Olanzapine/Samidorphan Program NDA 213/378
Psychopharmacology Drugs Advisory Committee and
Drug Safety and Risk Management Advisory Committee
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Alkermes. Inc.

Introduction, Lauren DiPetrillo, PhD, Alkermes, Inc.

Slide 2

Hello, my name is Lauren DiPetrIllo, and I'm the regulatory lead on the olanzapine/samidorphan program, hereafter referred to OLZ/SAM, being developed by Alkermes as a new potential therapeutic option for the treatment of schizophrenia and bipolar I disorder.

I would like to thank the advisory committee and the agency for this opportunity to present the key data supporting this application.

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Now on this slide represents an overview of our agenda. Following my introduction, Dr. René Kahn, an expert in serious mental illness from Mt. Sinai Hospital will present his perspective on the unmet medical need for both of these conditions.

This will be followed by Dr. David McDonnell who will provide an overview of the clinical efficacy of OLZ/SAM,

Then Dr. Sergey Yagoda will provide an overview on the clinical safety.

We have two unique clinical perspectives, one psychiatric from Dr. Ginger Nicol, a practicing psychiatrist, and also a site investigator on OLZ/SAM clinical trials. As well as a second on cardiometabolic from Dr. Evan Stein from University of Chicago, who's an expert in lipid disorders.

And then we'll wrap up with conclusions.

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We also have Dr. Kathleen Brady, who's an expert in opiate risk mitigation strategies for opiate receptor antagonists, as well as several other members of Alkermes to address questions.

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Now olanzapine is an effective antipsychotic agent. It's been approved by the FDA under the brand name Zyprexa since 1996. However, it's utility has been offset by its propensity to cause clinically significant weight gain, and we know that this weight gain doesn't, in fact, stabilize over time, but

increases so that patients can gain upwards of 50 pounds while taking olanzapine, which not only has an impact on cardiometabolic risk outcomes, but also affects patients' lives.

Samidorphan is an opiate receptor antagonist developed by Alkermes and is a new molecular entity. It was combined with olanzapine with the intention to mitigate olanzapine-associated weight gain but, importantly, to maintain the antipsychotic efficacy of olanzapine.

We have two proposed therapeutic indications. One for the treatment of schizophrenia and, two, for the treatment of bipolar I disorder, both as a monotherapy and adjunct to lithium or valproate. Importantly, both of these are identical to Zyprexa.

Our proposed therapeutic dose range is also identical to Zyprexa, namely 5-20 milligrams of olanzapine combined with a 10-milligram fixed dose of samidorphan given orally once daily.

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Now we've met frequently with the agency over the years, and at end of Phase 2, aligned on what would be needed for our pivotal Phase 3 registration package for the treatment of schizophrenia. This can comprise two Phase III clinical studies. One to evaluate the antipsychotic efficacy of OLZ/SAM versus placebo with olanzapine included for assay sensitivity. And two, to evaluate the weight efficacy of OLZ/SAM versus olanzapine in a 24-week trial in schizophrenia patients.

We also aligned that samidorphan is not a general weight loss agent nor has any antipsychotic properties and is included in the combination to mitigate a key safety risk of olanzapine, so thus a samidorphan alone arm was not required for Phase 3.

We had several additional meetings with the agency to align our clinical pharmacology study designs, our Phase 3 statistical analysis, as well as what would support a bipolar I disorder PK bridge.

At our pre-NDA meeting, we aligned at our NDA submission content and we also have an agreed pediatric study plan.

Slide 7

Now the program itself is extensive. It's comprised of 27 clinical studies, 18 of which with OLZ/SAM and 9 with samidorphan alone. Throughout the presentation, you'll hear about two pivotal Phase 3 studies conducted in schizophrenia patients, namely Study A305, which evaluated the antipsychotic efficacy of OLZ/SAM, and Study A303, which evaluated the weight mitigation efficacy of OLZ/SAM herein referred to as weight efficacy.

We also have three long-term open-label safety extension studies.

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Now throughout the program olanzapine/samidorphan has demonstrated consistent mitigation of olanzapine associated weight gain. This goes all the way back to nonclinical species where we saw decreased weight gain and adiposity versus olanzapine.

We then moved into healthy volunteers in Phase 1 and saw decreased weight gain.

And, importantly, this was replicated in schizophrenia patients not only in Phase 2 but also in Phase 3. And in Phase 3, in fact, we saw smaller increases in waist circumference and systolic blood pressure. And with long-term treatment, we see stabilization of weight gain, waist circumference, blood pressure, and metabolic laboratory parameters, all of which contrast to what's known for Zyprexa, as these all increase over time.

Slide 9

Now to focus on our bipolar bridging strategy, we met with the agency and aligned that there was two key points that we needed to establish. One, that the olanzapine exposure within OLZ/SAM must be bioequivalent to Zyprexa. This here is shown on this plasma concentration time curve with concentration on the Y axis and time on the X.

The OLZ/SAM olanzapine concentrations are represented in blue and Zyprexa in orange. And you can see that they're virtually overlapping, indicating bioequivalent olanzapine concentrations.

We also needed to demonstrate similar antipsychotic efficacy to olanzapine in our schizophrenia program. And you'll see this presented in Dr. McDonnell's slides.

Slide 10

Now the bridge is also supported by several other lines of evidence. Olanzapine associated weight gain is disease independent. We know in looking at the Zyprexa US PI weight gain is noted as an adverse reaction for both schizophrenia patients and bipolar patients.

We also know that the weight mitigation of olanzapine/samidorphan is disease independent as we've seen this in Phase 1 healthy volunteers as well as schizophrenia patients.

We have no drug/drug interaction with lithium or valproate, which supports our adjunct indication.

And, importantly, in looking at the literature, opiate receptor antagonists, when given concurrently with patients' antipsychotics, do not impact bipolar symptom control. In fact, in looking at treatment guidelines, opiate antagonists are actually recommended for patients with co-occurring substance use disorder.

All of these points support out bipolar bridge strategy.

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In summary, we have a favorable benefit/risk profile for the treatment of schizophrenia and bipolar I disorder.

We demonstrated antipsychotic efficacy versus placebo, as well as clinically meaningful mitigation of olanzapine-associated weight gain.

This was further supported by findings on our waist circumference and systolic blood pressure.

Our safety profile is well tolerated with a similar safety profile to that of olanzapine, yet we have an additional benefit of lower weight gain.

And with that, I'd like to turn it over to Dr. René Kahn to speak about the unmet medical need.

Unmet Need in the Treatment of Patients with Schizophrenia or Bipolar Disorder, René S. Kahn, MD, PhD

Slide 12

Thank you very much to provide me with the opportunity to talk about the unmet needs in the treatment of patients with schizophrenia or bipolar disorder.

I'm René Kahn, I'm Chairman of the Department of Psychiatry at the Icahn School of Medicine in New York.

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Schizophrenia is one of the most devastating psychiatric illnesses, and it starts early in life, in the second decade, with a lifetime risk of 1%, meaning that about 1% of the population has the risk to develop the illness, which is more than diabetes type one, more than multiple sclerosis, and more than Parkinson's disease.

It's characterized by positive symptoms, psychotic symptoms, delusions and hallucinations; called positive because it's present in the patients and not in the healthy populations.

Negative symptoms, which means negative because they're not present in the patients, but they are present in the healthy populations, such as decreased social interaction, decreased initiative, and decreased emotional expression, and cognitive impairment.

Unfortunately, the illness is life long and characterized by frequent relapses and rehospitalizations. And this leads to that fewer than 10% will eventually have gainful employment.

In addition, the life expectancy is decreased by 15 years, and which is multi-tributable to the high, the increased risk of suicide but it's also related to the risk of cardiometabolic comorbidities, which is quite prevalent in this population.

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Fortunately, we can treat the positive psychotic symptoms in schizophrenia quite well. And, in fact, olanzapine is one of the most effective antipsychotics in the treatment of schizophrenia, as you can see on the left-hand side of this slide.

The only more effective drug is clozapine, but that drug is characterized by a lethal side effect that occurs in 1% of the population that is treated with this drug because of a reduction in white blood cells.

Not only is olanzapine one of the most effective antipsychotics, it's also been adhered to most prominently.

This is a study we conducted several years ago where we compared how long patients stay on the medications that they had been randomized to, and there also, olanzapine beat the other antipsychotics in this study as well as adhere. So patients are compliant in the sense that they continue the treatment, which is very important because we know that continuation of treatment is one of the most effective ways to prevent relapse and rehospitalizations.

Slide 15

Now the other major psychiatric illness is bipolar illness, which has a lifetime risk even higher than schizophrenia of 2%. And this is characterized by manic episodes which are psychotic hyperexcitable episodes where patients are often in need for hospitalization. And, usually, patients also have additional depressive episodes.

Like in schizophrenia, the illness starts early, in the second decade of life, and it is characterized by frequent relapses, very often leading to hospitalizations. And these patients also have an impaired social and occupational functioning that lasts throughout life.

Life expectancy is decreased by ten years, and this is not just attributable to the highly increased risk of suicide, but there's also a result of high risk of medical comorbidities.

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Like in schizophrenia, olanzapine is highly effective in treating manic and psychotic symptoms in bipolar illness.

As you can see in the left-hand side of this slide, olanzapine is highly effective in reducing psychosis and mania and belongs to the most effective antipsychotics in bipolar illness.

Similarly to schizophrenia, as you can see here in a meta-analysis, patients continue to use olanzapine more than any of the other antipsychotics and, therefore, stay on olanzapine longer, which leads to less relapses and less rehospitalizations.

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The unfortunate characteristic olanzapine, however, is that it induces weight gain to a considerable extent. And although, as you can see here, the range is quite large, it's a very large percentage of patients treated on olanzapine who gain more than 7% of their weight.

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Now that is a major problem because we all know that increased weight is a problem because it leads in an almost dose-dependent fashion to increased risk for diabetes, hypertension, and dyslipidemia. The higher the weight, the larger the risk.

Slide 19

What's more, as you probably are aware, that increased weight is related to all-cause mortality. And that from about a BMI of about 26, there is a linear increase with increasing weight to the risk of all-cause mortality. So the problem with olanzapine is that it increases hypertension, diabetes and dyslipidemia, but moreover, because of the weight increase, it has a direct risk of all-cause mortality.

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So to summarize what I have presented here, is that schizophrenia and bipolar illness are lifelong debilitating illnesses starting early in life, characterized by treatment relapse and rehospitalizations.

Olanzapine, fortunately, is highly effective in treating psychosis as well as mania, and there's an excellent maintenance treatment for both disorders.

The problem with olanzapine, however, is that it severely increases weight, which associated with increased morbidity and mortality.

So the olanzapine/samidorphan combination may allow olanzapine to be used more widely again by limiting the weight gain associated with this effective medication.

Thank you.

OLZ/SAM Antipsychotic and Weight Efficacy – David McDonnell, MD, Alkermes, Inc.

Slide 21

Thank you, Professor Kahn. My name is David McDonnel. I'm a psychiatrist and the medical lead on the development of OLZ/SAM. I'm going to present the efficacy of OLZ/SAM, both the antipsychotic efficacy and the effects on weight gain.

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Here is the agenda for my presentation. I will cover the objectives of the clinical program, the data sources, and the data supporting the antipsychotic efficacy, and the differences in weight gain with OLZ/SAM treatment.

In addition, I will present the findings of the anthropometric and cardiometabolic parameters.

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The objectives of this clinical program were to demonstrate the combination of olanzapine and samidorphan maintain the psychotic efficacy of olanzapine alone and mitigated the weight gain associated with olanzapine treatment.

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The antipsychotic efficacy was established with a placebo-controlled study in patients with schizophrenia.

Additionally, across multiple studies in the program, OLZ/SAM demonstrated similar effectiveness to olanzapine in controlling the symptoms of schizophrenia, and the long-term control of symptoms was observed in the open-label studies.

The second part of our program was unique, to examine the effects of OLZ/SAM on olanzapine associated weight gain. The pivotal study focused on the differences in weight gain for OLZ/SAM compared to olanzapine after 24 weeks of treatment.

This six-month study is supported by findings in the Phase 2 dose ranging study, and the long-term stability of weight observed in the open-label studies with OLZ/SAM.

In addition to weight, other outcomes that could be affected by that change in weight were measured, including metabolic laboratory parameters, waist circumference, and blood pressures.

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The sources of the data in the program were as follows:

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There were two pivotal efficacy studies, the placebo-controlled study of four weeks in duration, and the olanzapine-controlled 24 week or six-month study examining the effects on weight.

Patients who completed these studies could enter a one-year extension study to be treated with OLZ/SAM, and patients who completed these extension studies could further enroll into a further two years of treatment with OLZ/SAM.

In addition to these pivotal studies, there were two Phase 2 studies, a dose-ranging study and a study in patients with schizophrenia and co-occurring alcohol use disorder.

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The antipsychotic efficacy of OLZ/SAM was established in a four-week double-blind randomized placebo-controlled study.

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This was in patients with schizophrenia who were 18-70 years of age and were acutely ill. This study included an olanzapine only treatment arm. Patients were hospitalized prior to randomization and

remained in hospital for at least the first two weeks of the study, and greater than 80% remained inpatient for the full duration of the study. 403 patients were randomized to treatment with OLZ/SAM, olanzapine, or placebo.

The primary and key secondary endpoints were met in this study. The primary endpoint was a change from baseline in positive and negative syndrome total score at week four for OLZ/SAM compared to placebo. The PANSS is a universally accepted scale that assesses the severity of symptoms in patients with schizophrenia.

The key secondary endpoint was the change from baseline in clinical global impression of severity at week four. The CGI-S is a more global measurement of severity of illness based upon the clinician's experience.

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Patients in this study were, on average, 40 years, the majority were male, white, and from outside the US.

In keeping with the requirements of the study, the baseline PANSS total score was greater than 100 for all treatment groups, indicating moderate to severe levels of illness.

The completion rate for this mostly inpatient study was high. Mean doses of olanzapine used in both OLZ/SAM and olanzapine treatment was approximately 18 milligrams per day.

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OLZ/SAM established antipsychotic efficacy in this four-week study. This figure represents the primary outcome measure of PANSS total score with the change from baseline on the Y axis and visits in weeks on the X axis.

The numbers below the X axis designate the number of patients on each treatment at each visit.

The OLZ/SAM is in blue, olanzapine is in orange, and placebo is in gray.

A decrease in PANSS score indicates improvement, and at the end of four weeks, we see 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.

The improvements compared to placebo occurred early in treatment, after one week for both OLZ/SAM and olanzapine.

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 observed in open-label studies with up to 76 weeks of treatment with OLZ/SAM.

The similarity in antipsychotic effects between OLZ/SAM and olanzapine in the pivotal four-week study is consistent with observations from studies across the program.

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Here are three studies. On the left is the Phase 2 12-week dose ranging study. In the middle is the 24-week study in which weight was assessed. And on the right is the study of patients with schizophrenia and co-occurring alcohol use disorder treated for up to 60 weeks.

The absolute changes in PANSS total scores are shown with OLZ/SAM in blue and olanzapine in orange. We see very similar control of symptoms across the three studies for OLZ/SAM and olanzapine with no evidence that there's a loss of efficacy with the addition of samidorphan to olanzapine.

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Having demonstrated that OLZ/SAM maintains the antipsychotic efficacy of olanzapine, we now move to the next objective of the clinical program, the mitigation of weight associated with olanzapine treatment.

Before I go to the design of the pivotal weight study, I would like to walk through some important considerations in the development of the study.

First, the study duration had to be balanced with patient retention. Olanzapine related weight gain occurs, continues over time and, therefore, an ideal comparison would follow patients for as long as possible.

However, the majority of studies in schizophrenia that are longer than six months have discontinuation rates in excess of 50%, making missing data a significant issue. Thus, Alkermes agreed with the agency on a 24-week or six-month study comparing OLZ/SAM to olanzapine.

A point of uncertainty in designing this study was the extent to which we'd be able to detect differences in metabolic laboratory parameters. We included these parameters as exploratory efficacy endpoints, understanding that the observed 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 the six months was sufficient to see differences in weight, it was not clear that this timeframe was sufficient to observe weight-driven changes in the metabolic parameters. Thus, the primary focus of the study was on weight gain associated with OLZ/SAM and olanzapine treatment, and with the metabolic laboratory parameters as exploratory endpoints.

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The effects of OLZ/SAM on weight were examined in a 24-week double blind randomized controlled study in patients with schizophrenia.

Patients who were suitable for outpatient treatment and were 18-55 years of age with a body mass index between 18 and 30 kilograms per meter squared.

561 patients were randomized to treatment with OLZ/SAM or olanzapine.

The coprimary and key secondary endpoints were met in this study. These coprimary endpoints were selected to evaluate the clinically meaningful difference in weight gain to both mean changes in the overall population and the proportion of patients gaining a large amount of weight in the study.

One coprimary, examined the percent change from baseline in body weight at week 24, and the other, examined the proportion of patients gaining greater than or equal to 10% of their body weight. And this 10% cutoff was chosen as it signifies clinically meaningful amount of weight gain. For instance, in a person weighing 170 pounds, this represents 17 pounds of weight gain in just six months of treatment.

The key secondary endpoint - examined the 7% cutoff, as this is widely used in psychiatry studies. And this cutoff has been used to determine potentially clinically significant weight gain, which is reflected in the labeling of all antipsychotic medications.

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Patients in Study A303 were, on average, approximately 40 years of age, predominantly male, and 70% were black. The body mass index was balanced between treatments at between 25 and 26 kilograms per meter squared.

Patients had a PANSS total score at baseline of approximately 70, indicating mild to moderate symptoms of schizophrenia in keeping with the outpatient study population.

In this study, 64% of patients completed the study and the completion rates were similar between the treatment groups. This completion rate is higher than most six-month studies of patients with schizophrenia and consistent with the high completion rates seen on olanzapine treatment.

The average dose of olanzapine in this study was approximately 17 milligrams per day in both treatment groups.

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The coprimary and key secondary endpoints were met in this study , and I'm going to talk in more detail about these endpoints in subsequent slides.

The difference in percent change of weight reflects the mean change of the whole population of the study. OLZ/SAM had 2.38% less weight gain than olanzapine, and this difference was highly significant.

For patients gaining greater than or equal to 10% of their body weight, the risk difference between OLZ/SAM and olanzapine was 14%, and for the 7% cutoff, it was 16%.

Both these values were lower for OLZ/SAM compared to olanzapine with high statistical significance.

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Now I'm looking at the percent change in body weight in more detail. This figure is showing the percent change from baseline in body weight by week in the 24-week study.

At the end of 24 weeks, the percent change in body weight with OLZ/SAM was significantly lower than with olanzapine. As OLZ/SAM is not a weight loss product, there was some initial weight gain which stabilized from four weeks on and remained stable for the remainder of the study.

This contrasts to what is seen with olanzapine. The weight gain on olanzapine treatment continued to increase throughout the 24 weeks.

As a result, the differences between OLZ/SAM and olanzapine continued to grow throughout the study.

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Now looking in more detail at the categorical cutoffs. First, to the table on the left. In the coprimary and key secondary endpoints, OLZ/SAM reduced the risk of gaining either 10 or 7% of body weight by 50%. This can be translated into a number needed to treat, or NNT. This is the number of patients needed to be treated with OLZ/SAM to show a benefit over olanzapine.

A number needed to treat of less than 10 indicates that this is an effect important enough so that the difference can be seen in routine clinical practice. For the 10 and 7% cutoff, the NNTs were 8 and 7 respectively for OLZ/SAM.

Now to the figure on the right, the cumulative responder plot. This is an important figure as it shows that OLZ/SAM shifted the entire weight gain distribution curve compared to olanzapine and reduced the risk of weight gain compared to olanzapine no matter how we defined clinically meaningful.

The X axis is all the cutoff points for weight. For instance, minus 15% represents a 15% weight loss. As you can see, almost 100% of patients gain more weight than this in the study, and you can see in the figure that the OLZ/SAM curve in blue is consistently shifting lower than the olanzapine curve in the orange.

The widest separation between these curves includes the cutoff points of 10 and 7%. And this indicates that the risk reduction with OLZ/SAM treatment is most pronounced in those patients who are most susceptible to weight gain associated with olanzapine treatment.

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To assess the impact of missing data, we looked at the pattern of weight gain in those patients who completed or dropped out early in the study.

In this figure we see the percent change in body weight by week in the study. The solid lines in blue and orange are those patients that completed the study and their average weight gain. The *n*s are the

numbers of patients. So in blue, 177 patients completed treatment with OLZ/SAM, and in orange 175 patients completed treatment with olanzapine.

The dotted lines represent the patients who discontinued at each of the visits during the study.

For example, look at week 16, with OLZ/SAM treatment in blue on the left, we note that 15 patients discontinued treatment at this visit, and the average weight gain for those 15 patients was approximately 3%.

For olanzapine on the right, we see that 16 patients discontinued at week 16 with a weight gain of approximately 7%.

Overall, for OLZ/SAM, we see that patients who discontinued treatment early had a trend of weight gain that appeared to be similar to those patients who completed the study.

This was not the case for olanzapine. We can see in general patients who discontinued treatment early on olanzapine, trended towards having higher weight gain than those patients completing treatment with olanzapine.

Given these observations, the multiple imputation mechanism used to handle missing data in the primary analysis was appropriate and actually may have underestimated the weight gain on olanzapine treatment.

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The findings in the Phase 3 study are supported by the findings in the dose ranging Phase 2 study.

On the left of the slide is our 12-week Phase 2 study, and on the right is the results from the pivotal Phase 3 study.

In this Phase 2 study, there were stabilization of weight gain on OLZ/SAM with continued weight gain on olanzapine throughout with very similar findings to the Phase 3 study.

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This figure demonstrates the long-term stability of weight on treatment with OLZ/SAM for up to 76 weeks. All patients are on OLZ/SAM treatment, and the findings are consistent with the findings in the Phase 3 study.

After an initial period of weight gain, weight stabilized and remained stable with continued OLZ/SAM treatment.

Importantly, while this is an open-label study and interpretation is limited, the long-term stability of weight observed here is different than the persistent weight gain that has been described with long-term olanzapine treatment.

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So, in summary, we've seen that OLZ/SAM has demonstrated antipsychotic efficacy compared to placebo treatment. Olanzapine demonstrated similar effects to OLZ/SAM.

The consistency in the control of symptoms of schizophrenia for OLZ/SAM and olanzapine has been demonstrated in multiple studies in patients with schizophrenia.

OLZ/SAM demonstrated a clinically meaningful reduction in weight gain compared to olanzapine treatment as assessed by both mean changes in weight as well as the risk of gaining either 10 or 7% of body weight. And this finding is supported by similar findings in the Phase 2 study.

Open-label studies show long-term stability of weight with OLZ/SAM treatment. And this is in contrast with the literature which demonstrates progressive weight gain with long-term olanzapine treatment.

As we can see, the addition of samidorphan to olanzapine has maintained olanzapine's known effects in controlling symptoms of schizophrenia, and there appears to be no loss of efficacy with the combination treatment.

In addition, OLZ/SAM demonstrated a meaningful mitigation of olanzapine-associated weight gain, demonstrating that OLZ/SAM has a weight profile that is lower and fundamentally different from that of olanzapine.

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In addition to weight, we did examine the changes in metabolic laboratory parameters, waist circumference, and blood pressure.

These are known as both weight dependent and independent risk factors for cardiometabolic disturbance.

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This figure demonstrates that OLZ/SAM mitigated increases in waist circumference. Waist circumferences is an accepted proxy for central adiposity, and we know that central fat is a major driver of downstream metabolic impairment.

The figure on the left is showing the change from baseline in waist circumference for OLZ/.SAM and olanzapine. Similar to the changes in weight after 24 weeks, there were lower increases of waist circumference for OLZ/SAM.

Interestingly, the differences in waist circumference occurred earlier than the differences in weight, suggesting that changes in how weight is distributed may occur earlier than the actual changes in weight.

On the right, we also looked at the categorical changes in waist circumference. We examined an increase of 5 centimeters, or 2 inches, in waist circumference. This was chosen as not only does it reflect a change in pant size in only six months of treatment, but, also, there is evidence that every 5-centimeter increase in waist circumference is associated with increased mortality for both males and females.

Again, OLZ/SAM reduced the risk of gaining 5 centimeters in waist circumference by 50% compared to olanzapine with a number needed to treat of six.

The changes in waist circumference was stable in patients continuing OLZ/SAM treatment for up to 76 weeks with a 1-centimeter change over this time period.

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Blood pressure on OLZ/SAM remained stable while it increased on olanzapine treatment.

One the left is change in systolic blood pressure in the 24-week study, and on the right are the changes in diastolic blood pressure.

In the 24-week studies, systolic blood pressure on all olanzapine treatment increased by greater than 2 millimeters of mercury, whereas it was unchanged on treatment with OLZ/SAM. Diastolic blood pressure was largely unchanged for both treatments.

In addition, OLZ/SAM reduced the number of patients shifting from a normal blood pressure to type 1 or type 2 hypertension compared to olanzapine in this 24-week study.

The long-term stability of blood pressure was demonstrated in patients remaining on OLZ/SAM treatment for up to 76 weeks with a 1-millimeter mercury change in systolic blood pressure over this time period.

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Unlike the changes in weight, waist circumference and blood pressure, we did not see differences in metabolic laboratory parameters between OLZ/SAM and olanzapine.

Here we are looking at a change by visit in total LDL and HDL cholesterol and triglycerides for OLZ/SAM and olanzapine. On the Y axis is the change from baseline, and on the X axis is weeks.

As you can see, the changes occurred very early in treatment for all the lipid parameters.

To demonstrate this, if we look at the top left-hand panel, this is changes in fasting total cholesterol from baseline over the course of 24 weeks.

For both treatment groups we can see early increases in the total cholesterol for the first two weeks of treatment, and then a recovery back to baseline levels over the remainder of the study.

There is a similar pattern for LDL cholesterol in the top right-hand panel, and in the bottom panels, early changes and stabilization occurred with HDL and triglycerides.

So, overall, at the end of 24 weeks of treatment, the level of changes in lipids was relatively small and not different between OLZ/SAM and olanzapine.

This is consistent with what is known about olanzapine. It is associated with early changes in metabolic parameters that are weight independent, and the addition of samidorphan does not appear to affect these changes.

The changes in metabolic parameters due to persistent progressive weight gain may take longer than the six months to emerge.

In the long-term open-label data with OLZ/SAM treatment for up to 76 weeks, stability was seen in these lipid parameters.

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And here we're looking at the changes by visit in the glycemic parameters with HbA1C on the left, fasting glucose in the middle, and fasting insulin on the right. Similar to the lipids, there was little difference in the glycemic laboratory parameters between OLZ/SAM and olanzapine, with stability in HbA1C and small increases from baseline for glucose and insulin.

The glycemic parameters like the lipids remain stable for patients remaining on OLZ/SAM treatment for up to 76 weeks.

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So, in summary, in the 24-week study, OLZ/SAM mitigated olanzapine associated increases in waist circumference and reduced the risk of gaining 5 centimeters of waist circumference by 50%.

There were smaller increases in systolic blood pressure for OLZ/SAM compared to olanzapine.

There were no differences between OLZ/SAM and olanzapine for lipid and glycemic laboratory parameters, and there was long-term stability for all the parameters.

The improvements in waist circumference and blood pressure further support the clinical impact of mitigating olanzapine associated weight gain.

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Finally, overall, we've demonstrated that in the pivotal studies OLZ/SAM met all primary and secondary objectives. OLZ/SAM demonstrated greater improvements in the symptoms of schizophrenia compared to placebo and mitigated clinically meaningful weight gain compared to olanzapine treatment.

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Thus the combination of olanzapine and samidorphan is an effective antipsychotic that retains the efficacy of olanzapine.

OLZ/SAM also results in a reduction of clinically meaningful weight gain compared to olanzapine. And this finding is further supported by the differences on waist circumference and blood pressure.

And with that, I will hand it over to Dr. Sergey Yagoda for an overview of the safety of OLZ/SAM.

Clinical Safety - Sergey Yagoda, MD, PhD, Alkermes, Inc.

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Thank you, Dr. McDonnell. My name is Sergey Yagoda. I'm a psychiatry medical director at Alkermes.

I will give you an overview of the safety data collected in OLZ/SAM clinical program.

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I will start with an overview of the safety profiles of olanzapine and samidorphan individual components of OLZ/SAM.

We will then review the exposure data and sources of safety information, including the pooling strategy that was applied for analysis of safety data in the current application.

I will show you adverse events profile, discuss the laboratory parameters, vital signs, and ECG data.

I will then discuss areas of special interest such as the risks associated with antipsychotic drug class, opioid antagonism, and mitigation strategies to address those risks.

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OLZ/SAM is a combination drug consisting of an atypical antipsychotic olanzapine and an opioid antagonist samidorphan.

Our understanding of its safety profile is informed by an extensive safety package accumulated for Zyprexa.

The effects of samidorphan have been studied in over 600 patients and healthy volunteers.

Supportive to that is a nonclinical experience with opioid antagonists which are used in the field of addiction psychiatry, including in patients with comorbid serious mental illness.

As we monitored our clinical studies, we focused on the known safety profiles of both components while being vigilant to new and expected adverse events or amplification of known signals that might have emerged from combined use of olanzapine and samidorphan.

Our overall experience to date suggests that the safety profile of OLZ/SAM is generally consistent with olanzapine with the exception of less weight gain.

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Let us review the known safety profile of olanzapine and samidorphan.

As a second-generation antipsychotic, olanzapine is known to commonly cause weight gain and increased appetite, somnolence, dry mouth, constipation, orthostatic hypotension, and extrapyramidal symptoms.

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There are other potentially serious risks of olanzapine and overall class of atypical antipsychotics. They are presented on this slide.

These less common risks are informed by over 20 years of olanzapine use.

Slide 55

Common adverse events of samidorphan are shown on the left. This is based on a 12-week study in adults with alcohol use disorder, where samidorphan was used as a monotherapy.

As we can see, there is an overlap with common adverse events of olanzapine treatment such as dizziness, dry mouth and constipation.

Additionally, nausea and vomiting were commonly reported.

Other important risks of opioid antagonism are potential of acute precipitated opioid withdrawal in opioid dependent patients, vulnerability to opioid overdose, and reduced or inadequate opioid analgesia.

Slide 56

Let's review the sources of safety data.

Slide 57

First, we have placebo and olanzapine controlled clinical studies. Study A305, a four-week study in patients hospitalized for acute exacerbation of schizophrenia. This study had both placebo and olanzapine comparators.

And Study A303, a 24-week long weight study in stabilized outpatients. Here we were able to compare safety profiles of OLZ/SAM and olanzapine.

Slide 58

These two studies had continued into long-term safety extensions. We have integrated and pooled the overall exposure to OLZ/SAM from those randomized controlled studies, long-term extensions, and one additional large study in comorbid alcohol use disorder in schizophrenia population.

This created a long-term safety pool with a total of 831 patients and up to three and a half years of exposure data for OLZ/SAM.

Slide 59

The overall safety profile of OLZ/SAM is informed by a total of 1,601 unique exposure to OLZ/SAM with 1,262 of those in population of 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 clinical studies going up to three and a half years.

Slide 60

Now let's review the adverse events , or AEs.

Slide 61

First, let me orient you to this slide.

Highlighted in blue is the four-week acute study, A305, with the adverse events counts represented by randomized treatments. OLZ/SAM on the left, followed by olanzapine and placebo.

The purple section represents the 24-week weight study, A303, with OLZ/SAM compared to olanzapine.

Finally, highlighted in yellow on the right is the long-term safety pool data that collects AE information from the randomized controlled studies with addition of long-term open-label extensions.

Looking at the rows, we can see that the rate of adverse events assessed as related to the study medications was similar between the OLZ/SAM and olanzapine treatment groups.

AEs were generally mild and moderate in severity. There were a few treatment discontinuations due to AEs across treatments. Most were related to the exacerbation of underlying schizophrenia.

Serious adverse events were infrequent and, again, were largely related to the exacerbation of underlying psychiatric disease.

One patient in OLZ/SAM treatment died of complications of COPD. This event was considered unrelated to OLZ/SAM treatment.

Slide 62

Presented on this slide are the most common adverse events listed in degrees and frequency. Similar to what we've seen from the Zyprexa label, most common adverse events in these studies were weight increase, somnolence, dry mouth, headache, increased appetite, and anxiety.

Events were similar between the studies and represent known olanzapine safety profile.

There were no new emergent trends with the long-term exposure. Neither there were new AEs that occurred in OLZ/SAM.

Overall frequencies were similar to those seen on olanzapine treatment with the exception of less reported weight gain in the 24-week study.

Slide 63

Changes in laboratory parameters were similar to olanzapine.

Slide 64

OLZ/SAM had no significant difference from olanzapine in changes from baseline in the 4- and 24-week controlled studies in clinical chemistries, including renal and hepatic measures, lipids, glycemic and hematologic parameters.

Long-term safety data showed no evidence of new safety findings.

Slide 65

Vital signs were stable and similar to olanzapine treatment with the exception of lesser increase in systolic blood pressure, weight and waist circumference, as was covered already by Dr. McDonnell.

Orthostatic blood pressure was measured as a drop in systolic and diastolic in an excess of 20 and 10 millimeters of mercury respectively upon standing from supine.

A total of 10 patients in OLZ/SAM met these criteria compared to 1 patient on olanzapine. This represents 3.7% and 0.4% respectively.

Rate of orthostatic blood pressure measured in a similar way in the long-term pool was 5.7% for OLZ/SAM.

Clinically, only one patient developed orthostatic hypotension, which was recorded as an AE on OLZ/SAM treatment.

Importantly, there were no patients who developed syncope on OLZ/SAM treatment.

Slide 66

Rates of the extrapyramidal symptoms were generally low. We did not see a difference in the frequencies of Parkinsonism, akathisia, or dyskinesias as measured by the reported adverse events and the EPS scales.

Suicidality was evaluated based on the adverse events and Columbia Suicide Severity Rating Scale. There was one suicidal attempt on the OLZ/SAM treatment across the long-term treatment pool with no completed suicides.

Slide 67

Evaluation of ECG parameters during the Thorough QT study showed no clinically relevant effect of OLZ/SAM on corrected QT interval, heart rate, and other ECG parameters.

Tested dose levels included supratherapeutic 30 milligrams of olanzapine and samidorphan in the patients with schizophrenia.

Slide 68

Our comprehensive review of safety included assessments of AEs of special interest for both the olanzapine and samidorphan components.

Slide 69

Our assessment further confirmed that OLZ/SAM profile is consistent with that of the individual components of this combination product.

These are specific risks of olanzapine antipsychotic drug class and the class of opioid antagonists that we continue being vigilant to.

Of these, risks related to opioid blockade deserves special attention.

Slide 70

In the final part of my presentation, I wanted to share with you our plans of mitigating these risks through the labeling, education and pharmacovigilance activities.

Slide 71

Let us first look at the epidemiology data. Lifetime estimates of opioid use disorder in the schizophrenia and bipolar disorder populations tend to be higher than that in the general population with estimates of approximately 5% up to 8.5% compared to approximately 2% in general population.

Slide 72

Recognizing the increased use of opioids in these patients as compared to the general population, we are proposing the full-on labeling to address risks related to opioid blockade with OLZ/SAM.

Label contraindicates use of OLZ/SAM in patients dependent on opioids due to the risk of precipitated opioid withdrawal.

Secondly, the label warns on the potential of opioid overdose that may result from increased sensitivity to opioids after OLZ/SAM treatment discontinuation. As well as the risk of attempting to overcome the opioid blockade by taking excessive amounts of opioid drugs.

The label also warns on potential of reduced or inefficient opioid analgesia, and provides guidance on pain management, including temporal replacement of OLZ/SAM with olanzapine or another antipsychotic should the short-term pain management with opioids being necessary.

Slide 73

Furthermore, our education plan includes a spectrum of clinician and patient-directed resources and activities that is aimed toward the reduction of risks.

This includes continued communication with clinicians, peer-to-peer speaker programs, medical conferences, and information services, including the support center, as well as tools such as a wallet card for the patient, information brochures, and the product website.

Our pharmacovigilance plan ensures safety data collection, signal detection, and regulatory reporting in accordance with the current regulations.

Slide 74

We have collected a comprehensive safety package for the OLZ/SAM combination. We have evaluated the adverse events, laboratory and ECG parameters, identified and analyzed areas of special interest based on the known mechanism of action and clinical experience collected for both components.

Slide 75

What we have found is that OLZ/SAM safety profile is generally consistent with olanzapine with the exception of less weight gain.

We have developed a number of strategies to address the potential risks associated with opioid antagonism through labeling, pharmacovigilance activities and education plan.

With that, let me turn it over to Dr. Ginger Nicol, who will share her perspective on the potential clinical application of OLZ/SAM.

Clinical Perspective and Benefit-Risk Profile – Ginger Nicol, MD, Dipl. ABOM, Washington University School of Medicine.

Slide 76

Hello. I'm Ginger Nicol, I'm an associate professior of psychiatry at Washington University in St. Louis. I have additional board certifications in child psychiatry and in obesity medicine. And, clinically, I specialize and research I specialize in characterizing and mitigating metabolic effects of antipsychotic drugs.

I'll be talking with you today about the clinical perspective considering that there's a mortality gap of 15-30 years between patients with severe mental illness, like schizophrenia and bipolar disorder, and the general population, as you've heard today, primarily attributed to by obesity and related illnesses like type 2 diabetes, cardiovascular disease, conditions that are accelerated by treatment with antipsychotic drugs.

This mortality gap is predicted to continue over the next 20 years unchanged without better treatment options. So, today, I'll be talking with you about the benefit/risk profile of OLZ/SAM.

Slide 77

What's represented on this slide is the depiction of a weigh gain curve over the course of four years of treatment with olanzapine.

This is a 28-year old man who was referred to me by his primary care doctor at approximately 38 months of treatment with olanzapine after he had developed hypertension and metabolic dysregulation, gained more than 60 pounds.

We worked with this young man over a period of a number of months to try and help him lose weight but, ultimately, he decided to discontinue the medication.

We went back to look and see what had charted his course, how had he gotten to this point. And at month one, when he started olanzapine, he had a normal metabolic profile.

You can see by six months that he's already gained 20 pounds, and by 12 months his metabolic profile remains normal, so he meets criteria for hypertension.

Then we start to see metabolic dysregulation at 24 months, and it isn't until 34 months that he begins treatment for hypertension.

This is an all too common occurrence with patients who are treated with olanzapine, this very significant weight gain that leads to metabolic dysregulation. Very significant dissatisfaction with weight and, ultimately, the decision to discontinue the medication.

In this young man's case, he rapidly decompensated and sadly did not recover back to his previous level of functioning.

Slide 78

So how common is the case I just described to you, about the decision to discontinue medication based on weight gain?

This represented on this slide is an online survey of 200 patients with schizophrenia asking about side effects of antipsychotic medications and their preferences specifically related to the side effect of weight gain.

And as you can see across the bottom of the slide, categories of weight gain that were asked about and the number of respondents who reported that they would not take the medication based on that amount of weight gain.

And you can see that the amount of weight gain as it increases across the bottom, the number of patients that say "I would not take this medication also increases."

Slide 79

Similarly, in a study of bipolar disorder patients online asked about side effects that they wish to be avoided with antipsychotic medications across the bottom of the slide. Some commonly reported adverse events or side effects associated with atypical antipsychotics and the number of patients who reported that side effect as being either very or extremely bothersome or reason to discontinue the medication, out of all of these side effects, weight gain is the number one reason patients with bipolar disorder also choose to discontinue medication.

Slide 80

So where does OLZ/SAM fit in all of this? You've seen a representation of this table earlier in the presentation, slightly modified here to include a column for treatment response.

Importantly, olanzapine is at the top as one of the biggest offenders in terms of clinically significant weight gain, right up there with clozapine, a medication that we also know is very effective but also has potentially life-threatening side effects like agranulocytosis and cardiotoxicity. Akathisia, a sense of internal restlessness, it's very uncomfortable. Prolactin elevation, a few main reasons that patients discontinue antipsychotic medications in addition to the weight gain.

And olanzapine here has a very favorable profile as well as a very high treatment response.

When samidorphan is added to olanzapine, as you've heard today, the substantial amount of weight gain is prevented, essentially moves it down this table to the category where we see medium or moderate metabolic risk and weight gain risk along the lines of what we might see with another commonly prescribed antipsychotic medication, risperidone.

Slide 81

So, to summarize, what is the risk-benefit balance for patients and prescribers like me? Olanzapine, as you've heard, a very effective medication for both acute and long-term symptom control. It's better tolerated than many of the other medications but is not used because of that long-term very significant weight gain leading to metabolic dysregulation and that mortality gap that we've been discussing all day.

OLZ/SAM, on the other hand, with the weight gain liability reduced, as we've discussed today, the long-term stability of the metabolic parameters and the preserved efficacy and tolerability profile makes olanzapine a medication that now can be chosen first line in our patients without that significant risk that leads to early mortality.

There is also the risk of the opioid antagonists, but as a practicing psychiatrist, I can tell you that this is the type of agent that we are familiar with and use commonly in the treatment of opioid use disorder.

So, in my view, this is a manageable risk and doesn't outweigh the benefits that are substantial with OLZ/SAM.

Thank you.

Clinical Perspective: Cardiometabolic – Evan A. Stein, MD, PhD, FACC, University of Chicago, Department of Medicine

Slide 82

Good morning. I'm Evan Stein from Preventive Cardiology and Lipid Clinic, at the University of Chicago, Department of Medicine. And I'm, pleased to be with you today to talk about the cardiometabolic aspects of olanzapine combined with samidorphan.

Slide 83

We've heard from Dr. Kahn and Dr. Nicol that cardiovascular disease is a serious problem in patients with serious mental illness and, in fact, a recent meta-analysis has confirmed that there's an 85% higher risk of patients with serious mental illness dying from atherosclerotic cardiovascular disease compared to matched controls.

Recently, the cardiology guidelines have now defined patients with serious mental illness as a population requiring special attention, similar to those patients that they define with diabetes and inherited forms of high cholesterol.

They also point out that preventive actions only occur in the minority of these patients.

Slide 84

Let's now turn to the weight gain that is associated with olanzapine versus that associated with the combination with samidorphan.

Firstly, we know with patients on olanzapine along there is a significant increase in weight, and that this weight is predominantly central adiposity and leads to metabolic dysfunction.

Slide 85

If one looks at starting patients with obesity, as one is used to in terms of obesity-related drugs, you start by definition in patients who are obese. You also make sure that they are enriched with metabolic abnormalities because it is a requirement to show an improvement in metabolic abnormalities over 24-52 weeks, and we have numerous trials to compare to over the years.

Slide 86

However, with olanzapine combined with samidorphan, this is a unique or novel drug where there is weight attenuation. By definition, in the 303 trial it started nonobese patients. In fact, anybody with a BMI over 30 was essentially excluded. Patients were also excluded if they had significant metabolic abnormalities such as diabetes and dyslipidemia. And we know from epidemiological perspective trials that it takes a number of months if not years of weight gain to develop these metabolic abnormalities. In addition, we have absolutely no prior trials to compare to.

Slide 87

So let's now turn to the data that was shown previously by Dr. McDonnell, and if we look firstly at the weight, we know that the combination of olanzapine with samidorphan attenuated weight gain starting at four weeks, as we see in the left-hand figure. And that this was maintained, if we look at the middle figure, for at least 76 weeks. And that just in 24 weeks, there was a 50% less risk of substantial weight gain, defined as more than 10% or three quarters of a pound a week, or 7%, which is about a half a pound a week over the initial six months or 24 weeks.

Slide 88

If we look now at historic data for olanzapine alone, you can see that the weight continues to increase at about a 45-degree trajectory over the same 76 weeks.

Similarly, when we look at the metabolically significant weight gain as reflected by the waist circumference, there's a separation of those patients on OLZ/SAM starting at about two weeks, which reflects the fact that the weight gain is predominantly central adiposity and that this separation continues for the 24 weeks during which there was active comparison.

If one then looks at the middle figure, you can see that those patients who entered and continued in the open-label extension with OLZ/SAM had significant attenuation, virtually flat for continued increase in waist circumference.

And looking at historic data from the CATIE trial, one can see that waist circumference in patients on olanzapine alone continued to increase at 45 degrees for the next 60 weeks.

Slide 89

So how does this translate into cardiovascular risk? Well, we know that the metabolic syndrome, which consists of central adiposity, hypertension, hyperglycemia and dyslipidemia, we see a reduction in risk difference of between 15 and 20% for Stage 1 and Stage 2 hypertension, for a reduction in waist circumference increase of greater than 5 centimeters, and there's also about a 10% risk difference in patients progressing from normal or overweight to obesity defined by a BMI greater than 30.

There's no difference in the glycemic or dyslipidemic parameters but we know, again, from epidemiological trials, that these take much longer to occur.

Slide 90

So, in summary, we know that patients with serious mental illness require special attention due to the increased risk of cardiovascular disease, and that olanzapine alone increases this risk due predominantly to long-term progressive central fat accumulation, and the combination with samidorphan versus olanzapine along results in significant attenuation of weight gain starting at 4 weeks, and stabilizes over the long-term, 76 week open-label study.

That this attenuation in weight gain is reflected by a significant reduction in increase in waist circumference which reflects metabolically significant weight gain, and that there is a significant attenuation in systolic blood pressure in just 24 weeks. And that the combination of olanzapine and samidorphan effectively addresses important long-term health risk in patients with serious mental illness treated with a highly effective antipsychotic drug.

And that the combination is the epitome of a drug where an ounce of prevention is worth a pound of cure.

Thank you.

Conclusions, Lauren DiPetrillo, PhD, Alkermes, Inc.

Slide 91

Thank you, Dr. Stein.

Slide 92

In conclusion, our Phase 3 studies we met all our primary and key secondary endpoints and, namely, demonstrated antipsychotic efficacy versus placebo in Study A305, as well as clinically meaningful mitigation of olanzapine associated weight gain in Study A303.

We see durable treatment effect with long-term treatment in regards to symptom control as well as stabilization of weight, waist circumference, blood pressure, and metabolic laboratory parameters.

Our overall safety profile is generally consistent to that of olanzapine with an added benefit of reduced weight gain.

The class risks associated with opiate receptor antagonists will be addressed through labeling and education.

This leads to a favorable benefit/risk profile for the treatment of schizophrenia and bipolar I disorder.

Thank you.