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

2019 Congress of the Schizophrenia International Research Society

Investor Presentation

APRIL 12, 2019

Forward-Looking Statements

Certain statements in this presentation may constitute “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: future business plans or prospects of Alkermes plc; timing and/or plans for development, regulatory and pre-commercial activities for ALKS 3831, including timing of submission of a new drug application (“NDA”) for ALKS 3831; expectations regarding continued submission for publication of data related to ALKS 3831; and the potential therapeutic and commercial value of ALKS 3831. Although the company believes that such forward-looking statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those expressed or implied in the forward-looking statements due to risks and uncertainties. The factors that could cause actual results to differ include, among others: whether an NDA for ALKS 3831 will be submitted in a timely manner; once submitted, the FDA’s view of the sufficiency of the pre-clinical and clinical data for ALKS 3831 in determining whether to accept for filing the ALKS 3831 NDA and/or approve the ALKS 3831 NDA; regulatory delays in filing the NDA with the FDA; whether preclinical and clinical results for ALKS 3831 will be predictive of future results; whether ALKS 3831 could be shown ineffective or unsafe during clinical studies; and those risks and uncertainties described under the heading “Risk Factors” in the Alkermes plc Annual Report on Form 10-K for the fiscal year ended Dec. 31, 2018, and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at www.sec.gov and on the company’s website at www.alkermes.com in the “Investors—SEC filings” section. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained herein.

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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

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Schizophrenia is a Disabling Neuropsychiatric Disease

- 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

3.5M

SUFFER FROM SCHIZOPHRENIA[1]

[1]Schizophrenia and Related Disorders Alliance of America, https://sardaa.org/resources/about-schizophrenia/ accessed on April 9, 2019.

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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**

[1]Kapur et al. *Am J Psychiatry* 2005; 162:939–946
[2]Leucht et al. *Lancet,* 2013; 382:951-62

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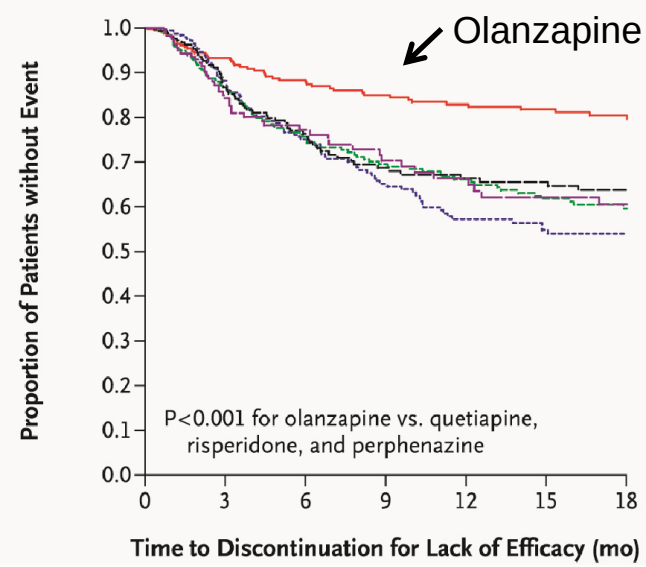
Olanzapine Demonstrated Superior Efficacy vs. Other Oral Antipsychotics; Metabolic Side Effects Drove Discontinuations

Efficacy

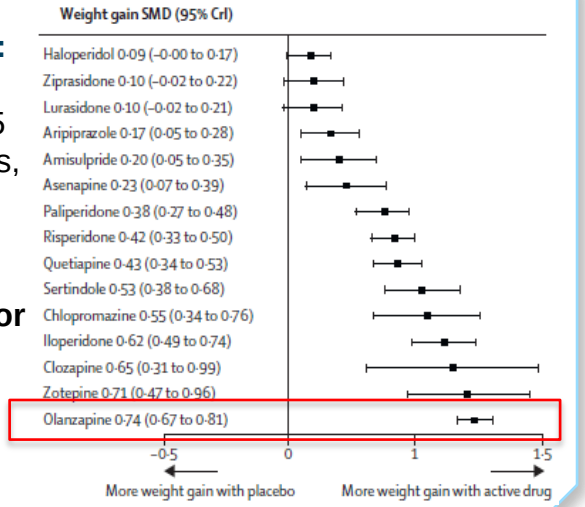
CATIE 2005[1]



Side Effects

CATIE 2005: Olanzapine exhibited a **higher rate of discontinuation** due to weight gain or metabolic effects compared to other atypical antipsychotics[1]

Leucht 2013: In a meta-analysis of 15 antipsychotics, olanzapine exhibited the **highest propensity for weight gain**[2]



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

[1]Lieberman et al. *NEJM*, 2005; 353:1209-1223
[2]Leucht et 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

Source: Bymaster FP, et al. *Neuropsychopharmacology.* 1996,14(2):87-96

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 ($p=0.004$)

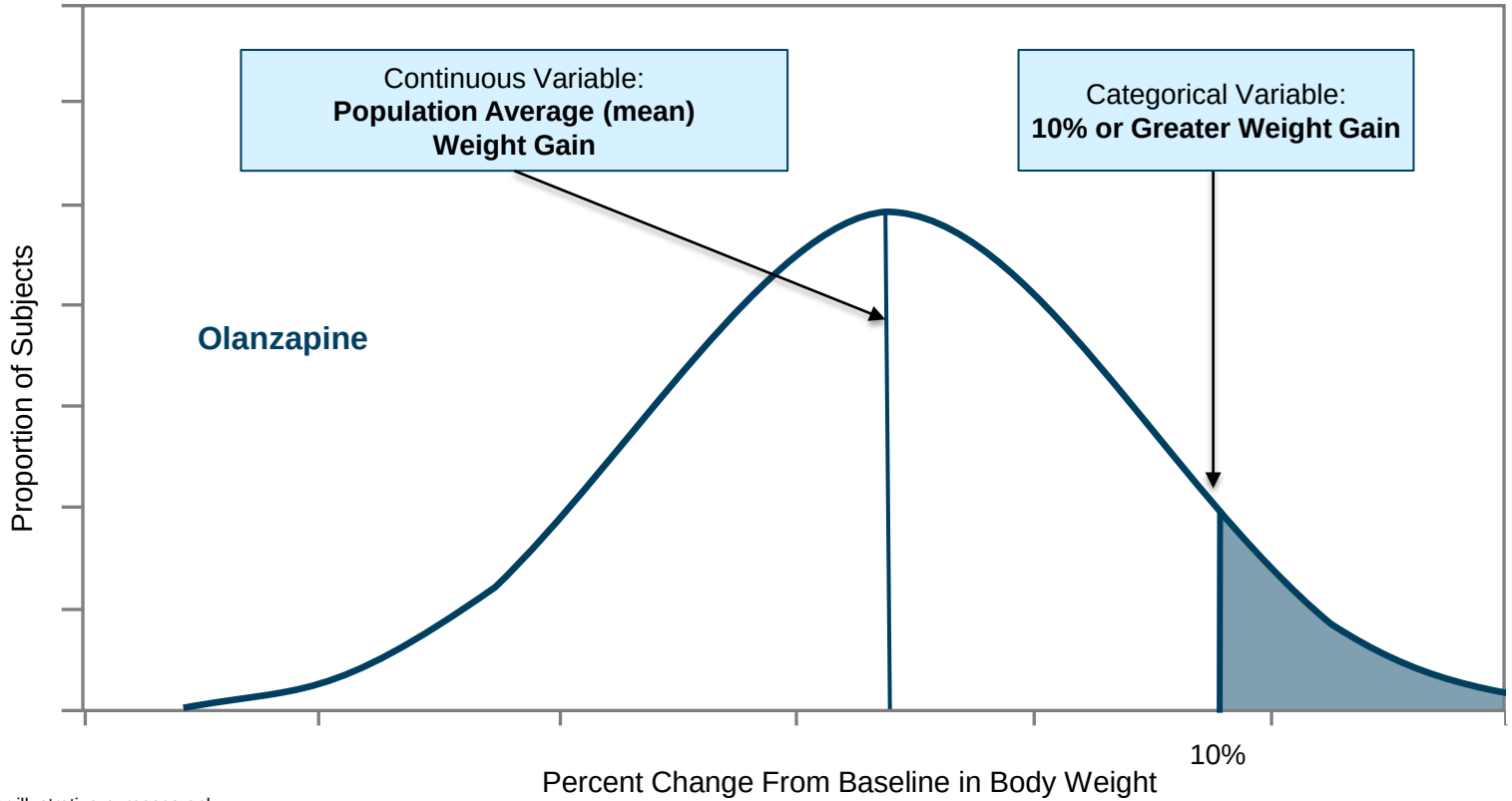
ENLIGHTEN-2 Weight Study

- 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

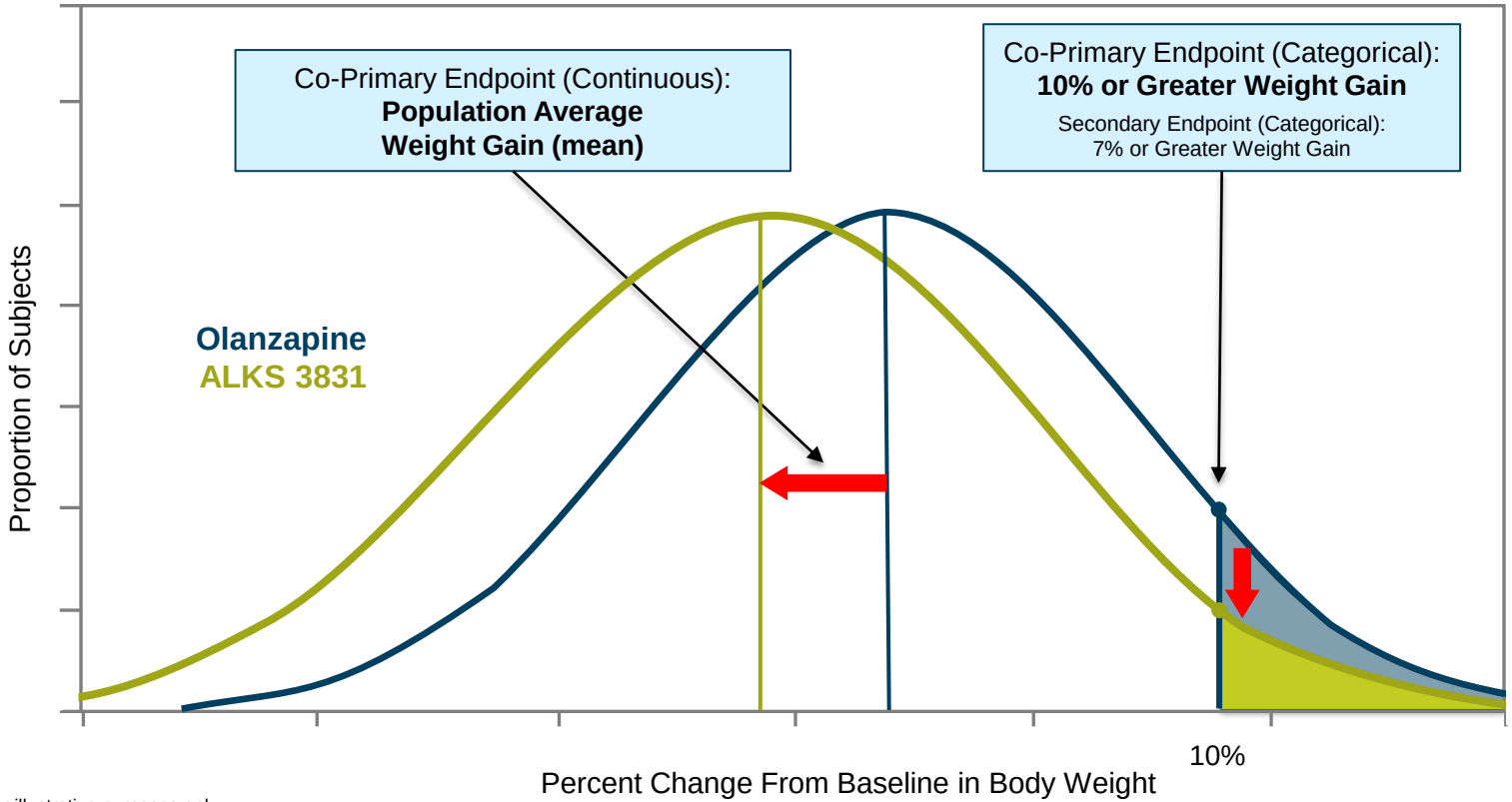
PANSS = Positive And Negative Syndrome Scale

ENLIGHTEN-2: Designed to Evaluate Weight Distribution



For illustrative purposes only

ENLIGHTEN-2: Primary Analysis Captures Shift in Two Dimensions



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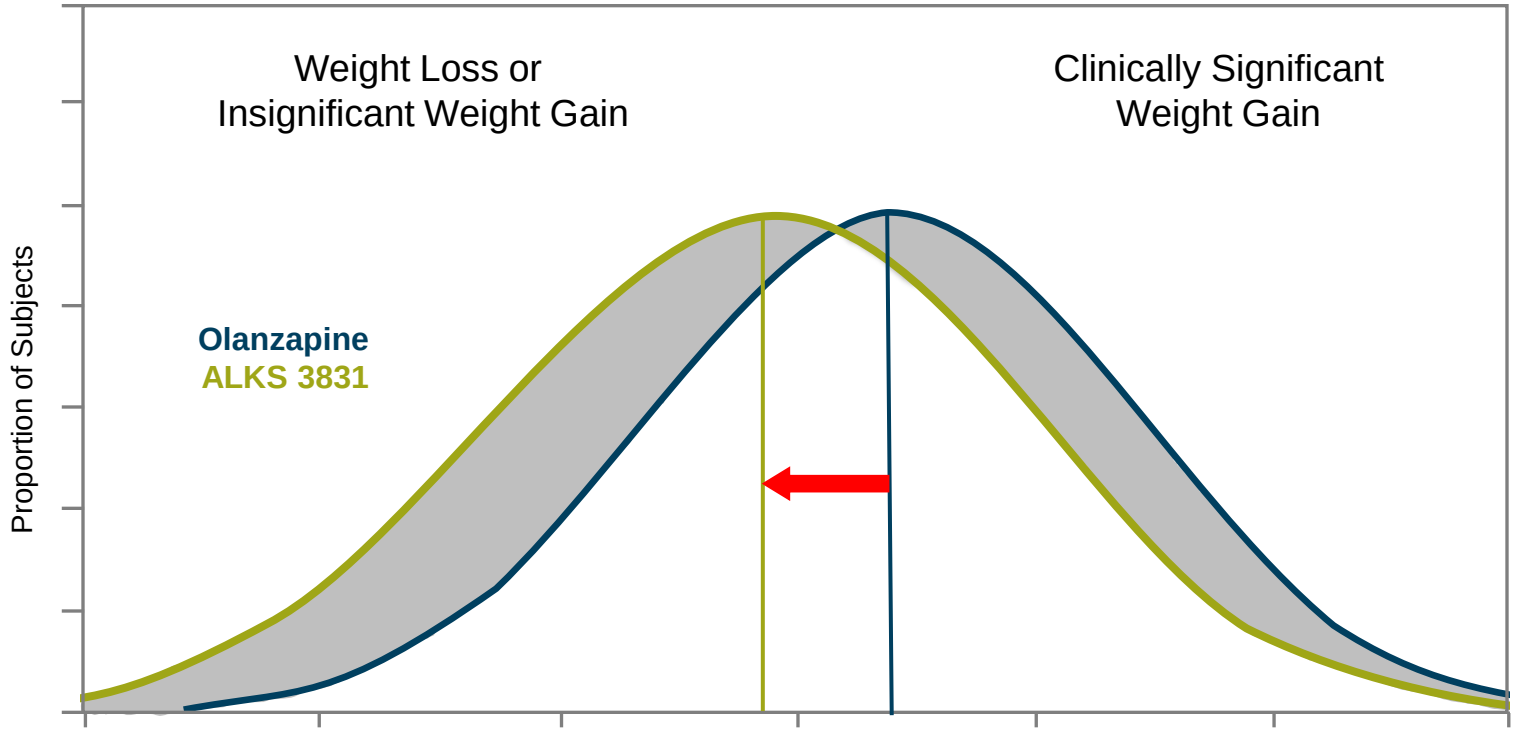
ENLIGHTEN-2: Shift in Mean Has Beneficial Weight Implications for Entire Study Population



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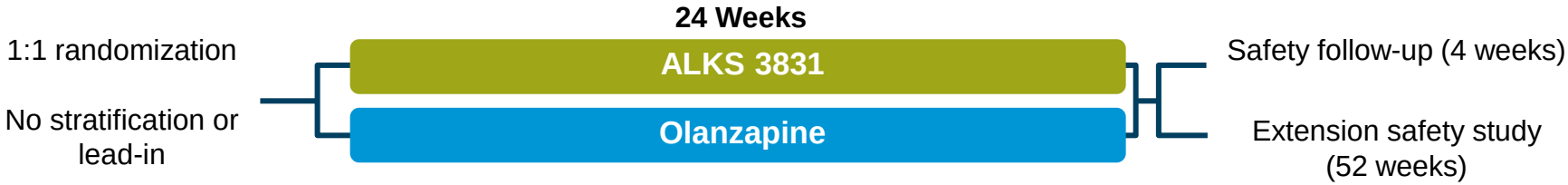
ENLIGHTEN-2:
Study Design and Baseline Characteristics

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/m^2
- 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)

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ENLIGHTEN-2: Baseline Characteristics and Subject Disposition

Baseline Characteristics†	ALKS 3831 N=274	Olanzapine N=276	All Subjects N=550
Age (years)			
Mean (SD)	40.3 (9.79)	40.1 (10.01)	40.2 (9.90)
Gender, n (%)			
Male	193 (70.4)	207 (75.0)	400 (72.7)
Race, n (%)			
Black or African American	199 (72.6)	193 (69.9)	392 (71.3)
White	63 (23.0)	65 (23.6)	128 (23.3)
Body Mass Index (kg/m^2)			
Mean (SD)	25.38 (3.13)	25.52 (3.19)	25.45 (3.16)
Subject Disposition	**ALKS 3831**	**Olanzapine**	**All Subjects**
Randomized, n	280	281	561
Efficacy Population, n	266	272	538
Completed, n (%)	176 (64.2)	176 (63.8)	352 (64.0)

†Baseline characteristics and completion rates for safety population; includes all randomized subjects who receive at least one dose of study drug

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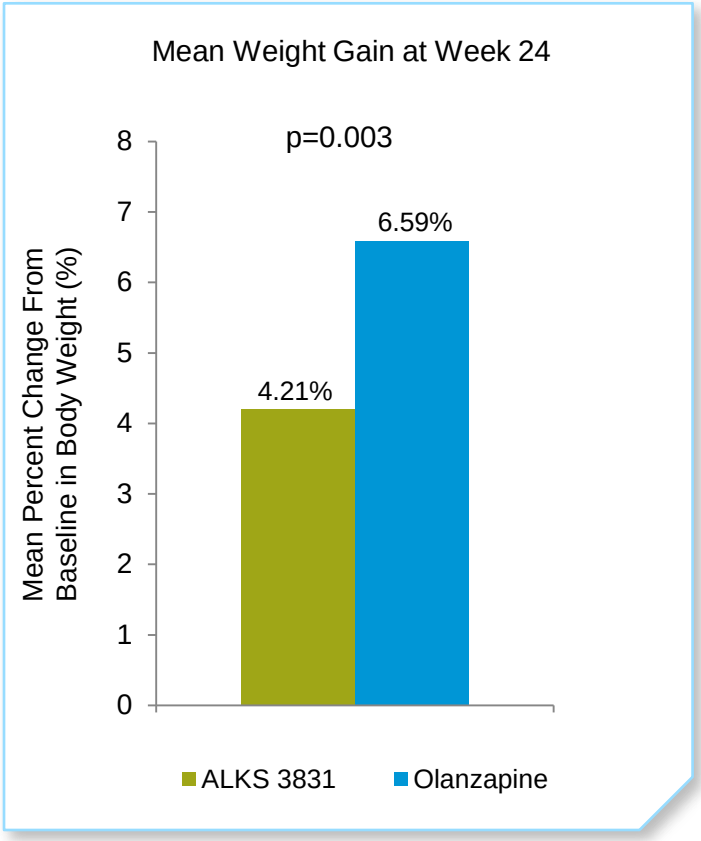
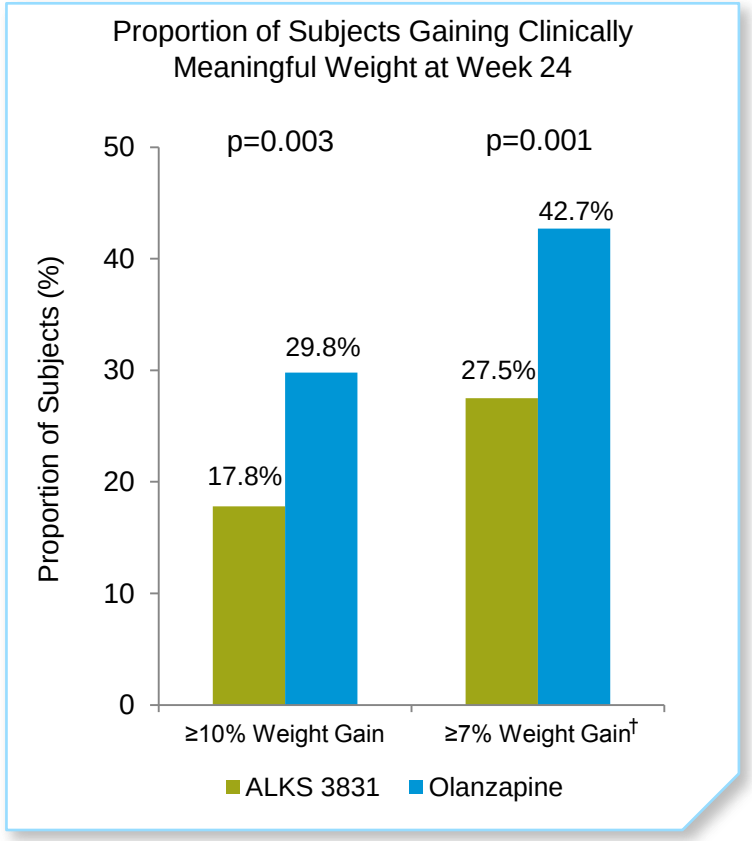
ENLIGHTEN-2: Weight Results

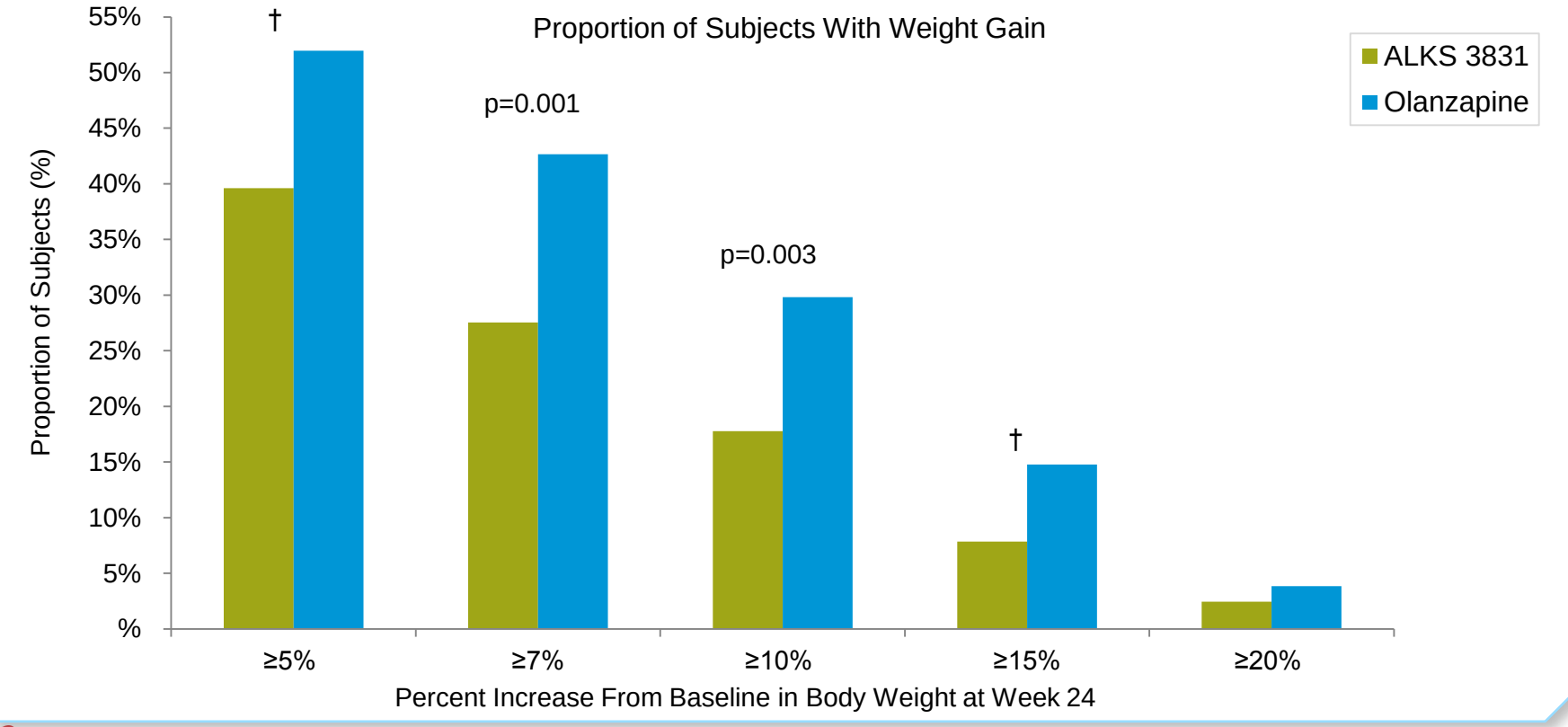
ENLIGHTEN-2: Achieved Prespecified Co-Primary and Key Secondary Endpoints





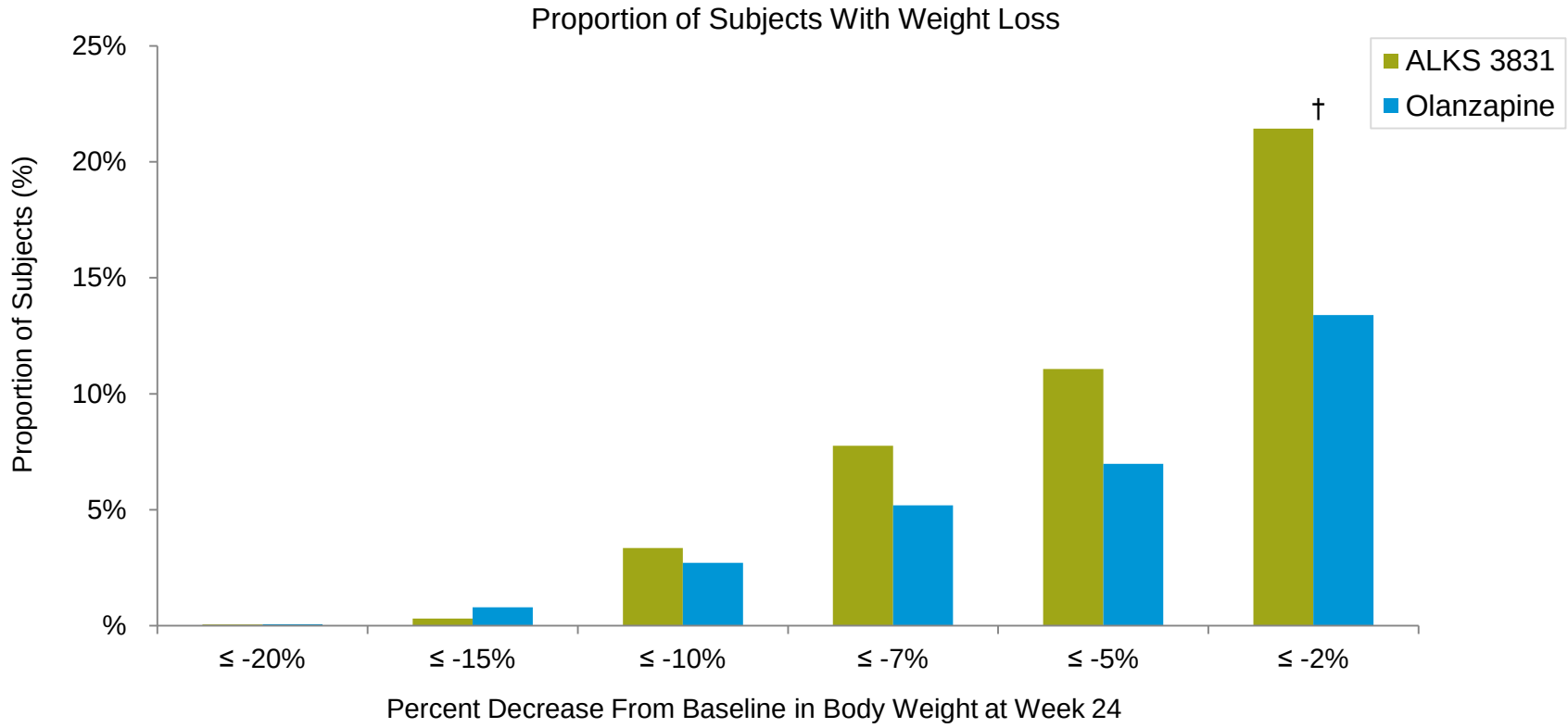
†Prespecified key secondary endpoint

ENLIGHTEN-2: Fewer Patients on ALKS 3831 Gained Clinically Meaningful Weight Compared to Olanzapine



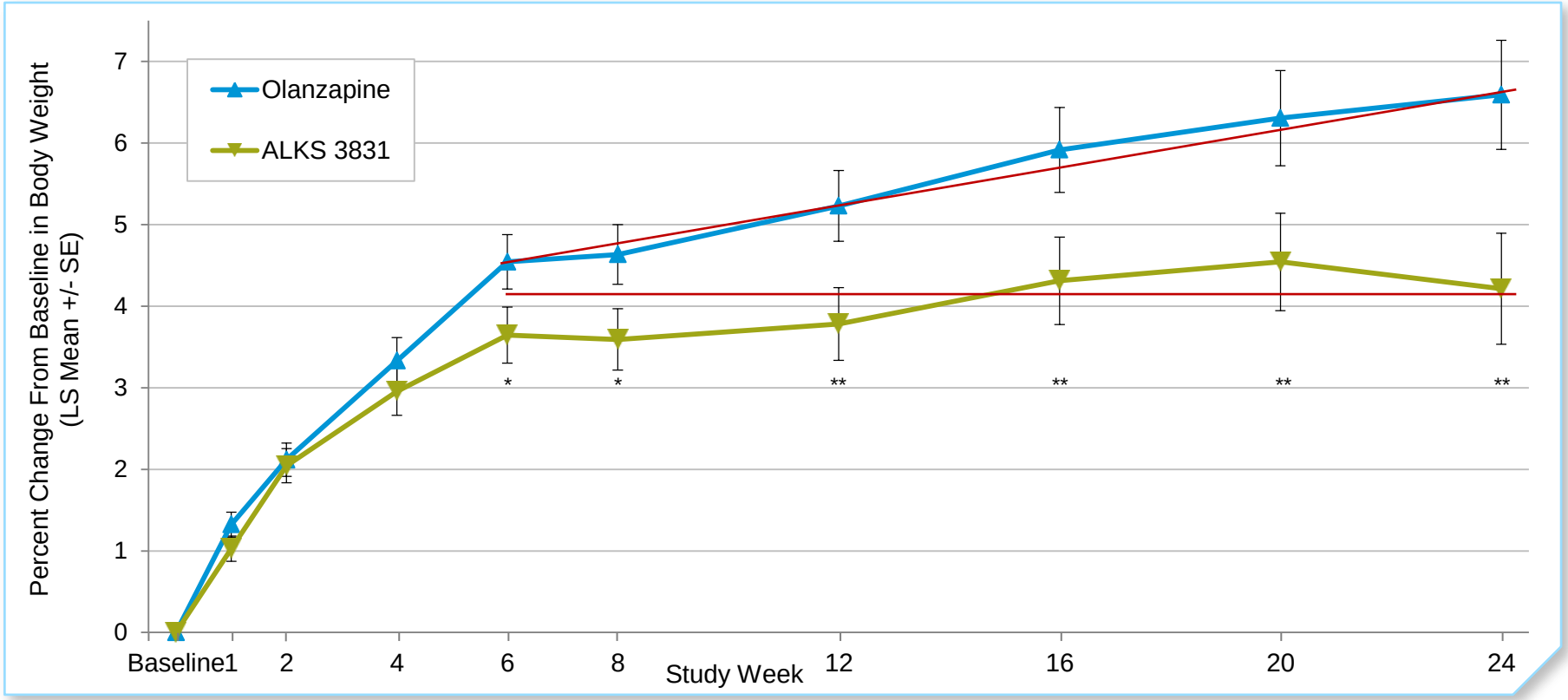
†p<0.05 based on post hoc analysis

ENLIGHTEN-2: More Patients on ALKS 3831 Lost Weight Compared to Olanzapine



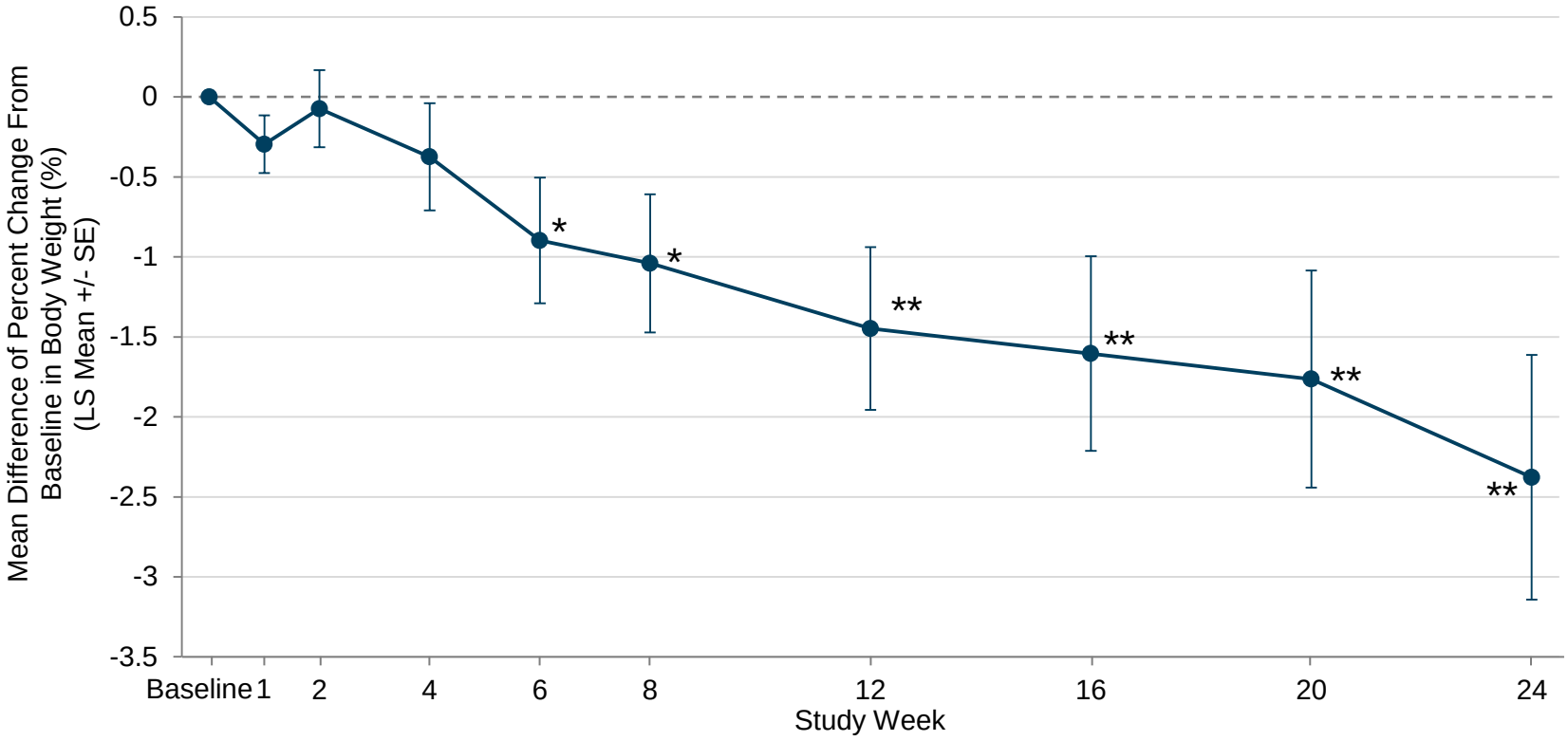
†p<0.05 based on post hoc analysis

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

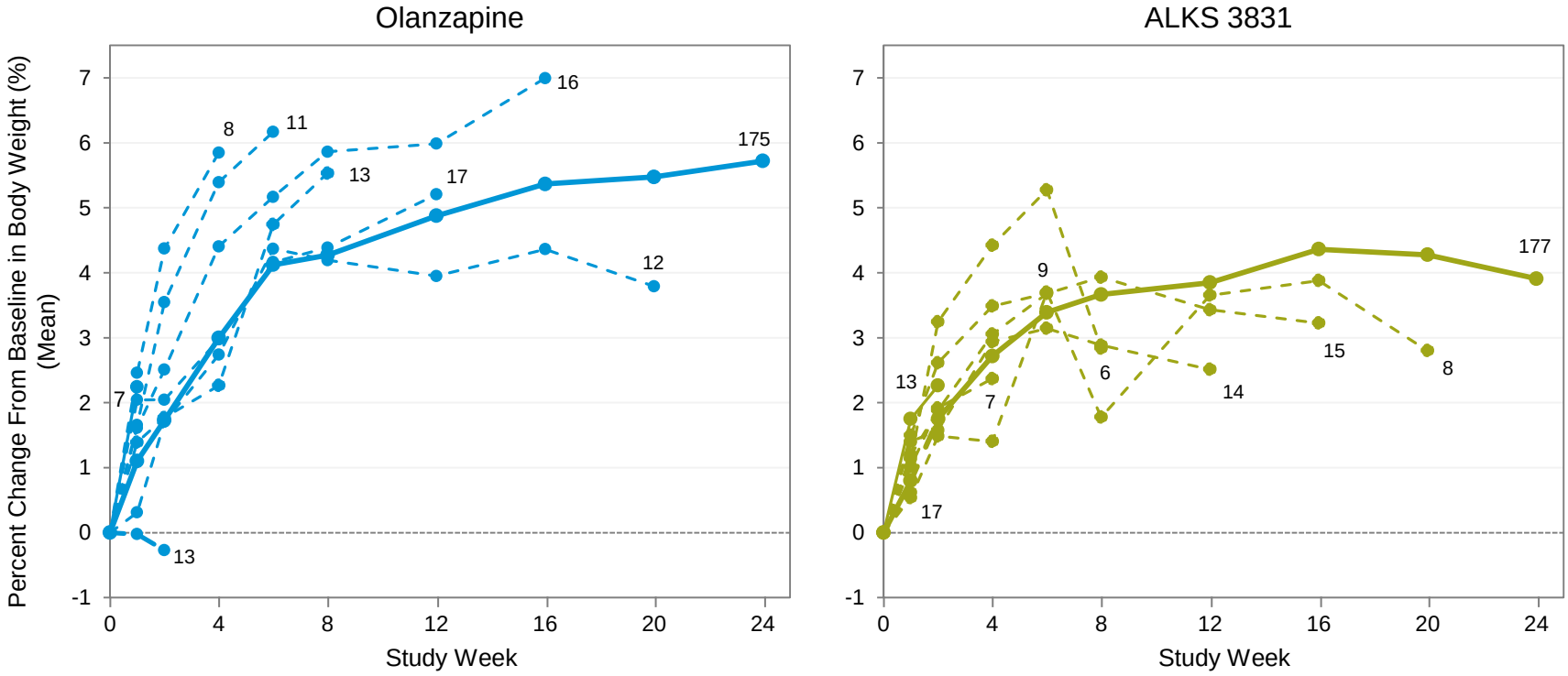


Note: Difference in weight change based on ANCOVA approach using MI for missing data.
*p<0.05 vs. olanzapine; **p<0.01 vs. olanzapine

ENLIGHTEN-2: Weight Gain Trajectory of Early Discontinuations

Percent Change From Baseline in Body Weight by Treatment

Completers vs. Premature Discontinuations



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

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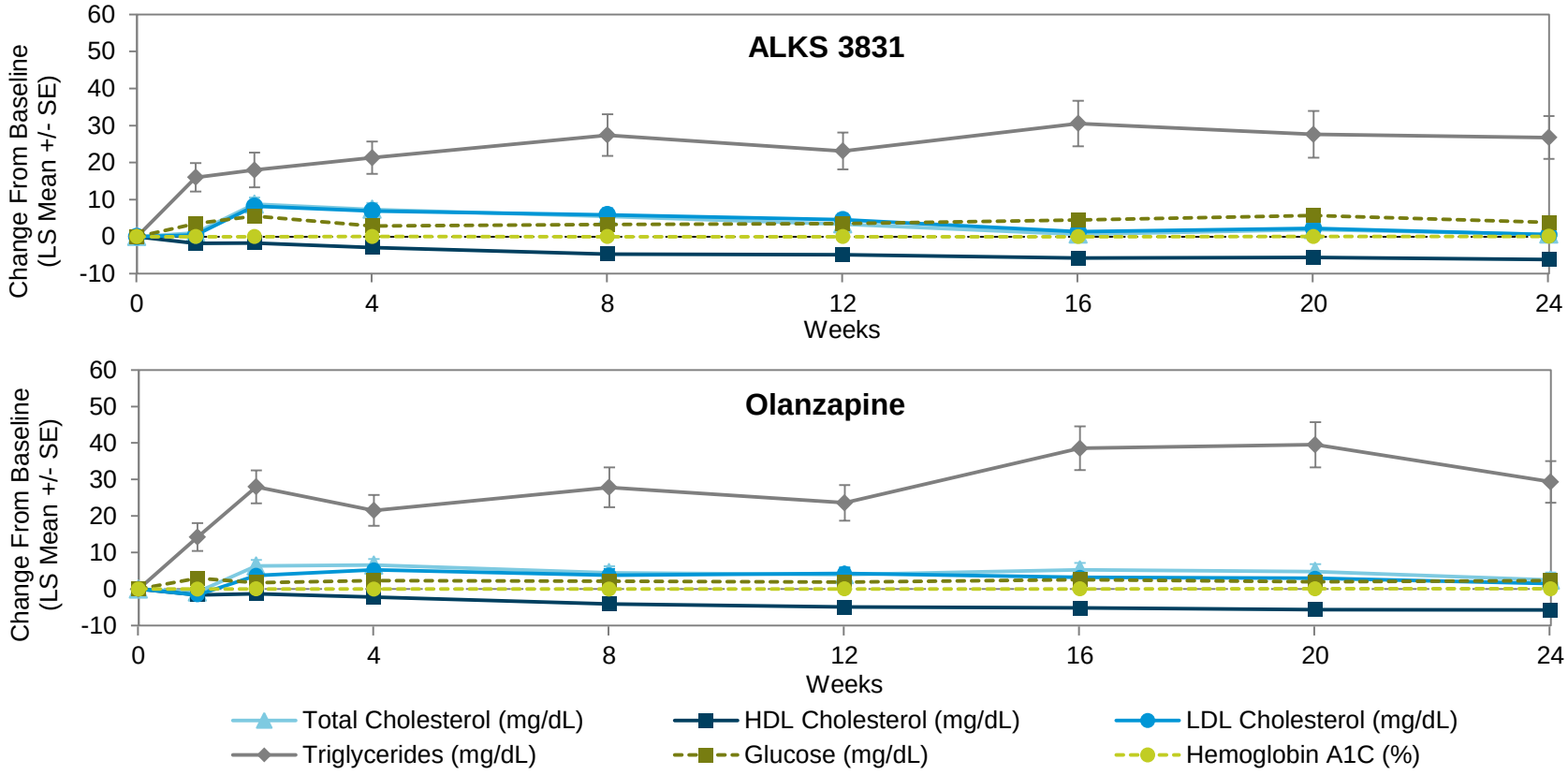
ENLIGHTEN-2: Metabolic Results

ENLIGHTEN-2 Metabolic Parameters: Changes Were Generally Small for Both ALKS 3831 and Olanzapine



Weight Gain Distribution Matters: Central Fat Accumulation Carries Significant Risk for Developing Metabolic Complications

Abdominal Obesity Correlated With Metabolic Syndrome[1]

Waist Circumference as Compared with Body-Mass Index in Predicting Mortality from Specific Causes

Michael F. Leitzmann[1,2*], Steven C. Moore[1], Annemarie Koster[3,4], Tamara B. Harris[3], Yikyung Park[1], Albert Hollenbeck[5], Arthur Schatzkin[1]

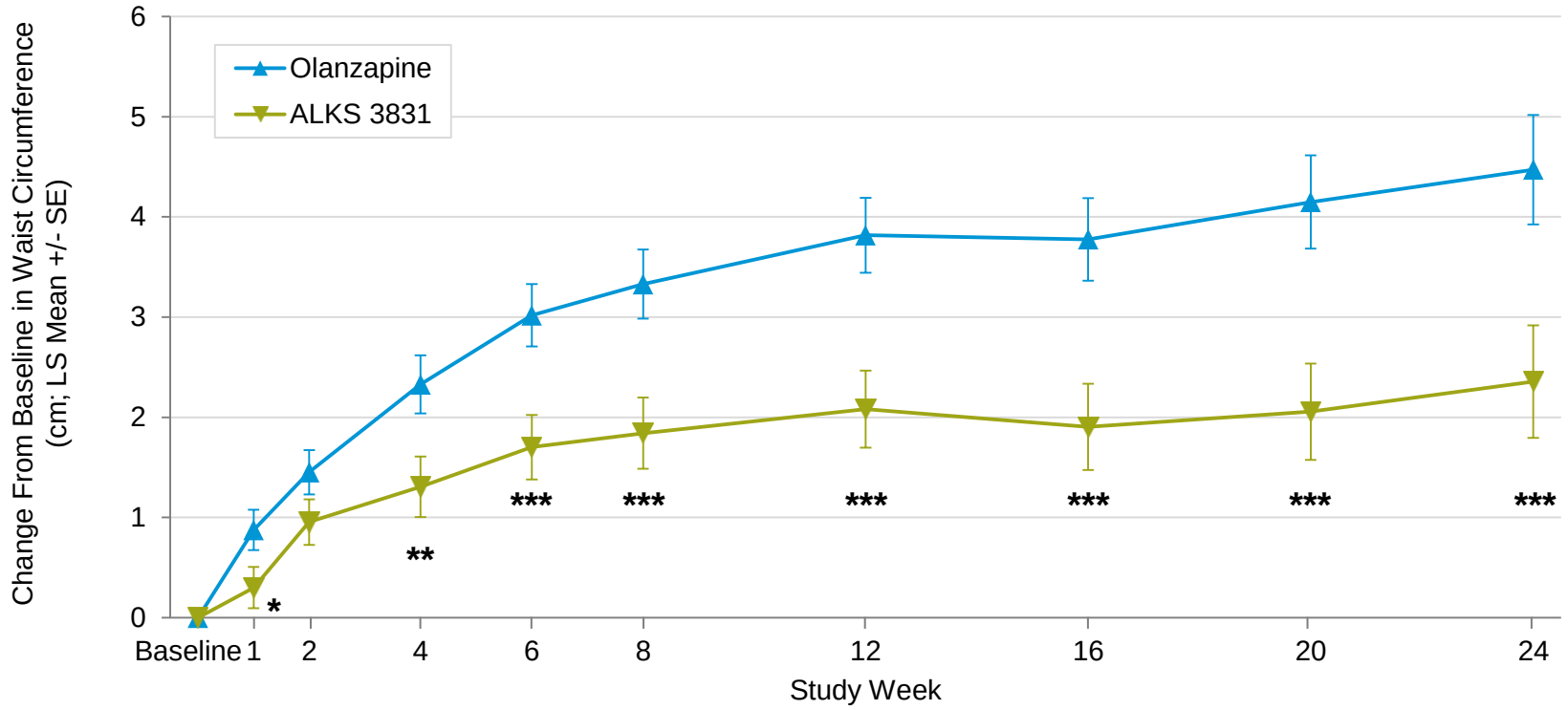
1 Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, Maryland, United States of America, **2** Department of Epidemiology and Preventive Medicine, Regensburg University Medical Center, Regensburg, Germany, **3** Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute on Aging, National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, Maryland, United States of America, **4** Department of Internal Medicine, School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, The Netherlands, **5** AARP, Washington, D.C., United States of America

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[2]

Conclusions: Increased abdominal fat measured by WC was related to a higher risk of deaths from major specific causes, including deaths from lung cancer and chronic respiratory disease, independent of BMI.

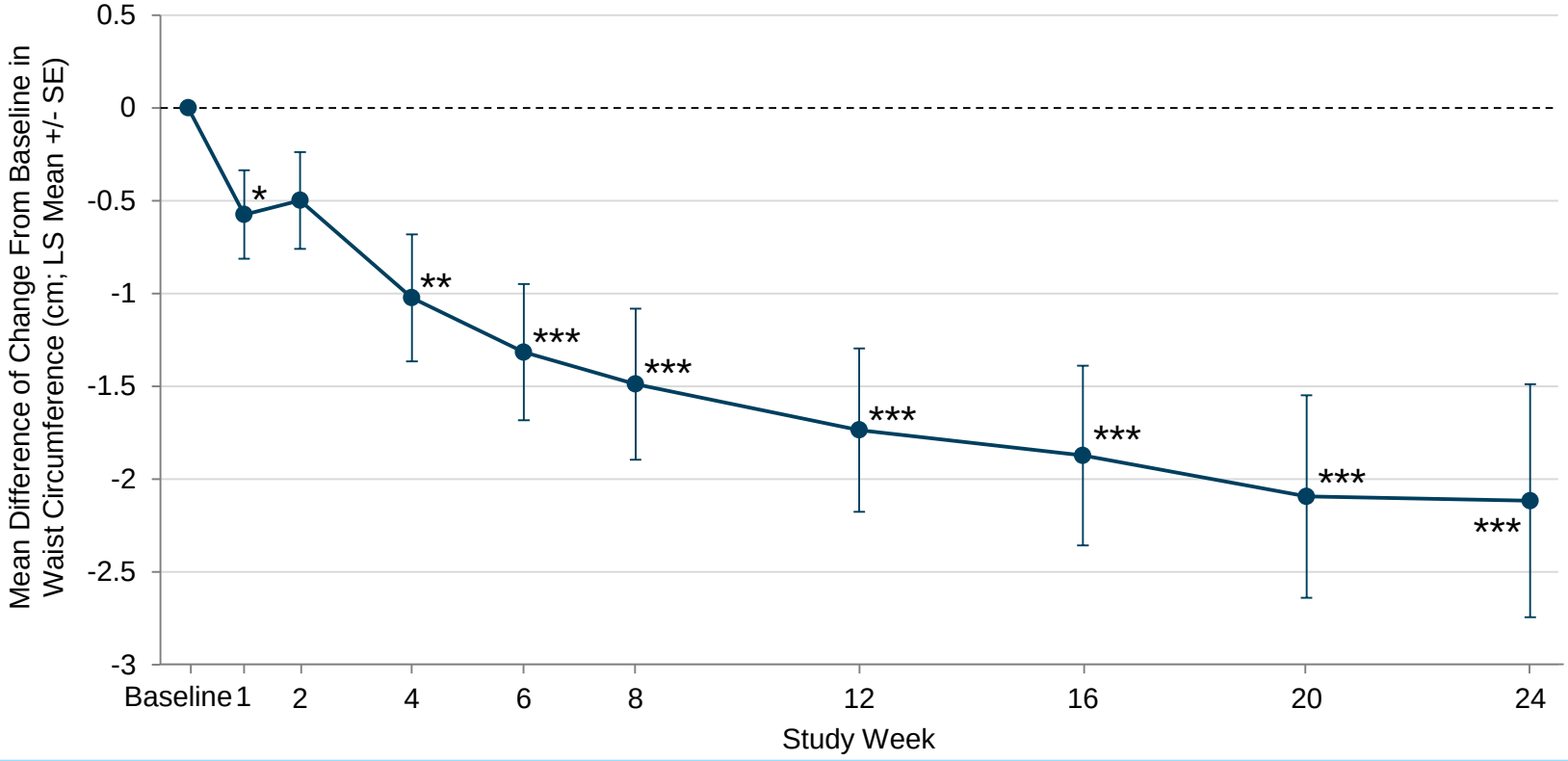
[1]Richie et al. *Nutr Metab Cardiovasc Dis*. 2007;17(4):319-26
[2]Leitzmann et al. *PLoS ONE*, 2011; 6(4): e18582

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

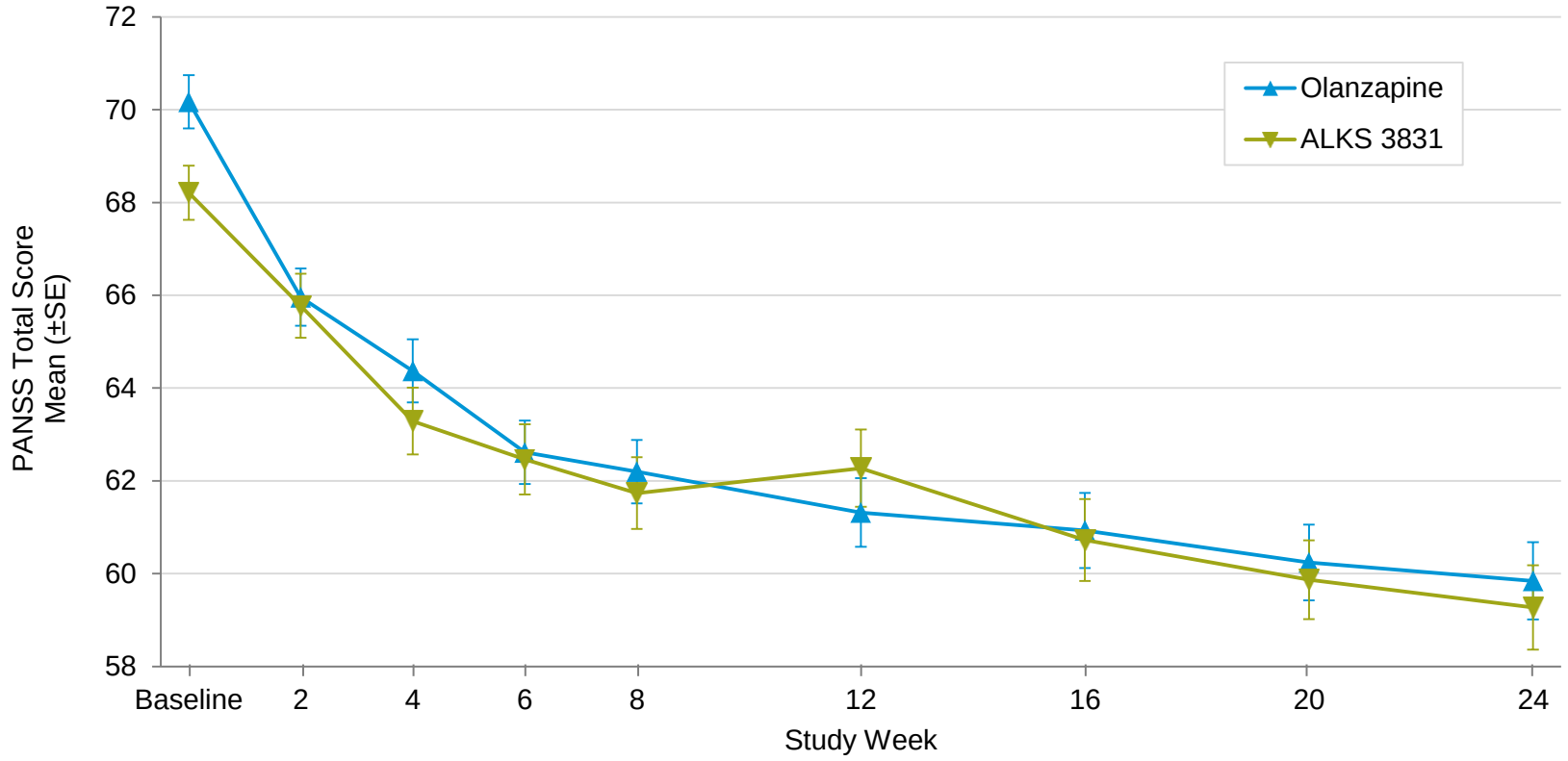
Summary Takeaways: ENLIGHTEN-2 Metabolic

- 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



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ENLIGHTEN-2: Most Common Adverse Events

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

- 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

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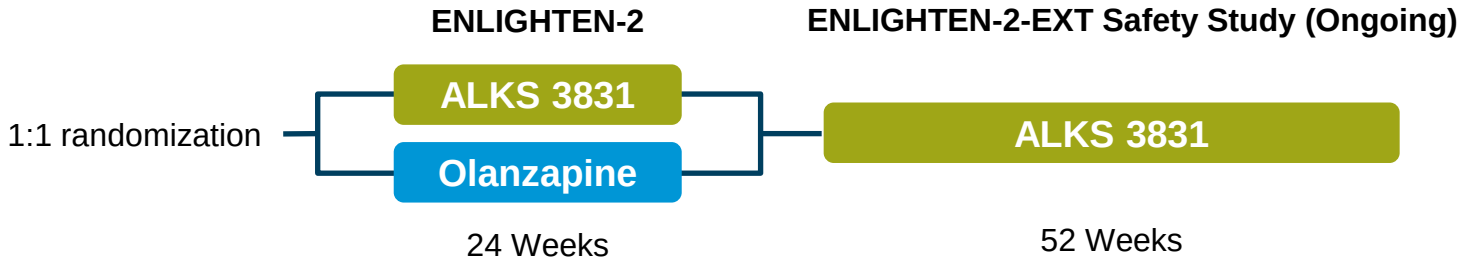
ENLIGHTEN-2-EXT: 52-Week, Open-Label Safety Study

Interim Results

ENLIGHTEN-2-EXT: Long-Term Safety Study Design



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

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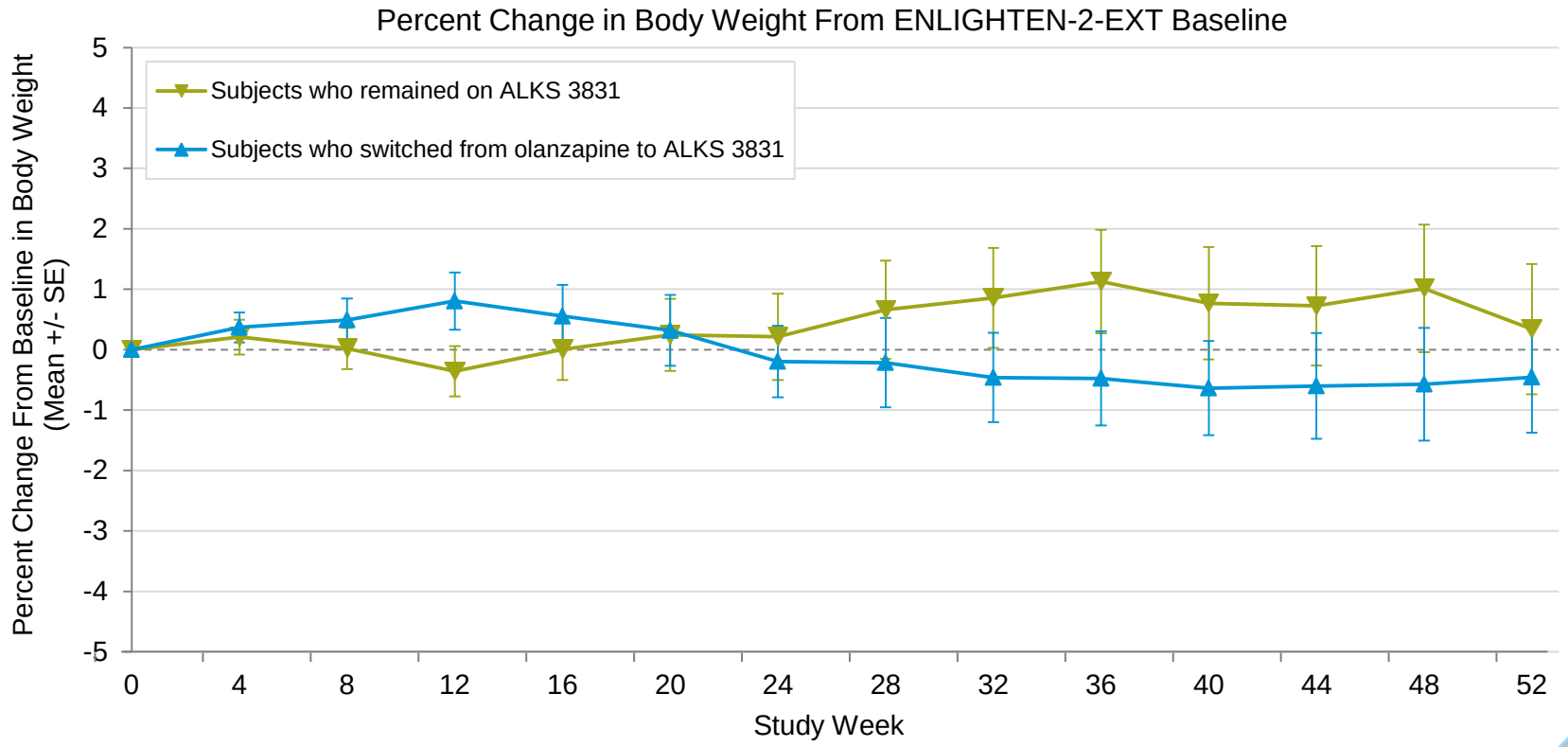
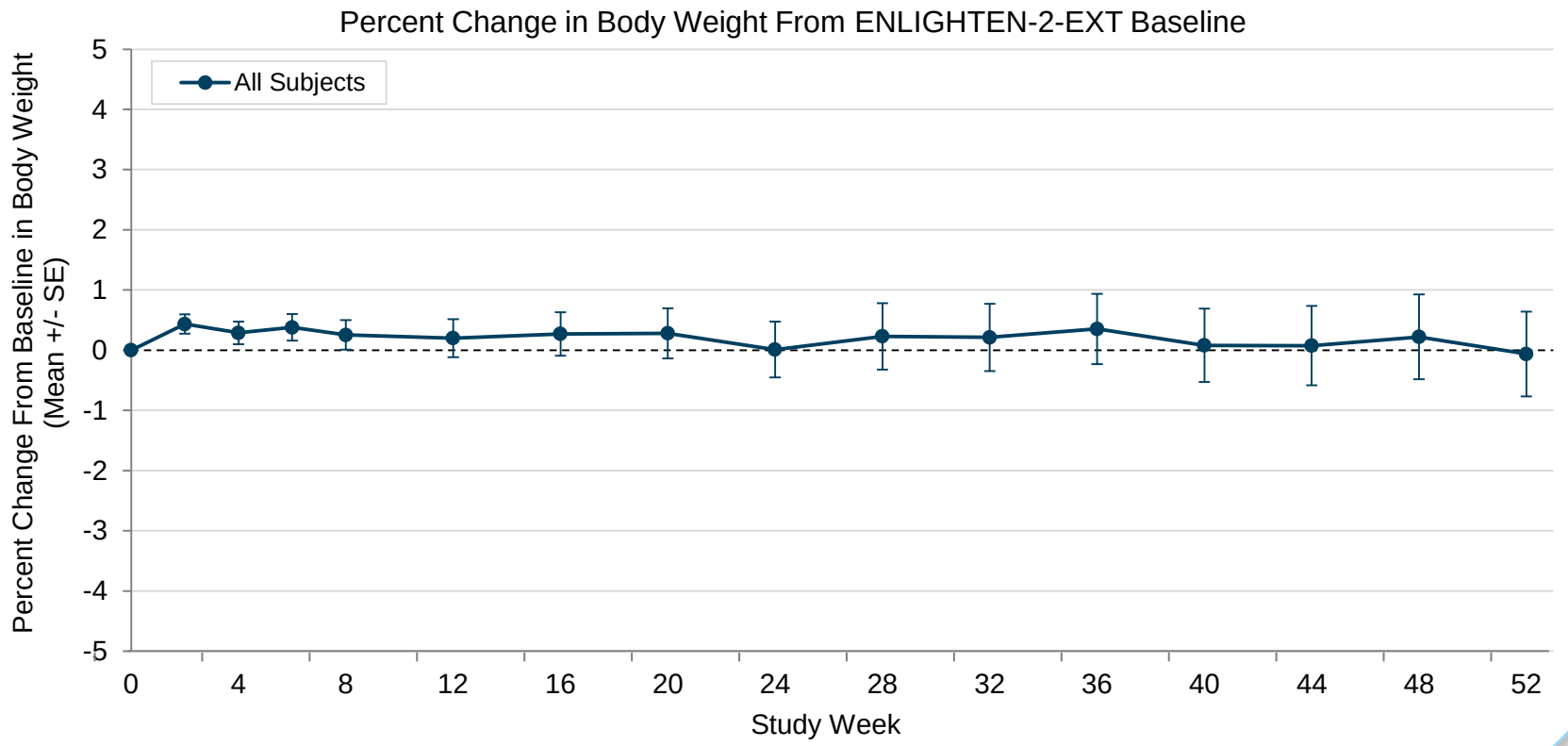
ENLIGHTEN-2-EXT: Interim Weight Results

ENLIGHTEN-2-EXT Interim Results: Weight Remains Stable Over 52 Weeks

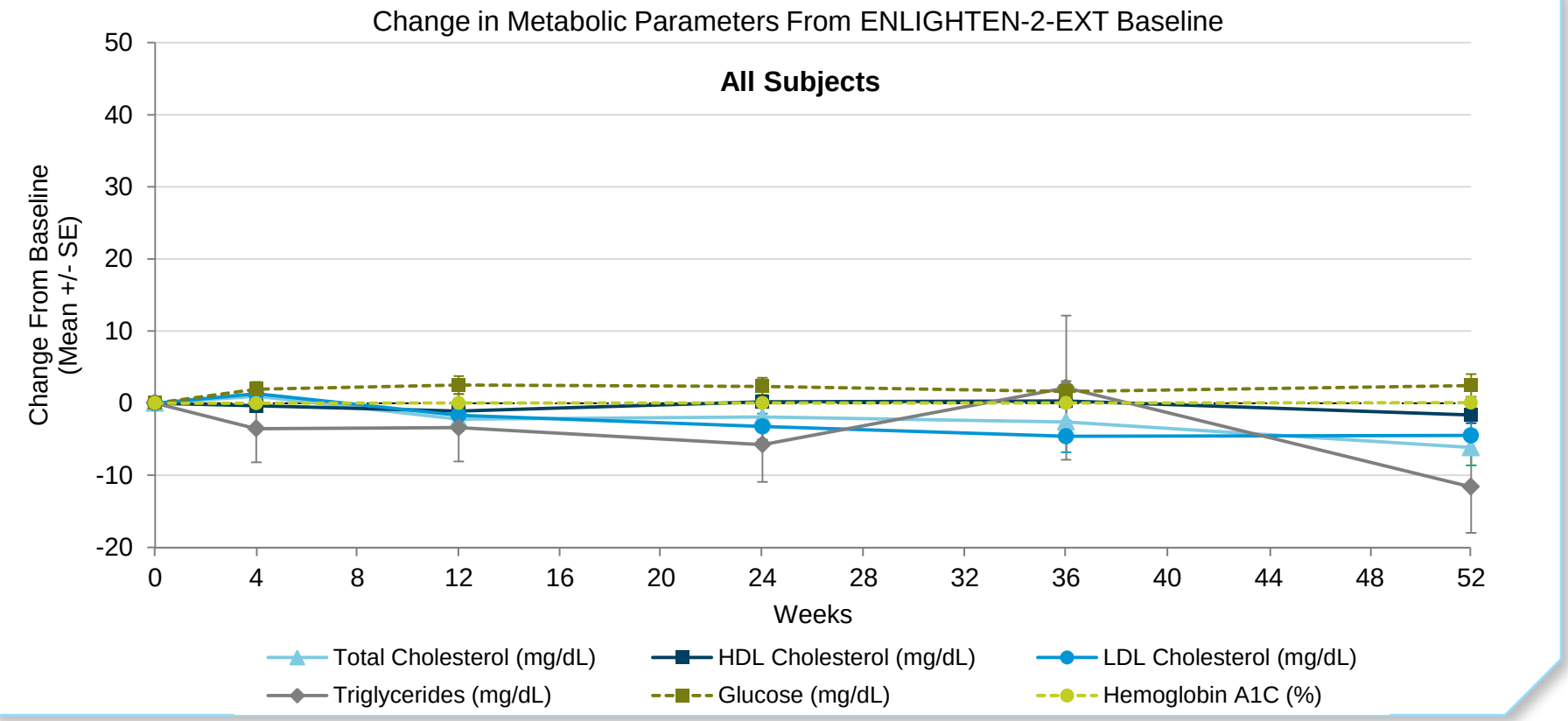


ENLIGHTEN-2-EXT Interim Results: Weight Remains Stable Over 52 Weeks

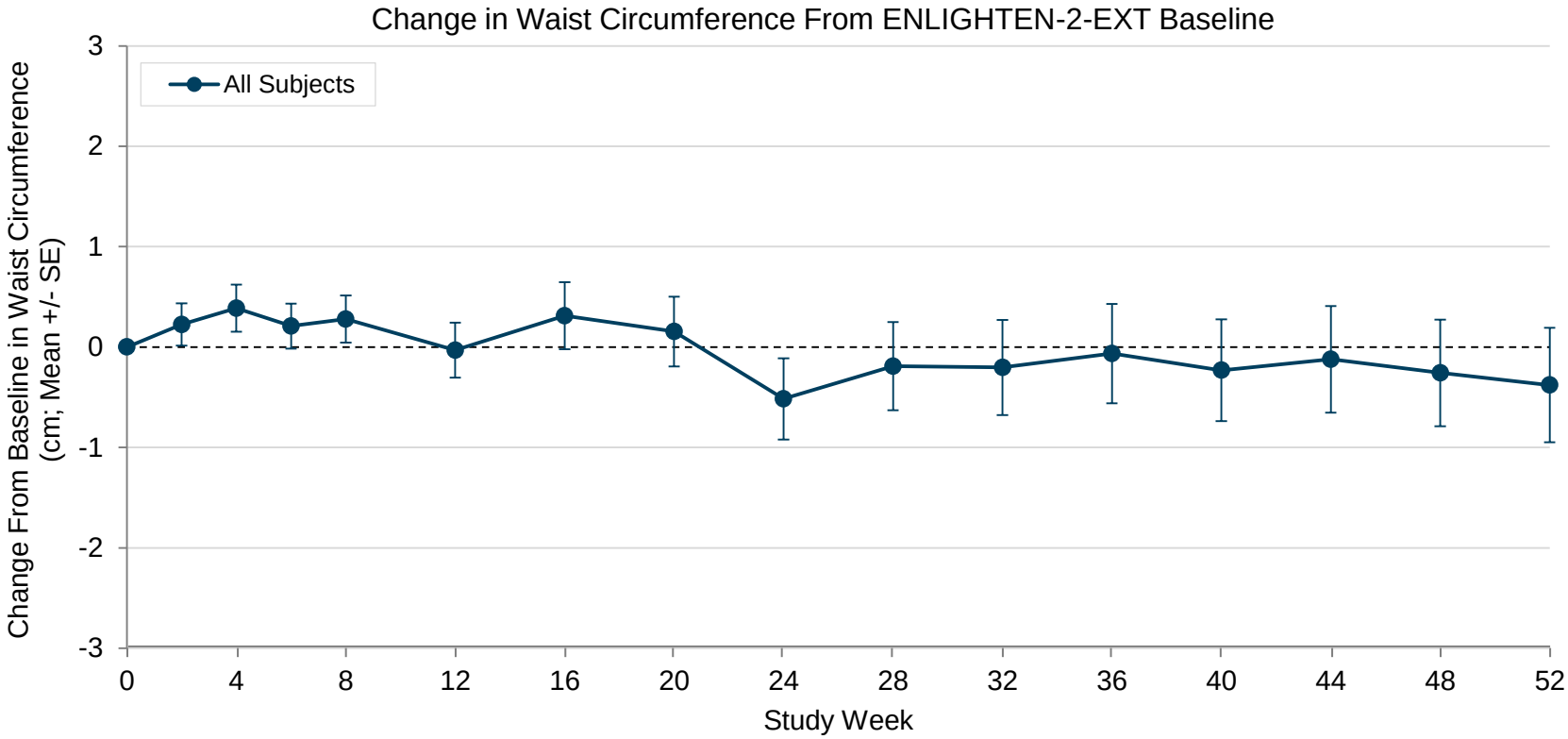


ENLIGHTEN-2-EXT: Interim Metabolic Results

ENLIGHTEN-2-EXT Interim Results: Metabolic Parameters Remained Stable

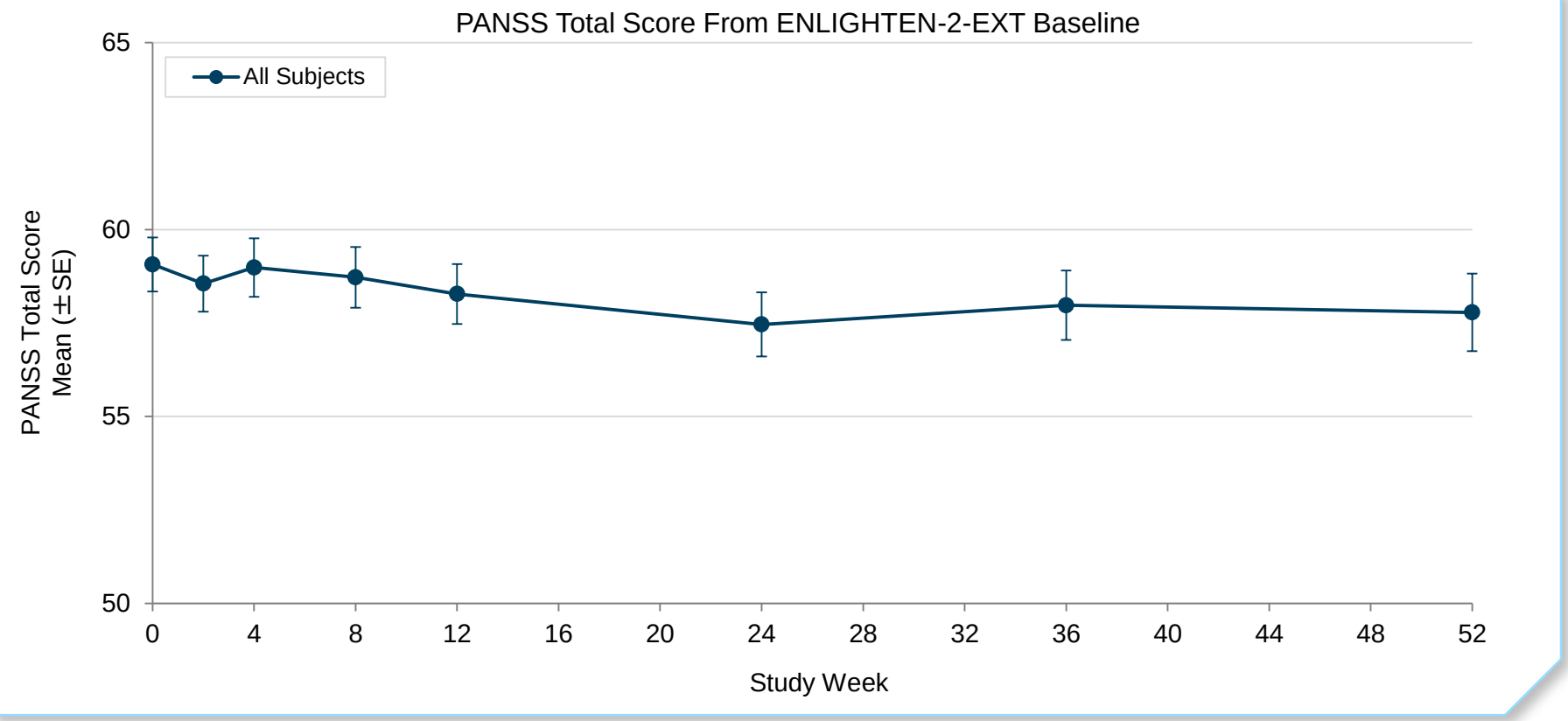


ENLIGHTEN-2-EXT Interim Results: Waist Circumference Remained Stable Over 52 Weeks



ENLIGHTEN-2-EXT Interim Results: Antipsychotic Efficacy

ENLIGHTEN-2-EXT Interim Results: Sustained and Durable Antipsychotic Efficacy



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

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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

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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

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