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EDITED TRANSCRIPT

ALKS - Alkermes Plc Conference Call to Discuss ALKS 3831
Development Program

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OVERVIEW:

ALKS discussed about its ALKS 3831 development program.



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PRESENTATION

Operator

Good morning, and welcome to the Alkermes 3831 conference call. My name is Brandon, and I'll be your operator for today. (Operator Instructions) Please note, this conference is being recorded. And I will now turn it over to Eva Stroynowski, Co-Head of Investor Relations. You may begin.

Eva Stroynowski - Alkermes plc - Co-Head of IR

Welcome to the Alkermes plc conference call to discuss the development program of ALKS 3831, our investigational agent for the treatment of schizophrenia. With me today are Mark Namchuk, Senior Vice President of Research, Pharmaceuticals, Nonclinical Development; Craig Hopkinson, our Chief Medical Officer and Senior Vice President of Medicines Development and Medical Affairs; and Richard Pops, our CEO. Please note that during today's call, we will reference slides that are available on webcast. If you've not done so already, please go to the Investor section of our website, alkermes.com, to access the webcast player. A PDF of this slide will be made available on our website following the completion of this call.

Our discussions during this conference call will include forward-looking statements. Actual results could differ materially from these forward-looking statements. Please see Slide 2 of the accompanying presentation and our most recent annual and quarterly report for important risk factors that could cause our actual results to differ materially from those expressed or implied in the forward-looking statements.

We undertake no obligation to update or revise the information provided on this call or in the accompanying presentation as a result of new information or future results or developments. After our remarks, we'll open the call for Q&A.

We have a lot of ground to cover today. Mark will start with a brief overview of ALKS 3831 and the pharmacology behind the potential new antipsychotic medication. Then he will share new insights on 3831's mechanism of action, which we have discovered to the length of our preclinical observation of olanzapine and samidorphan. Greg will then discuss clinical data for 3831, including our recently completed translational medicine study and data from the Phase II and Phase III clinical studies and our registration pathway. Finally, we will discuss our next steps and future plans to support the broad use of ALKS 3831 in psychiatry.

Now I'd like to turn the call over to Dr. Mark Namchuk.



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Mark Namchuk - Alkermes plc - SVP of Research, Pharmaceutical and Nonclinical Development

Thank you, Eva. And good morning to everyone. We've learned a great deal about olanzapine and samidorphan, and it's great to have a chance to share some data with you. I'll dive straight in and get started.

ALKS 3831 is an investigational, novel, once daily oral atypical antipsychotic drug candidate designed to provide robust antipsychotic efficacy with a differentiated weight and metabolic profile. It is a once-a-day bi-layer tablet composed of olanzapine and samidorphan, our proprietary opioid antagonist. While olanzapine is widely considered to be one of the most efficacious atypical antipsychotics, there are limitations to its use due to the weight gain and metabolic consequences that patients experience. We hypothesized that the addition of opioid antagonist may ameliorate the deleterious metabolic side effects associated with olanzapine, and we'll spend some time discussing the foundation of data that we've gathered to validate this hypothesis.

What we've discovered through our preclinical and clinical research is that olanzapine causes metabolic disturbances in both acute and chronic settings and that samidorphan plays an important role in ameliorating these effects. We're approaching the end of our clinical development program for 3831. Last summer, we announced positive top line results from ENLIGHTEN-1, which evaluated the antipsychotic efficacy of 3831 compared to placebo over 4 weeks in which Craig will speak to in greater detail later in the morning.

We expect data later this year from ENLIGHTEN-2, our 6-month Phase III study, assessing weight gain with olanzapine compared to ALKS 3831 and our planning for potential NDA submission in the first half of 2019.

So why olanzapine? One of the barriers that has haunted the design of novel medications for the treatment of schizophrenia is the polypharmacology. The most effective agents hit on multiple receptors. The wheel diagram shown here on Slide 6 give you a sense of how many receptors are being hit by each of these antipsychotics. Decades of excellent medicinal chemistry have been important to trying to understand which of these receptors drive efficacy and which are associated with side effects. But our success as an industry has been limited. We have yet to recapitulate a molecule as effective as olanzapine in terms of polypharmacology in the treatment of schizophrenia. Olanzapine hits on serotonin, histamine, dopamine D1 and D2 and other receptors. This blend of pharmacology endows us with an efficacy that makes it difficult to replicate. To date, all atypical antipsychotics are associated with some metabolic sequelae.

The concept with 3831 is different. We did not want to alter the successful assembly of receptors engaged by olanzapine. We want to retain that and instead focused on adding a second agent with distinct pharmacology to directly deal with olanzapine's associated metabolic liabilities. The agent we chose to combine with olanzapine is samidorphan, our receptor antagonist that works through 3 prominent opioid receptors mu, kappa and delta. The early foundation for this program was based on recapitulating in preclinical species the weight gain associated with olanzapine use in humans. If we could do that, then we had a valid experimental setting to test the effects of olanzapine and samidorphan's opioid modulation on attenuating weight gain. I will show you findings from both rodents and nonhuman primates. I'll point out that as opposed to humans, the weight gain associated with olanzapine is observed only in females in most preclinical species. This phenomenon has ended up being a very useful mechanistic tool for us, and I'll speak more on that in a moment.

For brevity, today, I'll review the data for olanzapine, olanzapine plus samidorphan and placebo, which we refer to as vehicle. The full preclinical data set has been submitted to peer review journal, and we look forward to having that manuscript published later this year.

Shown on this slide, our data from female rats that had normal diet for 28 days. The black line represents animals given vehicle. The light blue line on top represents animals treated with olanzapine, and the green line represents animals treated with olanzapine plus samidorphan. As one would expect for young rats, all the animals in the study gained weight on the normal diet over the course of the study. However, you can see that from the slide that the rate of weight gain observed for the olanzapine treated females is higher than that of vehicle. But when samidorphan is added to olanzapine, a clinically relative exposures of ALKS 3831, the observed weight gain overlays the black vehicle line. So by adding samidorphan to olanzapine, we're able to attenuate the weight gain associated with olanzapine use.

We conducted a similar study in female nonhuman primates that were fed a high-fat diet. Here, we recapitulated our findings that when samidorphan is administered in combination with olanzapine, there are benefits in terms of weight gain. Also, worth noting is the vertical dotted line on day 35.



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This represents when animals treated with olanzapine alone were switched to receive olanzapine plus samidorphan. The slope of weight gain for these animals leveled off and weight gain essentially flattened.

These preclinical observations provided a framework from which we build our broad development program. We have 2 lanes to the 3831 program. The registration development pathway shown on the left, and the mechanistic understanding pathway shown on the right.

I'll start with the pathway on the right and show you findings from our preclinical studies that provide insight into the mechanism underlying 3831. We've generated a lot of new data here with important implications for the program. What both olanzapine and samidorphan are doing preclinically is complicated and fascinating. Greg will then speak to the translational work we conducted in humans, which is beginning to confirm our preclinical findings. Starting preclinically, we first wanted to drill down and understand what exactly were we observing with olanzapine and samidorphan? What is olanzapine driving? And what effect is samidorphan exerting? To narrow our focus to these questions, we conducted weight and body composition assessments in preclinical species.

On Slide 14, on the left, is the same graph I showed you previously comparing weight gain in female rats at a normal diet. We also examined body composition in these same animals, shown on the right-hand side of the slide. Consistent with previous observations, olanzapine drove an increase in adiposity. Meanwhile, the addition of samidorphan decreases this accumulation of fat. As I alluded to before, the weight gain we see preclinically is limited to females.

Here on Slide 15 are the data for male rats that a normal diet, which helps build on the observation that olanzapine is driving the accumulation of fat. In the graph on the left, you see that the slope of weight gain is identical for male rats receiving olanzapine vehicle and ALKS 3831. The lines are parallel, because the animals take a couple of days to acclimate the samidorphan as is common with many CNS drugs. But after the first few days, the slopes were the same. We're not seeing a differentiating effect on weight in these male rats. However, even without an effect on weight, we see changes in body composition in these same male rats. On the right side, shown in the light blue line, you can see that olanzapine is, again, driving the accumulation of fat. This is similar to what we observed in female rats. In green, you see that olanzapine plus samidorphan resulted in a similar effect as normal diet alone. So one of the interesting findings for us as we dug deeper mechanistically was that olanzapine drives a change in adiposity that can be associated with or independent from weight gain.

However, when we add samidorphan to olanzapine, it attenuates the increase in adiposity in both circumstances. This observation goes across species. On the left hand side, are the data -- weight gain data I showed you previously for female nonhuman primates. On the right hand side of the slide, our data from a CT scan examining central adiposity measuring fat just below the kidney after 28 days. You can see that fat accumulates at a higher rate with olanzapine than for vehicle or the combination of olanzapine plus samidorphan. This is a second set of studies with the same observation that olanzapine drives accumulation of fat and that the addition of samidorphan attenuates it.

Now that we had insight into what was happening with olanzapine and samidorphan, we next wanted to ask how was it happening? There were 2 avenues of inquiry to pursue. How olanzapine might affect the reward pathway in the brain, and whether it was altering metabolic effects in peripheral tissues. We began by looking in the brain and asked how food reward may be disrupted by acute olanzapine exposure.

It is long been known that the consumption of palatable food triggers dopamine release in the brain's reward system making it feel good. This effect on food reward is what drives craving and tempts you to eat more like going back for a second helping of chocolate cake. One of the things clinically associated with the use of olanzapine is hyperphagia or increased appetite, which leads people to eat more. From our preclinical work, we observed that olanzapine is exaggerating food reward through access release of dopamine.

So look at how olanzapine and samidorphan affects normal food reward in the brain, we conducted our standard assay to examine dopamine release in the nucleus incubents of female rats following high-fat meal.

On the left hand side of the slide, you see that in response to a high-fat meal, the animals in the vehicle group shown in black had an increase in dopamine release. But when we added olanzapine, shown in blue, the reward is highly exaggerated. These rats really enjoyed the high-fat food, while they're taking olanzapine.



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In a second experiment shown on the right, we see that administration of samidorphan plus olanzapine showed in green, did not remove food reward, but normalizes it. 3831 looks very similar to the vehicle group on the left, but the exaggerated food reward associated with olanzapine has been removed.

With a better understanding of what is happening centrally, we then turned our focus to examine peripheral metabolic effects. This is a simplified model of how your body works to clear glucose from the central compartment. Shortly after eating food, glucose enters the bloodstream. In response, insulin is secreted by the pancreas and prompts the liver to turn off additional glucose production. Under normal circumstances, the remaining glucose is either utilized or stored by muscle, fat and liver.

It's known that olanzapine interferes with the normal glucose clearance process, and we once determined whether samidorphan played a role in counterbalancing olanzapine's peripheral effect.

So to characterize the activity occurring in these peripheral tissues, we conducted a series of detailed assessments on glucose utilization, glucose clearance and insulin sensitivity. So here's a study that was done after 2 days of exposure to either olanzapine vehicle or ALKS 3831. Before any significant changes in body composition have occurred, we use tracers to understand how glucose was being taken up in different tissues in the female rats. On the left, we are looking at muscle. And when you look at all the muscles in aggregate, we found that olanzapine decreased glucose utilization in muscle. Samidorphan partially offset this effect.

Shown on the right, is what happened in adipose or fat tissue where we saw the exact opposite effect. Olanzapine increases glucose utilization in fat tissue, and the addition of samidorphan fully blocked this effect. This imbalance in muscle and fat glucose utilization is clearly seen only 2 days into exposure of olanzapine. So we think this is a direct acute effect of olanzapine as we haven't seen any changes in weight or adiposity yet in these animals.

Another study we conducted evaluated whole body glucose clearance in female rats. We administered a bolus injection of insulin at resting glucose levels and looked at how well the animals were able to clear glucose from the central compartment. On the left side, in blue, is olanzapine, and in black, is the control. The animals who received olanzapine cleared less glucose than those who received vehicle as demonstrated by the reduced more shallow decline in glucose levels post insulin administration.

Moving to the right side, when animals received olanzapine plus samidorphan, shown in green, normal glucose clearance was retained.

Here on Slide 26, are more data from a primate study, I showed you before where female monkeys were fed a high-fat diet over a 58-day assessment period. The slide is a bit complex. So let me read you through it stage by stage. Shown on the very left-hand side is the prestudy baseline. These are monkeys who have not yet been exposed to samidorphan, olanzapine or a high-fat diet. After a fasting period, we gave the monkeys a bolus of glucose intravenously. This is a similar concept through oral glucose tolerance test done in humans, and the assessment is designed to evaluate how quickly monkeys clear glucose from the central compartment and how much insulin is required to drive that clearance.

The solid black line in the chart shows glucose levels with values listed on the left side y-axis. The hatch line shows how much insulin was required to clear that glucose with the levels listed on the right side y-axis of the chart. This prestudy baseline represents normal healthy glucose clearance in these animals.

Now in the middle column, you see that after 28 days on olanzapine, the animals' glucose clearance is still pretty normal. But look at insulin, the data suggest an increase in insulin secretion after a relatively short period of exposure to olanzapine. The data from day 58 are even more interesting. In the top right corner, we see data from monkeys that have been eating a high-fat diet with only vehicle treatment for 58 days. Although, their glucose clearance is still normal, the amount of insulin required to clear the glucose has gone up. This is a classic signature of a pre-diabetic phenotype and is associated with the fact that the animals have gained weight during the course of the study.

In the middle panel, on the far right of the slide, you see animals that were given olanzapine for 28 days and then switched to receive 3831 for the subsequent 4 weeks. Even though these animals weighed exactly the same as the control animals in the top right panel, the addition of samidorphan



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appears to have restored normal insulin sensitivity. Lastly, in the bottom right panel, when we administer their ALKS 3831 right from day 1, there was no change in glucose clearance or insulin levels compared with those observed at prestudy baseline.

We're able to retain normal insulin sensitivity throughout the entire study even though olanzapine was onboard. This is now a second study in a second species demonstrating samidorphan's ability to restore normal glucose clearance. Importantly, when samidorphan was co-administered with olanzapine from the start, it prevented the exaggerated insulin response.

So based on our preclinical data, we have an emerging model of olanzapine's effect in both the acute and chronic setting and what samidorphan is doing to help. In the acute setting, we've seen across multiple studies that olanzapine exaggerates food reward. We've also seen from our preclinical research that olanzapine acutely alters glucose clearance decreasing glucose utilization in muscle and increasing glucose utilization in fat. It also decreases insulin sensitivity in the liver. With the addition of samidorphan via ALKS 3831, we observed the normalization of food reward as well as the normalization of glucose clearance. We are unsure if the normalized glucose clearance is derived by restoration of insulin sensitivity or via a different mechanism. And this remains an open question that we are currently working on.

For example, we see restoration of normal glucose clearance in several preclinical assessments, but did not see an effect on insulin sensitivity using a classic diabetes and metabolic assay called the hyperinsulinemic euglycemic clamp. In the longer term, chronic setting, we believe that olanzapine drives a syndrome that has some of the hallmarks of classic type 2 diabetes, but is actually a distinct drug-induced metabolic syndrome. Our studies have shown that olanzapine increases weight and it also increases adiposity, both dependent and independent of weight gain. It is well established that one of the central tenets of conversion to metabolic syndrome is weight gain. And that the most deleterious type of weight 2 gain is an increase in central adiposity or central visceral fat like that seen with chronic olanzapine use. In all our preclinical studies, we have found that the addition of samidorphan attenuated this olanzapine-induced weight gain and decreased the accumulation of adiposity enabling the retention of a healthy metabolic profile. There are still open questions that we're investigating actively to understand at a deeper level what is going on. With a clear effects observed on weight and adiposity, we want to further interrogate what's happening to lipids, as we haven't seen definitive effects on lipid parameters in our preclinical studies. But collectively, our data argue that we have a good understanding of olanzapine-induced metabolic abnormalities as well as the potential benefits of 3831 in these acute and chronic sequelae. We're really excited about the preclinical data we've generated to-date and just recently submitted a publication of these data to a peer review journal.

Now I'd like to hand it off to my colleague, Craig, who will walk you through the results from our recently completed translational metabolic study in healthy volunteers as well as provide an overview of the clinical and regulatory development program for 3831.

Craig C. Hopkinson - Alkermes plc - Senior VP of Medicines Development & Medical Affairs and Chief Medical Officer

Thanks, Mark. The preclinical data that Mark just reviewed with you evolved our understanding of how olanzapine is causing metabolic changes both in the acute and chronic setting and the potential mitigating effects of samidorphan on these adverse metabolic sequelae. This is something we decided to investigate in the clinic as well. In order to corroborate the preclinical findings in the acute setting, we performed a 21-day translational medicine study in healthy volunteers examining a number of exploratory endpoints, including oral glucose tolerance testing, mixed meal tolerance testing and whole body insulin sensitivity. This assessments capture the body's glucose and insulin response under a variety of conditions and stimuli. Additional metabolic markers, such as blood lipids and indirect calorimetry were also captured. This is the most comprehensive evaluation of olanzapine's acute effects on metabolism in a healthy volunteer population that we are aware of from published literature.

Overall, the goal of this study was to gain insights into the acute metabolic effects of olanzapine and ALKS 3831 in humans, helping us isolate metabolic changes that are independent of weight changes. The study randomized 60 healthy volunteers to 3831 olanzapine or placebo at a ratio of 2:2:1. We included the placebo arm to make sure we were able to account for any study effects and to ensure assay sensitivity. Given the exploratory nonconformity nature of this trial, our prespecified threshold for significance was set at 0.1. There were no prespecified hypothesis or endpoints. For ethical reasons, 21 days was the longest duration we could examine the effects of an antipsychotic, particularly olanzapine, on healthy volunteers in a research study.



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This is also the reason why we selected 10 milligrams of olanzapine for the study despite 20 milligrams being the most commonly prescribed dose for the treatment of schizophrenia. All volunteers were inpatient for the duration of the 3-week treatment period, during which they were not permitted to exercise.

As expected, all treatment groups gained weight with a similar magnitude of weight gain observed from the olanzapine and 3831 groups. This is consistent with data from our previous clinical studies where we had not observed separation between olanzapine and 3831 until 3 to 4 weeks. This is a useful feature from a data interpretation standpoint since we're trying to isolate metabolic changes that are independent of weight changes.

Slide 32 represents data from an old glucose tolerance test, or OGTT, which is commonly used to detect prediabetic phenotypes and analogous to the insulin data Mark showed you in monkeys. After an overnight fast, subjects receive a bolus dose of 75 grams of glucose. Then over the next 3 hours, we measured the insulin and glucose levels in order to evaluate the body's ability to clear glucose over that time period. We conducted the OGTT twice, at baseline and on day 19. And these graphs represent the ratio of those 2 assessments.

On the left, for glucose, we see no change in placebo. There was small within group rises in the olanzapine and ALKS 3831 arms, but they did not differentiate from placebo. But we really need to look at glucose in the context of insulin, which is shown on the right-hand side of the slide.

Here we see a substantial 41% increase in insulin of the baseline for olanzapine, which was statistically significant versus both placebo and ALKS 3831. In the 3831 group, you see that the mitigating effect of samidorphan for hyperinsulinemia. Exaggerated insulin response during an old glucose tolerance test, such as what you see here with olanzapine, is strongly associated with a pattern of impairments of bodies handling glucose. These data replicate findings that Mark shared with you earlier from rats and monkeys. And so we were successful in recapitulating clinically what we observed preclinically.

Slide 33 shows data from a similar assessment called the mixed meal tolerance test. This assessment incorporates glucose, fats and protein. If you're familiar with Ensure protein shakes, this test essentially involves giving subjects 2 small bottles of Ensure. The addition of fat and protein macronutrients with glucose slows gastric emptying and also slows the rate at which glucose enters bloodstream. The aim of this assessment is to determine how much insulin is produced in response to the mixed meal. On the left side, we see a small study effect and that all 3 groups experienced an increase in glucose area under the curve from baseline to day 18. There were no significant differences between or among groups, but all arms did see within group increases in glucose.

On the right side with insulin, you see a pretty substantial study effect, whereby all groups had a drift up in metabolic parameters. This may speak to the nature of the study design, where we had young healthy volunteers coming into a confinement period where they had pretty substantial changes in lifestyle and dietary choices for the duration of the study. Numerically, olanzapine had the largest increase in insulin of 73%, which was statistically significant compared to ALKS 3831. 3831 looked similar to placebo and had the lowest numerical increase in insulin.

The study effect observed here makes these data a bit noisy, but the outcomes are similar to what we saw in the OGTT indicating that samidorphan mitigating olanzapine-induced hyperinsulinemia. Taken together with the preclinical data, this strengthens our foundational belief and the mechanistic underpinnings of ALKS 3831.

Given olanzapine's effect of adiposity over the long term, we're interested in determining whether we could identify any short-term lipid changes that might proceed weight gain. And so we assessed triglycerides, HDL and LDL over a 21-day period. The data shown here, we saw variable assay sensitivity and no statistical separation of 3831 from olanzapine. So the data were not particularly informative.

Ultimately, we remain interested in the long-term effect of olanzapine and samidorphan on lipids in patients with schizophrenia. If we're successful at significantly attenuating weight gain, our believe is that we will see positive effects on lipid parameters.

Overall, data from this translation metabolic study confirmed the acute findings from our preclinical studies with samidorphan mitigating olanzapine-induced hyperinsulinemia as demonstrated by the OGTT and mixed meal tolerance test assessments. This normalization of glucose clearance was observed despite undetectable changes in insulin sensitivity using hyperinsulinemic euglycemic clamp.



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This finding recapitulates what we observed preclinically. Altogether, these results have spurred our desire to further understand the mechanism underlying 3831. We know that samidorphan is playing an important role in ALKS 3831 and have learned a lot about how to design future mechanism studies to interrogate the chronic longer-term effects of samidorphan and olanzapine.

So ultimately, we have a lot of exciting opportunities ahead of us from a mechanistic standpoint as we pivot to gaining more insights on the potential long-term benefits from future studies in patients. So independent of the mechanism pathway, we've been busy progressing 3831 through clinical developments on its pathway to registration and are nearing the completion of the pivotal program.

I'll start off with an overview of our Phase II results, which gave us a lot of confidence in 3831's weight and antipsychotic profile. This was a randomized, double-blind, active-controlled Phase II study evaluating ALKS 3831 versus olanzapine in 309 patients with schizophrenia conducted in 2 12-week stages. For the first week of the study, all patients received an oral olanzapine lead in which all patients were randomized to receive olanzapine or one of 3 doses of ALKS 3831 for 12 weeks.

Following this 12-week double-blind treatment stage, those patients who had been on olanzapine were switched over to ALKS 3831 for a 12-week extension stage allowing us to observe the effects of initiating 3831 in patients actively in the process of gaining weight on olanzapine.

The patients who received ALKS 3831 in Stage 1 continued on the same dose of 3831 through the Stage 2 extension. Here are the weight data from the full 24-week study. We saw important differences between olanzapine and 3831. Notably, the separation started around week 4. At 12 weeks, there was a clinically meaningful and statistically significant difference in mean weight gain with the percentage change in body weight being 37% lower in the 3831 group compared to the olanzapine group.

Further, the risk of patients gaining more than 10% of their baseline body weight was 2.7x greater in the olanzapine group versus the 3831 group. The potential for increasing benefit at the time of ALKS 3831 is underscored and strengthened by the results of the second 12-week stage. The patients that switched from olanzapine to 3831 are represented here by the dash blue line. Their body weight remained stable with no additional mean weight gain and the slope of the curve clearly changed and became like (inaudible) was flat.

The Phase II study's primary endpoint was the antipsychotic efficacy of ALKS 3831 compared to olanzapine as measured by a reduction from baseline in Positive and Negative Syndrome Scale total score, or PANSS. PANSS is the standard psychiatric scale used for measuring symptom severity in schizophrenia.

As shown here on Slide 41, ALKS 3831 demonstrated to maintain equivalent efficacy to olanzapine over the 24-week study. This efficacy is a central component of this medicine and will be further exemplified in the Phase III data, which I'll get to in just a moment. The most common adverse events in the 3831 treatment groups relative to olanzapine in the Phase II study was somnolence, sedation and dizziness. And these were generally mild and transient lasting just a few days.

Now let's take a look at our Phase III program. The ENLIGHTEN development program is comprised of 2 foundational Phase III studies, ENLIGHTEN-1, our pivotal 4-week antipsychotic efficacy study read out with positive top line results last summer. We expect to report that in the first quarter of this year for ENLIGHTEN-2, a 6-month study focused on weight gain. And we're planning to submit an NDA for 3831 in the first half of 2019.

Here are the data from ENLIGHTEN-1, which is a randomized, multinational, double-blind, active controlled, 4-week study that evaluated the antipsychotic efficacy, safety and tolerability of 3831 compared to placebo in 403 patients experiencing an acute exacerbation of schizophrenia. An olanzapine arm was included in the study in order to confirm study validity and provide comparative information. These study we announced last summer and presented at ACNP in December. The efficacy results were clear. The study achieved as primary endpoint with 3831 demonstrating clinically important and statistically significant reductions from baseline in PANSS total scores compared to placebo at week 4 with a p-value of less than 0.001. The mean reduction from baseline in PANSS total score for the 3831 arm was 23.9 points compared to a mean reduction of 17.5 points for the placebo arm. Olanzapine achieved similar improvements from PANSS -- from baseline PANSS scores compared to placebo at week 4 with a p-value of 0.004. The mean reduction from baseline in PANSS total score for the olanzapine arm was 22.8 points.



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This study was crucial to the ultimate profile and value of ALKS 3831, as our goal is to replicate the powerful antipsychotic efficacy of olanzapine with a potentially differentiated weight to metabolic profile. With the intended antipsychotic efficacy demonstrated in ENLIGHTEN-1, we're eagerly awaiting the results from the ongoing ENLIGHTEN-2 study focused on weight.

ENLIGHTEN-1, the most common adverse events for both the ALKS 3831 and olanzapine treatment groups were weight gain, somnolence and dry mouth. We have now seen data from both a mechanistic and registration pathways for ALKS 3831. We're nearing completion of the development program as we await results from the ENLIGHTEN-2 study later this year.

Meanwhile, we are continuing to deepen our understanding of the mechanism of action of this potentially new medicine. Together we expect the data we are generating will position ALKS 3831 for broad use in the field. When we began our work on this program, our original hypothesis was that the chronic use of olanzapine led to long-term metabolic sequelae driven by abnormal food reward leading to weight gain. Ultimately, this increased weight can lead to drug-induced metabolic syndrome and eventually diabetes. What we've learned along the way is that olanzapine, unrelated to food reward, has a direct impact on body composition. Those changes can be associated with or can be independent of weight gain and are largely the accumulation of fat.

It is well known in the metabolic literature that a consequence of increased adiposity can lead to dysregulation in insulin sensitivity and the increase in baseline glucose and dyslipidemia. On top of that, we've learned that in addition to olanzapine's chronic effects, it also has acute effects on the dysregulation of metabolic functions. We've independently mapped out that olanzapine causes a decrease in insulin sensitivity in the liver. These data indicate that there are also abnormalities both in lipid content and glucose clearance that olanzapine is causing in the short term.

When we put the whole puzzle together, we believe that samidorphan has benefits in both of these short-term and long-term settings. In the acute setting, we have shown preclinically that samidorphan prevents olanzapine-induced exaggeration of food reward. Preclinically as well as clinically, we have demonstrated that olanzapine causes defects of clearance of glucose from the central compartment and the addition of samidorphan appears to normalize that effect.

Our preclinical data also show that we can attenuate the accumulation of weight and adiposity. This couldn't be studied in the context of our 21-day translational study. It was too short. But we did see attenuated weight gain in our 300-patient Phase II study. And these assessments are part of our ongoing 6-month ENLIGHTEN-2 study. In the chronic setting, our preclinical data indicate that 3831 is associated with mitigated weight gain and adiposity in comparison to olanzapine. These findings pose interesting new questions for future research to better understand 3831's potential long-term benefits.

So to summarize, our preclinical and clinical studies have shown us that samidorphan plays an important role in mitigating olanzapine-induced abnormalities on food reward, glucose clearance and attenuating increases in weight and adiposity. The unique pharmacology of ALKS 3831 may provide distinct clinical benefits for patients with powerful antipsychotic efficacy and a differentiated weight to metabolic profile compared to olanzapine.

We are nearing completion of our federal development program with top line results from 6 months weight study expected later this year and a planned NDA filing in the first half of 2019. We will continue to expand our mechanistic research activities in the future to more fully elaborate the potential of what we believe will be an important milestone.

With that, I thank you for your attention and turn it back over to Eva for Q&A.

Eva Stroynowski - Alkermes plc - Co-Head of IR

Thank you, Craig. We'll now take your questions. Operator?



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QUESTIONS AND ANSWERS

Operator

(Operator Instructions) From Crédit Suisse, we have Vamil Divan.

Vamil Kishore Divan - *Crédit Suisse AG, Research Division - Senior Analyst*

Thanks for all the detail on the product. I think it's one that people been trying to get their hands around. So appreciate the details. I guess, maybe, my main question just sort of summarizing all this as we wait for the ENLIGHTEN-2 data. What should we think about as being sort of clinically relevant information that we need to get out of there or what would be clinically meaningful benefit as we think about the difference between this and the benefits this provides on the weight gain and the metabolic changes? And then second, I'm just curious, I think, it's largely based around the payer side of this product. And maybe it is a little bit different from where the focus of this presentation is, but maybe if you kind of just comment on any sort of initial discussions on somewhat like what are the payers looking for from this product? And do you think that they would want to see people start on olanzapine and then switch if they start having an issue with weight gain? Or do you think this can be positioned where people can start on this initially given the benefit it might have?

Craig C. Hopkinson - *Alkermes plc - Senior VP of Medicines Development & Medical Affairs and Chief Medical Officer*

Sure. So I think, our take home is that we believe the virtue of olanzapine is its powerful efficacy. What limits use of olanzapine is the significant weight gain. And this leads to many patients to stopping medication. Patients suddenly stopping medication and most of the time this is without even consulting their physician leads to acute exacerbations and an increase in hospitalizations. So for us, the 2 most important aspects that we're focusing on is really to demonstrate the antipsychotic efficacy of olanzapine and I think, we've done that now in 2 studies. Phase II study demonstrated that we had equivalent antipsychotic efficacy based on PANSS scores and CGI from our Phase II study. And then in our Phase III acute study, once again we demonstrated a significant benefit in terms of antipsychotic efficacy. In terms of the weight gain, I think, we are encouraged by the data that we presented to you today and I presented previously on our Phase II study where we see a complete flattening of the weight gain that is observed with olanzapine. To us it is less about the absolute weight gain, as we said before, but it's more about the slope of the curve and unless we can completely flatten that slope then that is going to, obviously, be of significance. And we obviously are now looking forward to getting data from our 6-month weight study. I think, the additional data that we presented today gives further insights to our perspective on what 3831 is doing, and it also confirms in the acute setting some of the effects of olanzapine. And I think, what he saw there was that 3831 basically attenuates the hyperinsulinemic effects based on OGT and mixed meal tolerance test that we saw with olanzapine. The feedback that we've got from thought leaders is that this is going to be a clinically meaningful and significant product and that ultimately if we can curb the weight gain of olanzapine that this will force them to relook at olanzapine as a product through ALKS 3831. And I think on the payer side, I'll probably hand that over to Rich to maybe give his perspectives there?

Richard F. Pops - *Alkermes plc - Chairman & CEO*

Good morning. Obviously, briefly, I think all the evidence that is accumulating, and that's why we wanted to have this presentation today, show that there is more to 3831 than just weight. And even as you saw today, in the absence of weight gain, change in adiposity probably has long-term metabolic sequelae that are important for patients. So our ultimate goal is and what we hear from our thought leaders is that if 3831 exits with all these additional virtues and without additional liabilities, why would someone prescribe olanzapine.

Eva Stroynowski - *Alkermes plc - Co-Head of IR*

Any other questions [online]?

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Operator

From JPMorgan, we have Cory Kasimov.

Matthew Thomas Holt - *JP Morgan Chase & Co, Research Division - Analyst*

This is Matthew on for Cory. My first one is on the results that you saw from your metabolic study. I'm having a hard time understanding how the metabolic assessments square with what you saw in terms of weight gain in the study. So curious to hear your thoughts on what's happening here.

Craig C. Hopkinson - *Alkermes plc - Senior VP of Medicines Development & Medical Affairs and Chief Medical Officer*

Yes, as far as weight gain in this particular metabolic study, this was somewhat artificial setting and that this were healthy volunteers that were hospitalized for 3-week period when which we completely limited exercise in these patients and had fairly free access to calories. So we don't think that this is an appropriate setting for us to evaluate weight gain. Secondly, this was a short-term study. This was a 3-week study. And I think, what you saw from our Phase II data is that we only start seeing that inflection point with ALKS 3831 at about 4 weeks in terms of flattening the weight gain curve. And so I don't think we can read anything into this sort of weight gain in this particular study.

Matthew Thomas Holt - *JP Morgan Chase & Co, Research Division - Analyst*

Okay. That makes a lot of sense. And then just also on maybe the metabolic study as well as the Phase II and ENLIGHTEN-1 study. Do you see any metabolic differences based on starting BMI?

Craig C. Hopkinson - *Alkermes plc - Senior VP of Medicines Development & Medical Affairs and Chief Medical Officer*

Yes, I mean, I think previously we've actually said that in our acute study, we actually did see imbalances coming into the study. And so that does play a role. And so in our ENLIGHTEN-2 study, we are enrolling patients with BMI between 18 and 30. So that is something that we're controlling for in our ENLIGHTEN-2 study.

Matthew Thomas Holt - *JP Morgan Chase & Co, Research Division - Analyst*

Okay. And then, I guess, maybe last one for me. On the ENLIGHTEN-1 AEs, it looks like the weight gain increase was numerically higher than the olanzapine arm. I'm just curious to hear your thoughts on this and whether this was specifically significant?

Craig C. Hopkinson - *Alkermes plc - Senior VP of Medicines Development & Medical Affairs and Chief Medical Officer*

Yes, so, I mean, once again this was a safety finding. So we didn't perform any stats on it. But I think, more importantly, there were baseline imbalances in terms of weight coming to the study. I think, the second aspect is this is a study that was conducted in acutely ill patients coming into a hospitalized setting. And so you often see in acute schizophrenic studies, an increase in weight as patients are stabilized and have access to 3 square meals a day. So once again, over the course of 4 weeks, I wouldn't read anything into the weight gain observed in the study.

Operator

From Evercore ISI, we have Umer Raffat.



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Akash Tewari - *Evercore ISI, Research Division - Research Analyst*

This is Akash on for Umer. First question, and this is on the ENLIGHTEN-1. And it was on the weight increase. Is there any color on in terms of the AE. How was weight increase defined? Was it basically just patient assessor? Was there some level of weight gain that needed to be gained in order for that to be recorded as an AE? And then on these ongoing Phase III, what percent of patients are on the low dose versus the high dose in the olanzapine arm? And can you remind us what that looked like in the Phase II study?

Craig C. Hopkinson - *Alkermes plc - Senior VP of Medicines Development & Medical Affairs and Chief Medical Officer*

Yes, sure. So I'll take your first question. In terms of weight gain, this was not an endpoint in the study. It was not something we assessed and so we didn't believe that this was the appropriate setting for us to assess weight gain. So there weren't any standard procedures and standardized measures built into the study. So these were patients that gained weight from baseline. And once again, as I said, I wouldn't read too much into that. In terms of the -- I think, the second question is around doses used in the 2 studies. There was a significant difference in the design of the 2 studies between the Phase II and ENLIGHTEN-1 Phase III study. In the ENLIGHTEN-2 study, these were patients that were stable that came into the study with PANSS scores of less than 80. And essentially -- I think, a larger proportion of patients were on the 10 10 dose. In the ENLIGHTEN-1 study, these were acutely ill patients and so in our Phase III program, I think that you're going to see far higher use of the 20-milligram dose of enalapril, which was also the most widely used clinical dose.

Eva Stroynowski - *Alkermes plc - Co-Head of IR*

All patients are titrated up to that 20-milligram dose in ENLIGHTEN-2, and they only go back down if they have tolerability issues.

Operator

From Morgan Stanley, we have David Reisinger.

At this point, we're going to go ahead and turn it back to Eva Stroynowski for closing remarks.

Eva Stroynowski - *Alkermes plc - Co-Head of IR*

Hi, thanks, everyone, for your time today. If you have any additional questions, please feel free to reach out to us.

Operator

Thank you. Ladies and gentlemen, this concludes today's conference. Thank you for joining. You may now disconnect.

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