ALKS 3831: A Novel Drug Candidate for the Treatment of Schizophrenia

2019 Congress of the Schizophrenia International Research Society

Investor Presentation

APRIL 12, 2019
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Agenda

- Schizophrenia Treatment Landscape
- Introduction to ALKS 3831 for Schizophrenia
- ENLIGHTEN-2 Results
  - Weight
  - Metabolic
  - Antipsychotic Efficacy
- ENLIGHTEN-2 Extension Safety Study: Interim Results
- Summary and Next Steps
- Clinical Perspective
  - Dr. René Kahn, Icahn School of Medicine at Mount Sinai
- Q&A
Schizophrenia is a chronic serious mental illness that affects approximately one percent of the population.

- Onset typically occurs in late-adolescence and early-adulthood.

Characterized by an array of symptoms:

- Delusions
- Hallucinations
- Disorganized thinking and speech
- Disorganized behavior
- Negative symptoms (loss of motivation, blunted emotions)
- Impaired cognition

Schizophrenia is a Disabling Neuropsychiatric Disease

1Schizophrenia and Related Disorders Alliance of America, https://sardaa.org/resources/about-schizophrenia/ accessed on April 9, 2019.
Olanzapine: Profile of Unique Clinical Attributes

- Potent efficacy
- Rapid onset allows quick stabilization\(^1\)
- No titration required
- Did not cause significantly more extrapyramidal effects compared to placebo\(^2\)
- Smaller increase in prolactin compared to risperidone/paliperidone\(^2\)

- **Olanzapine associated with significant weight gain**

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Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

Olanzapine Demonstrated Superior Efficacy vs. Other Oral Antipsychotics; Metabolic Side Effects Drove Discontinuations

CATIE 2005: Olanzapine exhibited a higher rate of discontinuation due to weight gain or metabolic effects compared to other atypical antipsychotics

Leucht 2013: In a meta-analysis of 15 antipsychotics, olanzapine exhibited the highest propensity for weight gain

CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; SMD = Standard mean differences

1 Lieberman et al. NEJM, 2005; 353:1209-1223
2 Leucht at al. Lancet, 2013; 382:951-962
Introduction to ALKS 3831 for Schizophrenia
ALKS 3831: A Potential New Oral Treatment for Schizophrenia

- Investigational, novel, once-daily, atypical antipsychotic designed to provide robust efficacy of olanzapine while mitigating olanzapine-associated weight gain

- Combination of olanzapine and samidorphan
  - Bilayer tablet of olanzapine (5 mg, 10 mg, 15 mg, or 20 mg) with samidorphan (10 mg)
  - Proprietary novel chemical entity with patent protection to 2031

- Studied in 27 clinical studies and approximately 1,680 subjects exposed to ALKS 3831
ALKS 3831 Design Rationale: Retain Olanzapine’s Pharmacology and Address Weight Gain Liabilities via Brain’s Reward System

Neuroreceptor Binding Activity of ALKS 3831

Olanzapine

- D1
- D2
- 5HT\(_{2A}\)
- D4
- 5HT\(_{2C}\)
- Musc.
- a1
- a2

| Antipsychotic Efficacy |

Samidorphan

| Opioid Receptor Antagonist |

| Address Weight Gain Liabilities |

ALKS 3831

## ALKS 3831: Efficacy, Safety and Weight Profile Confirmed in Two Large, Phase 3 Studies

### ENLIGHTEN-1 Efficacy Study
- Antipsychotic efficacy vs. placebo
- 403 patients with acute schizophrenia
- ALKS 3831 demonstrated statistically significant reductions from baseline in PANSS scores at 4 weeks, compared to placebo (p<0.001)
- Olanzapine achieved similar improvements from baseline PANSS scores, compared to placebo (p=0.004)

### ENLIGHTEN-2 Weight Study
- Weight change vs. olanzapine
- 561 patients with stable schizophrenia
- Demonstrated statistically significant improvement compared to olanzapine at 6 months for both co-primary endpoints:
  - Percent change from baseline in body weight (p=0.003)
  - Proportion of subjects with ≥10% weight gain (p=0.003)
- Demonstrated continued reduction in PANSS total scores in stable patients

### NDA submission planned mid-2019

PANSS = Positive And Negative Syndrome Scale
ENLIGHTEN-2: Designed to Evaluate Weight Distribution

Continuous Variable: Population Average (mean) Weight Gain

Categorical Variable: 10% or Greater Weight Gain

For illustrative purposes only
ENLIGHTEN-2: Primary Analysis Captures Shift in Two Dimensions

Co-Primary Endpoint (Continuous):
Population Average Weight Gain (mean)

Co-Primary Endpoint (Categorical):
10% or Greater Weight Gain
Secondary Endpoint (Categorical):
7% or Greater Weight Gain

For illustrative purposes only
ENLIGHTEN-2: Shift in Mean Has Beneficial Weight Implications for Entire Study Population

Weight Loss or Insignificant Weight Gain

Clinically Significant Weight Gain

Proportion of Subjects

Percent Change From Baseline in Body Weight

Olanzapine
ALKS 3831

For illustrative purposes only

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ENLIGHTEN-2: Study Design and Baseline Characteristics
ENLIGHTEN-2: Study Design and Methods

Co-Primary Endpoints
- Percent change from baseline in body weight at Week 24
- Proportion of subjects with ≥10% weight gain at Week 24

Key Secondary Endpoint
- Proportion of subjects with ≥7% weight gain at Week 24

Key Study Design Elements
- Adults aged 18–55 years
- DSM-5 diagnosis of schizophrenia; PANSS 50-90
- BMI: 18–30 kg/m²
- Stable body weight (change ≤5%) for ≥3 months
- Upon study completion, all patients eligible to rollover into 52-week open-label extension safety study (ENLIGHTEN-2-EXT)

1:1 randomization
No stratification or lead-in

24 Weeks
ALKS 3831
Olanzapine

Safety follow-up (4 weeks)
Extension safety study (52 weeks)
### ENLIGHTEN-2: Baseline Characteristics and Subject Disposition

<table>
<thead>
<tr>
<th>Baseline Characteristics†</th>
<th>ALKS 3831 N=274</th>
<th>Olanzapine N=276</th>
<th>All Subjects N=550</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>40.3 (9.79)</td>
<td>40.1 (10.01)</td>
<td>40.2 (9.90)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>193 (70.4)</td>
<td>207 (75.0)</td>
<td>400 (72.7)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>199 (72.6)</td>
<td>193 (69.9)</td>
<td>392 (71.3)</td>
</tr>
<tr>
<td>White</td>
<td>63 (23.0)</td>
<td>65 (23.6)</td>
<td>128 (23.3)</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>25.38 (3.13)</td>
<td>25.52 (3.19)</td>
<td>25.45 (3.16)</td>
</tr>
<tr>
<td><strong>Subject Disposition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized, n</td>
<td>280</td>
<td>281</td>
<td>561</td>
</tr>
<tr>
<td>Efficacy Population, n</td>
<td>266</td>
<td>272</td>
<td>538</td>
</tr>
<tr>
<td>Completed, n (%)</td>
<td>176 (64.2)</td>
<td>176 (63.8)</td>
<td>352 (64.0)</td>
</tr>
</tbody>
</table>

†Baseline characteristics and completion rates for safety population; includes all randomized subjects who receive at least one dose of study drug.
ENLIGHTEN-2: Weight Results
ENLIGHTEN-2: Achieved Prespecified Co-Primary and Key Secondary Endpoints

Mean Weight Gain at Week 24

- **p=0.003**
- **ALKS 3831**: 6.59%
- **Olanzapine**: 4.21%

Proportion of Subjects Gaining Clinically Meaningful Weight at Week 24

- **p=0.003**
- **p=0.001**
- **≥10% Weight Gain**
  - **ALKS 3831**: 29.8%
  - **Olanzapine**: 27.5%
- **≥7% Weight Gain†**
  - **ALKS 3831**: 17.8%
  - **Olanzapine**: 42.7%

†Prespecified key secondary endpoint
ENLIGHTEN-2: Fewer Patients on ALKS 3831 Gained Clinically Meaningful Weight Compared to Olanzapine

Proportion of Subjects With Weight Gain

<table>
<thead>
<tr>
<th>Percent Increase From Baseline in Body Weight at Week 24</th>
<th>Proportion of Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5%</td>
<td>55%</td>
</tr>
<tr>
<td>≥7%</td>
<td>50%</td>
</tr>
<tr>
<td>≥10%</td>
<td>45%</td>
</tr>
<tr>
<td>≥15%</td>
<td>40%</td>
</tr>
<tr>
<td>≥20%</td>
<td>35%</td>
</tr>
</tbody>
</table>

p=0.001

p=0.003

† p<0.05 based on post hoc analysis

†p<0.05 based on post hoc analysis
ENLIGHTEN-2: More Patients on ALKS 3831 Lost Weight Compared to Olanzapine

Proportion of Subjects With Weight Loss

Proportion of Subjects (%) vs Percent Decrease From Baseline in Body Weight at Week 24

- ALKS 3831
- Olanzapine

†p<0.05 based on post hoc analysis
ENLIGHTEN-2: ALKS 3831 Weight Profile Stabilized

Note: Weight curve based on analysis of covariance (ANCOVA) approach using multiple imputation (MI) for missing data.
Red slope lines for illustrative purposes only
*p<0.05 vs. olanzapine; **p<0.01 vs. olanzapine
ENLIGHTEN-2: Mean Difference of Percent Change From Baseline in Body Weight for ALKS 3831 and Olanzapine Continued to Increase Over Time

Mean Difference of Percent Change From Baseline in Body Weight (%)

Study Week

Baseline

Note: Difference in weight change based on ANCOVA approach using MI for missing data.

*p<0.05 vs. olanzapine; **p<0.01 vs. olanzapine
ENLIGHTEN-2: Weight Gain Trajectory of Early Discontinuations

Percent Change From Baseline in Body Weight by Treatment
Completers vs. Premature Discontinuations

Olanzapine

ALKS 3831

Solid lines denote the weight gain curve of patients who completed the study. Dashed lines denote weight gain curves of subjects who prematurely discontinued at given visits. Numbers of patients summarized in each curve are noted.
Summary Takeaways: ENLIGHTEN-2 Weight

- ALKS 3831 mitigated olanzapine-associated weight gain over the six-month study
  - Patients in the ALKS 3831 group had half the risk of experiencing clinically meaningful weight gain compared to the olanzapine group
  - Continued divergence of olanzapine and ALKS 3831 weight gain curves throughout ENLIGHTEN-2

- ALKS 3831 weight curve stabilized at Week 6 and remained flat for the remainder of the six-month treatment period

- ALKS 3831 shifted weight distribution curve to the left, compared to olanzapine

- Weight trajectory of patients who discontinued early suggests the observed treatment differences in ENLIGHTEN-2 between olanzapine and ALKS 3831 may have been underestimated
ENLIGHTEN-2: Metabolic Results
ENLIGHTEN-2 Metabolic Parameters: Changes Were Generally Small for Both ALKS 3831 and Olanzapine

**ALKS 3831**

**Olanzapine**

Diagram showing changes from baseline in metabolic parameters over weeks for ALKS 3831 and Olanzapine. The parameters include:
- Total Cholesterol (mg/dL)
- HDL Cholesterol (mg/dL)
- LDL Cholesterol (mg/dL)
- Triglycerides (mg/dL)
- Glucose (mg/dL)
- Hemoglobin A1C (%)

The changes are generally small for both treatments.
Weight Gain Distribution Matters: Central Fat Accumulation Carries Significant Risk for Developing Metabolic Complications

Abdominal Obesity Correlated With Metabolic Syndrome

Increased waist circumference (WC) consistently predicted risk of death due to any cause as well as major causes of death, including deaths from cancer, cardiovascular disease, and non-cancer/non-cardiovascular diseases, independent of BMI, age, sex, race/ethnicity, smoking status, and alcohol intake.

1Richie et al. Nutr Metab Cardiovasc Dis. 2007;17(4):319-26
ENLIGHTEN-2: Early and Significant Impact on Waist Circumference

Note: Waist circumference curve based on ANCOVA approach using MI for missing data
*p<0.05 vs. olanzapine; **p<0.01 vs. olanzapine; ***p<0.001 vs. olanzapine
ENLIGHTEN-2: Mean Difference of Change From Baseline in Waist Circumference for ALKS 3831 and Olanzapine Continued to Increase Over Time

Note: Waist circumference curve based on ANCOVA approach using MI for missing data
*p<0.05 vs. olanzapine; **p<0.01 vs. olanzapine; ***p<0.001 vs. olanzapine
Summary Takeaways: ENLIGHTEN-2 Metabolic

- Changes in lipids, glucose and HbA1C were small for ALKS 3831 during the six-month treatment period

- ALKS 3831 demonstrated an early and significant impact on mitigating olanzapine-associated increases to waist circumference
  - Waist circumference separated before observed shift in weight at Week 6
  - Central adiposity is an important predictor of cardiovascular risk
ENLIGHTEN-2: Antipsychotic Efficacy
ENLIGHTEN-2: Antipsychotic Efficacy
PANSS Scores Show Continuous Improvement in Stable Patients

![Graph showing PANSS Total Score Mean (±SE) over Study Weeks for Olanzapine and ALKS 3831.](image)
ENLIGHTEN-2: Most Common Adverse Events

<table>
<thead>
<tr>
<th>Serious Adverse Events†</th>
<th>ALKS 3831 (N=274) n (%)</th>
<th>Olanzapine (N=276) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Adverse Event (≥5%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight increased</td>
<td>10 (3.6)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>203 (74.1)</td>
<td>227 (82.2)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased appetite</td>
<td>68 (24.8)</td>
<td>100 (36.2)</td>
</tr>
<tr>
<td>Waist circumference increased</td>
<td>58 (21.2)</td>
<td>50 (18.1)</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>35 (12.8)</td>
<td>22 (8.0)</td>
</tr>
<tr>
<td>Extra dose administered</td>
<td>30 (10.9)</td>
<td>34 (12.3)</td>
</tr>
<tr>
<td></td>
<td>17 (6.2)</td>
<td>22 (8.0)</td>
</tr>
<tr>
<td></td>
<td>14 (5.1)</td>
<td>12 (4.3)</td>
</tr>
<tr>
<td></td>
<td>14 (5.1)</td>
<td>17 (6.2)</td>
</tr>
</tbody>
</table>

Similar safety profile observed to date in ongoing extension safety study (ENLIGHTEN-2-EXT)

†Only 1 serious adverse event in each group deemed to be study-drug related
ENLIGHTEN-2-EXT: 52-Week, Open-Label Safety Study

Interim Results
Primary Objective:
- To evaluate the long-term safety and tolerability of ALKS 3831 in subjects with schizophrenia

Study Design Elements:
- All subjects started on same ALKS 3831 dose that they maintained at the end of ENLIGHTEN-2
- 76% of patients who completed ENLIGHTEN-2 rolled over into ENLIGHTEN-2-EXT
- All patients eligible to rollover into additional open-label safety study following completion of ENLIGHTEN-2-EXT
ENLIGHTEN-2-EXT: Interim Weight Results
ENLIGHTEN-2-EXT Interim Results:
Weight Remains Stable Over 52 Weeks

Percent Change in Body Weight From ENLIGHTEN-2-EXT Baseline

- Subjects who remained on ALKS 3831
- Subjects who switched from olanzapine to ALKS 3831

Study Week

Percent Change From Baseline in Body Weight

(Mean +/- SE)
ENLIGHTEN-2-EXT Interim Results: 
Weight Remains Stable Over 52 Weeks
ENLIGHTEN-2-EXT: Interim Metabolic Results
ENLIGHTEN-2-EXT Interim Results: Metabolic Parameters Remained Stable
ENLIGHTEN-2-EXT Interim Results:
Waist Circumference Remained Stable Over 52 Weeks

Change in Waist Circumference From ENLIGHTEN-2-EXT Baseline
ENLIGHTEN-2-EXT Interim Results:
Antipsychotic Efficacy
ENLIGHTEN-2-EXT Interim Results: Sustained and Durable Antipsychotic Efficacy

PANSS Total Score From ENLIGHTEN-2-EXT Baseline

Study Week vs. PANSS Total Score Mean (±SE)

All Subjects
ALKS 3831 ENLIGHTEN-2 and ENLIGHTEN-2-EXT: Clinical Implications for Patients

Weight
- ALKS 3831 mitigated olanzapine-associated weight gain
  - Weight gain separated at Week 6, continued to diverge through Week 24, and remained stable through an additional 52 weeks of treatment
- ALKS 3831 shifted weight distribution curve to the left
  - Patients in the ALKS 3831 group had half the risk of experiencing clinically meaningful weight gain compared to the olanzapine group

Metabolic Parameters
- Changes in metabolic parameters were small and remained stable with long-term treatment with ALKS 3831
- ALKS 3831 demonstrated an early and significant impact on mitigating olanzapine-associated increases to waist circumference. Waist circumference remained stable throughout 52-week extension study

Antipsychotic Efficacy
- Significant reduction of antipsychotic symptoms demonstrated in stable patients in ENLIGHTEN-2. Sustained and durable antipsychotic efficacy maintained throughout 52-week extension period
- Improvements in antipsychotic efficacy now demonstrated in both acute and stable patients, across short- and long-term studies
Next Steps for ALKS 3831 Program

- Advancing toward regulatory submission for schizophrenia
  - Anticipated pre-NDA meeting to discuss key FDA requirements, including efficacy, safety, weight and metabolic profile
  - NDA submission planned for mid-2019

- Continued publication of data and scientific education
  - Plan to present data at spring medical meetings, including APA and ASCP

- Enrollment ongoing for ENLIGHTEN-Early phase 3 study in young adults
  - Early-in-illness study in multiple indications

- Launching lifecycle management initiatives
  - Bipolar opportunity

- Commercial launch planning and preliminary payer discussions
René Kahn, M.D., Ph.D.

Icahn School of Medicine at Mount Sinai
Q&A

René Kahn, M.D., Ph.D., Esther and Joseph Klingenstein Professor & System Chair of Psychiatry, Icahn School of Medicine at Mount Sinai

Craig Hopkinson, M.D., Chief Medical Officer, Senior Vice President of Medicines Development and Medical Affairs, Alkermes

Richard Pops, Chief Executive Officer, Alkermes