me, for example? Is there any plan at this time to provide some kind of educational programs or materials to those potential prescribers?

DR. AKERMAN: Yes, absolutely. I think that's a very important point. We would most certainly be interested in informing anyone who could come into contact with a patient taking this medication, and we're happy to work closely with the agency to ensure that our educational plan is robust and gets to all HCPs and patients who need this information.

DR. ZACHAROFF: Okay. Then one more question with respect to slide CS-23.

While we're bringing up that slide, Dr. Akerman, my question would be in the event that OLZ/SAM does need to be discontinued because the patient does become a candidate to receive an opioid analgesic, on an acute basis let's say, how long after discontinuation of the medication would

prescriber of an opioid need to wait before they prescribe the opioid and wouldn't experience the opioid antagonism?

DR. AKERMAN: Yes, I would imagine that would be based on clinical judgment, depending on the opioid and how long the patient was receiving treatment. But I'd like to ask my colleague, Dr. Rege, to comment on what is known.

Dr. Rege?

DR. REGE: Yes. Bhaskar Rege, clinical pharmacology from Alkermes. In our clinical trial that was looked at, the effect of samidorphan in blocking the effects of remifentanil, which is a known very potent opioid antagonist, the data indicated about 48 hours of blockade, which would be the time period that we will be recommending, and within 48 hours, the new activity was recovered after stopping this.

DR. ZACHAROFF: So in the event that somebody is on this medication and is in a motor vehicle accident, for example -- I heard you say remifentanil. I'm assuming that's the only opioid

agent that the testing was done with?

DR. REGE: The clinical trial that was done, that used the remifentanil as an opioid to test against the samidorphan, there are other opioid agonist data that's available. The half-life of samidorphan is around 7 to 11 hours, which, again, I think within 24 hours, one would remove at least 90 percent. The patient would clear about 95 percent of the drug within 24 hours. So that's an indicator of any other less active opioid antagonist that may be able to get up to 24 hours rather than something very potent like remifentanil that could take about 48 hours.

DR. ZACHAROFF: Okay. I'm going to keep it to clarifying questions and we can save the discussion for this afternoon. Just one last question to you then, sir, and that would be, is there any study of people needing acute opioid analgesia before the 24 to 48 hours has passed, for medical purpose?

DR. AKERMAN: We do have issues of instances within our clinical trial program. I can ask.

Dr. Yagoda to speak to those, and then I'd like to turn to Dr. Kathleen Brady who can let us know what is known in the field about analgesia in the context of opioid antagonists.

Dr. Yagoda?

DR. YAGODA: Sergey Yagoda, medical director. The use of opioids was restricted in our clinical program, however, we have an example when one of the patients had gotten into a car accident and was injured. They had pelvic fracture. The patient was well informed of the pain management aspect. They were carrying the emergency card with them, and they were able to communicate with the ER physicians.

On the ongoing participation in the study, where they received opioid antagonist, the ER physician was able to contact the investigator, and they worked out the pain management plan. The patient received acute opioids in combination with paracetamol in the immediate acute stage, and then they transitioned to oxycodone/paracetamol. The patient recovered. They did not report inadequate

analgesia throughout the recovery period.

DR. AKERMAN: Dr. Brady, could you comment on what is known about analgesia and the context of opioid antagonists?

DR. BRADY: Certainly. Hi. This is Kathleen Brady. Can everyone hear me? I just want to make sure I've got my off-mute ok.

DR. ZACHAROFF: Yes, I hear you. Thank you.

DR. BRADY: Okay. Great.

The opioid antagonists have been around in the treatment of alcohol dependence for 20 some years now, and so are increasingly commonly used. There are pretty well-defined protocols for analgesia in the face of opioid antagonists that I think most physicians, and ED docs, and trauma surgeons are aware of.

These certainly include the use of regional blockades, the use of non-opioid analgesics, and then careful application of opioids to overcome the blockade, where patients are in hospital and can be scrutinized very carefully. I think we've learned a lot about how to produce analgesia in the face of

opioid antagonists, and then I think the field is well versed in this.

DR. ZACHAROFF: Okay. Thank you. That concludes my questions.

DR. NARENDRAN: Thank you. This is Raj Narendran. I'm going to ask my question because it's sort of related.

Does Alkermes have any PET occupancy data at the mu receptor in humans for samidorphan at 10 milligrams to definitively say what percentage of mu receptors are occupied, and for how long? Do you have any PET data?

DR. AKERMAN: We do not have PET data, but what we do have is animal data that I could ask Dr. Rege to speak to.

DR. NARENDRAN: That's fine. If you don't have PET data, it might be worth considering down the line. Thank you.

The next question, I'll pass it to Dr. Dunn.

DR. W. DUNN: Hi. This is Walter Dunn from UCLA. My question is -- actually I'd like to hear a comment from both the sponsor and the FDA,

perhaps starting with the sponsor. This is not the first time that the advisory committee has heard about samidorphan. There was an application for ALKS 5461 back in 2018. This is the combination product of buprenorphine and samidorphan.

In that briefing document, they mentioned that samidorphan is metabolized to 2 full mu opiate receptor agonists. So you start with the antagonist, but it metabolites to 2 agonists. There wasn't any mention of that in any of the material that I saw this time. Can you comment on what's the role of agonists? What potential problems may arise from that; both a comment from the sponsor and FDA, please? Thank you.

DR. AKERMAN: Thank you. I'll ask Dr. Rege to comment on this question.

DR. REGE: Bhaskar Rege, clinical pharmacology in Alkermes. Slide up, please.

Yes, there are two major metabolites for samidorphan. You're right that in the RDC-9986, that is the main metabolite that has opiate agonist effects. What you see on the slide here is the

affinity values. For mu kappa and delta for 9986, they were at least 20-fold lower than the parent molecule. In fact, kappa is around 200-fold lower. So in a clinical situation, in the presence of samidorphan, we expect that the samidorphan antagonism will out-compete any agonism, and there won't be any likelihood of this metabolite engaging any of the receptors.

In terms of the receptor occupancy data, we did look at the rat, and we see about over 90 percent receptor occupancy at mu receptor at a concentration of a 10-milligram dose. So again, there is no likelihood of any of these metabolites having ability to engage any mu receptors and confer any effects. So the overall in vivo situation, we don't expect any of those metabolites contributing to any pharmacological effect to samidorphan, and all we see is the receptor antagonist effect for samidorphan and mu receptor.

DR. AKERMAN: And I'll just add this is confirmed by no evidence of abuse potential for either olanzapine or samidorphan across the

clinical program.

DR. W. DUNN: So that's based off the assumption that the patient is taking consistent doses of the medication. I think in this patient population, consumption is inconsistent adherence. So if you've got a patient who is taking it one day and not the other, and as you mentioned previously, in 24 hours, you're losing about 90 percent of the blockade, how does that factor into the safety equation then?

Could you also comment on the half-life of the metabolites?

DR. AKERMAN: I'll ask Dr. Rege to comment on the half-life, but I will note that we saw good adherence across our clinical program, which is consistent with adherence, which is known to be the case for [inaudible - audio fades].

Dr. Rege?

DR. REGE: Bhaskar Rege, clinical pharmacology from Alkermes. Can I have the slide CT-3, please? The half-life of 996, which is the metabolite that we were discussing, it's around

24 hours versus the half-life of samidorphan, which is around 7 to 11 hours. There's a third metabolite that, in fact, has a similar half-life as samidorphan.

Again, as we saw, none of the data that we indicate in the remifentanil study, where we see a 48-hour blockade, that none of that data really indicated that any of the 996 metabolites contributed to any effects because we actually see a receptor blockade rather than any of the agonist effects due to the metabolites, even if it has a longer half-life.

DR. W. DUNN: Just as a quick follow-up just to clarify, hypothetically, patients taking the combination product consistently for, let's say a month, and then start to take it inconsistently once every 2 days or so, in that window where their samidorphan concentrations are achieving less than 90 percent occupancy, you've got more new opioids or antagonist activity present, and that hypothetically could put the patient at increased risk for an overdose if they took another opiate

agonist?

Would that be a correct interpretation of the safety concern?

DR. AKERMAN: Well, I'd like to ask Dr. Kathleen Brady to comment on what is known about opioid overdose risks associated with antagonists, but just to note that opioid use would be contraindicated in conjunction with OLZ/SAM use.

Dr. Brady, could you comment on opioid risk of overdose?

DR. BRADY: Yes. The risk of opioid overdose as associated with antagonist therapy is generally thought to be associated when an individual with opioid-use disorder is placed on an opioid antagonist, which again that would be contraindicated with OLZ/SAM, and then they abruptly stop and resume their usual dose of opioids.

One of the things that happens with opioids is people get tolerant very quickly, so they'll lose that tolerance very quickly when they're taking an antagonist. And if they administer the

same dose of opioids that they're used to administering, they're likely to overdose.

There is a little bit of animal data that suggests using opioid antagonists when they abruptly discontinue, there is super sensitivity of the new receptors, but that has not been demonstrated in clinical populations at all. In fact, there's a human laboratory study by Cornish and colleagues where they gave individuals -- they tested morphine sensitivity, gave a couple of weeks of daily naltrexone, tested morphine sensitivity with abrupt discontinuation, and found no change in terms of CO2 or respiratory depression.

DR. W. DUNN: Could the FDA comment about these metabolites? Is it a concern of yours? I don't have, off the top of my head, the binding affinities of a standard opiate versus these metabolites, so I'm wondering if the binding affinities are not high enough for you to be concerned about that agonist activity of the metabolites; if you could comment on that. Thank you.

DR. NARENDRAN: Dr. Dunn, we're going to wait for agency because they have their own time.

DR. W. DUNN: Okay.

DR. NARENDRAN: Okay? They'll have 30 minutes.

The next question is going to be Dr. Krishna.

DR. KRISHNA: Hi. This is Sonia Krishna, affiliate faculty at Dell Medical School at Austin. I just wanted to clarify what the demographics were for A303, what the average age was and baseline weight with absolute numbers. I've appreciated the percentages but really want to see what the absolute weight reduction or at least prevention of gain was. I saw 3 to 6 kilograms. I just wanted to clarify that. Thank you.

DR. AKERMAN: Yes, absolutely. I'll ask Dr. McDonnell to speak to this, but noting that you've asked about the demographics and the absolute weight change.

Dr. McDonnell?

DR. McDONNELL: David McDonnell, Alkermes.

Slide up, please. This is a slide looking at the baseline characteristics in the A303 study, and we see the baseline characters were generally well balanced between the treatments. The body weight at baseline was 77 kilograms and the BMI between 25 and 26, very similar between both treatment groups.

DR. NARENDRAN: Did that answer your question, Dr. Krishna?

DR. KRISHNA: Yes, that covered most of it, but if you could remind me what the absolute percentage change changed to in terms of kilograms, that would be helpful.

DR. McDONNELL: Yes. The absolute change in body weight with OLZ/SAM was 3.18 kilogram. With olanzapine, it was 5.08 kilogram, and the difference of 1.9 kilogram.

DR. KRISHNA: Thank you.

DR. NARENDRAN: The next question is from Ms. Witczak.

MS. WITCZAK: Good morning. Thanks for your presentation. I had two questions, one that just came out of the one from prior speaker. But the

first is, given that we know that antipsychotics, Zyprexa, has a lot of off-label use, I'd love to hear what your thinking is behind that because, obviously, this is a great concern with what's happening in the real world, off-label with Zyprexa and the weight gain, so I'd be interested about that.

Then, I noticed on the slide -- so that's question 1. Question 2 was in that slide on the demographics. I just wanted to make sure that I understood something correct, that only 64 percent of the people actually completed the study. Is that what the completion rate was, completion percentage? And if it was only 64 percent completed, what were the reasons for dropping out?

DR. AKERMAN: Your first question, the indications proposed for OLZ/SAM would be consistent with that of Zyprexa, which we'll be recommending. To your second question, the reasons for dropout, I'll ask Dr. McDonnell to speak to that, noting that the dropout and missing data is what was anticipated in a schizophrenia trial of

this duration.

Dr. McDonnell?

DR. McDONNELL: David McDonnell, Alkermes. The treatment completion in the study, you're right, was over 64 percent in the study. That's high for a study of this duration in this study population. Most antipsychotic studies that are 24 weeks duration or longer tend to have discontinuation rates that are higher than that.

The reasons for discontinuation in this study -- slide up, please -- the majority of the reasons that patients discontinued in our clinical studies is for withdrawal by subject, loss to follow-up, and they tend to be the highest reasons for discontinuation, and then the adverse events were similar between the treatment groups for OLZ/SAM and olanzapine.

MS. WITCZAK: Okay. Thanks. This helps right here. I see that the adverse events are a little bit higher with the combined product. Again, going back to the question on off-label, I know this is what was studied, but there are a lot

of knowns out there, given the fact that olanzapine has been on the market for a long time and there's been all kinds of issues with off-label; so just being more proactively looking at this and what could be anticipated.

That would be a comment, or I would love to hear your comments based on what I just said. Thank you.

DR. AKERMAN: Yes, absolutely. Thank you. Dr. Rene Kahn is joining us and has extensive experience with research on olanzapine.

Dr. Kahn, could you comment on the question about off-label use?

DR. KAHN: Yes. Thank you, Dr. Akerman. This is Dr. Rene Kahn, and just for my conflict of interest, I do get honoraria and consulting fees from Alkermes.

Yes, there's a lot of experience with olanzapine since the approval in 1996, and I do think it is really mostly used in schizophrenia and bipolar illness and maybe sometimes in psychotic depression. But I'm not so sure that the off-label

use is really extensive in olanzapine because it's really only approved in the indications that I just mentioned. So I'm not so sure whether it's, in the clinical, normal practice, going to be a major problem. Thank you.

MS. WITCZAK: Okay. We can discuss that later this afternoon on my concerns. Thank you.

DR. NARENDRAN: Thank you.

People who've asked the questions and have their questions answered, if you could lower your arm, that would be helpful. The next question is Dr. Thomas.

(No response.)

DR. NARENDRAN: Dr. Thomas, we can't hear you.

DR. THOMAS: Okay. Sorry. Dr. Thomas, Baylor College of Medicine. I have two questions. One is in two parts, and this is directed towards Dr. Brady and Dr. Rege; apologies if I'm mispronouncing that.

The first question is, my understanding of samidorphan is not only that it has a longer

half-life but also higher binding affinity than naltrexone, which the presenters have compared it to in terms of efficacy and safety or other safety data for it. I guess, one, is that accurate?

Two, if that is, especially for Dr. Brady, do you think that the protocols that exist for dealing with acute pain management for people on antagonists would be altered or import more morbidity if they had to overcome this over a longer time and with a higher affinity binding antagonist?

DR. AKERMAN: I'll ask Dr. Rege to speak to the binding affinity first, and then to Dr. Brady. Thank you.

DR. REGE: Bhaskar Rege, clinical pharmacology at Alkermes. Can I have slide CP-91, please? From a binding affinity perspective, in regards to the mu receptor naltrexone, samidorphan only is twice -- has more affinity than naltrexone. Per kappa, they have a very similar affinity between naltrexone and samidorphan, and for delta, it is about 30-fold more affinity for samidorphan.

DR. AKERMAN: Dr. Brady, could you comment on pain management with an antagonist?

DR. BRADY: Yes. This is Kathleen Brady, and I am a paid consultant for Alkermes, just for conflict of interest. As you know, pain management is a very clinically driven process and so individual. Pain thresholds as well as pain regimens differ tremendously from one individual to the other.

So I would say that these fairly minor differences in binding and half-life are something that would fairly easily be managed using the protocols that are already well established with careful patient monitoring, because no matter which antagonist an individual is on, there will be a time when the antagonism is wearing off and agonists become more potent. It's hard to say precisely for any individual what that time point is, so clinicians know to monitor carefully. Thank you.

DR. THOMAS: Hi. It's Dr. Thomas. My second question is related to the slide regarding

labeling. Having the antagonist there, there's the question of if you have someone who is in a using population of opioids, whether that would import increased risk of death and relapse.

There's actually some good data, and Dr. Brady's has already brought this up, around I think a 6-month study of Vivitrol versus Suboxone in which one of the outcomes was that there actually wasn't an increased risk of overdose, at least relative to one another, but you could potentially extrapolate that with this. However, these were people that were in a recovery program and actively working on it.

So I guess my question is, is there any thinking about the labeling to designate if people are on this, they either become opioid-dependent or they come into treatment opioid-dependent, labeling around them being in recovery or their stage of recovery? Certainly, if they're early in recovery and they're not in treatment, there might be more risk around that as opposed to someone who's been in recovery or working a recovery program. Thank

you.

DR. AKERMAN: Yes, thank you. This is something we considered very carefully, and I'd like, again, to have Dr. Brady weigh in on her clinical impression. But there will be a contraindication for patients who are currently physiologically dependent on opioids and would really be clinical judgment if someone had a remote history of opioid use.

Dr. Brady, could you comment as well?

DR. BRADY: Yes. I'd say this is definitely an issue of clinical judgment, but if we think about current opioid-use disorder, it's actually any time in the last three months. Really, the gold standard for this is going to be the clinical interview. I think that anybody probably who has had opioid dependence or actually is even at high risk is somebody you'd probably want to think very carefully about using this particular drug.

It's a very small percentage of the population of individuals with schizophrenia. It's only somewhere between 5 to 10 percent, so there's

still 90 percent of patients for which this would not even be an issue. So I think one would want to tread very cautiously in people with recent histories of opioid-use disorder.

DR. THOMAS: Just one follow-up question for that. Is it the idea that the labeling would be contraindicated in people with opioid-use disorder and cover even if they were not initially and then became or started to have that issue, as opposed to designating anything around recovery, or how that works if they were to become dependent?

DR. AKERMAN: The current contraindication we're proposing would be in people who are physiologically dependent on opioids. Because opioid-use disorder is a broader diagnosis, it would be at the discretion of the clinician if someone had a remote history of opioid use.

DR. THOMAS: Okay. Thank you.

DR. NARENDRAN: Thank you.

We have 12 minutes. I've got another four questions. I would appreciate it if you guys could now stick to one question at a time, and that way

everybody has a chance to ask their question; then if there's extra time, you can come back again.

The next question is from Dr. Boudreau.

DR. BOUDREAU: Yes. Hi. A quick question because a lot of mine were answered. With regards to the educational materials -- and sorry if this was discussed, as I might have gone in and out a little bit with my cell -- do the materials contain information about the risk of opioid overdose, even post-discontinuation of the medication?

I know that you addressed the fact that the data is pretty limited around -- I think it's only animal studies with regards to the upregulation of mu receptors with naltrexone, which is one of the hypothesized mechanisms by which they've observed elevated risk of overdose after treatment discontinuation.

It doesn't sound like you've looked at that in your clinical program with regards to animal studies, but I'm just curious about educational materials with regards to that, given that adherence to these medications sometimes isn't

great, and that these patients could present in emergency departments and places and not say that they're taking the medication because they have discontinued it, but still could be at risk for an undetermined time following discontinuation. Thank you.

DR. AKERMAN: Yes, we agree it's important to include all of these potential risks associated with opioid antagonists, and that would include the risk of overdose if someone were to attempt to overcome the blockade, if there was risk of precipitated opioid withdrawal, and the risk of inadequate analgesia. These risks will be included in the contraindications and warnings and precautions, as well as any educational material for both HCPs and patients.

DR. BOUDREAU: Thank you.

DR. NARENDRAN: The next question is from Dr. Iyengar.

DR. IYENGAR: This is Satish Iyengar from the University of Pittsburgh. I have what's maybe a discussion question. The studies that I see here

are on schizophrenia. How strong is the evidence that extrapolation to bipolar disorder is feasible?

DR. AKERMAN: Yes. I'd like to ask my colleague, Dr. DiPetrillo, to comment. We align with the agency on a bridging strategy.

Dr. DiPetrillo, could you outline this?

DR. DiPETRILLO: Yes. Lauren DiPetrillo, regulatory affairs. As mentioned by Dr. Fischer this morning, we did align with the agency on a bipolar bridge.

If I could have slide up? This really rests on two key points, one in regards to demonstrating that the olanzapine exposure in OLZ/SAM is bioequivalent to Zyprexa, which is shown here, and then also showing similar antipsychotic efficacy to olanzapine across our schizophrenia program.

If I could have slide up? The bipolar bridge is also supported by several other lines of evidence, namely that we know that olanzapine-associated weight gain is disease independent and noted as a concern for both patients with bipolar and schizophrenia. We also

know that the weight mitigation Of OLZ/SAM is disease independent, as we've seen this in healthy volunteers and in schizophrenia patients. We have no drug-drug interaction with lithium or valproate.

Then importantly, in looking at the literature, opiate antagonists, when given concurrently with patients' antipsychotic agents, does not affect bipolar symptom control, and in fact are included in treatment guidelines right now for patients with co-occurring substance-use disorder. But in regards to your question on how this translates, I'd like to actually turn it over to Dr. Kahn to speak about his clinical expertise of using olanzapine in both bipolar and schizophrenia patients.

Dr. Kahn?

DR. KAHN: Yes. Thank you very much. If I can just show up the slide on the efficacy of olanzapine in slide number 16, in bipolar illness. You can see there that olanzapine is highly effective as a treatment of mania, and also the time to discontinuation is actually the shortest or

the least pronounced in patients with mania. I really think that olanzapine is very well shown and very well studied.

You can see that also in the confidence intervals in bipolar illness, a highly effective antiemetic agent and a highly effective drug to maintain mood stability in bipolar illness. So I think there's a very long history of both efficacy in the short term and the long term in bipolar illness. I think a drug that includes the high efficacy of olanzapine in bipolar illness with the mitigated weight gain is really something we need currently. Thank you.

DR. NARENDRAN: Thank you.

The next question is from Dr. Jeffrey.

DR. JEFFREY: Hi there. Jessica Jeffrey from UCLA. For Study A303, I found it interesting that participants did not report changes in quality of life. Will you please review the tool used to assess quality of life and discuss your interpretation of these results? Thank you.

DR. AKERMAN: Yes. I'd like to ask

Dr. McDonnell to speak to these data, followed by Dr. Ginger Nicol to give her impression of the importance of weight gain to patients.

Dr. McDonnell?

DR. McDONNELL: David McDonnell, Alkermes. We did look at the quality of life in our clinical studies, and as you may expect, the results may have been confounded by the fact that both patients will be treated with active treatment, both patients receiving olanzapine. We know that patients who are treated with olanzapine tend to have high quality of life.

Slide up, please. These are the quality-of-life measures that we used in our clinical program. We used the EuroQol in 303 and the Impact of Weight on Quality of Life in 303. The Impact of Weight on Quality of Life, we were trying to look for a measure that could look at the effects of weight, and we chose this one because it is used in weight-loss products, however, probably was not well suited to a product that prevents weight gain.

What we saw in the outcome of the scale is we saw patients entering with high levels of quality of life, so a high score indicates a high level of quality life, and those levels stayed high for the full duration of the study. When you look at the individual items on the impact of quality of life, it may well be that the actual well being on the treatment affected them.

So this is something we've seen consistent in the clinical program, that both patients are all on olanzapine, so they tend to do well in the quality of life. One of the things we did look at is we did a patient exit interview for patients who were on OLZ/SAM in our open-label extension study.

Slide up. This is only a subpopulation of the patient. It's biased, but there are patients who remained on OLZ/SAM, so obviously they chose to remain on it. But what we saw was in those patients, generally speaking, quite positive effects on their emotional and mental well-being, on their self-esteem, and social activity. The patients were doing well when treated with OLZ/SAM,

obviously, within the limitations of how this interview is done.

I'll ask Dr. Nicol to talk to the effects of weight on quality of life in general.

Dr. Nicol?

DR. NICOL: Hello. This is Ginger Nicol. I'm a child and adult psychiatrist and obesity medicine specialist at Washington University in St. Louis, representing the clinical risk-benefit perspective here. For disclosure, I'm a paid consultant for Alkermes.

One of the things that we know about quality-of-life measures and randomized clinical studies of patients with schizophrenia is that, just as Dr. McDonnell said, most of the people that entered the study, there are limitations on how sick or well they can be. So when they're already on a medication that's very effective or they are stabilized, these measures tend to be high, and I think it's meaningful that they didn't change over the course of the study.

What we know from at least one

study -- slide up, please -- asking patients with schizophrenia what influences their decision to take medication -- but I know there are many psychiatrists here listening today. This is a population that we really do struggle with treatment compliance. This is an online study, so everybody was anonymous. But patients with schizophrenia, asking them what's the most important thing in terms of medication side effects that drives your decision to take a medication, you can see here, in that study, looking across the spectrum of potential weight gain, the number of respondents saying, "Yes, that would mean I don't want to take the medication."

This is really, I think, pretty obvious here with the slide, but in general, and working with patients with first-episode schizophrenia in particular, which is more typical in my population, these folks are very concerned about weight gain. They may not really understand or care about some of the other longer term side effects associated with weight gain, but weight gain is very important

and having the discussion with patients and families, especially in that critical period where we need to get them treated so we can impact long-term functioning. Thank you.

DR. NARENDRAN: The next question is from Dr. Bohnert.

DR. BOHNERT: Hi. Thank you. I was curious if I understood correctly in the dose-finding study, or Study 302, there was a lack of dose response effect on weight of the samidorphan. I hope you could comment on why you went forward in the next studies with the highest dose.

DR. AKERMAN: I'll ask Dr. McDonnell to speak to the dose-finding study.

Dr. McDonnell?

DR. McDONNELL: David McDonnell, Alkermes. In the phase 2 302 study, which is our dose-finding study, it's important to point out that the primary outcome of that study was actually an efficacy outcome, and as you would expect, the different doses of samidorphan that were studied in that study did not have an effect on the efficacy

outcome because olanzapine was treated as required by the clinician.

With regard to the weight effects, this was an important secondary endpoint in the study. We did study three different doses of samidorphan in this study. We studied a 5-milligram dose, a 10-milligram dose, and a 20-milligram dose, and I acknowledge that the FDA said that they didn't see a dose difference in this study.

Slide up, please. But when we got the results of this phase 2 study, based upon this data -- which here we're looking at the percent change from baseline and body weight by week. In orange is the olanzapine-treated patients and in blue is the patients who had samidorphan. The solid blue line is the 10 milligrams of samidorphan and the dotted lines are the 20 milligram and 5 milligrams of samidorphan.

What we saw is we saw the best mitigation of weight with the 10-milligram samidorphan dose, and obviously when we're looking at a medication that doesn't cause weight loss, we want to try and

maximize the amount of weight that it prevents. We looked at this data, and there are some other data in the clinical side where samidorphan was tolerated at all three doses. There was no real difference in the tolerability of samidorphan, but we felt that this was the dose that maximized that mitigation of weight in our phase 2 study, and we chose that dose as a fixed dose to move forward. Slide down, please.

DR. BOHNERT: Thank you.

Clarifying Questions to FDA

DR. NARENDRAN: Thank you.

It's about 11:30. I still see a couple hands up. I wasn't sure if Dr. Dunn and Dr. Iyengar have questions, but I was thinking we can move to the agency's question session, and if there is extra time, we can give you a chance to complete it.

So let's move to the agency's questions, clarifying questions to the FDA. Again, please use the raised-hand icon to indicate that you have a question. State your name for the record. If you

have a specific presenter, please address that question to the presenter. If there's a specific slide you have, address it to the slide. At the end of your question being answered, please say thank you so it would be easier for me to figure out to move to the next person.

Our first question is Dr. Dunn because he had that follow-up question.

DR. W. DUNN: Great. Thank you. Walter Dunn, UCLA. Yes, this is a follow-up question to the agency. Regarding the presence of the mu opioid agonists, as far as the metabolites, how problematic is that? Is that a concern. Then as a related question, what's your stance on fluctuating levels of mu blockade? So again, observation within this patient population, medication adherence is highly inconsistent and, again, that's the presumption rather than the exception.

As a related question, what's your position on the use of this on a PRN basis?

DR. FARCHIONE: Sorry. The last one threw me a bit. This is Tiffany Farchione, by the way.

What do you mean by on a PRN basis?

DR. W. DUNN: Yes. Basically, the two clinical situations I can envision are a patient is taking a standing dose of OLZ/SAM, and then occasionally you prescribe, let's say, a 5-milligram dose of olanzapine for any potential exacerbations of symptoms or treating psychotic episode before they get bad, allowing the patient to take it on an as-needed basis, based off --

DR. FARCHIONE: I think that that's kind of outside the scope of what we're talking about here. We're really talking about the indication that they're seeking, which is chronic treatment indication for schizophrenia or bipolar I disorder. But as far as the previous question about -- and again, this is not something that we brought up in our briefing document or anything like that because it really wasn't an issue that we were particularly concerned about.

I know that you referenced previous briefing materials from the last advisory committee, and really under that application, the main reason that

we were concerned was because with that other application, that samidorphan was combined with buprenorphine, which is an opioid agonist. So we had concerns about the -- and they were hypothetical concerns, but we had hypothetical concerns about potential additive, new agonism effects between buprenorphine and samidorphan metabolite.

So that's where the concern came from in the past, but we don't have anything really to add on this application. The other thing, too, to think about is that, again, with the previous application, there was a human abuse potential study, and samidorphan didn't produce positive effects in the human abuse potential study either.

DR. W. DUNN: Dr. Farchione, just as a follow-up on your first comment about this use in a chronic population, I guess maybe the better question is, is there a concern for safety if there is fluctuating levels of new blockade?

DR. FARCHIONE: Again, we haven't evaluated it in that context, and I don't anticipate that it

would be used in that manner. If that's related to the PRN question, I'm not sure why someone would use this as a PRN basis.

DR. W. DUNN: I guess, again, under the presumption that patients -- even if we prescribe it to them chronically or just kind of standing, they're not going to use it every single day, right? They're going to be on and off maybe 60-70 percent of the time they're taking their medications. I guess maybe that would be the closest --

DR. FARCHIONE: Perhaps I can throw this over to Judy Staffa because I think your question might be coming from some of what was in the OSE presentation, so let me pass that over to her.

Judy?

DR. STAFFA: Hi. Judy Staffa here. Yes. I think that is one of the concerns that was raised in Dr. Celeste Mallama's presentation, is the fluctuating levels of the antagonist sitting on the receptor, and I think that related to some of the concerns about overdose. I think those fluctuating

levels come not from a prescribed PRN regimen, but more from, what we know, as you mentioned, about the difficulties with adherence to medications in this patient population.

So I think that's where those concerns are reflected. Yes, we've posed them and are anxious to hear what folks think about that, who treat these patients and know even more about this condition and this concern.

DR. W. DUNN: Great. Thank you.

DR. NARENDRAN: Our next question is from Dr. Zacharoff.

DR. ZACHAROFF: Hi. This is Kevin Zacharoff from Renaissance School of Medicine at Stony Brook University. This is in reference to the presentation that we previewed by Dr. Celeste Mallama with respect to considerations of risks associated with real-world settings of opioid use.

Dr. Mallama, in one of your slides, at the conclusion of that prerecorded presentation, there was mention about use of alternatives in the event that somebody requires acute analgesic treatment if

they're on this medication. I'm just wondering what alternatives were being referred to because, as we heard, in the example given earlier to my question from the sponsor, there was a situation where somebody was in a motor vehicle accident and suffered a fractured pelvis and presumably presented to the emergency department requiring analgesic treatment.

I know there was some mention of acetaminophen, but I don't think most clinicians would consider acetaminophen to be adequate analgesic treatment for someone who's post-MVA with a fractured pelvis. So I just want clarification about what alternatives were being referred to.

DR. MALLAMA: Hi. This is Celeste Mallama with FDA. In regards to pain management alternatives, those would be non-opioid alternatives. I think I can also pass this question to my colleague, Dr. Alicia Lopez, if you want to add something.

DR. LOPEZ: Yes. This is Dr. Lopez with the FDA. The case that's referenced that you were

referring to, that was based on the literature review, within the literature it was stated that the surgical team used a multimodal approach to pain management. They did use opioids. In this case for post-surgical pain, they used a hydromorphone pump, pain pump. Non-opioids that they used, at the end of surgery, they used a nerve block and then they also used the acetaminophen. They reported that they didn't believe the nerve block alone would be sufficient to manage the post-surgical pain, but that was the combination that they opted for within that case that was reported. Thank you.

DR. W. DUNN: Thank you. That answers my questions.

DR. NARENDRAN: The next question is from Dr. Fiedorowicz.

DR. FIEDOROWICZ: Yes. This is Jess Fiedorowicz in Ottawa. My question is for the FDA. I heard the rationale for the bridging strategy to a bipolar I indication rests on bioequivalence for olanzapine and a trial in schizophrenia. There

were some studies cited by the applicant in bipolar disorder, and those included two small trials with comorbid alcohol-use disorders; a practice guideline recommending naltrexone for use of alcohol-use disorder; and then a very small trial that was just a research letter, and all of those studies were with naltrexone.

So in my mind, I'm struggling with seeing how there's a single bridge here. It seems more like a series of bridges, perhaps something more familiar to what my colleagues in Pittsburgh might be familiar with. We have links from schizophrenia bipolar disorder, and then from naltrexone to sam. If that's the case, I think the rationale for each of those may be somewhat tenuous. The first is if naltrexone holds and why not just use that, which is much cheaper, and then the second, there's a lot of burgeoning literature on opioid neurotransmission, and it's relevant to the mood disorders.

So I'm just wondering what your thoughts are on this sort of complicated and tenuous bridging

strategy, and also, is there any precedent for that, for this sort of complex bridging strategy?

DR. FISCHER: Hi. This is Bernie Fischer. Usually when an applicant comes in and is going through a 505(b)(2) pathway, we make sure that they have compared the bioavailability, and that lets us generalize that their drug has the same blood levels and would lead to the same efficacy and safety as a listed drug or a drug that's already approved.

In this case, the applicant did do that, and what we really wanted to see was does the samidorphan interfere with the blood levels, interfere with the action at the receptor, and interfere downstream somehow. So we didn't think that they needed to do a bipolar study and a schizophrenia study because most of the drugs that are approved for both indications we assume act, at least partially, through a B2 receptor blockade.

So we were satisfied that if there was no interference in the efficacy with the schizophrenia study, that we didn't feel that there was going to

be a unique interference with the bipolar group as far as efficacy.

DR. NARENDRAN: Does that answer your question, Jess?

DR. FIEDOROWICZ: It answers my question. I'm not sure that I find it compelling, but I appreciate the answer.

DR. NARENDRAN: Our next question is from Dr. Krebs.

DR. KREBS: Hi. Thank you. This is Erin Krebs. My question is related to the weight gain issue, specifically with switching from olanzapine to the OLZ/SAM formulation. I'm referring specifically to figures that were in the FDA documents, really looking at the extension studies where there's an open-label extension after an initial randomized trial, and then included in the FDA presentations we watched earlier.

At least my impression here is that the weight gain is happening early when the drug is started, whether that's olanzapine alone or the olanzapine/sam. The benefit that seems to be

there, in terms of prevention of additional weight gain or of excess weight gain, seems like it's with the patients who are olanzapine naive starting initially. At least from the figure that I'm looking at, it didn't seem that that was occurring with patients who were switching from olanzapine to olanzapine/sam.

The reason, I'm just wondering if you could comment on that or have conversation about that. I imagine if this product becomes available as something to prevent weight gain, that patients who had been on olanzapine and had weight gain may want to switch to this new product with the hopes that that would halt the weight gain.

Is that something that can be commented on at this point or do we just not have data that are adequate?

DR. GOLDEN: Hi. This is Julie Golden. I'm a clinical reviewer with the Division of Diabetes, Lipid Disorders, and Obesity at FDA, and I collaborated with the Division of Psychiatry on this application. I am also looking at the figures

that you cite in the FDA briefing document. These were basically patients, when they switched over in the open-label phase to ALKS 3831, we're following those patients from the beginning of the controlled period. So they are not randomized from the beginning. That's the first point.

The second point to make is that while these longer term switched data seem potentially suggestive of a stabilization of weight, I think it's premature to make that statement at this point because we don't have randomized data at that time. We don't have any data suggesting that patients who have been on olanzapine for, say, 3 months or 6 months, and then switch over to ALKS 3831, will mitigate the weight gain. That would require an additional randomized period post-olanzapine.

The only data that we have that's potentially suggestive was in the FDA presentation of 302, which included a 1-week olanzapine lead-in period, and then patients who gained weight were stratified in that period.

So although that's a very exploratory early

study and we can't make any comments about whether that pattern would be seen in future studies, there was some suggestion of an enhanced treatment effect in patients who gained weight with olanzapine in that 1-week period. Beyond that, I think it's just speculation.

DR. NARENDRAN: Does that answer your question, Dr. Krebs?

DR. KREBS: Yes, I think so. Thank you.

DR. NARENDRAN: I do not see any more questions for the agency. Does anybody else have any more questions for the agency? We have 10 more minutes. I see a couple of hands.

Dr. Dunn, do you have a follow-up question?

DR. W. DUNN: Yes, a follow-up question maybe for one of the biochemists at the agency.

Can you comment on the binding affinity of those metabolites compared to a standard opiate that someone would be taking? I appreciate that metabolites have a 10-fold lower binding affinity compared to samidorphan, but how does it compare to a standard mu agonist people will take for

analgesia?

DR. FARCHIONE: This is Tiffany Farchione again. I think the person we would need in order to actually answer that question is not in the presenter room, so we would have to actually get that person and call them in and everything. We'd also apparently have to look up the answer as well, but we can try to get that to you. There's no direct comparison studies, but we can try to get that response to you before the end of our part of the session here.

DR. W. DUNN: Yes, that would be great. I'm just trying to -- yes, if you could get --

DR. FARCHIONE: Yes.

DR. W. DUNN: -- if you can give me some idea of how problematic it's going to be, how does it compare to morphine, or oxycodone, or something like that. Thank you.

DR. FARCHIONE: Yes. I also wonder if perhaps the applicant has a ready answer to this. Again, like I said, we have to look this up, but perhaps they're prepared with a backup slide or

something of that nature.

DR. AKERMAN: Yes. Just to clarify the question, are you asking about the binding affinity of samidorphan?

DR. W. DUNN: No, the metabolites, the metabolite that has the mu agonist activity.

DR. AKERMAN: Yes. And maybe before I turn it over to Dr. Rege to speak to that, I want to also mention that we've conducted a thorough human abuse potential study, and in our clinical data, we see no evidence of abuse potential.

Dr. Rege?

DR. REGE: Yes. Bhaskar Rege, clinical pharmacology in Alkermes. I think your concern is whether the metabolite would impart any pharmacologic effect. I think there's a bit of evidence clinically speaking. I mentioned remifentanil, but I can also show you the human abuse potential study data that also confirm that there was no indication of any [inaudible - audio fades] metabolite, which in vitro has shown to be a mu agonist.

Slide up, please. As the slide is coming up, what you will see on the slide is I'm going to show you the primary endpoint analysis data, and that relates to the [inaudible - audio fades]. The slide is going to take a little bit of time to come up, but let me explain in terms of -- [inaudible].

Actually, the human abuse potential study for samidorphan, that was done up to 30 milligrams, which is 3 times the target dose of samidorphan. The study was conducted in accordance -- yes, that's the study. On the screen here, you will see that the data for the primary endpoint, which is the difference of the Emax drug liking visual analog scale relative to placebo, is plotted, and what you see is a point estimate, as well as a 90 percent interval.

There were 5 treatments in this study, but there were 2 doses of samidorphan used, the 10-milligram, which is a target dose, and a 30-milligram, which is a supratherapeutic dose but 3 times higher. The study also included a negative control, which is naltrexone at 100 milligram, and

also 2 positive controls with oxycodone, and then pentazocine.

With the positive control of oxycodone and pentazocine, which you see as a dotted line and a B at 15, it was considered to test whether the study had an adequate assay sensitivity, and the criteria there was the lower interval to be at least above 15, and that's in accordance with FDA guidelines. You see that both oxycodone and pentazocine data suggested that the study had adequate assay sensitivity.

The next point of comparison was whether samidorphan was different than placebo. The criteria that was used in accordance with discussion with the agency is that the upper 90 percent interval to be below 11, and that 11 threshold was set based on VS1 [indiscernible] analysis on multiple, historical HAP study data, looking at the placebo responses. Prespecified criteria that was set as 11, both samidorphan doses 10 and 30 were well below that 11 threshold and similar to naltrexone.

Again, I think these data also suggested that the data we have in terms of in vitro for a metabolite really didn't confer any effects clinically speaking, whether it's an abuse potential signal or any of the PK/PD data that has been looked at in the ability of samidorphan to block remifentanil effects.

DR. W. DUNN: Yes, a quick follow-up question. The way these studies were conducted, how long after the last administration of samidorphan were the subjects interrogated about their liking for the compound?

DR. REGE: It was up to 72 hours after the dose of samidorphan.

DR. W. DUNN: So the assumption is, at that point, there should have been no more new blockade from the samidorphan, and if there was any effect from the metabolite, it would be unopposed activity at the mu receptor. Would that be correct?

DR. REGE: That's correct. So at 72 hours, there shouldn't be any mu blockade [inaudible -

audio fades].

DR. W. DUNN: Okay. Thank you.

DR. NARENDRAN: Two more questions for the agency.

DR. FARCHIONE: Sorry. Raj, this is Tiffany. Before we move on, I do just want to emphasize that the agency agrees with what the applicant just presented as far as their human abuse potential study is concerned. I'm hoping that that covers Walter's question adequately.

DR. W. DUNN: Yes. Thank you.

DR. FARCHIONE: Okay. Thanks.

DR. NARENDRAN: Thank you, Tiffany, for the clarification.

The last two questions, Dr. McAninch?

DR. McANINCH: Actually, this is Jana McAninch from FDA.

DR. NARENDRAN: Oh.

DR. McANINCH: I wanted to just follow up on a question that was asked earlier, but if there's a new question, we should probably go to that first, and then I can comment afterwards.

DR. NARENDRAN: Dr. Meisel?

DR. MEISEL: Hi. Thanks, Raj. Steve Meisel from Fairview, a question for the agency here. There is a drug called Contrave that the agency approved a year or two ago for weight loss that is in many respects comparable because it's got naltrexone in it. It's designed for weight loss, but has the same risks, at least in principle; if somebody needs emergency opioids because they come into the ED after a trauma or something like that, or require surgery, or dental procedures or something.

Could the agency please comment on the relative risk of opioid overdose, or lack of effectiveness, or those kinds of elements with Contrave versus the product the applicant is asking for today?

DR. STAFFA: This is Judy Staffa from FDA. We did look into this, as you'll remember from our background materials, as well as Dr. Mallama's presentation. There are some similarities because we saw this as a product that was approved for a

population that contains an opioid antagonist, but it's not approved for use in a population that actually has opioid-use disorder. So it was a different group than the other populations out there who are administered naltrexone, as was talked about before.

We looked into our postmarketing experience, and I'll turn it over to some of our speakers that are more familiar with those detailed data. But again, we also noted that this population is not exactly the same as the population taking a product that contains an opioid antagonist for weight loss. This is a different population.

So we included it because it is the only product we know of that has that particular characteristic, so I'm glad you brought it up because I think we do think it might be relevant. But we've done the review, and I think there's some limited information available, and I'll turn it over to I think Dr. Lopez for that part of the review.

Is that correct, guys?

DR. MEISEL: If I could just clarify my question because in both of these cases, the prescriber of the target drug, whether it's this one or Contrave, would be different than the people who would be prescribing an opioid for an unrelated condition. So it's that educational, phase 4 type of stuff.

DR. STAFFA: That's correct, yes. That's what we thought, because we also noted that in the Contrave label, opioids are contraindicated, yet in one of our reviews, we noted that I think around 11 percent of those patients did have evidence of an opioid when we looked at prescription data.

We did also note that when we look at the olanzapine population, the current patients treated with olanzapine, when we look at national prescription data, we also see that in those patients, if we take a snapshot and look over the most recent year, that about 20-21 percent of those patients have a prescription for an opioid.

So we were trying to get an understanding of the differences between those populations. But

again, Dr. Lopez can provide a little bit of information about what we saw in the Contrave review. But just remembering that samidorphan is not approved as part of any other product, so we really can't look directly at another product with samidorphan, and I think we've already talked about some of the differences between samidorphan and naltrexone.

Dr. Lopez, can you just provide a high-level view of what you saw in the review?

DR. LOPEZ: Yes. This is Alicia Lopez. The review looked at data that came from the FDA adverse event reporting system. Within that review, we were looking specifically at interactions or patients who had an adverse event who were using both an opioid at the same time as they were using Contrave.

What we ended up seeing was there were 13 specific cases where we could identify somebody using those two medications concomitantly and where they did experience symptoms that were associated with an opioid withdrawal syndrome. We also

identified one case, which was previously discussed, about an inadequate analgesic effect for somebody who was not taking an opioid regularly and had an acute incident where they needed to have an opioid for surgery.

Now with that, it is important to note the limitations of the FAERS data as well as the strength of it. So as far as strength goes, that data includes all marketed products approved and off-label uses, as well as all patient populations. So it is looking at a large portion of the patient population. The limitations to it, though, are that we cannot assess a causal relationship between the event and the product, but fortunately it contains enough information for us to fully extract the relationship to the event. Also, we don't receive every report of an event that can occur, so there is usually an underreporting of the events within that data.

Something else that I would like to point out that we did notice, that there were some cases where a patient who was prescribed an opioid or

prescribed Contrave and were using those concomitantly, and the prescriber wasn't always aware of that concomitant use. So the prescriber may have prescribed Contrave to somebody who was previously established on an opioid without being made aware by the patient that they were using an opioid or vice versa.

There was also evidence of nonmedical use or somebody may have used a product that was not prescribed to them, or misused I should say. They were not using a product prescribed to them, but it may have been prescribed to somebody else, so then they had these two medications on board and they wouldn't have had the opportunity to be counseled by a prescriber about the potential for an adverse event.

DR. STAFFA: This is Judy Staffa again. I just want to add some more clarification. Thank you, Dr. Lopez.

When I spoke about the prescription data that we saw, that about 11 percent of patients who had a prescription for Contrave also had a

prescription for an opioid, that raises concern because, clearly, they were prescribed an opioid, but what we don't have a window into is to whether that was prescribed with instructions to stop taking the other product while taking the opioid or to hang on to the opioid. We don't know what specific instructions may have come with that. We just know that the patient had a prescription in their name for both.

DR. MEISEL: Thank you. That's helpful.

DR. NARENDRAN: We don't have any more questions from the members, so Dr. McAninch, if you could take over.

DR. McANINCH: Sure. Thank you.

This is Jana McAninch from the Division of Epidemiology. There was a question earlier about off-label use of olanzapine. I just wanted to point out some information that is in your FDA briefing document on diagnoses associated with use of olanzapine based on an office-based physician survey. This is on page 107 of the PDF or page 49 of the attended Division of Epidemiology review.

Basically, it looks like 31.5 percent of mentions were associated with a diagnosis of schizophrenia; 21.3 percent schizoaffective disorders; and 20.3 percent bipolar disorders. So cumulatively, it's about 73 percent of those top three with the remainder consisting of different depressive disorders, anxiety, adjustment, and psychosis codes, in case that's helpful.

DR. NARENDRAN: Thank you, Dr. McAninch.

I think with that, we will now break for lunch. We can reconvene in one hour sharp, at 1 o'clock as scheduled, a 55-minute lunch. Panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin a little bit earlier, 12:45, to ensure you're connected before we reconvene at 1 o'clock. Thank you.

(Whereupon, at 12:06 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

Open Public Hearing

DR. NARENDRAN: We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in the meeting.

Likewise, FDA encourages you at the

beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listen to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected now.

MS. FOXWORTH: Dear committee members, thank you for the opportunity to address you today. My

name is Phyllis Foxworth, and I am with the Depression and Bipolar Support Alliance. DBSA was created for and led by individuals who themselves have a lived experience. It is this first-person experience that informs our comment. We have not received funding from the sponsor to speak at the meeting today, however, we have received funding from the sponsor for activities at DBSA.

Living with bipolar can be life-threatening. The risk of death by suicide is 10 to 30 times higher than the general population. It is estimated that 20 to 60 percent will attempt suicide at least once in their life, yet, the history of therapeutic interventions to treat bipolar have been delayed due to societal stigma and negligence. Until the mid-90s, the only medication available was lithium salt.

Bipolar is far from a problem solved. Many people discontinue a therapeutic intervention because of the side effects. A DBSA study revealed weight gain as a side effect that most led patients to discontinue medication. This side effect cannot

only have a severe impact on individual's physical health, but can take a tremendous toll on their mental health.

For example, the report for the 2018 DBSA Patient-Focused Drug Development meeting identified the inability to live up to one's professional potential as a major impact of the disorder. While there are a myriad of reasons behind this challenge, the role of weight gain brought on by therapeutic interventions must be considered.

Not only do studies reveal that discrimination around body weight is rampant in our society, but employers often make hiring and promotion decisions based on a person's weight. This includes access to highly visible projects that can lead to promotion or outright dismissal.

Whole health is just as important. Forty percent of respondents to a DBSA survey stated their overall health was worse since first experiencing symptoms. Contributing to this revelation is that many people are forced to weigh the risks-benefits of side effects and make

difficult decisions on whether to prioritize treatment of their physical health or their mental health. This is a very personal decision, yet many within the medical and scientific community label people who choose to make a difficult decision to prioritize their physical health over there mental health as non-compliant.

DBSA holds it's not patients that are non-compliant, but the medical and scientific community that is non-compliant by not providing adequate therapeutic interventions. DBSA urges the committee to put the patient at the center of decision-making around approval of this application. When treating bipolar, success should be defined by considering the patient's whole-health requirements and their own unique definition of a life well lived.

If I have communicated anything, I hope it is this. Patients count. Bipolar is not a problem solved. Patients want and need solutions that support a pathway to whole health and thriving. Individuals will evaluate the risks and benefits of

solutions based on their own life circumstances. I respect there are many variables taken into account when considering this application, however, I urge the advisory committee to prioritize patient-desired treatment outcomes as part of your evaluation. Thank you for your time today.

DR. NARENDRAN: Thank you.

Speaker number 2, your audio is connected now. Please introduce yourself.

MR. SPERLING: Good afternoon. My name is Andrew Sperling, and I'm with the National Alliance on Mental Illness. I've received no compensation from the sponsor to appear here today. NAMI does receive financial support for support programs and other activities from the sponsor.

I've been at the National Alliance on Mental Illness now for more than 20 years, and I can tell you in all honesty that NAMI is the nation's largest advocacy organization, advocating on behalf of people living with mental illness and their families. Maybe in all my years at NAMI, I have yet to meet someone living with schizophrenia, or

any other major mental disorder, or their family members, that's completely content with the treatments that are available. They all have complicated side effects. They take a long time. There is often 6 to 8 weeks, after you initiate therapy, before you see any clinical benefit.

But we do know that some are better than others, and this was validated in the NIMH CATIE trial more than 15 years ago, and olanzapine had the lowest switch rate; in other words as the proxy for efficacy. But we also know from the CATIE trial that there was significant weight gain and metabolic syndrome associated with olanzapine that you've heard about this morning.

We believe at NAMI that patients should not have to choose between significant weight gain or efficacy and effectiveness in dealing with their side effects, and that's why we want to see newer, better treatments. This is not an incremental lens [indiscernible]; this is a game changer for people that are at risk of obesity and all the complications of diabetes that come with it.

I'm going to close on a personal note. My brother James has been living with schizophrenia since 1996. He has tried just about every medication that's out there. I could go through the long list, but I don't have time. But his longest period of clinical stability was from about 2008 to about 2015 when he was on Zyprexa, when he was on olanzapine. But I can tell you, he put on significant weight. My estimation during that period, probably close to 70 pounds. He now faces that dilemma, do I go with the most efficacious drug knowing that I have significant weight gain associated with it?

Patients should not have to make this choice. We need to do better and we need better treatments. I appreciate your time, and thank you for your attention.

DR. NARENDRAN: Thank you.

Speaker number 3, your audio is connected now.

MR. KRAMER: Thank you. Good afternoon. My name is Luke Kramer. I'm the executive director

for the STARR Coalition. We're a nonprofit organization, bridging the gap between mental health, research, and advocacy. In disclosure, the STARR has received one grant from Alkermes since our inception six years ago, but we have not received any honorarium or other reimbursements for our participation today.

I once worked with a man who I would watch cling to a telephone pole screaming. He later described being at the top of a tall building, being battered by storms, and about to fall to his death, and he lived his life in terror. I also worked with another gentleman who spent every waking moment convinced he was dying, and all he could do was smell his own flesh rotting.

There are countless stories like this, and I know many of us know countless people who right at this moment have had their lives torn apart by schizophrenia and bipolar. I'm honored to have my office in a day treatment facility where over 100 brave individuals with treatment-resistant mental illness come each day. They all know that we're

meeting, and several have submitted letters to you guys. But we talked extensively about this particular compound, especially the opioid component and their concerns.

Even with those with a history of dependency, every comment came back around to, "Look, we trust our treatment team and we're willing to try anything that can relieve our symptoms." Someone even asked would we even be talking about an opioid component if it was a proven drug for prostate cancer or heart disease?

I've been watching the transcript kind of come up through the bottom and imagined, what if we substituted the word "schizophrenia" and "bipolar" with the term "terminal cancer"?

If we had a medication that we showed that reduced tumors but had adverse side effects, and then the company decided to invest years of research and untold resources to transform that compound into something that would still stop the growth of tumors, but then would drastically reduce harmful side effects; if it was any other

indication, would we be sitting here today debating whether people should have access to this life-saving therapy?

We're not here with really any concern about the efficacy of this compound; we believe that the data speaks for itself. But we are concerned with people like me, and my peers, and others who are living with the diagnosis and the lack of urgency for getting new therapies to the public. We are concerned when we see respected biopharmaceutical companies peel away from this space because they've given up on this process or they see inequity with mental health therapies.

We all know that recovery is much much more than just swallowing a pill, but we also know, without medications that are proven to be effective, we, many of us, cannot even begin to get a foothold to begin that journey. Please consider those who are looking to all of us to be a voice for them. Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 4, your audio is connected

now.

MS. BERNSTEIN: Good afternoon, and thank you for allowing me the opportunity to speak with you today. I've not received financial consideration from the sponsor to speak, however, DBSA does receive funding for sponsorship programs.

My name is Kathy Bernstein, and while I work with the Depression and Bipolar Support Alliance, today I speak on behalf of myself, a daughter and a caregiver to my mother. Today I speak from our family's experience in caring for our mother, a woman who raised 6 kids, a husband, and managed a chaotic household, who now at the age of 84 lives with dementia in an assisted-living community and is in need of complete care.

Today I will share how medications designed to stabilize moods have had a life-changing impact on my mother, her ability to care for herself, and subsequently our family. Mom has lived with anxiety and depression for which she has taken medication most of her adult life. The untimely death of two children only exacerbated her

symptoms. As she aged, she began showing signs of dementia. Her cognitive and executive functioning deteriorated slowly, accelerating at times with increased anxiety. At the same time, Mom began losing feeling in her hands and feet, limiting her mobility.

As we mentioned, Mom was superwoman. She was an amazing cook, social, and smart. She loved to read books. She could do the New York Times Sunday crossword puzzle, and she was an avid bridge player. Two years ago, my mom fell and fractured her femur, which changed her life. She was hospitalized and surgery was performed. Because of her dementia and anxiety, and perhaps heightened by the quickness in which things around her happened, as well as pain medication she was given, she became unhinged, disoriented, verbally abusive, and combative.

Her doctor added olanzapine to her medication regimen, and while it helped settle her down and made it easier to care for her, it had negative consequences, too. Weight gain, one of

the known side effects, was dramatic. Mom quickly shot up in weight from 140 to 160 pounds. For a woman who had limited mobility to begin with, this was a game changer. Rehabilitation was impossible. She was too weak to carry the excess weight that occurred in what seemed like overnight.

Today she's a hundred percent wheelchair-bound. She cannot get up on her own out of a chair. She can't leave her room. She can't toilet herself or shower herself. She needs complete care. Because she's dead weight, I am no longer to take her out of the facility she lives in. She's stuck. And while she's less combative and calmer, her executive functioning has decreased significantly and she gets very disoriented at times. She can no longer play bridge, read books, or do those crossword puzzles.

My mom, the patriarch of our family, is gone. Her quality of life is gone. She tells me every day that she prays for God to take her. There has to be more options that may help people like my mom who need medications to be well in one

aspect of life that don't take away from other areas. Thank you.

DR. NARENDRAN: Speaker number 5, your audio is connected now.

MS. STALTERS: I'm Linda Stalters, the CEO of Schizophrenia and Related Disorders Alliance of America or SARDAA. We've received no financial support from the sponsor to participate in this hearing and we have received sponsorship funding for our activities from the sponsor.

I was formerly an APRN with a background in education, in-patient home health care, and a solo practitioner specializing in schizophrenia spectrum, bipolar, and borderline personality illnesses. I now serve as an executive and advocate for the most rarely neuropsychiatrically ill and pursuing improved treatments and services while educating and supporting diagnosed individuals, their families, professionals, and the public.

It is critically important for you to acknowledge these illnesses can be terminal

illnesses without treatment. Over 50 percent of individuals living with psychosis do not receive medication or care. Thus, without treatment, approximately 170,000 are homeless and almost 380,000 are incarcerated.

I have cared for and heard reports from many patients that olanzapine was very effective in managing their symptoms, but they either discontinued without notifying their clinician or changed to a less effective medication due to the unacceptable weight gain, and slid into psychosis that's leading them to homelessness or incarceration.

People with a brain illness such as schizophrenia or bipolar deserve treatment and care, not brutality of homelessness or incarceration. I actually had a patient once who said they would rather die of diabetes than give up taking olanzapine because of their symptom relief. We know that people with these illnesses die on average 10 to 28 years earlier than the general population. Some of these early deaths can be

attributed to the side effects such as metabolic disorder, sometimes related to medications.

There is more hope for people with schizophrenia spectrum and bipolar if they receive well-tolerated, efficacious treatment. Don't people with these illnesses deserve a meaningful and fulfilling life? Of course they do. Antipsychotic medications, including olanzapine, are the primary medications for people living with schizophrenia and bipolar disorder, however symptomatic individuals and their caregivers continue to suffer and beg for symptom relief without side effects such as weight gain.

There is little research and development for new and improved medications for schizophrenia and bipolar illnesses. Development of new efficacious medications is vitally important to improve and actually save millions of lives affected by these illnesses. The introduction of Alkermes 3831 and olanzapine/samidorphan, showing similar symptom management of olanzapine without the weight gain, is an important medication advancement for people

who struggle to live a meaningful life in the space of psychosis. Therefore, I support the approval of Alkermes 3831.

DR. NARENDRAN: Thank you.

Speaker number 6, your audio is connected now.

MS. HAMMER: Hello. Hi. I'm Michelle Hammer. I created the Mental Health Clothing Brand, Schizophrenic NYC to start conversations about mental health, and I received no funding from the sponsor. I think what's different about me speaking right now is that I have schizophrenia, and I take olanzapine, and I have to say that olanzapine really did kind of change my life. It made my head calm, it made my brain quiet, and I was warned before I took olanzapine that it could really make me gain weight.

The first week I took olanzapine, I believe I gained about 10 pounds, but what I did is I told my doctor I gained 10 pounds in a week, and he said, "Oh. Here's another pill. Just take this pill, and you'll lose that weight." And that was

really convenient. All I had to do is take another pill, which is the good, but it would be convenient if I didn't have to take another pill.

I think the more frustrating side effects of olanzapine is the complete sedation. If I take olanzapine before I go to bed at night, which I do, just like last night, my partner started vomiting up blood, and I had no idea this even happened. Apparently, I said things in the middle of the night like, "Oh, I'm sleeping. Leave me alone," which is extremely rude, but I have no memory that I said that. And if I had not taken olanzapine, I would have been able to help my partner who was vomiting up blood, but I couldn't because olanzapine knocks you out so hard.

Also, I've slept till 4 p.m. in the afternoon because of olanzapine. There are a lot of things that need to be changed, and I think it's not just the weight gain. I think there are a lot more options that can be changed about olanzapine and psychiatric drugs, and everything for schizophrenia drugs. There's more than just weight

gain options I would say, and that's really what I wanted to mostly get across because weight gain is a big deal.

I have friends that have gained a lot of weight on psych meds, and it just makes them extremely depressed, and that's going to affect your mental health as well. When you're extremely depressed because you're overweight, how does that help your depression? It really doesn't make any sense, does it?

So really, there's my story. I take olanzapine. I like it. I wish there was something where I didn't have to take something for the side effects, but there are tons of side effects with it. So I think we do need to come up with something better, and I support what Alkermes is doing. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 7, your audio is connected now.

DR. SEYMOUR: Thank you for the opportunity to speak today on behalf of the National Center for

Health Research. I am Dr. Meg Seymour, a senior fellow at the center. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

We agree that weight gain and metabolic risk is a major problem with atypical antipsychotics because of the health risks and because weight gain can result in patients discontinuing their medication. Although ALKS 3831 studies suggest that fewer patients taking the drug gain more than 10 percent of their baseline body weight than those taking olanzapine alone, we have concerns regarding its safety compared to an absolute difference between the groups below 14 percent, and perhaps as low as 12 percent.

The risk-to-benefit equation is particularly questionable because most of the patients in the weight gain study were male, black, overweight at baseline, and were adults 55 years old or younger.

None of us can predict how generalizable these findings would be for most patients who take antipsychotics. Many of them are white, some of them are women, and many of whom are teenagers or over 55.

As FDA scientists noted in their review, there's a considerable risk that as an opioid antagonist, samidorphan may lead to opioid withdrawal symptoms or to accidental overdose. Regardless of whether patients are prescribed an opioid or are abusing them, these risks are present. These risks are especially concerning for patients with bipolar disorder, who are more likely to be abusing opioids in the general population.

Labeling alone is not enough to mitigate these risks. Patients and providers should have actual data on the safety of the drug for those with opioid dependence. It is not enough to assume that patients and prescribers will heed or understand the warnings of the label. Although fewer than 14 percent of patients may benefit from this drug by experiencing lower weight gain, the

risks are too high to justify approval. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 8, your audio is connected now.

DR. AQUILA: Good afternoon. My name is Ralph Aquila. I am a psychiatrist. I have had the good fortune of having different roles in my 30-year career. I was actually involved in the HGAJ trials, which were the trials that helped launch olanzapine, commercially known as Zyprexa back in the day.

What I do nowadays, I work on the west side of Manhattan, an area called Hell's Kitchen. Nowadays, it's actually referred to more as Hell's Kitchenette because the neighborhood's changed quite a bit since when I started there. But what I continue to do is treat hundreds of patients, mostly that have been on olanzapine. I will say that olanzapine has been a major benefit for the vast majority of the patients that I've treated.

One of the things that I think is important to underscore and something that I, along with my

team, have been looking at since the early '90s is medical comorbidities. I think some of the previous speakers underscored excess mortality, particular in schizophrenia, of anywhere from 15 to 25 years sooner than the general population; anything that can help us to mitigate these horrible adverse events.

In particular, I think the new Alkermes product with the addition of samidorphan is something that can be extremely helpful in the trenches when we're looking at how do we get patients with schizophrenia to move forward with their lives.

Again, I've been involved in numerous research trials. I do believe that second-generation agents are superior to first-generation agents. And again, what I've seen is that olanzapine has been an extremely helpful medication. The weight gain that then can lead to other metabolic factors is certainly something that is a major concern, but I would say, as I have looked at the data of the new product, the Alkermes

product, I think that it's certainly worth trying in patients. I have spoken with my patients about it, and I know that they also would very much like to try an olanzapine that might mitigate the weight gain. So I am really interested in doing that.

I do apologize. I left out at the beginning, I am not receiving any compensation for this presentation at the moment, but I am on the advisory board for Alkermes for this specific molecule and have received compensation in the past for that, but not receiving anything for today. I want to thank you for your attention, and good afternoon.

DR. NARENDRAN: Thank you.

Speaker number 9, your audio is connected now.

(No response.)

DR. NARENDRAN: Speaker number 9, you may want to unmute yourself.

DR. PODAWILTZ: Alright. Can you hear me?

DR. NARENDRAN: Yes, we can hear you now. Thank you.

DR. PODAWILTZ: Thank you for this opportunity to address the joint meeting. My name is Alan Podawiltz and I am not being remunerated for this presentation today. However, I am a primary investigator at study sites for the Alkermes A307 and 308 studies, which supports the activities here in my department. I have no other sponsorship conflicts to report.

I'm a psychiatrist working in Fort Worth, Texas. I participated in the Texas Medical Algorithm Project in the '90s that included, at that time, the newly released olanzapine medication. I've been familiar with olanzapine for treatment of schizophrenia for 23 years. I found olanzapine to be one of the most effective medications in the treatment of psychosis caused by schizophrenia and bipolar. I've seen patients recover quicker from their acute psychosis, remain in remission from their psychosis longer, and attaining a significantly higher quality of life.

However by 2005, it became evident that the patients prescribed olanzapine could gain weight

and contribute to what we now call metabolic syndrome. The weight gain and metabolic concerns often limited my long-term use of olanzapine. I was pleased to be invited to the study of this new medicine. There are three cases I'd like to report, one from 1998 and the two most recently from the medication being discussed today.

Case 1, a 38-year-old male, 20 years of debilitating symptoms of schizophrenia. He had been hospitalized greater than 20 times in local and state psychiatric facilities and initiated treatment with olanzapine. As he improved, not only did his psychosis stabilize, but he gained insight into his chronic illness.

As a standard, I asked about the dose of medication, side effects, and if he thought the medication could be increased or decreased. After about 2 months, he, without my prompting this time, stated that he thought the dose should be increased. I increased the dose of olanzapine.

He had worked as a bellman at a local hotel off and on for years. In the spring of our work

together, he decided to start a lawn care company. By the end of the first summer, he had 5 employees. He diversified for the winter to include holiday lights. He never returned to the hospital in that 3 years I worked with him. He did gain 30 pounds.

I'd like to note that I'm not aware of which arm of olanzapine/samidorphan study; the next two cases were randomized.

Case 2, a 21-year-old female, first-break schizophrenia caused her to drop out of college her junior year. She was really psychotic with derogatory internal stimuli and intrusive paranoid thoughts that others could hear her voices in her head. Over the course of about 4 weeks, she admitted to less and less intrusive thoughts and the belief that others could hear her thoughts. She stabilized over the next 9 months and subsequently returned to school; no weight gain.

Case number 3, 20-year-old male, first-break schizophrenia going to school on an athletic scholarship, experiences significant psychotic break requiring psychiatric hospitalization. Over

the course of a year, he's no longer isolating at home and does not think that others are out to hurt him. He is currently in the process of interviewing for a public service job; no weight gain.

The medication discussed today would be my choice for acute and long-term treatment for schizophrenia and bipolar disorders. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 10, your audio is connected now.

MR. BULLARD: Thanks. My name is Chris Bullard. Thanks for having me. I live with bipolar I diagnosis. I work in the field of mental health with Sound Mind Live. We're an organization focused on ending the stigma around mental health through the power of music. I've also, for the past two years, led a music support program for those diagnosed with mental illness at NAMI here in New York City. I've not received payment from the sponsor to be here today. Sound Mind Live as an organization has received fiscal support for some

of our events.

I'm here to tell the committee about the huge impact and side effects that olanzapine has had on myself and those I've worked with who live with bipolar disorder. After each time I've been hospitalized, I've been put on olanzapine, and each time, while it's really helped me to stabilize, I've also been extremely reticent to take it because of the side effects it's been known to have.

Since my initial diagnosis, I've also sat in countless bipolar support groups, and while these groups are, more than anything, usually a source of hope for those attending, they can also sometimes breed a sense of fear and discouragement around certain medications because of the side effects, and olanzapine is definitely one of those in some cases.

In these groups I've attended, we've consoled people who now live with severe weight gain issues, diabetes, and women who have pointed to olanzapine as being a big contributor to this,

and also seeing a number of people go off their meds and refuse to take olanzapine after their first hospitalization because they fear they'll see the same kind of side effects or weight gain in the long term.

I myself have really struggled also with that sedation impact of it, missing work, leaving me personally to take less of the drug than prescribed in the past, which I regret and hope we as a mental health community can really work towards this weight gain issue and the sedation effects that also were mentioned earlier.

I think all medications tend to have side effects, but these side effects shouldn't make the very prospect of living a healthy life unachievable. Olanzapine has this immense potential to really help stabilize individuals and, speaking from lived experience, can really help with psychotic features. However, it's still currently among those drugs that, with people I've worked with and spoken to, has led to people having medication fatigue of continually searching for a

medication that's not going to lead to these side effects that are causing things like severe weight gain or heavy sedation.

If we can make any strides towards lessening those side effects, I think it's a huge step in the right direction, which is why I definitely support trying to reduce these side effects in terms of weight gain associated with the drug. So again, I really appreciate you taking the time to listen to me today, and thanks.

DR. NARENDRAN: Thank you.

Speaker number 11, your audio is connected now.

MR. WRIGHT: Hi. My name is Jason Wright, and I received no compensation from the sponsor but have in the past been involved in an advisory board. I'm happy to be able to tell you my story, not the story of where I'm going but where I've been. The story of where I'm going is being written still.

Real quick though, I'm the editor and founder of Oddball Magazine and the president of

the Oddball Foundation, a 501(c)(3) pending nonprofit foundation, newly established to promote mental health and social justice advocacy through art. I'm also a podcaster for the Oddball Show, have written two books and a third on the way, and I'm a proud husband of a great wife, and I have a dog, Obie [ph]; good to know. But it wasn't easy to get where I am today. My life medicated began at 15 when I was diagnosed ADHD. I did not realize that this medication that I would take would soon become a catalyst to more medications.

Over 25 years later, I think that I might be on the right regimen but still think there's room for adjustment. In that 25 years, I've struggled to find the right medication, the right living situation, the right doctor, the right job, the right life. I went from a happy carefree kid to a problem-riddled, confused and sad adult. I was a smoker and a drinker, and I used that along with my medication to get through, and I did. I also wrote poetry and practiced guitar as well.

In that 25 years, I went from a thin kid, to

a fat kid, to a thin adult, to a fat adult, to where I am now, which I would say was the former, and sadly now the latter due to an unprecedented time full of uncertainty in walking out in the street and jeopardizing my safety of myself or others.

The extreme nature of this pandemic and the sedative nature it has caused has made me gain about 27 pounds from where I was at before. But before that, before this pandemic, the weight was from the meds. That 25 pounds that I gained back I had lost from the 30 pounds I gained from the weight-gaining antipsychotic, olanzapine.

I tried my hardest to get off olanzapine though I noticed the effects were good, but I had to make a choice, a slightly effective medication with horrible weight gain causing me a bad self-image and possibly so much more problems, or make a change, a leap of faith to basically the last med that there was that I could take. And it's not great, but it's what I have right now.

I live a good life. If I stayed on the

olanzapine, I don't know where I would be. I've heard people gain much more than 30 pounds on that drug, and I still know people who take it. I couldn't let myself be a med statistic due to medication. I wanted to speak up and say that the reason that this medication doesn't always work for people is because the side effects are often worse than the original feelings of sadness, auditory hallucination, or whatever it may be. And sadly, once one is on medication, it seems impossible to get off of it. That is a difficult pill to swallow.

But where I am at now, drug-free, healthy, successful, smoke-free for over 4 years now, I didn't get there without the help of the right medications. I am still working on the right balance and we are trying to balance something. But one thing that I think I might have finally got right is my meds, and that took about 25 years to do. There are still days when I feel that I'm not where I want to be, but that's the ups and downs of life, I guess.

Please consider my story only as a recovery story because that sad, confused adult is no longer confused or sad. I'm doing really well, excited for what the Oddball Foundation is going to do for the mental health community and how this world will change once we can change it. Thanks for listening. I am Jason Wright, editor of Oddball Magazine, podcast host of the Oddball Show, and the president of the Oddball Foundation. If you want to find out more about us or the Oddball Foundation's mission, please visit oddballmagazine.com, the Oddball Foundation. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 12, your audio is connected now.

DR. McINTYRE: Nice to be with you all this afternoon, and good afternoon. I'm Roger McIntyre, psychiatrist and Professor of Psychiatry and Pharmacology at the University of Toronto. I also head the Mood Disorders Psychopharmacology Program at University Health Network in Toronto. I'm very

pleased to say I'm also the chair of the Scientific Advisory Board for the Depression and the Bipolar Support Alliance.

Affiliations, professional aside for a moment, what I am is an advocate, and I've been a passionate advocate of people who have been affected by mood disorders, where I've been privileged to be employed for the better part now of almost two and a half decades now. Throughout that journey, wearing the hat as an advocate, as a clinician, as a researcher, and as a person involved in policy and best practices, it is abundantly clear that the state of the union for treatments in bipolar must improve. It is a national health high priority that treatments must improve, and access to alternatives is a priority. We didn't need COVID-19, but COVID-19's only amplified the urgency.

In my experience and certainly in my research, what has certainly been the case is that individuals who are so privileged to have access in a timely way to high-quality coordinated health

care, the great majority either do not sufficiently respond and/or have problems with intolerability.

Weight gain with psychotropic agents broadly, especially with the second-generation class, with certain members of the class including but not limited to olanzapine being, in fact, one of the most common offending agents, the implications of weight gain, you've been hearing about it. It's obvious. I think it's very clear. It's not something that people desire. You have weight that's inappropriate to their height and their overall health, and we know that it not only leads to people stopping medication but also people not even starting medications in the first place, and that unnecessarily prolongs the suffering, and that unnecessarily leads to what could be progression of illness.

There's also a story unfolding, and a very concerning story. As people gain more weight, it could have very significant adverse effects on their cognitive abilities, and certainly we don't want to make more harm for people who are affected

for bipolar disorder.

So it's very clear that having an option would be generally welcomed. Having a specific option addressing the unmet needs in serious mental illness, who are candidates for antipsychotics, and a treatment with lower weight-gain liability would certainly be a tremendous alternative and option for our field. I'll finish by saying I have not been provided any compensation for being here today. Thank you everyone for giving me your attention.

DR. NARENDRAN: Thank you.

Speaker number 13 has withdrawn, so we'll proceed to speaker number 14. Speaker number 14, your audio is connected now.

MS. PLOTNICK: Thank you. My name is Debbie Plotnick, and I am the vice president for state and federal advocacy at Mental Health America. I have received no compensation for being here today, although Mental Health America does receive some financial support for its programs from the sponsor.

I come here today to talk about my personal experience as a family member of a daughter with bipolar disorder and through my personal training as a social worker. My daughter was experiencing the effects of her bipolar disorder, including extreme suicidality in early adolescence. One of the medications that she was given straight away was olanzapine. As I look back at her pictures at that time, she had been a skinny kid. She's built like her dad. She's long and lean, but her pictures from late in middle school and high school show a very chubby individual, and that is because of olanzapine, and that was something that she then refused to take going forward.

At the same time that my daughter was experiencing this, I was in graduate school as a social worker, and one of the programs that I worked for was Clubhouse, where I met people of all different ages, many of whom were taking olanzapine. The reason I know they were taking olanzapine was as soon as they started taking it, or when I met them -- they didn't necessarily tell

me their medications, many of them did -- they were very heavy. The young people would tell me how uncomfortable this made them, how do you find a boyfriend or a girlfriend, and they would go off their medication.

The people who are my age -- and here I was a slightly older student going back to graduate school -- they were my age, and they had diabetes, and they weighed a lot, a lot more than they should have. Many of the people that I worked with started dying, and they would have heart attacks, and they would die from many things related to metabolic disorder, and it was heartbreaking.

But in my work now, one of the things that I work on is making sure people have access to medication. Well, many people don't want to take the medications that they have access to such as olanzapine, and they are blamed for that as being non-compliant. But what we have to do is we have to offer people an alternative that will help them in getting better, in feeling better, and engaging in life, and not having to choose whether or not

they die in their 40s or they're able to have ongoing relationships. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 15, your audio is connected now.

DR. BALLON: Good morning. My name is Dr. Jacob Ballon. I'm a clinical associate professor at Stanford University. I am the medical director of our locked, inpatient acute unit at Stanford, as well as the co-director of the INSPIRE Clinic, which is our psychosis clinic, focusing primarily on people in early psychosis.

I have previously been on an advisory board with the sponsor and am an investigator in one of the trials. I want to focus a bit on my experience with this drug and with the patients in trials, as well as thinking about where this drug fits in clinically beyond that.

I have been part of the enlightened early study, looking at the use of this medication in people in the early stages of bipolar illness or schizophrenia. It's been remarkable to me that

when I look at not just the part which has been randomized, where I'm not sure which medication a person might be on, but when I look beyond to the extended phase of the study where I know it's open label and people are on this medication, how tenacious people have been in wanting to maintain this medication, including traveling at great personal expense in order to be able to stay in the study that they might otherwise have to discontinue because they would be too far away to logistically return otherwise.

Many of the patients that I have in this continuation phase of the study are working full-time or have resumed going to school full-time, a testament largely to the efficacy of olanzapine that we have heard many people talk about, but also their general willingness to stay on this medication because of the fact that they've been able to tolerate it very well.

It's no secret that olanzapine is an excellent medication, but that the weight gain can cause all kinds of problems such that I would

otherwise want to use olanzapine for people in the early stages of illness, but I often cannot because of that risk. Beyond the issues with adherence to medication, I don't want to subject people to potentially life-shortening side effects and life-altering morbidity.

I'm looking forward to hearing more of the results of early psychosis because I think this medication fits very well in that stage of illness for people, where we can hopefully get people to take a medication that they find both very effective for their psychiatric illness and tolerable to take, setting them on a course for staying engaged in a psychiatric treatment and feeling comfortable with their medication for long term. We've heard people talk already today about how challenging it can be.

Weight gain is an important side effect. It is not the only side effect, but it is one that sets the course for a number of other metabolic problems that can come down the line. So I'm very strongly in support of this medication. I have

seen the benefits for people already, and I thank you all for your attention.

DR. NARENDRAN: Thank you.

Speaker number 16 has withdrawn, so we will proceed to speaker number 17. Your audio is connected now.

DR. ABRAMS: Good afternoon. Can you hear me ok?

DR. NARENDRAN: Yes, we can hear you.

DR. ABRAMS: Oh, very good, and thank you for teeing up my slides there for me. I'm Michael Abrams, a health researcher at Public Citizen, and I have no financial conflicts of interest to disclose.

Regarding efficacy, the primary endpoint for this medication is of course weight gain as we've heard. Evidence presented shows that the addition of samidorphan does not eliminate weight gain associated with olanzapine administration. It only reduces that weight gain by an absolute amount of approximately 2 percent, well below the 5 percent goal for weight-loss drugs cited in the FDA

briefing document on page 8 specifically.

Additionally, this small effect was not coupled with same-direction, significant differences across a number of metabolic and cardiovascular health indicators, including mixed results regarding waist circumference, blood pressure changes, and unfavorable glycemic trends summarized by these two slides from the sponsor on the left and the FDA on the right.

Next slide, please. Moreover, unfavorable or null results regarding lipid parameters -- evident in the left panel, a slide from the sponsor -- and unfavorable glycemic trends are highlighted in the center graph of the right panel as well. As I said, both slides here are taken from the sponsor.

Regarding safety, there's of course been expressed a clear concern, noted by both the sponsor and the FDA, that use of an opioid receptor antagonist, samidorphan, comes with substantial risk for opioid overdose and death, as persons with psychosis have especially high risk for

substance-use disorders, the slide on the left from Dr. Goda. I must add, individuals taking olanzapine, as we know, have substantial risks for medication discontinuity, which adds to that concern. Additionally, use of samidorphan carries with it risk of inadequate pain control from opioids when such pain control is needed. The right-hand slide from the FDA reminds us that over 1 in 5 adults on olanzapine concurrently use opioid analgesia. Moreover, data on quality of life, which should be noted as a key patient-reported outcome, does not support this medication's overall benefit-to-risk profile over olanzapine alone.

Accordingly, Public Citizen concludes that this particular application for olanzapine/samidorphan as a treatment for schizophrenia or bipolar offers only marginal benefits in weight gain reductions at best, with no or few physiologic or patient-oriented improvements demonstrated by clinical trials. Moreover, it intensifies what can be regarded as real risks for opioid overdose and death.

We thus recommend that the advisory committee vote no on the three basic questions listed here on this slide, which you'll be talking about later today, and moreover that the FDA not approve this combination medication. Thank you very much.

DR. NARENDRAN: Thank you.

Speaker number 18, your audio is connected now.

DR. NIERENBERG: Thank you. My name is Dr. Andrew Nierenberg. I am the director of the Dalton Family Center for Bipolar Treatment Innovation at Massachusetts General Hospital and Professor of Psychiatry at Harvard Medical School. I have been doing clinical practice now for close to 40 years, and I've also been deeply engaged in research, mostly in mood disorders and depression, and for the past 20 years, focusing on bipolar disorder.

Within bipolar disorder, my expertise, both in terms of clinical practice and research, is in bipolar depression, and as many of you may know,

the options for bipolar depression are limited, and currently there are only four FDA-approved treatments for bipolar depression, including the olanzapine/fluoxetine combination, quetiapine, lurasidone, and cariprazine. Out of those, the olanzapine/fluoxetine combination has the largest risk of weight gain and metabolic syndrome, and because of that, it is actually rarely used.

In many of the talks that I give -- and I ask people what they're actually using out of those four -- it's usually less than 1 percent. The paradox is that for some patients, for reasons unclear, they will only respond to olanzapine/fluoxetine. So the fact that they cannot, only not, be prescribed it by their prescribers, and they can frequently reject that as an option because of weight gain, emphasizes the importance of having the samidorphan/olanzapine combination together.

Now, I failed to mention that I am not being paid to be on this call, but I have been on the scientific advisory board for Alkermes, but it is

really in my role as a clinician and a researcher that I advocate that this be approved. Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 19, your audio is connected now.

DR. McEVOY: Thank you. My name is Joseph P. McEvoy, MD. I am a Professor of Psychiatry at the Medical College of Georgia. I do clinical trials and have done so for multiple decades. I have done clinical trials supported by Alkermes. My clinical research has focused on the biology and treatment of severe mental illness, schizophrenia and bipolar disorder. In particular, I served as the co-principal investigator of the CATIE schizophrenia trials.

The goal of somatic treatment and psychosocial management for severe mental illness is sustained remission of positive affect of psychopathology. Sustained remission implies that psychopathology like hallucinatory perceptions, delusional beliefs, and disorganization of thought

are brought to levels of mild or less. In other words, they do not interfere with or drive behavior. They're not intrusive or distressing. Uninterrupted long-term treatment with an effective antipsychotic medication is necessary for sustained remission.

The primary outcome measure of the CATIE schizophrenia trials was time to all-cause treatment discontinuation. Treatment continuation implied that both treating clinicians and treated patients agreed that an assigned medication was adequately effective and tolerable enough to keep going. Olanzapine won the CATIE schizophrenia trials; that is among the non-clozapine antipsychotic medications, patients and clinicians kept it going longer.

As many of the clinicians who've already spoken attest, olanzapine helps patients with severe mental illness to sleep, it rarely produces subjectively distressing extrapyramidal side effects such as akathisia, and I believe the evidence is compelling that it reduces the

intensity of positive psychopathology more effectively than the other non-clozapine antipsychotic medications.

I believe that for these reasons, patients with severe mental illness assign value to olanzapine in their economies. They take it more consistently and they're more likely to achieve sustained remission. However, as has been noted, weight gain and undesirable changes in metabolism greatly reduce the use of olanzapine, denying its benefits to many patients.

The olanzapine/samidorphan combination is only a small incremental step towards making olanzapine more tolerable and therefore more available to patients with severe mental illness. I believe that the addition of samidorphan only partially reduces the associated weight gain and does little, if anything, to mitigate olanzapine's unwanted metabolic effects. However, this is very much the same pattern, the same constellation, we see in the broader population struggles with obesity, insulin resistance, and dyslipidemia.

There are no single agents that produce miraculous improvement across everything. We combine treatments.

I believe that the olanzapine/samidorphan combination takes us an important step closer to improve management of psychopathology with olanzapine, accompanied by very acceptable levels of tolerability, and I hope to be able to welcome it into our armamentarium. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 20, your audio is connected now.

MS. McGOUGH: Hi. My name is Cecilia McGough. I am the executive director of the nonprofit Students With Psychosis, formerly known as Students With Schizophrenia. Our mission is to empower student leaders and advocates worldwide through community building and collaboration. Students with Psychosis and me personally were not financially compensated for our time or contribution to this testimony today. Students with Psychosis has not received grant funding

through this sponsor.

The community of people living with schizophrenia deserve more treatment options. Weight gain side effects from medications can lead to or contribute to unhealthy eating patterns, self-image struggles, and staying compliant to medication. As a person who lives with schizophrenia and an active voice and participant within the schizophrenia community, I speak to students living with psychosis every single day. I can say with confidence that we are not satisfied with the limited options in treatment and advocate for more variety in care, such as in medication choices, to help empower schizophrenia community members. We want more options.

I started my medication journey back in 2014 during my sophomore year at Penn State. Admittedly, no one comes fully prepared when faced with a diagnosis of schizophrenia, but what I was most certainly not prepared to navigate through was an additional eating disorder due to the side effects of medication, which impact my quality of

life to this day.

I gained 60 pounds in my first treatment, which further shattered my self-image issues and put strains on the romantic relationship that I was in, but more importantly put strains on my relationship with myself. Tackling this eating disorder consumed my life and was an additional burden that should not have been carried. This changed how I ate, this changed how I spent my time, this changed my self-image, and ultimately contributed to going off medication multiple times, sick psych work days, an additional behavior of self-harm, suicidal thoughts, and depression. I felt like both my mind and my body were against me and at war. If I chose to take my medication, I sided with my brain health. If I stopped taking medication, I sided with maintaining a healthy weight.

Schizophrenia treatment should not feel like a war within yourself. This war can lead to serious consequences such as unhealthy eating patterns, self-image struggles, and staying

compliant to medication. Empower schizophrenia community members by giving them more treatment options and help mitigate weight gain side effects. Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 21, your audio is connected now.

DR. KOSTEN: Thank you very much. This is Dr. Thomas Kosten. I'd like to thank you for this opportunity and note that I've got no compensation from the sponsor for today's presentation, but in the past I have had some grant support from the sponsor related to studies in opiate dependence, not related to this particular medication. I'm a Professor of Psychiatry, Pharmacology and Neuroscience at Baylor College of Medicine, and I'm the director of the substance-abuse division there.

What I'd like to talk about is opiate antagonist safety and that there is a lack of interactions with older drugs, except opioids, which are blocked, and if an opiate-dependent person were to take it, it would precipitate

withdrawal. Samidorphan, though, is safe at the doses it has been given, and there are actually several studies supporting that. Samidorphan is an opioid antagonist.

I've worked clinically with antagonists like naltrexone and samidorphan for over 40 years and established the naltrexone treatment program at Yale in 1980. It was the first treatment program in the country for this, and this was for opioid relapse prevention. I've published review papers on the safety of naltrexone and other opioid antagonists such as nalmefene.

As an example, naltrexone daily dose is 50 milligrams a day and has been safely given at up to 500 milligrams per day. That's 10 times the usual dose. However, at 600 milligrams, which is, again, about 10 times that dose, some obese patients have had elevations of liver function tests, but these were transient and reversible after stopping the naltrexone. Thus, this very low dose of samidorphan will be safe even with potential overdoses of the combined medication.

If opiates are used while taking the samidorphan combination, nothing will happen. They'll be no adverse reactions. There will be simply no effect of the opiates on pain or respiration. You cannot overdose. It's completely safe. However, in response to one of the previous speakers who wanted to ask about pain management, pain management opiates is in fact possible. Sentinel can be used at larger dosages, and it will in fact provide analgesia.

Samidorphan itself also has no increase in overdoses and, in fact, it's reducing overdoses. It's a blocker. And the potential after discontinuing samidorphan, or this medication, or any opioid antagonist, that you'd be more sensitive to having an overdose is a myth. There is no data to support that whatsoever. So this is a completely safe drug, and I laud the company for putting it together, and I think it is a service to the patients with bipolar and schizophrenia. Thank you very much.

DR. NARENDRAN: Thank you.

Speaker number 22, your audio is connected now.

DR. CORRELL: Thanks very much. My name is Christoph Correll. I'm Professor of Psychiatry and Molecular Medicine at Zucker School of Medicine in New York as an adult psychiatrist, and I'm also a child psychiatrist, and I'm the Chair and Professor of Child Psychiatry at the Charité University in Berlin. I've been a consultant, advisor, and data safety monitoring board member for most of the companies that make antipsychotics and other psychotropic medications. I've been an advisor and also author on data for Alkermes ALKS 3831. I am not receiving any compensation for my giving my opinion during this public hearing.

Since I've been involved in part of the data collection and interpretation, I will not speak at all on the data. Obviously, the committee has a difficult task of evaluating the benefits and potential risks, and that's never easy, and obviously there are lots of data on the table to do that with. But I want to speak as a clinician and

clinical researcher with over 20 years of experience and also having spent really half of my life researching side effects because as a child psychiatrist, I see side effects quite a bit in a vulnerable, antipsychotic naive population.

To put the olanzapine risk into context, in our satiety study that we published in 2009 in JAMA -- and these were children and adolescents who were antipsychotic naive, no more than one week of exposure, and many people now get olanzapine as one of the first choices in the emergency room or also on units -- the mean, the average weight gain in 12 weeks, was 19 pounds; 19 pounds with olanzapine. This is not the chronic patients you're seeing in these studies.

Actually, the number needed to harm, again, more than 7 percent or the same, was 1 for olanzapine; 14 percent in these youngsters was 2 for olanzapine; and 21 percent of weight gain in 12 weeks, the number needed to harm was 4.

So we have a medication that can be quite helpful, and you've heard other testimonies, but it

has a lot of weight gain. Making the weight gain smaller, even though this will not be a perfect drug, even though we have other antipsychotics that have less weight gain or almost no weight gain at the moment, there are patients that require olanzapine and who only respond to olanzapine.

If you or I had to take a medication that works for us and has special efficacy, and it has a lot of side effects, and we could take the exact same medication in terms of efficacy but had less weight gain, would we not want that? While weight gain has multiple implications, adherence goes down.

Melissa DelBello, who also put a written statement in, and I were co-PIs at PCORI, Patient-Centered Outcomes Research Institute, funded study, where we randomized children and adolescents who are on antipsychotics, including also olanzapine, to receive Metformin or not, 1460 patients that have already been randomized. We did a survey with NAMI and the Depression and Bipolar Support Alliance, asking family members and

patients what should be our primary outcome for this Patient-Centered Outcomes Research Institute funded study, and we were dead set, it must be quality of life.

What did the patients choose? Weight, where the biological marker that's easy to measure, that is our primary outcome, because patients and families recognized that many of the problems that come with second-generation antipsychotics, including poor quality of life, being bullied, having also problems with adherence, center around weight.

Now, you've seen that at least in the data, there seems to be little of a metabolic signal, but we know that weight gain over time and waist circumference increase is related to metabolic outcomes, and when real-world patients are treated, as I told you in these antipsychotic naive patients, there will be a lot of weight gain, and mitigating this can be helpful.

When asking family members -- and that's the study that Roger McIntyre published who spoke

earlier --

DR. NARENDRAN: Sorry. I think we have to conclude. I apologize.

DR. CORRELL: Okay. Then the last point is there must be also a consideration of risks, obviously, and I want to say that less than 10 percent of people with schizophrenia have opioid dependence. I believe that with a REMS program, that should not deter the 90 percent of people with schizophrenia who can potentially also be treated with olanzapine --

DR. NARENDRAN: Thank you.

DR. CORRELL: -- to not receive --

Questions to the Committee and Discussion

DR. NARENDRAN: Thank you. I appreciate your point. Thank you.

The open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will proceed with the questions to the committee and the committee discussion. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording, then we will proceed with the voting. Our first three questions are voting questions. Dr. Bonner will provide the instructions for the voting.

Dr. Bonner?

DR. BONNER: Thank you, sir.

LaToya Bonner, DFO. Questions 1, 2, and 3 are voting questions. Voting members will use the Adobe Connect platform to submit their vote for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be

moved to a voting breakout room. A new display will appear where you can submit your vote. There will be no discussions during the voting. You should select the radio button -- that is the round circular button -- in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected. Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote.

You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, the DFO will announce that the vote is closed. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record, then the chairperson will go down the roster, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did if you choose. We will continue in the same manner until all questions have been answered or discussed.

Are there any questions about the voting process before we begin?

(No response.)

DR. BONNER: Okay. I will turn the meeting back over to the chair.

DR. NARENDRAN: Thank you.

Question number 1, has the applicant presented adequate evidence that samidorphan meaningfully mitigates olanzapine-associated weight gain?

Are there any questions about the wording of the question from the panel members? Please raise your hand if there are.

(No response.)

DR. NARENDRAN: I don't see any questions, no hands, so I think we could proceed. You will now begin voting on question number 1.

Dr. Bonner, you can take over.

DR. BONNER: LaToya Bonner, DFO. We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. NARENDRAN: The voting has closed and is now complete. The vote results are displayed. I will read the total votes into the record. For question 1, 16 yeses, 1 no, zero abstain. I will turn the meeting over to the chair.

DR. NARENDRAN: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote if you wish to. We'll start with the first person on the list, and then you guys can kind of go down and proceed.

Dr. Iyengar?

(No response.)

DR. NARENDRAN: Dr. Iyengar, if you could unmute yourself.

DR. IYENGAR: Hello?

DR. NARENDRAN: Go ahead, Dr. Iyengar.

DR. IYENGAR: Okay. Sorry. This is Satish Iyengar from Pittsburgh, and I voted yes. I was largely convinced by Study 303. Thank you.

DR. NARENDRAN: Dr. Racher?

(No response.)

DR. NARENDRAN: Dr. Matthew Racher, can you please unmute yourself?

MR. RACHER: Hi. This is Matthew Racher, certified recovery peer specialist and patient representative from Miami. I voted yes. I do believe that there's a meaningful mitigation of weight gain associated with this medication.

DR. NARENDRAN: Dr. Jain?

DR. JAIN: Hello. This is Dr. Felipe Jain. I voted yes. Thank you.

DR. NARENDRAN: Dr. Krebs?

DR. KREBS: Hi. This is Erin Krebs. I voted yes for the populations studied. I do think it's an important question about whether there would be mitigation of weight gain in people who are already on olanzapine, because I think many people will wonder if switching to this new product would help them with weight gain or not.

DR. NARENDRAN: Dr. Boudreau?

DR. BOUDREAU: Hi. Denise Boudreau, and I

voted yes for some of the reasons that have already been stated and would echo what Erin Krebs just said, and will also say it will be interesting to see in real-world populations the difference, and I'm curious if there is significant difference in weight gain.

DR. NARENDRAN: Thank you.

Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. This is Jess Fiedorowicz in Ottawa. I also voted yes. I did want to add some clarification here as well about why I did. My expertise is in psychiatry and obesity medicine, and usually we have a 5 percent threshold for clinically meaningful weight loss. This 2.8 percent doesn't cross that, but I felt like we really need to consider the tremendous individual variability in risk for weight gain with olanzapine and some other antipsychotics, and for me that made the co-primary categorical outcome of more than 10 percent weight gain compelling and for which a 50 percent reduction was shown.

I don't often advocate for dichotomizing

continuous data, but I think, given the individual variability here, a good argument can be made. I also think there's compelling reason to prevent and focus on prevention of weight gain, given that once a new weight setpoint is set, but the brain continues to defend that fat mass. So I felt that this is indeed clinically meaningful even though it doesn't cross the traditional 5 percent threshold for weight-loss studies.

DR. NARENDRAN: Thank you.

Dr. Meisel?

DR. MEISEL: Hi. This is Steve Meisel from Fairview in Minneapolis. I voted yes. I do believe the data are compelling that the mitigation of weight gain is statistically and clinically meaningful. That said, I do worry that in the real world, the impact will be less than in controlled trials as it is with most drugs and most conditions.

I echo what Dr. Krebs talked about, that there will be a desire to switch people stabilized on olanzapine to this with the hopes that there

would be weight loss. That's going to be a nuance, and that's going to be very, very important should this drug be approved. That's not what this is all about. This is for de novo.

They're going to be a fair number of patients who are still going to gain weight, just maybe not as much. So whether that is something that is noticed in the community of patients who need to use this is I think an open question. If you're only gaining 10 pounds and you otherwise would have gained 20 pounds or that sort of thing, you're still gaining weight; and how noticeable is that going to be in terms of the, "yes, but it could have been worse" sort of messaging. But unbalanced, I think the data is pretty compelling that it's meaningful mitigation.

DR. NARENDRAN: Thank you.

Dr. Krishna?

DR. KRISHNA: This is Dr. Sonia Krishna from Austin, and I voted yes. Thank you.

DR. NARENDRAN: Dr. Dunn?

DR. W. DUNN: Hi. This is Walter Dunn from

UCLA. I voted yes. Based on the clinical trial data, I do believe the evidence suggests samidorphan does mitigate olanzapine-associated weight gain. However, this is a very narrow yes, as I still have reservations about the generalizability of the data.

First, the mean weight of the subjects in these studies was barely overweight, with a BMI slightly over 25. In my clinical experience, this is not representative of chronically ill patients, a large percentage which were overweight or clinically obese. So if you start with a subject population at lower risk for weight gain, indicated by their BMI status, either through a combination of genetics, diet, or behavior, you're not really seeing how effective this drug might be in a high-risk population.

The second issue is that I don't know if this effect would be replicated in a real-world clinical population, for adherence will certainly be much more variable. And will the weight advantages of this compound be seen if patients are

only 50 percent adherent to their medication?

This is a theoretical concern based primarily on the half-life of olanzapine and samidorphan. Half-life of olanzapine is 33 hours and for samidorphan it's 7 to 11 hours. When you're taking the compound regularly, both drugs are at steady state and you have good coverage. But what happens when you lose 90 percent of the mu blockade after 24 hours, which is akin to skipping one dose, and this was cited by the sponsor. So what is the effect of olanzapine on appetite and weight gain when you're losing that new blockade?

Now, I don't imagine you lose total weight prevention benefit, but perhaps the weight advantages are attenuated. That's to say that this is not necessarily limitation of the study because this is something that wasn't addressed, but we could use this to actually clinically motivate our patients to remain consistent. You can tell them we're going to give you this medication. This could be very helpful for your psychosis or mood

symptoms, and you're not going to gain as much weight as you otherwise could, but you need to stay on it every single day.

So potentially, if we have that information, we could use that to help motivate our patients to be more adherent to the meds. But this is information we don't have, but that's needed to guide patient care and education. Thank you.

DR. NARENDRAN: Thank you.

Ms. Witczak?

MS. WITCZAK: Kim Witczak, consumer rep. I voted no, and I voted no for the word "meaningful" mitigate weight gain. Percentage is one thing, but when you actually looked at the absolute weight gain, it is minimal, and then compared to what we use as the weight-loss standard.

I also think the quality-of-life information that was patient reported falls into this as well. Again, even what Walter, the previous speaker, had said, a real-world -- what's going to really happen -- this clinical trial was -- it's very much set up in one -- we heard some of the things like

who was in the clinical trial, the type of BMI weights. But also I'm concerned -- people are still gaining weight, and I would be more interested in why has one person gained and the other one doesn't against some of those. But again, the word "meaningful" is where I got stuck. Thank you.

DR. NARENDRAN: Thank you.

Dr. Calis?

DR. CALIS: Hi. This is Karim Calis from the NIH, and I voted yes. I don't think anyone here would be debating the efficacy of olanzapine or the combination with samidorphan, certainly not for schizophrenia. But in terms of the point at hand, which is the reduction in weight and weight mitigation, we don't have any specific guidance on how to best assess the mitigation of antipsychotic induced weight gain in non-obese individuals. We do know that weight gain is a treatment-limiting adverse effect of olanzapine, which by all accounts is a very effective drug for these indications.

What concerns me still is that we have a

very modest effect, at best, on weight gain mitigation and certainly less than compelling effects on metabolic parameters, and that's been demonstrated here. But again, mitigating weight gain and inducing weight loss are quite different entities, and I think the standards for that or how we look at them is going to be different.

I still would have reservations and concerns about long-term safety data with samidorphan and also with regards to the positive information on long-term adherence and long-term effects on metabolic parameters, but I still think that in terms of meeting the study endpoints as discussed with FDA, I think that the applicant has met that bar. Thank you.

DR. NARENDRAN: Thank you.

Dr. Jeffrey?

DR. JEFFREY: Hi. Jessica Jeffrey, UCLA. I voted yes for the reasons previously stated. But additionally I want to make mention that I believe it's important to note the participants taking ALKS 3831 in Study A303 experienced less increasing

waist circumference and had favorable systolic blood pressure. Notably, both central adiposity and higher blood pressure are associated with poor medical outcomes. Thank you.

DR. NARENDRAN: Thank you. This is Raj Narendran, and I voted yes. I would like to just re-echo the comments of Dr. Fiedorowicz and Dr. Jeffrey, the categorical delineation of number of people who gained over 7 percent, 10 percent as to less central adiposity based on the weight size is what guided my vote.

I will pass it to Dr. Thomas.

DR. THOMAS: Patrick Thomas from Baylor College of Medicine. I voted yes.

DR. NARENDRAN: Thank you.

DR. AMIRSHAHI: Maryann Amirshahi from Georgetown University. I voted yes for the same reasons.

DR. NARENDRAN: Dr. Bohnert?

DR. BOHNERT: Hi. Amy Bohnert. I voted yes. My motivation for doing so is very similar to those outlined by Dr. Meisel, so I won't repeat

those comments. Thank you.

DR. NARENDRAN: Thank you.

Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff, Stony Brook Medicine. I voted yes, but would echo that it was a narrow yes, and that was with respect to Ms. Witczak's comments. I think the word "meaningfully" could be determined to be different things to different people. I would certainly agree that for patients, any kind of weight loss or diminished weight gain would be a positive thing. But with respect to quality of life, metabolic outcomes, et cetera, et cetera, I wasn't a hundred percent convinced. So it was a narrow yes from me. Thank you.

DR. NARENDRAN: Thank you.

We will now move to voting question 2.

Voting question number 2, has the applicant adequately characterized -- one second. I've been told to pause.

(Pause.)

DR. NARENDRAN: Okay. We'll proceed again.

Question number 2, has the applicant adequately characterized the safety profile of ALKS 3831, olanzapine/samidorphan?

Are there any questions about the wording of the question from the panel members?

(No response.)

DR. NARENDRAN: I do not see any raised hands, so I guess we could proceed to voting.

Dr. Bonner?

DR. BONNER: LaToya Bonner, DFO. We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. BONNER: The voting has closed and is now complete. The vote results are displayed. I will read the vote result into the record. For question 2, 13 yeses, 3 nos, 1 abstain. I will turn the meeting back over to the chair.

DR. NARENDRAN: Thank you, Dr. Bonner.

We will now go down the list again, and everyone who voted, state their name and vote into

the record. You may also provide justification for your vote if you wish to. We'll start with Dr. Meisel.

DR. MEISEL: Thank you. Steve Meisel with Fairview in Minneapolis. I voted yes. I do believe that we understand what the safety profile of this product is. I saw no serious signals about anything that would be unexpected or untoward. Clearly, the issue of what happens when a patient needs to have an opioid because of whatever, surgery, fracture, dental procedure, whatever it may be, I think that's an open question, but I think we understand the question. I think it's characterized that that's going to be an issue to manage going forward. So I believe we understand what the safety profile is, so I think it's been as well characterized as we can get. Thank you.

DR. NARENDRAN: Thank you.

Mr. Matthew Racher?

MR. RACHER: Hi. This is Matthew Racher, patient representative. I decided to abstain from voting on this question. Thank you.

DR. NARENDRAN: Thank you.

Dr. Jain?

DR. JAIN: This is Dr. Felipe Jain of Massachusetts General Hospital. I voted yes, however, it's qualified. The risks associated with use of an opiate antagonist in general are well known and were well characterized with regard to schizophrenia in the studies we were presented. Regarding the schizophrenia/bipolar bridge and 20-plus years of clinical research evidence we have with regard to use of an opiate antagonist in bipolar disorder, it's reassuring but not conclusive, and that's because samidorphan is a new molecular entity.

I'm concerned that bipolar disorder has symptomatology and neurobiological underpinnings that overlap with but are not identical to those with schizophrenia and that further safety research in bipolar disorder should be conducted. Thank you.

DR. NARENDRAN: Dr. Krebs?

DR. KREBS: Hi. This is Erin Krebs, and I

voted yes.

DR. NARENDRAN: Thank you. This is Raj Narendran. I voted yes.

I will pass it on to Dr. Fiedorowicz.

DR. FIEDOROWICZ: Yes. This is Dr. Fiedorowicz at Ottawa. I voted yes. I agree with Dr. Jain about the need for future research in bipolar disorder. Thank you.

DR. NARENDRAN: Thank you.

Next is Dr. Iyengar.

DR. IYENGAR: This is Satish Iyengar from Pittsburgh. I also voted yes. I also agree with the comments that Dr. Jain made about the need for further study for bipolar.

DR. NARENDRAN: Thank you.

Dr. Krishna?

DR. KRISHNA: This is Sonia Krishna at Dell Medical School at University of Texas in Austin. I voted yes. Thank you.

DR. NARENDRAN: Dr. Dunn?

DR. W. DUNN: This is Dr. Walter Dunn from UCLA. I voted no. I still have questions

regarding the implications of these metabolites of samidorphan in terms of their mu agonist activity, though not so much in the context of abuse potential, as I think those have been adequately addressed. The question I have is, is there going to be interactions of these metabolites with the opioids?

So theoretically, in the 1 or 2 days post-discontinuation of olanzapine/samidorphan, you're going to lose the mu blocking properties of samidorphan and only have the mu agonist activity of the metabolites. So during this period, would patients be at a higher risk for complications with prescribed opioid use greater than that would be expected from naltrexone? I'm not aware of any mu agonist metabolites with naltrexone.

What's not clear is if the binding affinity of these metabolites is of any clinical relevancy. For example, after you discontinued samidorphan, would a standard safe starting dose of oxycodone or hydromorphone result in a greater incidence of adverse events due to an adverse effect with these

metabolites? What should the label say? Should the label say, in the 1 or 2 days after you discontinue this, you need to lower your dose of your opiates or avoid opiates in this window of high risk?

Now again, I appreciate that this is somewhat of a high safety standard to have to consider multiple, what if, clinical situations with regard to safety, but I think this is a burden shared with any intervention designed to prevent a harm rather than addressing existing illness or disorder. And this is the role of samidorphan, not to treat an illness or disorder, but rather to prevent weight gain, which is the potential pathway for increased morbidity and mortality. Thank you.

DR. NARENDRAN: Thank you.

Dr. Thomas?

DR. THOMAS: Patrick Thomas, Baylor College of Medicine. I voted yes for some of the reasons stated, but do share some concerns about potential interaction of opioid agonists, not knowing the binding affinity, as well as if someone were to

abuse taking advantage of having that present, plus another dose. Thank you.

DR. NARENDRAN: Thank you.

Dr. Calis?

DR. CALIS: Hi. This is Karim Calis from the NIH, and I voted yes, and it's a qualified yes. I agree with Dr. Jain. I won't repeat what he said, but I would like to say that certainly with the new molecular entity like samidorphan, we'd certainly like to have more long-term safety data. But I believe that with the long-term safety extensions with the combination, I feel like the sponsor has attempted to gather additional information. But I think we need to continue to look at long-term safety with this combination product, and I'm particularly interested in metabolic parameters as well, and glucose in particular. Thank you.

DR. NARENDRAN: Thank you.

Dr. Jeffrey?

DR. JEFFREY: Hi. Yes. Jessica Jeffrey from UCLA. I voted yes for the reasons previously

stated, however, I want to support the comments of Dr. Jain.

DR. NARENDRAN: Thank you.

Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff, Stony Brook Medicine. I voted no, and my no was really based on some of the reasons mentioned by Dr. Dunn; in addition to while I do feel that there was very good characterization of the safety profile of olanzapine, I have very strong concerns with respect to whether or not the safety profile of samidorphan was adequately characterized. I don't necessarily consider testing with remifentanil to be representative of what would happen in real life. I think there are other opioids that could have been utilized, such as morphine, for example.

I have no clear understanding as to what the appropriate course of action would be in the event that somebody does have an unintentional overdose. Do we reach for a different antagonist? Do we give more of this medication? It's really not clear to me, so I have a number of questions with respect to

the safety profile of the samidorphan component of this medication. Thank you.

DR. NARENDRAN: Thank you.

Ms. Witczak?

MS. WITCZAK: Kim Witczak, consumer rep. I voted no. I voted no for some of the reasons that Dr. Zacharoff just mentioned. But it's a new entity, a combined product. We don't know if there's long-term safety that I'd like to see, the real world, as well as all the off-label, like kids, the elderly. I'm concerned who's prescribing these and are they going to really understand it, and I think even within the population that was studied with having a higher than the general public with abuse disorder. So I think there's just a lot of concerns of the unknown that we don't know at this time. Thank you.

DR. NARENDRAN: Thank you.

Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi, Georgetown University. I voted yes. I think that, overall, they did a good job of characterizing the

safety profile as best they could. I think that there are some limitations, particularly with regard to the metabolites of samidorphan. Also, one area that I think needs further study is going to be how we do manage an opioid overdose when this medication is on board. Thank you.

DR. NARENDRAN: Thank you.

Dr. Bohnert?

DR. BOHNERT: Hi. Yes. This is Amy Bohnert. I voted yes. Dr. Amirshahi just characterized all of my reasons very well, and I think there's a need for -- sorry, all of my limitations to that yes, and I think there's a need for well-designed, postmarketing surveillance for this.

DR. NARENDRAN: Thank you.

Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau. I voted yes, and nothing to add.

DR. NARENDRAN: Thank you.

We will now be moving to question number 3. Question number 3, is labeling sufficient to

mitigate the risks related to the opioid antagonist action of samidorphan?

Are there any questions about the wording of the question from the panel members? I see Dr. Iyengar.

DR. IYENGAR: Yes. This is Satish Iyengar from Pittsburgh again. This question is pretty narrowly stated. I was just looking at the applicant's proposed risk mitigation strategy section, and there's a good bit not only about labeling but also education. I was wondering are we voting on just the narrow statement.

DR. FARCHIONE: This is Tiffany Farchione. I would say that we're voting on the narrow statement. I think in terms of the educational materials and things like that, if they happen to be promotional or even just voluntary type stuff, we're not necessarily looking at a REMS per se. What we would really like to hear from the committee as you do register your votes is your rationale on why you voted the way you did.

Again remember, all of these things that are

part of labeling can be part of your considerations, and if you say yes, you should tell us in what way you think labeling can help. I realize that may have been a little circuitous. Hopefully that got to your question.

DR. IYENGAR: Thank you. Yes.

DR. NARENDRAN: We have another question from question from Dr. Dunn.

DR. W. DUNN: Hi. This is Walter Dunn from UCLA. In terms of the question, is it regarding labeling in general or is it labeling based off of what information we currently have with the current studies? I guess maybe what I'm really asking is, is it sufficient provided we get more information or is it just a general question that if we get more information, labeling would be sufficient?

DR. FARCHIONE: This is Tiffany Farchione again. We're obviously talking about the application that we have in front of us with the information that we have for review. We do have the discussion question coming up, where you can talk about what additional data, if any, you would

like to see.

DR. W. DUNN: Thank you.

DR. NARENDRAN: We don't see any further questions, so I think we can proceed with the voting. I'll pass it to Dr. Bonner.

DR. BONNER: LaToya Bonner, DFO. We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. BONNER: This is LaToya Bonner. The voting has closed and is now complete. The voting results are displayed. I will read the vote results into the record. For question number 3, 11 yeses, 6 nos, zero abstain. Now I will transfer the meeting back over to the chair.

DR. NARENDRAN: Thank you. We'll do the same thing. We'll go down the list and have everyone who voted state their name and vote into the record. Please also provide justification as requested by the agency. I think it would be very helpful. We'll start with Dr. Meisel.

DR. MEISEL: Thank you. Steve Meisel with Fairview in Minneapolis. I voted no. In fact, I think labeling will do absolutely nothing to mitigate the risks related to the opioid antagonist, the qualities of this drug. I'm mindful of the fact that the prescribers of this drug will generally be psychiatrists. The psychiatrist will seldom be prescribing opioids. The people who'd be prescribing opioids are emergency room doctors, orthopedic surgeons, oral surgeons, anesthesiologists.

Since they're not the prescribers of this, all they're going to see, if they happen to look at a patient's medication list, would be the fact that they're on some form of olanzapine antipsychotic, and the idea or the notion that there's going to be an interaction, a negative interaction, or have a problem with the prescribing of opioids is going to fly right by them. It's just not going to compute. There's not going to be any alert. There's not going to be any knowledge of that. They're not going to go back and read the label of this drug

when they're prescribing an opioid in an emergency room, or a dentist office, or a post-op floor, or places like that.

So I think the conundrum here is that the labeling is designed for the prescriber, but the risks are not when the prescriber uses it because they're not prescribing the opioids in general. It's going to be with the people who are caring for the patient in non-psychiatric situations. So I don't think labeling is a strategy that's going to be very effective at all. Thank you.

DR. NARENDRAN: Thank you.

Dr. Thomas?

DR. THOMAS: Hi. Patrick Thomas, Baylor College of Medicine. I voted yes, answering the question narrowly about labeling sufficient to mitigate the opioid antagonist action. I don't know that you can say it about the other action, that we just aren't as characterized. I share some of the concerns that were previously stated, however, in the real world, even though naltrexone is a little more well known, sometimes people don't

say it, there are ways to manage that in ER. So I think that that would be manageable. Thank you.

DR. NARENDRAN: Thank you.

Dr. Bohnert?

DR. BOHNERT: Hi. Yes. This is Amy Bohnert. I voted yes. I share the concerns of the other two, but I felt like, on balance, the labeling would be sufficient for patients to make an informed choice about those potential adverse consequences of insufficient analgesia and overdose risks if they were already on long-term [indiscernible] but did not take the medication, and that's all.

DR. NARENDRAN: Thank you.

Dr. Jain?

DR. JAIN: This is Felipe Jain, Massachusetts General Hospital. I agree with Dr. Meisel one hundred percent that those prescribing the opiates are often going to be not those who are starting the olanzapine/samidorphan combination, and that it will be far too easy for non-psychiatrists to not realize what medication

the patient is taking, and what its properties are, and that it has opiate antagonistic properties.

Additionally, I struggled with this piece, but I think that this is important. Although labeling has been sufficient for opioid antagonists when used for other purposes, the combination medication is different and poses unique risks. Particularly, this could be started when a person is manic or psychotic, or suffers from cognitive disorganization, which often accompanies those states, and that improves markedly once they're on the medication.

They may not realize what they have been placed on and the implications of it being an opiate antagonist, and the time when they're most likely to have been explained that it's also an opiate antagonist is when they're initially started on the medication. That's when the drug label will be provided to them.

So it's also well validated that people who are manic, and sometimes those who are psychotic, do not remember everything that occurred prior to

becoming stable on the medication. I think we're at risk of this, for the patient to not realize the implications of this medication having been started on them due to their unique vulnerability in the time period when it is likely that they will be started on the medication. Thank you.

DR. NARENDRAN: Thank you.

Dr. Krebs?

DR. KREBS: Erin Krebs. I voted yes. Given that labeling is never really sufficient, in the context of everything else, I think with this narrow question, I thought yes was appropriate.

I just want to say I think there are these three main risks of the opioid antagonism. The first two that are really related to patient selection are the risks of precipitated withdrawal that could occur in any one who has ongoing regular use of opioids and physiologic dependence, and then the risk of overdose that might occur with someone who has a behavioral opioid-misuse pattern.

Those things, the prescriber is really the one who's going to be reading the indication,

reading the label, and needing to know that information in terms of patient selection because certain patients will be at much higher risk or only at risk of those; not everyone would be. So I think labeling is most helpful there.

The third area, and I think the others have brought up, is this risk of ineffective analgesia, other prescribers not being familiar with the drugs and not looking and recognizing that this opioid antagonist effect could affect the benefits that patients might receive from prescribed opioids. Here, this is a real issue in clinical practice right now as we see increasing use of opioid antagonists for a variety of conditions. Certainly, in my facility, we have ongoing quality improvement activities, trying to develop systems and processes to catch these things.

Where it is most important is in the patients who have acute pain with a severe trauma or a planned surgical procedure. It's really a relatively narrow group of clinicians who are involved in those clinical scenarios. That's not

all doctors; that's ER doctors, surgeons, and anesthesiologists. I think there's a lot of increasing awareness of the issues here because these are common issues with lots of other antagonists or combination drugs right now.

The broader group of patients and probably that 20 percent prescribed olanzapine and opioids concurrently, the broader group of patients is not having that very severe acute pain but is having maybe acute or chronic musculoskeletal or dental, less severe pain conditions for which, frankly, opioids usually aren't the best choice and are not more effective than other analgesics.

So here, if a doctor doesn't catch it, the level of harm is likely to be low and there are plenty of alternatives. Frankly, often an opioid isn't effective and you try something else anyway. So I think there is some likelihood that that word won't get out in terms of that, but I think the magnitude of harm there is much smaller. So that's my long story. Thank you.

DR. NARENDRAN: Thank you, Dr. Krebs.

Dr. Boudreau?

DR. BOUDREAU: Hi. Denise Boudreau, and I voted no. My colleague Steve Meisel articulated very well my thoughts. The thing I would add to that is I think patients that are on opiate antagonists, they're at risk even after, for a time period for which they discontinue, and you have a population that's at high risk for using opioids in general and a higher risk for substance-use disorders. I really would want to see some broader education and also some postmarketing data. Thank you.

DR. NARENDRAN: Thank you.

Dr. Iyengar?

DR. IYENGAR: This is Satish Iyengar. I voted yes largely in response to the narrow question. This is not an area that I know enough about, and I defer to the earlier speakers, especially people like Steven Meisel, who have articulated
their reasons for saying no. Thank you.

DR. NARENDRAN: Thank you.

Dr. Krishna?

DR. KRISHNA: This is Sonia Krishna from University of Texas, Austin. I voted no for the reasons that Dr. Meisel and Dr. Jain brought up. I would add that most patients are reluctant to even reveal their opiate use, and if they did have some rare emergency and they did have to go to an emergency room, they probably would just say that they're on a medicine for schizophrenia. Maybe they would say olanzapine, but in general, I don't think that they would remember the combination of it, and I think the other providers who are non-psychiatric would be very hesitant to stop such a medication. Most of those doctors who have called me have just said, "Oh, we're going to leave the psychiatric meds alone. We don't want them to all of a sudden have a flare or relapse." So I think that there would be hesitation to stop the medicine and people would only treat it as a psychiatric medicine.

That said, I also would say that it is going to be marketed and sold -- even to

psychiatrists -- as a medication that mitigates weight gain and heading toward some level of weight loss. So I don't think that they'll be much focus on this being an opiate antagonist. I think it will just be remembered as an antipsychotic with less weight gain. Thank you.

DR. NARENDRAN: Thank you.

Dr. Dunn?

DR. W. DUNN: Walter Dunn, UCLA. I voted yes based off a very narrow interpretation of the question. Based on the first part, is labeling sufficient, I interpreted that as asking can labeling be sufficient, and I said yes. But based off of what's been discussed and what's been available in the presented data, I don't think the current information we have can provide sufficient labeling. I think more questions need to be answered.

This is of course related to the second part of the question. My concern remains about the metabolite, and the question asked specifically about the opioid antagonist action of samidorphan.

I think if we're only addressing that aspect of it, I think labeling is sufficient. If the question had said related to the action of samidorphan, I probably would have voted no. Thank you.

DR. NARENDRAN: Thank you.

Ms. Witczak?

MS. WITCZAK: Kim Witczak, consumer rep. I voted no. I voted no because I think there are -- well, first of all, there is the assumption that psychiatrists are the ones that will know this, but the reality is, if you've looked at the FDA slide, nurse practitioners and GPs are handing this out, and I do think that the patient will be thinking about it from a weight loss or less weight gain.

So the fact that it has -- then I think the people who would be prescribing the opioids, the ER doctors, the orthopedics, the dentists, people necessarily that may or may not know or be familiar, I think one of the previous speakers said with the psychiatric medications, people who are not in that space tend to realize you never stop

and you've got to be really careful with psych meds. So I think they'll just be some hesitations. I think it's really important -- and I think the sponsor did say the training. But I think it is going to be extremely important to all the non-psychiatrists, physicians, dentists, everybody.

I think also something else that the FDA should be looking at is how it's marketed and really look at the advertising and the marketing materials that are going to go to physicians as well as the patients, because I think the general public is going to see the idea that it's less weight gain, and I think that's going to be an advantage. I mean, it is a sales advantage over the current products on the market, however, to be able to say the other part of it and not just in the little box that probably gets fastly red and over some pretty pictures because that's not what people are going to hear. They're going to hear the weight loss and the less weight gain. So I think it's going to be really an important part should this drug get approved. Thank you.

DR. NARENDRAN: Thank you.

Dr. Calis?

DR. CALIS: Hi. This is Karim Calis from the NIH, and I voted yes. Again, it's a qualified yes based on the narrow wording of the question. I certainly agree with a lot of the comments that have been made so far of Dr. Meisel, Dr. Jain, and Ms. Witczak. I think those are very reasonable and certainly things that I've taken into consideration.

Labeling of itself with any drug, as another individual said earlier, is limited, but nonetheless, it's something that is important. I think one of the things that I'd really like to see -- and this is part of more of an educational campaign -- is to avoid any kind of misinformation about expectations. This is not a weight-loss drug. The modest effect that we see on mitigation of weight gain does not obviate the need for healthy lifestyle, diet, exercise, et cetera. So I think these are all important considerations. Certainly, we can address some of the safety issues

that have already been brought up in the warning section and also in limitations of use about this not being a weight-loss drug and so forth.

Lastly, I would leave with this comment, and that is I think it's also incumbent on the applicant, if this drug were approved, in their promotional material and their educational campaigns to not exaggerate the weight mitigation efficacy of this particular drug because it is certainly very modest. There's still certainly very limited information that we do know about the metabolic effects and the metabolic parameters. So there are limitations, and I think it's really important to keep those in context. So I will stop there. Thank you.

DR. NARENDRAN: Thank you.

Dr. Jeffrey?

DR. JEFFREY: Yes. Hi. Jessica Jeffrey from UCLA. I voted yes for the reasons previously stated most closely aligned with Dr. Dunn. But I did want to add that I do believe potential risks could be mitigated through careful labeling and

broad education to patients and medical providers, including physicians, dentists, and MPs.

I think one of the challenges here is broad education about potential risks to providers and multiple specialties, including psychiatry, emergency medicine, anesthesiology, and primary care, of course among others. So really, the devil's in the details of the labeling and the educational plan. Additionally, I think there should be thorough postmarketing surveillance. Thank you.

DR. NARENDRAN: Thank you. This is Roger Narendran. I voted yes. I have the utmost confidence that the agency can fix it with labeling, always; no. I really think we know a lot. There's a lot more awareness about opioid antagonists. We have so many products like buprenorphine and naltrexone. There's long-acting Revia. People are a lot more in tune in ER and surgical places to be aware, and I think when they're not, it could always be caught by a good pharmacy-based program to flag that.

So I think with labeling, there's no reason to hold this drug to a completely different standard than where we hold naltrexone just because it's more widely known. I think we need to definitely do an education of all the other providers, like surgeons and ER docs, but it's going to be very hard to overdose and override such a high antagonist effect if the occupancy of this drug is pretty high. So I think labeling and education can probably sufficiently address this concern.

I'll pass it to Mr. Matthew Racher.

MR. RACHER: Yes. Hi. This is Matthew Racher, patient representative. I just want to echo some sentiments that were previously described. I voted yes. I believe labeling is sufficient. I do also believe, as people were saying before, broader education from psychiatric providers and the healthcare treatment network is needed. It's definitely not a replaceable service to have that broader education to help patients understand the importance of any adverse effects

from the medication as they adhere to their treatment. So, yes. I voted yes.

DR. NARENDRAN: Thank you.

Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi, Georgetown University. I voted yes. Once again, this is a limited yes in the context of a drug label. I think we need to keep in mind that, really, a drug label is a guidance but, really, in the day-to-day operation of prescribing medication, it actually plays a small part. When you consider the relative risks of this medication from a toxicological standpoint and what we know about other opioid antagonists and the risk of poorly treated pain or precipitated withdrawal, while it is an adverse effect, it is very rarely life-threatening; whereas obesity and the consequences of obesity, which are often poorly controlled in the patient population that this medication would be approved for, is actually much more real.

I think that we do need to have targeted

intervention and educational initiatives with this medication, particularly focused on providers that will be prescribing opioid medications for sure. Then I think we also have to consider that these are not the only hard stops, particularly, because there are clinical pharmacists and clinical decision support, particularly within EMRs now. So I don't think we necessarily need to withhold this medication just based on the labeling alone. Thank you.

DR. NARENDRAN: Thank you.

Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. Jess Fiedorowicz from Ottawa. I voted yes, although I'm reconsidering the word "sufficient." I don't feel I answered the question accurately, and a robust education campaign targeting more than prescribers is certainly needed. If you read the question carefully, I guess it implies that maybe you only need labeling and I would strongly disagree with that.

I share the concerns with Dr. Meisel, and

even though we have a lot more experience now with opiate antagonists, I think some of these concerns could be magnified because this is a new entity and it's not well known. The well-known antagonist naltrexone might be easily recognized by emergency room physicians or anethesiologists, but they may not recognize that samidorphan is an opiate antagonist, especially when it's buried in with olanzapine in the same name.

DR. NARENDRAN: Thank you.

Dr. Zacharoff?

DR. ZACHAROFF: Hi. This is Kevin Zacharoff, Stony Brook Medicine. I voted no for a variety of reasons, including what we heard from Drs. Meisel, Dr. Jain, and Dr. Krishna. But there are a couple of other issues that guided me towards the no, including what we just heard from Dr. Fiedorowicz with respect to the lack of familiarity with samidorphan.

The first point is that all opioid antagonists are not the same. I have no clue as to what this medication really would behave like in

terms of opioid antagonists that I am familiar with. We heard the sponsor mention this morning something like what Vivitrol has, which is a card that a patient would carry along with them.

I have the Vivitrol card in front of me, and what it says is, "Vivitrol is an opioid inhibitor. Suggestions for pain management include regional analgesia and non-opioid analgesics. In the event that opioid therapy is required, it should only be administered by healthcare providers specifically trained in the use of anesthetic drugs and management of respiratory effects of potent opioids.

"Specifically, in the establishment and maintenance of patient airway and assess ventilation, the patient should be monitored closely in a setting equipped for cardiopulmonary resuscitation in the event that an opioid is given."

To that point Roger Chou published a case report on the website in January 2018 for the Agency for Healthcare Research and Quality, titled

"The Painful Medication Reconciliation Mishap." Basically, it was a patient who was on naltrexone, who broke their neck and obviously required opioid analgesic therapy. He states that the dosage necessary in naltrexone blocking effects could be as much as 6 to 20 times higher than the normal therapeutic doses required in the absence of an opioid antagonist. I have no clue as to what that would mean with patients who were still within the window of effectiveness of samidorphan.

Speaking about Vivitrol, which has a REMS -- I think it was Tiffany who mentioned a REMS earlier -- it's not clear to me as to why this medication wouldn't have a REMS, but I would not consider this medication with its opioid antagonist effects for both people who are candidates for opioid therapy or who are unintentionally overdosing as a result of abuse. I cannot understand why this would be treated as a traditional education initiative as compared to a REMS.

In line with that, I'd just like to

reiterate the idea that when we did look at the briefing materials, we saw the demographics of who's prescribing olanzapine, and there were many other healthcare providers other than psychiatrists that were doing the prescribing, many other disciplines, and a lot of primary care. I have no clue as to what the disciplines were of the osteopathic physicians, or the nurse practitioners, or the PAs because it wasn't broken up for those groups by discipline. But in no way, shape, or form would I consider this to be a traditional label, a black boxed warning that covers the risks.

In the event that there is going to be that card that the sponsored discussed this morning. that sounds to me much more like a REMS initiative, and I'm not understanding whether this is some kind of blend of a traditional risk mitigation strategy versus a modified REMS approach, but that's why I voted no. Thank you.

DR. NARENDRAN: Thank you.

I think this concludes our voting questions. We move to question number 4, which is a discussion

question.

Question number 4 is a discussion question. What, if any, additional data are needed to address outstanding issues with Alkermes 3831 or ALKS 3831, olanzapine/samidorphan?

Are there any questions about the discussion question, the wording of the discussion question?

(No response.)

DR. NARENDRAN: I don't see any raised hands. I would suggest if there's no hands, people can feel free to raise your hand to start the discussion.

I'll start. This is Raj Narendran. I don't think it's like an outstanding issue, but I would like to see a receptor occupancy study in humans to characterize what the mu receptor occupancy is after acute dosing, chronic dosing, and also after you stop it, how long does the occupancy persist?

I think if we know that, I think that could be helpful to tell providers there's 50 mu occupancy after 24 hours of stopping, or 48 hours of stopping, and then the pain management

could be cut by half of what it traditionally should be or should be more than half of what it should be. I think it would be important to get that PET occupancy data, which is typically done around phase zero/phase 1.

So hat would be one of my thoughts. It would also be good to see a long-term study with a comparator like olanzapine past what was done for a year, and see if the weight mitigation persists. Those are my thoughts.

Dr. Krebs, I'll pass it on to you.

DR. KREBS: Hi. Two things. First on the benefit side, I mentioned this before, but we don't have evidence that switching to this drug from plain olanzapine would have any benefits in terms of preventing further weight gain, much less, weight loss. One concern would be that a lot of people would be switched for no benefits but greater costs with this new product.

So I do think that additional research on people who are currently on olanzapine and have experienced weight gain would be necessary, and

just needing to be very careful that this isn't marketed in such a way that a lot of switching occurs that is not beneficial to patients or that there's no evidence for that yet.

On the harm side, I voted yes on the labeling thing, but I am concerned that the wording of the label, and the educational materials, and the advertisements do need to be carefully looked at in terms of making sure that the language is clearly understood, especially because words like "opioid dependence" really do not have a shared meaning among physicians, healthcare providers, or the general population these days. So making sure that it's very clear what the contraindications are, and what the risks are, and who's at risk, I think really careful work on that will be needed. Thank you.

DR. NARENDRAN: Thank you.

Dr. Dunn?

DR. DUNN: Thank you. This is Walter Dunn from UCLA. Before I begin talking about my concerns about additional data, I just want to say

that I agree with many of the public comments about how olanzapine is a really important tool in our armamentarium, and anything that we can do to make it safer could only benefit the patients; so taking that into consideration as you hear my comments.

The first thing is -- and I mentioned this before -- having more information about how narrowly does this weight benefit exist, meaning that if we drop below a 90 percent adherence rate, is most of the benefit lost? Because again, I think we have to think about real-world implications. Even though we prescribe medications and expect our patients to take it every day, that's not the reality.

So I think it's important for the clinician to know does adherence have to be at such a high rate that these benefits are not going to be achieved in the clinical practice.

I think that's important for us to know when we start the patient on this because there's no guarantee, even if they take it a hundred percent, that it's going to prevent the weight gain. If

that benefit is further mitigated by the necessity to be a hundred percent adherent, then I think for some clinicians it might not be worth the risk to place them on something with olanzapine.

Second is the issue about will this be effective for patients who are well into the overweight range or obese range. The study population, and I mentioned before, these were patients who were barely overweight, and I suspect for a lot of these patients in clinical practice, they're not going to be below a BMI of 25, and will the same benefits be seen there? Unfortunately, I don't think some of these questions can be answered with postmarketing surveillance. Those are designed to look at adverse events, so I think perhaps a long-term or a phase 4 study would have to be conducted to do this.

The second issue -- of course, I think I mentioned this -- is the metabolite properties in regards to interaction with opioid analgesics. Again, it's still unclear to me. I don't know if the actual study has to be done to see if there is

some type of added effect. Perhaps the labeling could say there is a theoretical risk that there may be increased risk of adverse events if you take an opioid analgesic within 24 to 48 hours of discontinuing samidorphan, but I think that study can be easily done. You place the patient on samidorphan; get the steady state. You discontinue within that acute window afterwards. You give them a standard dose of oxycodone or something like that and see if there is an increased rate of side effects.

Then finally, I think it's important to be clear in the label to really specify what this medication can and cannot do. I think one of the most important outcomes is really that of metabolic syndrome as a potential outcome. That was not addressed in this study; it was only 6 months. We saw that it did mitigate weight gain. We didn't really see that much difference in terms of the other measures, but I think metabolic syndrome is really what we're hoping to prevent long term.

You heard from many of the public

commentators that they're excited about using this in first-episode patients or they're already using it in first-episode patients, early psychosis patients. It's clear from important guidelines that olanzapine and clozapine are ones you should not start with in early-episode patients. But the reality is you've got really sick patients on the inpatient ward, and this is one of the most effective medications, and you have to go to it because there's really not other options. But my concern is if there's not good data about if this has an effect on metabolic syndrome, clinicians are going to assume, well, if I mitigate weight gain, I'm lowering the risk of metabolic syndrome, so maybe my threshold to use it in an early-episode patient is lower.

So that would be my concern. I think data really showing either that it does or does not have an advantage for metabolic syndrome would be important in guiding prescribing practices. Thank you.

DR. NARENDRAN: Thank you.

Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. Hello. Jess Fiedorowicz in Ottawa. I'd like to see studies that focus on the many concerns we've brought up about generalizability. In addition to the mention of switching from olanzapine to olanzapine/samidorphan not being studied, I agree with Dr. Krebs that we need to be very careful that we don't present this as a weight-loss medication but one that prevents weight gain, and this needs to be very clear in the indication. And as I read it, that's not super clear.

As mentioned by Dr. Dunn and others, it's also not clear if there's generalizability to those with obesity, which may represent over half of those with bipolar disorder or schizophrenia, and those that would be most interested in preventing further weight gain.

I'm somewhat concerned of a running theme that came up in the public comments that may represent some sort of early premarketing, with statements suggesting that this medication may

prevent weight gain altogether. That's simply not true. This committee seems to be in agreement that any weight mitigation is fairly modest, and this combination product is still absolutely obesogenic.

I also have to respectfully disagree with the agency and the applicant related to the rationale for this bridging to a bipolar I indication. I think there's a series of somewhat tenuous bridges here between naltrexone and samidorphan, and those naltrexone studies, as I mentioned before, were already pretty limited; as well as schizophrenia to bipolar disorder, while it's likely that these may be similarly effective, I don't think this bridging strategy establishes that indication.

With the FDA clarification, there seems to be this assumption that effects are entirely D2 mediated, and that ignores the burgeoning literature on the relevance of opioid neurotransmission in circuitry and mood disorders. I think this concern is relevant for both efficacy and safety.

So those are some of the concerns I wanted to bring up for a future study to address generalizability. Thank you.

DR. NARENDRAN: Thank you.

Next is Dr. Krishna.

DR. KRISHNA: I agree with the previous questions and comments and discussion. I also wanted to add that I would like to see this research done in younger patients. I know a pediatric study would be planned for the future, but even the current demographics were done in age 40 with the average being there. And if we're looking at first episodes, trying to prevent the weight increase to the same extent that would be on just olanzapine alone, I would like to see it done in maybe 18 to 25-year-old patients.

I feel, from data and experience, that the weight gain risk is much higher in younger patients. So if there is a medication that states that it mitigates some weight gain, it's going to be used even off-label in pediatric patients prior to getting the FDA indication, and I would just

like more data showing that hopefully there's a greater mitigation because the risk would be much higher for them. Thank you.

DR. NARENDRAN: Thank you.

Next is Dr. Meisel.

DR. MEISEL: Hi. Thank you. Steve Meisel with Fairview in Minneapolis. One of the elements here that I don't think I heard discussion about, and it wasn't intended to, but would be important for the real world, and that is a person who was already stable on olanzapine, what are the implications of switching them over to this product; good, bad or indifferent? I haven't seen any data to that effect or a discussion to that effect.

At first blush, it's not intended to do that, but you know full well that in the real world it would be a temptation to switch somebody over in the hopes that it would cause a weight loss. Well, what are the implications of doing that, both in terms of any value whatsoever and what additional adverse events might crop up should that happen in

the real world?

So that would be an area of additional data that I think would be really valuable to characterize this particular product. Thank you.

DR. NARENDRAN: Anybody else who wants add? I'm just going to scan for any other raised hands.

Ms. Witczak?

MS. WITCZAK: Kim Witczak. Somebody just said this, but I really want to see more on the common, off-label use of the drug with bipolar depression. It's being used in sleep disturbances. This is the real world. I know that some psychiatrists cannot believe it, but it is happening in the GPs and children's PTSD. So I'd love to see more study in those populations and what's happening.

Then as well, I'm going to reiterate communication. I think we have to be all over this, watching the way it is presented to not only the public through direct-to-consumer advertising, but also how it is promoted to the doctors, the meetings that are happening, the communications,

because that is one of the concerns with Zyprexa and some of those antipsychotics, is the weight gain.

So it sounds like a really great product, and definitely from a sales perspective, it is going to be the point of differentiation, and it's going to be an easy thing to go into a physician's office. So I think we have to be really careful about how it gets promoted because we could have a lot of potential issues down the road. Thanks.

DR. NARENDRAN: Thank you.

If people could take the opportunity to lower their hands so I don't call on you again. I see a couple raised hands. Okay.

Dr. Fiedorowicz, do you have comments, further comments?

DR. FIEDOROWICZ: Sorry. I didn't put my hand down.

DR. NARENDRAN: Okay.

If there's no additional comments -- I don't see anybody else -- I could try to summarize this. What I heard in terms of from the panel members for

additional data would be maybe a PET occupancy study to look at the mu receptor occupancy studies to look at switching from olanzapine to olanzapine/samidorphan to see if it's beneficial; studies to see if patients were not really adherent as prescribed at a hundred percent and what does that mean in terms of the benefits and risks of weight mitigation, as well as opioid overdoses and opioid antagonists risks.

It would be useful to see more patients with high BMI being enrolled to take this and see if it helps them as well. Definitely some questions were raised about studies required to look at the metabolic properties of samidorphan, especially if it has agonist efficacy and how that interacts with potential other opioid agonists when prescribed; is it going to lead to increased harm? Studies to address that could be helpful.

Also, people are interested to see whether there'd be longer term studies not just to mitigate the weight gain and the waist circumference, but also can it prevent the occurrence of metabolic

syndrome or mitigate the occurrence of metabolic syndrome. Data on bipolar disorder was raised. Also, people want to see data in younger patients, not just pediatric, but also 18 to 25-year-old patients who tend to be first episode with psychosis and mood disorders. There was also an interest in looking at additional data in PTSD and other off-label uses for which this medication could be prescribed. There was also some thought of better characterized long-term adverse events could be helpful as well in postmarketing data.

Are there any other thoughts or closing comments from the agency? I hope this is useful and helpful.

DR. FISCHER: Hi. This is Bernie Fischer. Yes, very helpful. Thank you very much. No additional comments from me. Thank you.

Adjournment

DR. NARENDRAN: With that, I would like to thank members of the public, the FDA staff, especially the technical staff. Specifically, I'd like to call out Dr. Bonner for having conducted a

great meeting through the virtual format and also the sponsor for having done a great job. We will now adjourn the meeting. Thank you.

(Whereupon, at 3:39 p.m., the meeting was adjourned.)