

THOMSON REUTERS STREETEVENETS

EDITED TRANSCRIPT

ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

EVENT DATE/TIME: APRIL 12, 2019 / 12:00PM GMT

OVERVIEW:

Co. provided data for ALKS 3831 ENLIGHTEN-2 study.



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

CORPORATE PARTICIPANTS

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

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

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

Sandra Coombs *Alkermes plc - Co-Head of IR*

CONFERENCE CALL PARTICIPANTS

Biren N. Amin *Jefferies LLC, Research Division - MD and Senior Equity Research Analyst*

Chi Meng Fong *BofA Merrill Lynch, Research Division - Research Analyst*

Danielle Catherine Brill *Piper Jaffray Companies, Research Division - VP & Senior Research Analyst*

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

Pamela Ann Barendt *Cowen and Company, LLC, Research Division - Associate*

Umer Raffat *Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research*

René S Kahn

PRESENTATION

Operator

Greetings, and welcome to the Alkermes Conference Call to discuss ALKS 3831 ENLIGHTEN-2 data. (Operator Instructions) Please note that this conference is being recorded. I'll now turn the call over to Sandy Coombs, Vice President of Investor Relations. Sandy, you may begin.

Sandra Coombs - *Alkermes plc - Co-Head of IR*

Thank you, and welcome to the Alkermes plc conference call to discuss ALKS 3831 our investigational agent for the treatment of schizophrenia. Last fall we announced top line data from ENLIGHTEN-2, and today, we're presenting detailed results of the study from the Congress of the Schizophrenia International Research society in Orlando. With me today are Richard Pops, our CEO; Craig Hopkinson, our Chief Medical Officer and Senior Vice President of Medicines Development and Medical Affairs; and special guest, Dr. René Kahn. Dr. Kahn is the Chair of the Department of Psychiatry at the Icahn School of Medicine at Mount Sinai. Please note that during today's call we will reference slides that are available on the webcast. A PDF of the slide will be made available on our website following the conclusion of the call. If you've not done so already please go to the Investor Section of our website, alkermes.com, to access the webcast player. We will be making forward-looking statements based on our current expectations relating to, among other thing, the future clinical development of ALKS 3831, its therapeutic value and commercial potential and our regulatory filing strategy and timelines. These forward-looking statements are neither promises nor guarantees and are subject to a high degree of uncertainty and risks.

Please see our press release issued earlier this week and our SEC filings for important risk factors that could cause our actual performance and results to differ materially from those expressed or implied in the forward-looking statements. We undertake no obligation to update or revise statements provided provided on this call as a result of new information or future results or development. After our remarks, we'll open the call for Q&A. Now, I'd like to turn the call over to Craig.

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

Thank you, Sandy. And good morning, everyone. We're here in Orlando at the Congress of the Schizophrenia International Research Society, or SIRS, to present data on both of our schizophrenia programs, ALKS 3831 and ARISTADA. Alkermes has been deeply involved in the area of serious

APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

mental illness for many years now, and we have a growing leadership position in this space. Before we get to ALKS 3831, I'd like to spend a brief moment on ARISTADA. Earlier this week, we announced positive top line results from ALPINE, first of its kind, 6-month study, evaluating the efficacy, safety and tolerability of ARISTADA and INVEGA SUSTENNA when used to initiate patients experiencing an acute exacerbation of schizophrenia in the hospital and maintain treatment in an outpatient setting. These preliminary data were also presented yesterday here at SIRS and represent another data set in the growing clinical body of evidence supporting ARISTADA as an increasingly important treatment option for schizophrenia. We're excited about these results and look forward to showing more details from the ALPINE study in the coming months.

In the interest of time today, I'll focus on ALKS 3831 and the results from ENLIGHTEN-2 pivotal weight study as well as our interim data from the ongoing long-term safety extension study. Then I'll turn it over to Dr. René Kahn, who will share his perspective on the schizophrenia treatment landscape.

So let's get started. Schizophrenia is a disabling disease that affects an estimated 1% of the population or roughly 3.5 million people in the United States and generally emerges late in adolescence and early adulthood. This devastating disease is characterized by symptoms that include hallucinations, delusions, disorganized thinking and speech, blunted emotions as well as cognitive impairment. Given the progressive neurodegenerative nature of schizophrenia, patients need effective, well-tolerated medicines to help tolerate -- control the symptoms and prevent relapse. And while we no longer injecting atypical antipsychotic on important treatment options that have proven long-term benefits. The vast majority of patients still use [our own] medications. Olanzapine has played an important role in the treatment paradigm of schizophrenia since its approval in 1996. Known for its efficacy, olanzapine offers other clinical attributes including no required titration and a rapid onset of antipsychotic efficacy that make it an important treatment option for healthcare providers and patients. These characteristics make it a leading choice for quickly stabilizing acutely ill patients.

Interestingly, in meta-analyses, olanzapine did not cause significantly more extra pivotal effects compared to placebo and was associated with the smaller increase in prolactin compared to risperidone and paliperidone reinforcing olanzapine's reputation for being generally well tolerated outside of its significant weight and metabolic liabilities. This [protocol] was underscored by data reflected in the NIH sponsored CATIE study, one of the largest studies ever conducted in schizophrenia where 5 antipsychotics including olanzapine were studied in a head-to-head manner in nearly 1,500 patients. What you see on the left side of the slide is the rate of discontinuations on the antipsychotics based on lack of efficacy. Olanzapine shown on the red line at the top of the graph stands out from the pack with the lowest rate of discontinuation due to lack of efficacy. At its peak, olanzapine was the most widely-used antipsychotic in the country. However, as its profound effect on weight and long-term metabolic liabilities became more broadly understood, regulated and the treatment community were forced to reconsider its use in the treatment paradigm and more restrictive guidelines were put in place. Today, olanzapine remains an important treatment option for patients and clinicians because of its efficacy, but it has dramatically decreased over the years in favor of weight-sparing antipsychotics.

This leads me to ALKS 3831. ALKS 3831 is an investigational, novel, oral antipsychotic drug candidate designed to provide the robust efficacy of olanzapine while mitigating its weight gain and many other related long-term metabolic consequences.

It's a once-daily bilayer tablet composed of olanzapine and samidorphan, our proprietary opioid receptor antagonist. The efficacy, safety and weight profile of ALKS 3831 is now being demonstrated across multiple studies and patient populations, including 2 large Phase III studies and more than 1,600 subjects have had exposure to 3831. The broad spectrum agents in the brain, olanzapine's efficacy are sought to be mediated primarily through a combination of dopamine and serotonin receptor antagonism. Samidorphan is our new molecular entity that functions as an opioid receptor antagonist and works through 3 prominent opioid receptors, mu, kappa and delta. Samidorphan has a unique binding pharmacokinetic and activity profile compared with other opioid antagonists.

Our nation-wide purposes was to leverage combination pharmacology of these 2 agents to retain the antipsychotic efficacy provided by olanzapine and see whether the addition of an opioid antagonist would effect the reward system which is known to play a role in mediating food intake. By doing so, we aim to harness the antipsychotic properties of olanzapine while mitigating the deleterious effects of weight gain and associated long-term metabolic sequelae. The registration program for ALKS 3831 that was agreed upon by the FDA is comprised of 2 foundational Phase III studies, ENLIGHTEN-1 and ENLIGHTEN-2. ENLIGHTEN-1 was designed to test the antipsychotic efficacy of ALKS 3831 versus placebo in acutely ill patients. And olanzapine almost included as an active comparator. This Phase III study was successfully completed in June of 2017 and subsequently presented at the 2017 ACNP meeting. ENLIGHTEN-1 was critical to the registration program for ALKS 3831 as it provided the clear demonstration



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

that 3831 retained a robust antipsychotic efficacy of olanzapine. The second key study in our registration program, ENLIGHTEN-2, was a 6-month, head-to-head comparison of weight gain for 3031 versus olanzapine. We completed this study last fall, achieving statistical significance on the 2 co-primary endpoints.

Before diving into the results of ENLIGHTEN-2, I'd like to spend a moment on our rationale for the study design. This figure is the model of how we predicted the distribution of weight gain for patients receiving olanzapine might look in a 6-month study based on CATIE as well as our own 300-patient Phase II study. The histogram captures the magnitude of weight gain on the X axis and the percentage of patients on the Y axis. Two specific measurements matter. The first is a center dotted line which represents the average or mean weight gain across the whole population. A continuous variable, the mean catches information across all patients in this study. The second measurement is the shaded area on the right which measures just the proportion of patients who gained more than 10% of their body weight. By focusing on both these measures, we aim to capture a sense of the entire distribution. Our hypothesis for ENLIGHTEN-2 was simple, ALKS 3831 would shift the overall distribution to the left. You can see how we arrived at the 2 co-primary endpoints for the study, one focused on the population mean change in weight and the other on the proportion of patients gaining an excessive amount of weight at a level prespecified at 10%. By shifting the entire distribution, you would favorably affect both of these measurements.

Importantly, this is key potential clinical implications for patients. You can see here that a shift in the distribution to the left means that on the right side of the figure fewer patients gained clinically significant amounts of weight and on the left side there are more patients who lose weight or gain insignificant amounts of weight. This theoretical model informed that designed for ENLIGHTEN-2, which I'd like to walk you through now.

ENLIGHTEN-2 was a multi-sensor, double-blind, randomized Phase II study that evaluated the weight gain profile of ALKS 3831 compared to olanzapine over 6 months in patients with stable schizophrenia. The study's 2 co-primary endpoints of statistical analysis plan were developed in collaboration with the FDA. In order to reach a positive study result, both of the co-primary endpoints had to achieve a P value of less than 0.05. Subject to completed ENLIGHTEN-2, we're eligible to roll over into a 52-week expansion safety study, and I'll speak to that later on this call.

The baseline characteristics and subject disposition for ENLIGHTEN-2 were similar for both ALKS 3831 and the olanzapine treatment groups as shown here on Slide 16. A total of 561 patients with stable schizophrenia were randomized in this study and 550 patients who received at least one dose of study drug were included in the safety population. We know that gender, race and BMI are characteristics known to be associated with weight gain. And as you can see here, that these co-variants were well balanced between the 2 groups. At the bottom of this slide, we list the completion rates for patients. For ENLIGHTEN-2, we knew that the retention throughout the 6 months duration and particularly keeping those patients experiencing substantial weight gain would be of critical importance in order to capture the separation between olanzapine and 3831.

We modeled for discontinuation rate of 40% in ENLIGHTEN-2 which is typical for schizophrenia trials of this duration. Our overall discontinuation rates were slightly lower than those expectations and similar between arms. Treatment of missing data is an important consideration in clinical trials.

Historical data tells us that olanzapine-associated weight gain is underrepresented in controlled settings and early discontinuation have an important effect. While there are a number of statistical methodologies to address missing data, we aligned with the FDA that multiple imputation was the most appropriate method for the co-primary weight-related endpoints in ENLIGHTEN-2.

Moving to the results of ENLIGHTEN-2, Picking out the data which demonstrate that ALKS 3831 successfully mitigated olanzapine-associated weight gain. The 2 co-primary endpoints met statistical significance at a P value of 0.003. We had prespecified the key secondary endpoints, the proportion of patients reporting weight gain of 7% or more from baseline and their hit as well with a P value of 0.001. Importantly, this mitigation of weight gain was maintained when we conducted our subgroup analyses based on race, gender, age and early weight gainers. Expressed in terms of odds ratio the olanzapine group had 2x of risk of gaining clinically meaningful weight in the categorical 10% and 7% cuts compared to the 3831 group.

Going now a level deeper into these data, let's look at how 3831 impacted overall distribution of the weight curve. Here on Slide 19 is the right side of the distribution or the proportion of patients who gained meaningful weight gain. In addition to our primary and key secondary endpoints of 10% and 7% weight gain, we also observed a clear differentiation from olanzapine at the 5%, 15% and 20% weight gain thresholds. At each of these categorical cuts, ALKS 3831 consistently demonstrated fewer patients with these levels of weight gain than olanzapine.



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

Now let's examine the left side of the distribution curve. Here we see that more patients on 3831 lost weight as compared to olanzapine. Together, these data reinforced the success of our [design] intent for ENLIGHTEN-2, a clinical -- clinically meaningful shift in weight distribution creating a distinctive profile for ALKS 3831.

Shifting the weight distribution for ALKS 3831 was a necessary prerequisite to achieve success on the primary endpoints of ENLIGHTEN-2. However, clinicians and patients are also concerned with the olanzapine's weight gain trajectory, which is well mount to persist consist over many months and potentially years before subsiding. It was important for us that we replicate the flat profile demonstrated in our large Phase II study for 3831, and as you can see here we did just that. This is the longitudinal plot of weight gain in the 2 groups over the 6-month period. There are a number of important conclusions from this plot. First, the curves begin to separate early and reach statistical separation by week 6. Second, as the study progressed, you see continued divergence between the 2 arms. And perhaps most importantly, the 3831 weight curve stabilized at week 6 and remained flat for the rest of the 6-month treatment period in contrast to the ascending olanzapine weight curve.

Another way to capture the continued divergence between ALKS 3831 and olanzapine is to plot the mean difference in body weight over the 6-month study. You can see here that the line continues to creep down, reflecting the growing difference between the 2 treatment groups. It's important to us as the results from patients who completed ENLIGHTEN-2 are the profiles of the patients who did not.

Here are side-by-side depictions of the subjects who discontinued early by treatment group. The solid blue and green lines denote the weight gain curve of patients who completed the entire 6-month study for olanzapine and 3831 while the dashed lines denote mean weight gain curves for those patients who discontinued prematurely. The numbers by each line reflect the number of subjects who discontinued at each week. For example, in the olanzapine chart from the left, 8 subjects dropped out of the study at week 4. The dotted line reflects the mean weight gain for those 8 subjects. So you can see, despite similar overall retention rates between the treatment groups, the weight gain trajectories are different for the patients who discontinued olanzapine versus ALKS 3831 and the majority of those patients in the olanzapine group who discontinued prematurely gave a greater percentage of baseline weight than olanzapine completers, consistent with historical data that suggests that olanzapine-associated weight gain is typically underrepresented in controlled settings. This [pattern] of discontinuations is reflective of what you'd expect to see in the real world. Patients who gain a lot of weight stopped taking their medications.

In contrast, you see a different pattern on the right-hand side of -- for 3831. This tells us that they observe treatment differences between olanzapine and 3831 may have been underestimated in the study. The bias that these discontinuations introduce further underscores the significance of the separation that was observed in the ENLIGHTEN-2.

In summary, the weight profile of ALKS 3831 demonstrated ENLIGHTEN-2 was consistent with our expectation. ALKS 3831 mitigated olanzapine-associated weight gain with mean weight stabilizing at week 6 and remaining flat thereafter. And for the first time we showed you that ALKS 3831 clearly shifted the weight distribution curve as compared to olanzapine with fewer patients from 3831 who gained significant amounts of weight.

Lastly, we showed you the weight trajectories of those patients who discontinued the study early. While we're extremely pleased with the positive results from ENLIGHTEN-2, those discontinuation plots are important clinical reminder that the observed treatment differences between olanzapine and 3831 may have been underestimated.

Let's turn now to the metabolic data from ENLIGHTEN-2. Presented here on Slide 26 are the combined metabolic parameters observed across the 6-month treatment period. Premises include HDL, LDL, total cholesterol, triglycerides, HbA1c and glucose. The top panel shows these parameters for ALKS 3831 and the bottom panel for olanzapine. The observed changes in these parameters from baseline were generally small with similar changes for both treatment groups. In this study, we saw that LDL and total cholesterol shown in light blue remained essentially flat for both treatment arms and showed no clinically meaningful change over the 6 months. HDL, shown in dark blue, went down approximately 6 milligrams per deciliter for both groups and then remained stable. This effect on HDL may be olanzapine-induced and a parameter of samidorphan may not impact.

For triglycerides, shown in grey, we saw a small increase for both groups of just under [30] milligrams per deciliter. When we look at the 32-week extension study in a few moments, we will show you that this acute phase phenomenon stabilized and then returned towards baseline.



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

For glucose, we saw small changes from baseline over the 6 months treatment period for both olanzapine and ALKS 3831, while HbA1c, which is considered a clinically superior measurement for 6-week glycemic control, remained completely flat in both groups. The small changes observed in ENLIGHTEN-2 were not surprising to us given the study of this length.

The literature demonstrates that the impact of olanzapine on lipids and HbA1c are variable from study to study, sometimes showing noteworthy changes in these metabolic parameters and other times demonstrating little change from baseline. In real-world practice, olanzapine's long-term metabolic disturbances are likely driven by weight gain associated with its long-term exposure.

As we talk to the differentiated weight and metabolic profile for ALKS 3831 compared to olanzapine, it's important to remember that it's not only absolute weight gain that matters but way that the weights accumulates. Olanzapine is known to leave not just too excessive weight gain in some patients, but weight gain's highly concentrated around abdomen. This is referred to as central or visceral fat and is generally stored in the abdominal cavity around a number of important internal organs, such as the liver, pancreas and intestines. Carrying a high amount of visceral fat is associated with a number of long-term health problems and is a leading indicator for developing metabolic complications such as cardiovascular disease and diabetes.

Here are the results for the change in patients' waist circumference from baseline measured in centimeters. Change in waist circumference is a well-established metabolic parameter and is an indicator of metabolic risk as denoted by the guidelines from the American Diabetes Association.

In ENLIGHTEN-2, ALKS 3831 demonstrated a clinically meaningful and statistically significant difference from olanzapine very early in the study with continued separation for the entire duration of the 6-month treatment period. Notably, the separation in waist circumference for ALKS 3831 versus olanzapine occurs earlier than the separation in weight curves.

So in another way, the mean difference from baseline in waist circumference between olanzapine and ALKS 3831 continued to increase over time.

Overall, the changes in key metabolic parameters observed in the 6-month ENLIGHTEN-2 study were small and remained stable. ALKS 3831 demonstrated an early and significant impact on waist circumference which occurred earlier than the observed shift in weight at week 6. The last data I'll review for ENLIGHTEN-2 is antipsychotic efficacy as measured by the Positive and Negative Syndrome Scale, or PANSS total score. While the study's co-primary endpoints were focused on weight, we also measured efficacy as an exploratory end point. Because at the end of the day, efficacy is what will differentiate ALKS 3831 in today's treatment landscape.

Here on Slide 32, you see that both ALKS 3831 and olanzapine demonstrated and maintained improvements in PANSS total scores over the 6-month study, underscoring the powerful efficacy of these agents.

Put these data into context, patients in both groups entered the study with stable disease, however, still moderately ill as based on the entry PANSS scores of approximately 70. By the end of the study, both groups had demonstrated meaningful improvements in their symptoms with PANSS scores considered to be moderately ill. The continued and sustained improvements in symptoms in the stable population is important as it reinforces the potent efficacy of olanzapine and ALKS 3831 over the 6-month period.

The most common adverse events reported in the ALKS 3831 treatment group were weight gain, somnolence and dry mouth. And the most common adverse events reported in the olanzapine group were weight gain, somnolence and increased appetite.

Now let's take a look at the ongoing open-label extension study. We're excited to share the interim results with you as you begin to see how ALKS 3831 performs over the long term. As a reminder, all patients who completed ENLIGHTEN-2 were eligible to enroll in the open-label, 52-week extension study. 76% of subjects who completed ENLIGHTEN-2 chose to do so. The subjects who were randomized to 3831 and ENLIGHTEN-2 remained on 3831 in the extension period and those who'd received olanzapine were switched to 3831.

So let's take a look at what happened to the weight and long-term exposure to 3831. Here on Slide 37, you see the weight curves of patients of the extension study normalized by each group's baseline. The green line represents the weight curve for those patients who continued on 3831. Their weight remained stable for the duration of the 52-week extension. Shown in blue are the patients who switched from olanzapine to 3831, their



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

previously ascending weight curves stabilized and remained flat during the extension period. This is in contrast to what we know about the long-term olanzapine use where weight gain is noted to continue for many months and years.

The stabilization of mean weight for the newly switched patients and the durability of effect for the 3831 continuation patients replicate the findings from our Phase II study.

Here are the weight results for all subjects in the extension period regardless of previous treatments. Our 3831 demonstrates durability of effect over the 52-week period. This extension was a single-arm, open-label study and all patients received 3831 and it's more appropriate to show you the combined data. So I'll focus on all subjects for the remaining slides.

Next, I will turn to the interim metabolic results, where all parameters remained stable with long-term treatment with ALKS 3831. On Slide 40 is a graph showing that metabolic parameters in the extension period remained remarkably stable with no clinically meaningful changes observed. The previously observed bump in glycerides reverted, suggesting the previous variability may be an acute effect that is sustained in the long term. The decrease in HDL observed in ENLIGHTEN-2 was maintained but remained stable throughout the 52-week extension, reinforcing our hypothesis that HDL may be one parameter where samidorphan does not mitigate olanzapine-induced effect.

At week 52, the mean change in fasting glucose for patients in extensions was about 2.5 millimeters per deciliter and the change in HbA1c was 0.07%.

Slide 41 shows the change from baseline in waist circumference over 52 weeks. The line remains flat, demonstrating ALKS 3831 durable stabilization of central fat accumulation.

Finally, let's look at the antipsychotic efficacy, which was sustained by ALKS 3831 in the extension. After completing ENLIGHTEN-2, patients rolled over into the extension with a mean PANSS score of approximately 59. Durability of antipsychotic efficacy was maintained with patients reaching a mean PANSS score of 57 at week 52, representing a moderately-ill, well-controlled patient.

You've now seen detailed results from ENLIGHTEN-2 Phase III study and interim results from the ongoing 52-week extension. Our 3831 mitigated olanzapine-associated weight gain, demonstrating clear separation at week 6, which continued to diverge through week 24 and remained flat for up to 76 weeks of treatment. The data also showed how ALKS 3831 shifted the weight distribution curve to the left compared to olanzapine, resulting in fewer patients who gained clinically meaningful amounts of weight. ALKS 3831 demonstrated small and nonclinically meaningful changes in metabolic parameters, which remained stable with long-term treatment. The exception here was the waist circumference. ALKS 3831 demonstrated an early and significant impact on mitigating olanzapine-associated increases to waist circumference, which may represent a long-term metabolic benefit.

Finally, the antipsychotic efficacy of ALKS 3831 should not be overlooked. Both 3831 and olanzapine demonstrated significant reductions in psychotic symptoms and, thus, efficacy was sustained for patients throughout the 52-week extension period. ALKS 3831 performed exactly as we expected it to, demonstrating a favorable impact on weight and clinically meaningful antipsychotic efficacy.

With the ALKS 3831 registration program complete, the team is busy preparing the new drug application. We expect to have a pre-NDA meeting with the FDA in the coming months to ensure alignment on our interactive [subject] to the NDA later this year. We're very excited about the profile of ALKS 3831 and its potential to help address the unmet needs of people living with schizophrenia. Now, I'd like to introduce Dr. René Kahn, who'll provide his insights on the schizophrenia treatment landscape and clinical relevance of these data. Dr. Kahn is Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai with more than 30 years experience in clinical research. We're pleased to have him here with us this morning. Dr. Kahn.



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

René S Kahn

Thank you very much, Craig. Yes, I am happy to say a few things about schizophrenia in general and about this particular drug and the treatment of schizophrenia. As Greg mentioned, I've been working in the field of schizophrenia for the last 30 years, and actually have conducted quite a few large clinical trials with one of the drugs that we used was olanzapine, so I have both clinical and actually scientific experience in the field.

Just to give you the context, schizophrenia is, as you probably know, quite prevalent disease, as Craig said, with a lifetime risk of 1%. But again, put it in perspective, it's more prevalent than Parkinson's disease, type 1 diabetes and multiple sclerosis. And different from many other illnesses, it starts very early in life. It starts late adolescent, so in the very productive period of people's lives. So people very often don't marry, don't get a job, have to discontinue education. So it's a very costly disease for the society, and obviously, also very costly from a personal perspective. So that's important to realize that may be it just sound 1%, but it's 1% throughout the lifetime, which is very different, for instance, compared to Alzheimer's disease, which is more prevalent, but that only starts when you're in your 80s usually.

So olanzapine is an extremely effective drug. In fact, we have used it. Craig presented the CATIE data and we have an equivalent study, more or less, in the first episode schizophrenia, called the [FES] study. We found the exact same thing. That the patients stayed longest on olanzapine because of its efficacy. And that's particularly important in first episode schizophrenia because that's when you want to have an effective treatment from the [get go]. And also from all the meta-analyses that have been done, the most effective drug is clozapine, but immediately followed by olanzapine. And so there's no question why this drug was so widely used when it was introduced to the market because it is indeed one of the most effective antipsychotics that we have around. Unfortunately, as you know, it became clear that patient weight -- gained considerable weight especially as Craig has also said, weight distribution was extremely unfavorable but it increased around the waist with all the subsequent consequences for cardiovascular disease and cancer.

So unfortunately, more or less, we've lost one of our most effective antipsychotics because of the side effect. So I think this particular combination with samidorphan has now provided -- or provides the opportunity to, kind of, reintroduce olanzapine. And what's important, as you've just heard, is that the efficacy is -- which is not surprisingly, is the same for the combination drug, the Alkermes drug and olanzapine alone because it's obviously the same active compound that's in there but it's important that samidorphan doesn't detract from its efficacy. So we have a very effective antipsychotic without the potential of excessive weight gain. And I think there is a real need to that. I mean, I know from clinical practice that olanzapine has hardly been prescribed anymore, that doctors go for the newer antipsychotics, which, as meta-analysis show, has not been showing as effective as olanzapine and clozapine, for instance, or use some of the other antipsychotics like risperidone, which has also probably less efficacy according to the meta-analyses and the other studies and also has a lot of side effects like sexual side effects. So there is, I think, a real need for a drug like this.

Just to emphasize a few things that I think are particularly important, one was Slide 23 that Craig has shown is the early dropouts. Why is that so important? Because it's never caught in clinical trials, those -- these are the patients that don't complete the study. And in fact, what -- this is one of the main clinical impediments of olanzapine that many patients drop out early on because of their weight gain, especially women, but men also. So this is really -- they don't -- therefore, the patients don't get the opportunity to be treated with the most effective drug. The other thing I want to emphasize is that there is a separation between the Alkermes drug and olanzapine in weight gain at week 6, but then there's a stabilization on the Alkermes drug. And olanzapine, as we know, and that's also shown in the first 6 months, is actually still increasing in weight. So that's -- this -- that's exactly what you -- what we know about olanzapine that the weight gain continues to accumulate. And that's very important in the 52-week extension of the ENLIGHTEN study that in fact there's no additional weight gain. So it's important to know that although there is some weight gain after 6 weeks, it stabilizes and then for the rest of the year and a half follow up almost there's no additional weight gain. So my conclusion is that this really is a great opportunity to, kind of, reintroduce one of the most effective antipsychotics that we have that we know are available and so the patients are able to be treated with it again. So doctors will again prescribe it, which is -- there really is a need for a drug like this with a greater potential for the -- treatment of patients. Thank you very much.

Sandra Coombs - Alkermes plc - Co-Head of IR

Great. I'll now turn it back to the operator so we can open the call for Q&A.



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) And your first question comes from the line of Cory Kasimov with JPMorgan.

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

This is Matthew on for Cory. So the first one is on the weight gain chart on Slide 23. Apologies if I missed this in the prepared remarks, but what did you observe with the 13 olanzapine treated patients that lost weight, but discontinued treatment nonetheless prior to 4 weeks? And then any thoughts on why this wasn't seen in the 3831 arm?

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

So I get to slide 23 here.

Sandra Coombs - *Alkermes plc - Co-Head of IR*

Okay, could you please repeat the question?

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

So on Slide 23, that looks like there's 13 patients in the olanzapine arm that lost weight that discontinued treatment prior to 4 weeks?

Sandra Coombs - *Alkermes plc - Co-Head of IR*

Yes.

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

Just curious to get your thought on this patients' group? And why we didn't observe this in the 3831 arm?

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

I mean, patients -- these are -- I think, it's really important to emphasize that these are in variably patients who came off of study not for reasons of weight gain but for other reasons. And as you can see across the entire profile of the olanzapine this continues. These patients had substantial amounts of weight gain in addition to their reasons for coming off of study. For those 13 patients they are the patients that discontinued early and could have been for a number of different reasons outside of weight gain. And this may be very variable amongst the individual patients in that subgroup of 13.

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

Got it. And then a question for Dr. Kahn. Out of all of the efficacy measures provided on the call today, what do you see is the most relevant for you in the real world setting?



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

René S Kahn

I think the reduction in the PANSS score is the most important. It's a very widely used gauge for not only psychosis but also negative symptoms and general symptoms. And in both studies, this is only -- in the weight gain study, these were not very old patient. They started out with the PANSS score of 70. Despite that not being a very high score, they still go down to 60. And don't forget that 0 is not 0, it depends. I think it's around in the 30s or 40s but -- so I mean they came even though they were moderately ill, they still improved. And in the ENLIGHTEN-1 study, the efficacy study, there was actually a very large drop. So I think the PANSS is most important gauge for treatment response.

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

Great. And then if I can sneak one more in. Just curious if you began discussions with payers any if there is any color if you can provide around these?

Richard F. Pops - Alkermes plc - Chairman & CEO

Matthew, this is Richard. No, we're just starting that now that we these data now, getting them out is an important part of that because now we can begin the medical affairs and education's process that will be necessary to make sure the payers are ready for this medicine.

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

And maybe just to add to what Richard just said, I think the first step of engaging payers really begins with showing the data with the clinical community, and we did that yesterday. And there's a lot of excitement around the product with some physicians coming up to us after the presentation yesterday, asking when this would be available. So I think this -- that education which needs to occur over the coming months and then obviously as Richard said, we'll start working with the payers and educating them as well.

Operator

The next question comes from the line of Chi Fong with Bank of America.

Chi Meng Fong - BofA Merrill Lynch, Research Division - Research Analyst

This is Chi Fong for Jason Gerberry. Just going back to Slide #21, the 24-week data, it looks like olanzapine, weight gain as probably feel on the up work trajectory where Alkermes drug has stabilized. Can you talk about maybe like how much that sort of that 24-week cutoff that I've underappreciate the potential weight gain difference between two trial on longer-term exposure, because that looks like when I look at the 52-week expansion, ALKS 3831 stayed more or less flat, may be like [1%] change of difference. And then I'll have a follow-up after that.

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

Sure. So I'll give my perspective and then I'll ask René to give his as well. Essentially, what you're seeing there is exactly as you described it is that there is continued divergence through 24 weeks of treatment for the olanzapine arm.

The 3831 on for week 6 onwards is completely flat, and we see that all the way through 76 weeks of follow up. Once again, I'll go back to the discontinuation curve, because I think there's a lot that lies on -- within that curve. And that is really that as we know in controlled clinical settings that olanzapine weight gain is often underappreciated. And I think when you look at those discontinuations, you're seeing virtually all of the olanzapine discontinuations are above the line of completers within the olanzapine group for weight gain. And that tells a story because these patients and they have become often study for reasons other than of weight gain. And yet, they were experiencing significant amounts of weight



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

gain. And I think -- our believe is also that patients on olanzapine who experience large amounts of weight gain just stop taking their medications. And so there's an adherence component there, and I think the other component is also that, that will lead to relapses and hospitalizations. So from our perspective, we continue -- we would have expected to see those curves continue to diverge if we had managed to apply the study through the 52-week extension. Obviously, it wasn't ethical for us to do that. And I think there's a lot of literature as well which demonstrates now that patients who were on olanzapine long term are especially coming in with lower BMIs, experience weight gain which goes -- which can stand out the years. And -- so obviously, the flatness of 3831 curve is incredibly important, but I'll ask René maybe to give his perspective as well.

René S Kahn

Yes, I agree with Craig. I think the impressive finding is here that there's separation in 6 weeks which is quite early. And then there's no additional weight gain in the Alkermes arm which is impressive, because like you said, the olanzapine goes out and we know from clinical experiences will continue to go up. And I also want to emphasize, although it was not one of the main outcome measures that the waist circumference actually separates even earlier, it separates at one week and then again at 4 weeks. And so it precedes the overall weight gain, which is very important because, like I said, the distribution of the weight gain is actually one of the biggest risk factors for cardiovascular disease and cancer as well. So I think that is very important that there is almost an immediate benefit in reducing the largest risk factor for long-term complications.

Chi Meng Fong - BofA Merrill Lynch, Research Division - Research Analyst

Got it. And if I may, I want to sneak in a follow-up on that. If I look at Slide #37 on the expansion interim analysis through 52 weeks, it looks like subjects who switched from olanzapine to ALKS 3831 had -- panned a way to -- has stopped the weight gain from going. Just going to want to see the clinical meaningfulness of stopping the weight gain of olanzapine? And whether that is clinically meaningful enough for our physicians to switch current olanzapine patients from using olanzapine to ALKS 3831?

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

Let's get -- I'll give my perspective and then I'll hand over to René to give his clinical perspective. I think what we're seeing is that patients who switch from olanzapine to 3831, you do you see that stabilization, but the damage that's already done is there. And I think, from our perspective, it's most efficient to stop patients on 3831. However, having said that, olanzapine patients gain weight over the years. And so what you're seeing here is, at very least, you can stabilize those patients by switching them over to 3831 which we believe is clinically meaningful. And also bear in mind that you see similar patterns on the waist circumference as well as René has said, that's a really important cardiometabolic risk factor as well. So our belief is yes, but ideally, we'd like to have patients initiated on 3831 but I'll hand over to René to give his perspective.

René S Kahn

Yes, so I echo that. I think the clear advantage is to start patients on the drug like this because you don't want to have the long-term weight gain that the patients who have been treated with olanzapine have. It is, however, remarkable that there is no additional weight gain after those first 6 weeks. I mean, that's -- it's essentially what this is, like a 1.5 follow-up, there is only weight gain in 6 weeks and then there's stabilization which is -- I think is a very potent finding because a 1.5-year follow-up is a really long term for clinical trials. So yes, you could switch patients from olanzapine to the Alkermes drug, but that's not the main strength of this drug. The main strength is that this should be a first-line drug in schizophrenia.

Operator

The next question comes from the line of Biren Amin with Jefferies.



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

Biren N. Amin - *Jefferies LLC, Research Division - MD and Senior Equity Research Analyst*

Just the question for the company, were the patients on the trial on exercise or diet regimen during the double-blind phase or the open-label extension period of the study?

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

No. The patients did come in with stable weights -- weight profiles over the 3 months coming onto the study, but we did not implement any additional measures in the trial that would be too difficult to implement.

Biren N. Amin - *Jefferies LLC, Research Division - MD and Senior Equity Research Analyst*

Got it. And then I've got a couple of questions toward Dr. Kahn. Given these data, how would you compare the 3831 to other weight-mitigating treatments like, I think, there's some literature on metformin and topiramate potentially as add-on therapies?

René S Kahn

Yes. Well, there are 2 things. One is, this is extremely well demonstrated. I think all the other trails are small trials, not very large, not very well controlled, not very well demonstrated, that's one. Two, it's very difficult to combine it what dose to use, at what point to use it. So I think this has an added advantage, one's because of simplicity, of course, of administering a single compound drug. And -- but the most important thing is the long-term follow-up. I have been emphasizing that several terms now. This is a 1.5-year follow-up. You don't have those data on any of the drugs you mentioned.

Biren N. Amin - *Jefferies LLC, Research Division - MD and Senior Equity Research Analyst*

Got it. And then maybe just one additional follow-up Dr. Kahn. What -- so if the drug is approved in second half 2020, what percentage of your patients would you switch off of olanzapine to 3831? And what percentage of patients on other atypical antipsychotics would you switch off of those therapies and prescribe 3831?

René S Kahn

Yes, the first one is easy, that's everyone. I mean, there's absolutely no reason to -- for them to continue on olanzapine if you have this drug, which is as efficacious and has no additional weight gain. And then to switch, you would switch a patient only if there is a need for better efficacy. There are many patients who are partial responders, who are still psychotic, I showed you in the ENLIGHTEN-2, they still had the PANSS of 70 which is not that high, but most of our patients will still, in fact, have a PANSS of 70. And if I would then give the Alkermes drug, you could still olanzapine, which you won't do. You could still have an additional 10 point reduction in the total PANSS score, that's worth it, So everyone who would be moderately ill and is not responding totally, I would definitely try to switch and we try to switch, and like I said, the current data suggests that, that'll be beneficial. But again, the most important thing is that you would start new patients. So in short, everyone who's currently on oral olanzapine, I would switch. The patients who are partially respondent -- responsive, which are most of the patients, I would probably switched unless they are doing really, really well. And the new patients, I would start on this drug.

Operator

The next question is from the line of Chris Shibutani with Cowen.



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

Pamela Ann Barendt - Cowen and Company, LLC, Research Division - Associate

This is Pam on for Chris. First, I have a question about the metabolic results. Were any of the results significantly different between arms?

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

So let me start off by just putting the metabolic results into context. So the shifts in the metabolic parameters were small and what we believe to be not clinically meaningful for the most part. The study wasn't actually designed to look at just a little separation between the arms, but numerically, in the 24-week study, we saw similar separations from baseline for olanzapine and 3831, but these were not clinically meaningful, just very, very small shifts from baseline. However, in terms of long-term follow-up, whatever shifts in metabolism that we saw on the lipid parameters except for HDL, these trended back towards baseline for 3831. If you look at HbA1c, which is probably the better marker for 6-week glycemic control, there was really no separation from baseline all the way through 0.07%. And then, obviously, there's one of the most important metabolic parameters is waist circumference and we already discussed that where there was very early separation of waist circumference that after the profile looks very similar to the weight curve where you see a complete flattening on 3831 and divergence with olanzapine throughout the 24-week study period. And obviously, this has long-term cardiometabolic consequences, so we believe that represents a metabolic benefit over the long term with 3831.

Pamela Ann Barendt - Cowen and Company, LLC, Research Division - Associate

Got it. And then for Dr. Kahn, are any of the differences in laboratory parameters observed between arms clinically meaningful regarding the metabolic parameters?

René S Kahn

Yes, I think the most meaningful, although there's no other difference because there was no control, is that you can actually see the triglycerides normalize in the long-term follow-up study. I think that is quite significant for the rest. And in the first 24 weeks, there was much difference -- not much change in general, but I think it's very important that in the 52-week follow-up, you see a normalization, a total return to baseline of the triglycerides. So that's very encouraging, I think.

Operator

The next question is from the line of Umer Raffat with Evercore ISI.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

I just wanted to zoom in on the data in a little more detail, just to understand each of the moving pieces of it because I know we had very good visibility on it previously as well and there's some incremental more information. So I'm just trying to focus more on some of the newer things. The first thing was, so as I look at the image on weight gain by percentage of patients that gained more than 5%, 7%, 10% weight, et cetera, what catches my eye is, if patients gained more than 7% then, obviously, 3831 clearly outperforms and I think it's 27% versus 43% in that ballpark. But if I dip below that, so if I say patients that only gained 5% to 7%, et cetera, then the number of patients that gained weight is actually lesser on just olanzapine. So I'm just trying to figure out why that is? And is that 7% sort of like a threshold? If a patient is going to gain more than 7% then you should be on 3831, and if it's going to be less than then 7% then maybe you just stay on the generic olanzapine. So I just wanted to get your thoughts, both from company's side and also from Dr. Kahn on that, and I had a follow-up?

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

So let me start off, first giving our perspective. So with prespecified 7% and 10% weight gain as clinically meaningful thresholds, but in addition to that we had prespecified an ASCO physical analysis plan where we'll be looking at a number of different thresholds. So we looked at weight gain

APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

of 2%, 5%, obviously, the 7% and 10%. We also looked at 15% and 20%. And on all of those cuts, there were significant separation in favor of ALKS 3831. In actual fact, in terms of the actual weight distribution curve which Dr. Kahn presented yesterday, virtually that entire curve across the entire distribution is shifted to the left in favor of 3831 and that's a range from...

Umer Raffat - *Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research*

If I may just, sort of, quickly add to that. So I guess what I'm doing is, I'm separating out the vintages, 5% to 7% separate from 7% to 10% instead of a more cumulative above 5% and above 7%, you see where I'm getting at? So if I just do 5% to 7%, the percentage of patients that gained weight is actually slightly more on 3831, which is sort of the genesis of the question. What is it about that 7% magic number?

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

Because, I think, more patients are then following -- are getting more weight on olanzapine. So the curve has shifted further to the right. So I think that's, kind of, an artificial way of looking at it. I mean, because when you look at the actual data and you look at the weight distribution curve that entire curve for the entire distribution is shifted to the left.

Umer Raffat - *Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research*

Fair point. And the second one was, I was just trying to understand -- I know there is a slide showing 3831 in one graph and just olanzapine in the graph below it on the metabolic parameters. And I know wasn't then at sort of in -- on the same graph, so what I'm curious about is, is there more hyperglycemia on 3831? And also if you could also just compare head-to-head the LDL on both the drugs?

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

Yes, sure. So in terms of the glycemic control, there was a lot of variability in the measure for glycemic control because it's very difficult in this population of patients to ensure a fasting status. So they were really small shifts in serum glucose. Numerically, it was slightly higher in the 3831 arm. The better measure to be looking at is obviously HbA1c which is an indicator of 6-week glycemic control and they're less dependent on fasting status and there you see the exact opposite that you actually see numerically lower separation from baseline for ALKS 3831, but I would say in both of these parameters, these are not clinically meaningful shifts. And so that dynamic range of -- in terms of these shifts from baseline is really not clinically meaningful but I'll ask for René for his clinical perspective on that as well.

René S Kahn

Yes, I agree. I'll be with both points. It's very, very difficult to do in these studies to have everyone really fasting and, I think, the changes are clinically not meaningful.

Umer Raffat - *Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research*

Got it. And if you could just quantify for us exactly how much did blood sugar go up on the active arm? And exactly how much went up on the comparator arm?

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

Yes. Let me just -- the other aspect I will sort of the -- probably jump in and add is the shift we've seen from baseline, we feel -- we don't think are clinically meaningful. So it's really difficult to tease apart differences and they really weren't differences across the 24-week study. And out of the long-term, these trended towards baseline except for HDL. I think the most important aspect to capture is also what we would have expected to



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

see in terms of the long-term weight gain of olanzapine. Because I think that's more tied to, as the waist circumference increases, as the weight increases, you start seeing longer-term metabolic consequences with olanzapine and which start to kick in. And that's where you start seeing a more significant aberrations in terms of lipid profile, glycemic control, et cetera, et cetera. The data that we're seeing from this study is actually not that different from what you would have expected to see in the, sort of, 12-week olanzapine studies. That's pretty much in the same dynamic range of about a 5 -- there, it's slightly higher 5% shift in total cholesterol; 3%, 4%, LDL; and about 24% for triglycerides. So I think, at the end of the day, it's really the long-term consequence that's sort of really need to be focused on, to really get the clinical message out of this, but once again, I'll ask René just for his perspective.

René S Kahn

No, I agree with you. The changes are very minimal. And in fact, any increase in HDL is what you want to see. That's actually a good thing -- an increase.

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

Sorry and your follow-up question?

Operator

The next question is from the line of Vamil Divan from Crédit Suisse.

Unidentified Analyst

This is (inaudible). Just have a few basic questions. So first on -- I just want to know like how long do patients typically stay on olanzapine? And secondly, the metabolic lab data, at least from the way I was looking at, it doesn't seem like there was -- as you (inaudible) meaningfully significant difference. But you also said that, it wasn't designed to measure these differences. So I just -- I'm just wondering like, does the -- and you know, is this what is typically seen? And does it suggest that, perhaps, there's no -- the weight does not have an impact on these labs? Or its just study not long enough? I just want to have a better understanding at that. And the third question is, when the data was presented yesterday, just want to know what the receptivity of the data was, were people excited?

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

So let me start off with your metabolic lab question, where -- I mean, I think, once again, let me reinforce what I said earlier on and that is, that we don't think these are clinically meaningful changes. And yes, we do think that the data that we saw on weight and waist circumference data are critically important in terms of really, sort of, analyzing what we expect to see long term with olanzapine and with continued weight on olanzapine and with continued increases in waist circumference, we would expect to start seeing more significant metabolic aberrations in terms of both lipid profile as well as glycemic control. And so we actually think that, that's how this would, sort of, have met out if we'd managed to perform a longer-term blinded metabolic study, which obviously, would not have been ethical to do so. In terms of the receptivity of the data, yesterday, I think there's a lot of excitement. I'm going to ask Dr. Kahn because he actually presented the data yesterday. And I will also ask him to speak to the duration of olanzapine use. René?

René S Kahn

Yes, I mean, I did get a pause and no one walked out during my presentation. So I think that was about as much as I could expect. So I think, it was well received but it's always very hard to gauge how that exactly is. I think there is enthusiasm about it to all the people approach me afterwards. There was certainly a lot of interest from the media, I can tell you that. And we're doing at least 3 interviews today with various media outlets. So



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

I think that tells you something about the interest in this drug. How long patients usually stay on olanzapine, it depends very much on the kind of study. In our own studies, it's actually in a 1-year follow-up, it's about 60%. So that's not bad despite side effects, but again, those are in controlled circumstances and that's because it's a highly effective drug. And you've seen probably also here that it's -- (inaudible) 67% or something 2/3, which is more or less reflecting the clinical practice and the trials that we have done. So the compliance is actually pretty good despite the side effects. Although, you've seen that the patients who do dropout mostly dropout, while that may not be the cause, but they gain more weight than the efforts. So actually the patients stayed on the drug may actually even be higher than 2/3 if you mitigate the weight increase.

Unidentified Analyst

Can I just add a follow-up questions. So like a patient is on olanzapine already given the data just presented, do you see some, sort of, emerging profile for -- to put in the clinical practice such as when would you switch patients over, like at what percent weight gain?

Unidentified Company Representative

As you know -- again, I mean, one of your colleagues asked more or less the same question. I think switching -- of course, some patients you'll switch, but I think the strength of this study -- of this compound, really, is to use it as a first-line drug because you want to use the most effective drug at the earliest possible stage. And unfortunately -- and that's exactly what happened with olanzapine. I mean, Olanzapine was the first-line drug used for patients. And then it was, more or less, fall into disuse because of the side effect. But it actually regained this position of the first-line drug. If you have a patient with psychosis, this is a drug you should give because it's the most effective one. But, again, apart of clozapine, which is now the first-line drug and then just keep them on it and the patient will probably stay on it. Now your questions about which patients would you switch? Yes, patients on olanzapine and I've been -- the irrespective of weight gain, except for the patients who really tolerate olanzapine very well with no weight gain, I would leave them on it. There's no reason to change. If the patients are early in their treatment, I would switch them because of the ultimate risk that we know about olanzapine as a treatment. And then, like I said, there are quite a few newer antipsychotics on the market with their own problems. Some have EPS, some has sexual side effects and some are just not as effective as, for instance, olanzapine. So there the patients don't do really well are not, as we call it, in remission, meaning they still have a PANSS score of round 70, they're still totally functioning, they still not have, may have hallucinations, all those patients, as I think, will be eligible to switch -- to be switched to this compound.

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

And I think, maybe just to add to that, we've -- most of our study, which is ongoing at the moment, the ENLIGHTEN early study, which is really looking at younger patients, early in illness population of patients the away we expect there to be significant amounts of weight gain on olanzapine because they're especially vulnerable to weight gain. And so that study is ongoing at the moment. And Dr. Kohn is actively involved in that study with us as well.

Eva Stroynowski - Alkermes plc - Co-Head of IR

We've got time for one more question.

Operator

And that question is coming from the line of Danielle Brill with Piper Jaffray.

Unidentified Analyst

This is (inaudible) on for Danielle Brill. I just had a quick question. And it is relating to something you've covered before, but there is a lower difference in the 5% threshold between the 2 groups. So I was just wondering if there would be some sort of, I guess, separation between -- for clinicians for



APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

prescribing generic olanzapine, for patients who are at lower risk of gaining weight, particularly for the ones who are going to be gaining weight for less than 5%?

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

Yes, it's interesting. One of the aspects that we looked at that when we analyzed the data was really early weight gain that's because we expected that there may be a differential profile there. And it turns out there's absolutely no difference in the patients who gained early weight versus the entire population of patients. The same benefit has constituted across the population. On top of that, as I said earlier on, when you look at the distribution curve of the weight that entire curve is shifted to the left. So I think, from a clinical perspective, it's really difficult to try and piece out which patients are going to gain early weight and there's really no clinical benefits, the entire population benefiting in ENLIGHTEN-2.

Unidentified Company Representative

And just to add, it's very -- it's impossible. I wish we could -- it's impossible to predict who will gain 5% and who will gain 15%, we don't know. So there's no marker that can predict that.

Danielle Catherine Brill - *Piper Jaffray Companies, Research Division - VP & Senior Research Analyst*

Got it. So in the threshold that were defined, there was no demographic specificities that were seen between the 7% or 5%, right?

Unidentified Company Representative

No, well, I mean, if I may jump in, this is, obviously, a great study, but it's only 500 patients. We've done studies in thousands and thousands of patients on olanzapine, and we haven't found a single predictor of gaining weight. There is a lot of effort being put in that because, obviously, everyone would like to know that. But there are no predictors of who's going to gain weight or not.

Operator

I'll now turn the call back to Sandy Coombs for closing remarks.

Sandra Coombs - *Alkermes plc - Co-Head of IR*

Thank you everyone for joining us on the call this morning. And if you have any follow-up questions, please don't hesitate to reach out to us at the company. Thank you.

Operator

This concludes today's conference. You may disconnect your lines at this time. Thank you for your participation.

APRIL 12, 2019 / 12:00PM, ALKS - Alkermes Plc Webinar on ALKS 3831 ENLIGHTEN-2 Data

DISCLAIMER

Thomson Reuters reserves the right to make changes to documents, content, or other information on this web site without obligation to notify any person of such changes.

In the conference calls upon which Event Transcripts are based, companies may make projections or other forward-looking statements regarding a variety of items. Such forward-looking statements are based upon current expectations and involve risks and uncertainties. Actual results may differ materially from those stated in any forward-looking statement based on a number of important factors and risks, which are more specifically identified in the companies' most recent SEC filings. Although the companies may indicate and believe that the assumptions underlying the forward-looking statements are reasonable, any of the assumptions could prove inaccurate or incorrect and, therefore, there can be no assurance that the results contemplated in the forward-looking statements will be realized.

THE INFORMATION CONTAINED IN EVENT TRANSCRIPTS IS A TEXTUAL REPRESENTATION OF THE APPLICABLE COMPANY'S CONFERENCE CALL AND WHILE EFFORTS ARE MADE TO PROVIDE AN ACCURATE TRANSCRIPTION, THERE MAY BE MATERIAL ERRORS, OMISSIONS, OR INACCURACIES IN THE REPORTING OF THE SUBSTANCE OF THE CONFERENCE CALLS. IN NO WAY DOES THOMSON REUTERS OR THE APPLICABLE COMPANY ASSUME ANY RESPONSIBILITY FOR ANY INVESTMENT OR OTHER DECISIONS MADE BASED UPON THE INFORMATION PROVIDED ON THIS WEB SITE OR IN ANY EVENT TRANSCRIPT. USERS ARE ADVISED TO REVIEW THE APPLICABLE COMPANY'S CONFERENCE CALL ITSELF AND THE APPLICABLE COMPANY'S SEC FILINGS BEFORE MAKING ANY INVESTMENT OR OTHER DECISIONS.

©2019, Thomson Reuters. All Rights Reserved.