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Olanzapine/Samidorphan Combination (OLZ/SAM) for Patients With Schizophrenia or Bipolar I Disorder

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APA Members

Financial Relationship Disclosure

Dr. Correll:

Consultant and/or advisor for or has received honoraria from:

- AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, Intra-Cellular Therapies, Jamjoom Pharma, Janssen/Johnson & Johnson, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedinCell, Merck, MindPax, Mitsubishi Tanabe Pharma, Mylan, Neurelis, Neurocrine, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viartis;
- has provided expert testimony for Janssen and Otsuka; has served on a data safety monitoring board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva;
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Dr. Cutler:

Consultant, Advisory Board:

- AbbVie, Acadia, Actinogen, Alfasigma, Alkermes, Anavex Life Sciences, Arrivo BioVentures, Autobahn Therapeutics, Axsome, Aytu Biopharma, BioXcel, Boehringer Ingelheim, Bristol Myers Squibb, Collegium Pharmaceutical, Corium, Definium Therapeutics, 4M Therapeutics, Helus Pharma, Incannex Healthcare, Helus Pharma, Incannex Healthcare, Intra-Cellular Therapies, J&J Innovative Medicine, Jazz Pharma, Knight Therapeutics, Kye Pharmaceuticals, Kuvatris Therapeutics, LivaNova, Lundbeck, Luye Pharma, MapLight Therapeutics, Mentavi, Neumora, Neurocrine Biosciences, NeuroSigma, Noven, Otsuka, Relmada, Sensorium Therapeutics, Sirtsei Pharmaceuticals, Supernus, Teva, Thynk, Transneural Therapeutics, Tris Pharma, Vanda Pharmaceuticals, and Vistagen

Speaker Bureau:

- AbbVie, Alfasigma, Alkermes, Axsome, Aytu Biopharma, Boehringer Ingelheim, Bristol Myers Squibb, Collegium Pharmaceutical, Corium, Intra-Cellular Therapies, J&J Innovative Medicine, Knight Therapeutics, Kye Pharmaceuticals, Lundbeck, Luye Pharma, Neurocrine Biosciences, Noven, Otsuka, Supernus, Teva, Tris Pharma, and Vanda Pharmaceuticals
- Data Safety Monitoring Board: Compass Pathways
- Stock options/equity: EMA Wellness, Evolution Research Group, 4M Therapeutics, Sensorium Therapeutics, Transneural Therapeutics

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What Could It Take to Change the Treatment Paradigm?

Expanding the Impact of OLZ/SAM

Evidence for Regulatory Approval

Treats Acute Exacerbations

Maintains Symptom Control

Reduces Acute Weight Gain

Established Safety Profile

Extending the Clinical Evidence Base

Reduces Negative Symptoms

Maintains Long-term Symptom Control

Minimal Long-term Weight Gain and Metabolic Changes

Effectiveness in Early-in-Illness Patients

Real-World Evidence

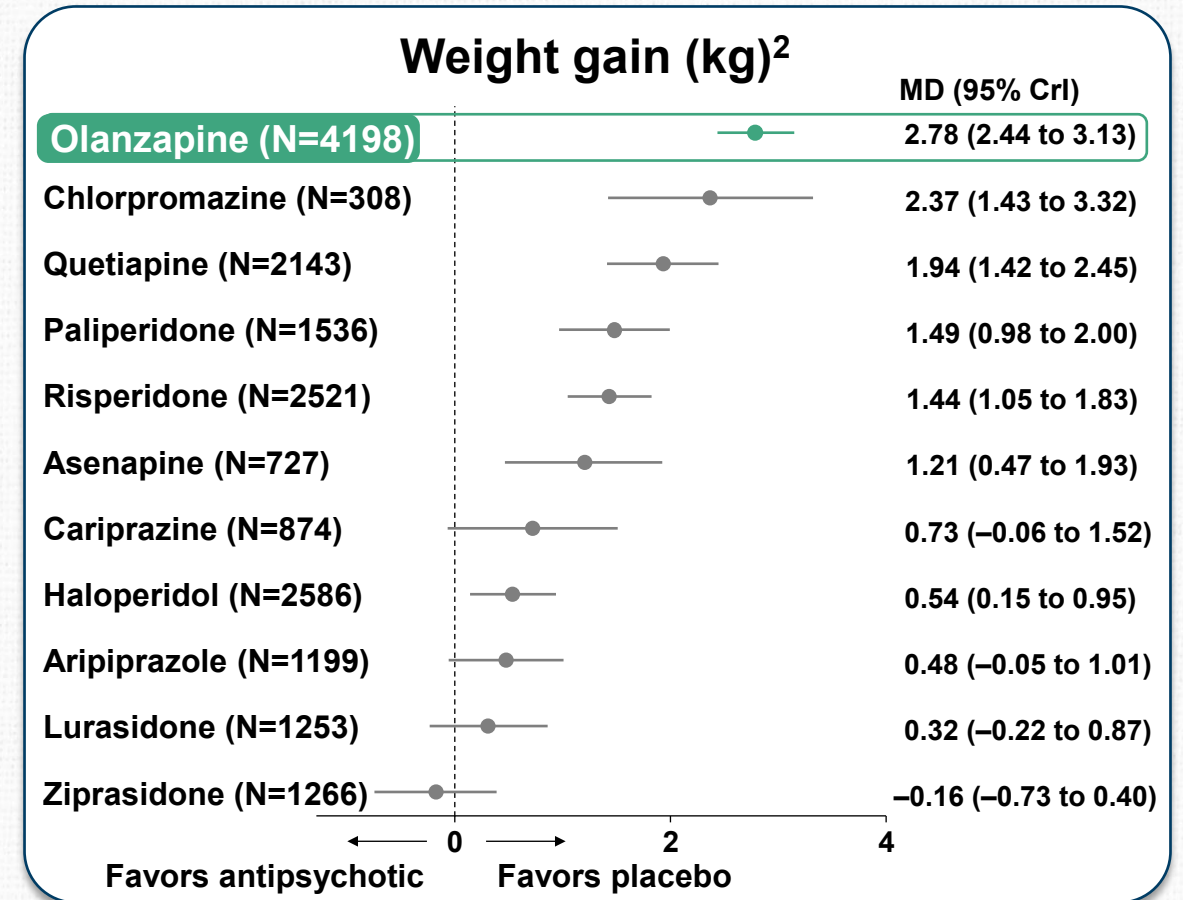
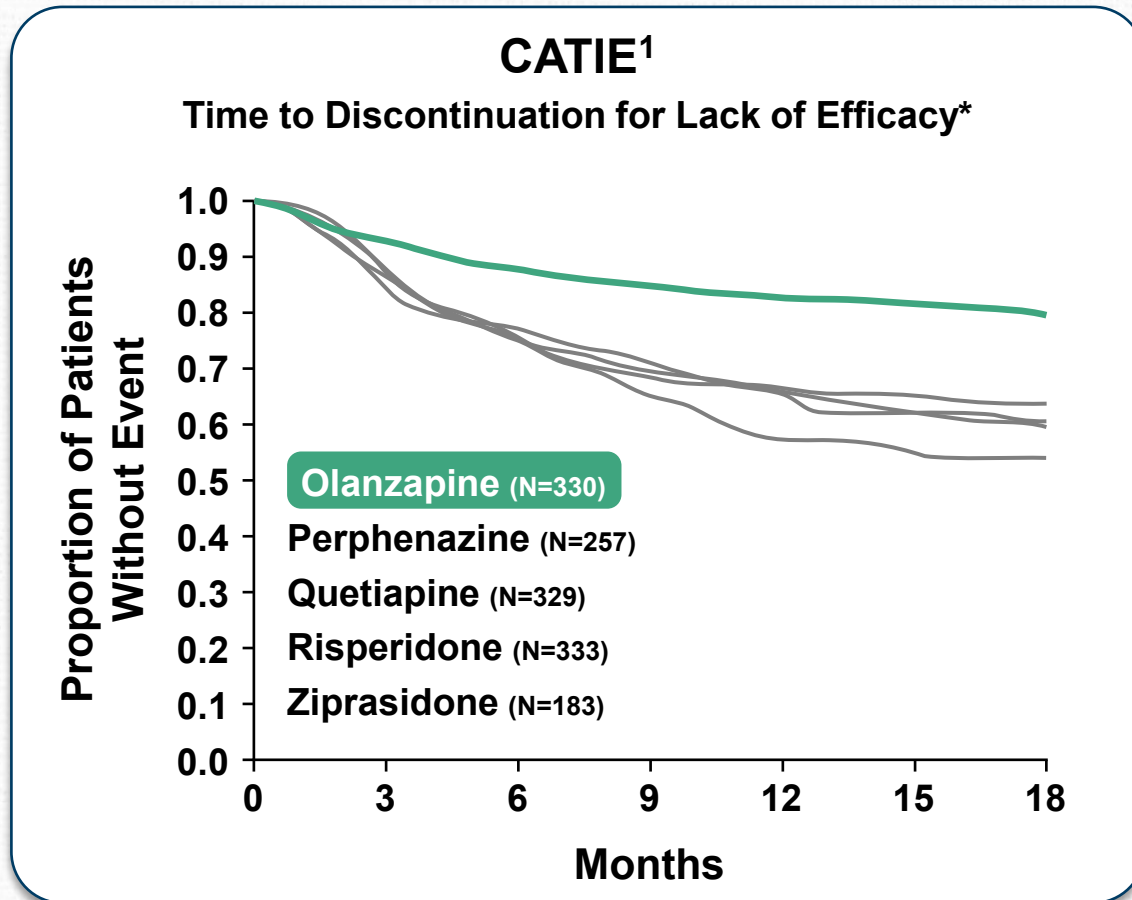
Reduced Risk of Relapse

Better Treatment Adherence

Better Treatment Persistence

Greater Effectiveness in Young Adults

Olanzapine Is Among the Most Effective Antipsychotics But Is Associated With Significant Weight Gain

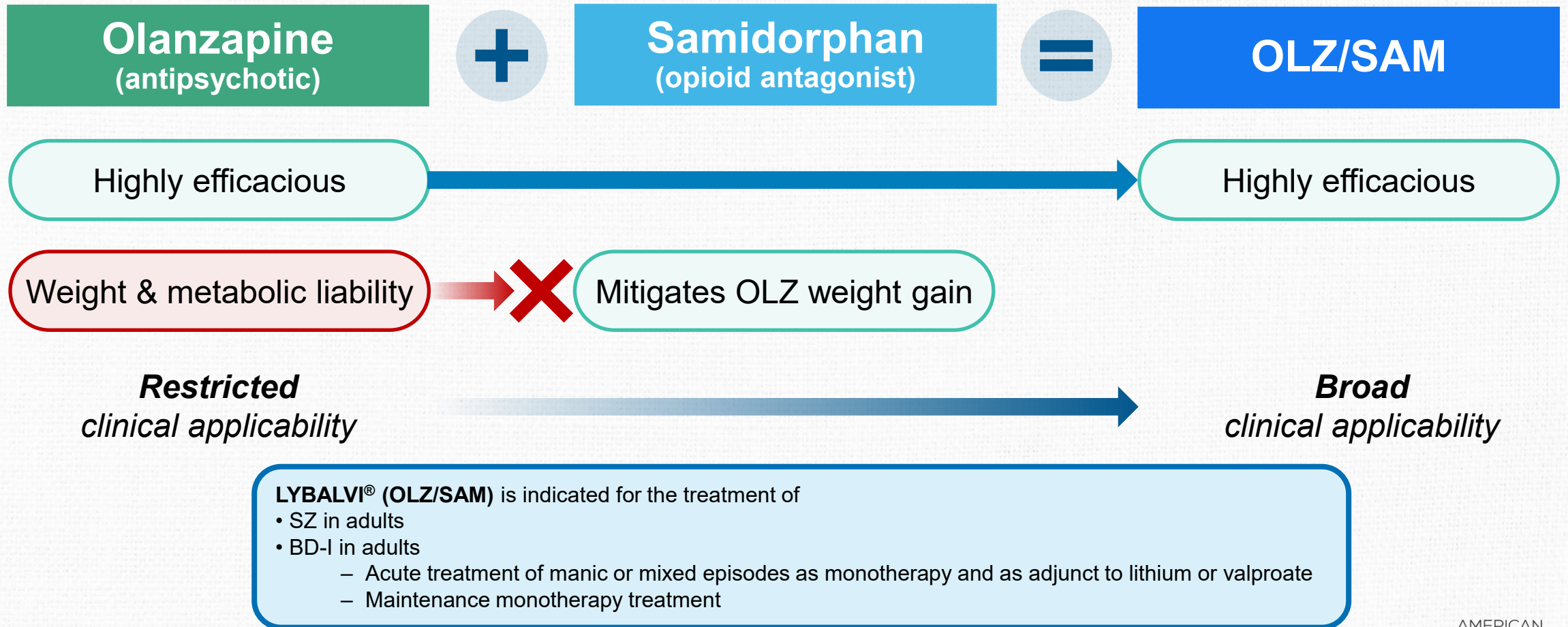


* $P < 0.001$ for olanzapine vs quetiapine, risperidone, and perphenazine.

CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; CrI, credible interval; MD, mean difference.

1. Adapted from Lieberman JA, et al. *N Engl J Med.* 2005;353(12):1209-1223. 2. Adapted from Huhn M, et al. *Lancet.* 2019;394:939-951.

Olanzapine/Samidorphan (OLZ/SAM) Was Designed to Mitigate the Weight Gain and Long-term Metabolic Effects of Olanzapine



BD-I, bipolar I disorder; SZ, schizophrenia.

LYBALVI (olanzapine and samidorphan) tablets, for oral use (US prescribing information). Waltham, MA: Alkermes, Inc.

Expanding the Impact of OLZ/SAM

Evidence for Regulatory Approval



Treats Acute Exacerbations



Maintains Symptom Control

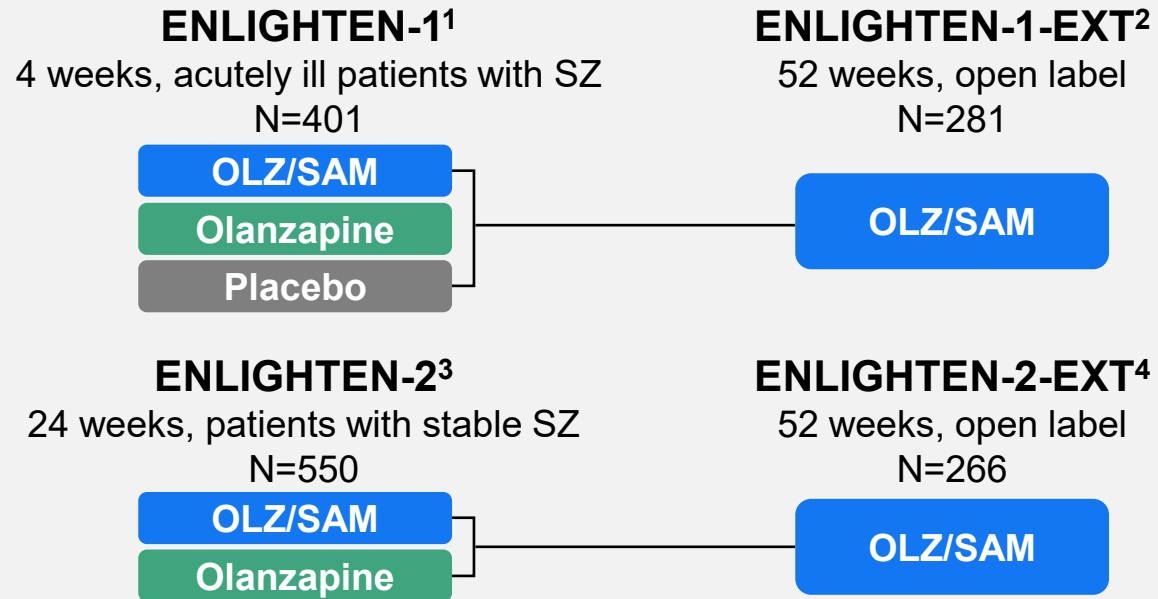


Reduces Acute Weight Gain



Established Safety Profile

Phase 3 Clinical Program*



*The efficacy of LYBALVI in the treatment of adult patients with bipolar I disorder has been established based on adequate and well-controlled studies of orally administered olanzapine.

EXT, extension; OLZ/SAM, combination olanzapine and samidorphan; SZ, schizophrenia.

1. Potkin SG, et al. *J Clin Psychiatry*. 2020;81(2):19m112769. 2. Yagoda S, et al. *CNS Spectr*. 2020;26(4):383-392. 3. Correll CU, et al. *Am J Psychiatry*. 2020;177(12):1168-1178. 4. Kahn RS, et al. *Schizophr Res*. 2021;232:45-53.

Expanding the Impact of OLZ/SAM

Evidence for Regulatory Approval

- ✓ Treats Acute Exacerbations
- ✓ Maintains Symptom Control
- ✓ Reduces Acute Weight Gain
- ✓ Established Safety Profile

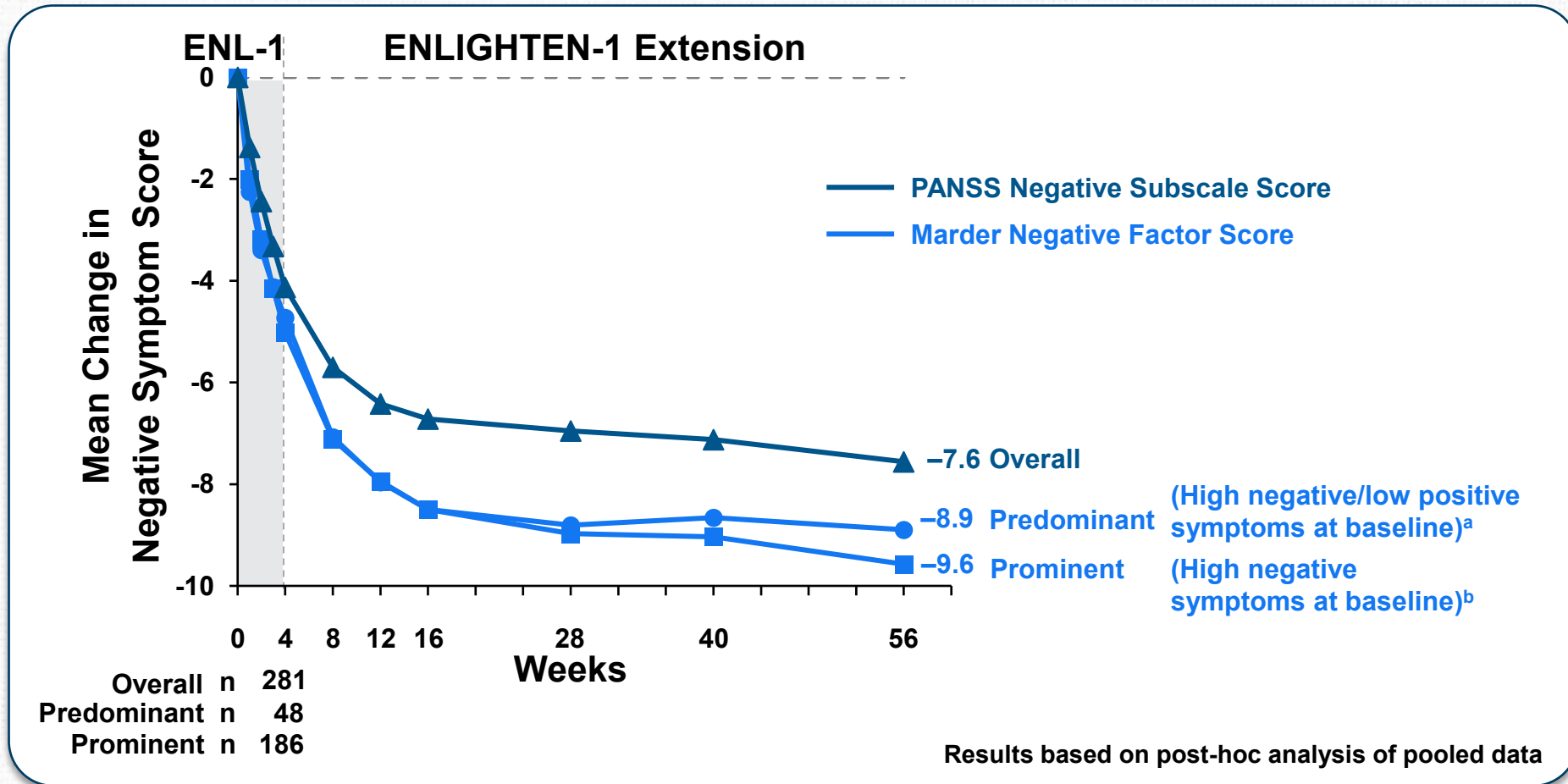
Extending the Clinical Evidence Base

- Reduces Negative Symptoms
- Maintains Long-term Symptom Control
- Minimal Long-term Weight Gain and Metabolic Changes
- Effectiveness in Early-in-Illness Patients

Real-World Evidence

Changing the Treatment Paradigm

Over 56 Weeks of Treatment, OLZ/SAM Led to Significant and Durable Improvement in Negative Symptoms of Schizophrenia

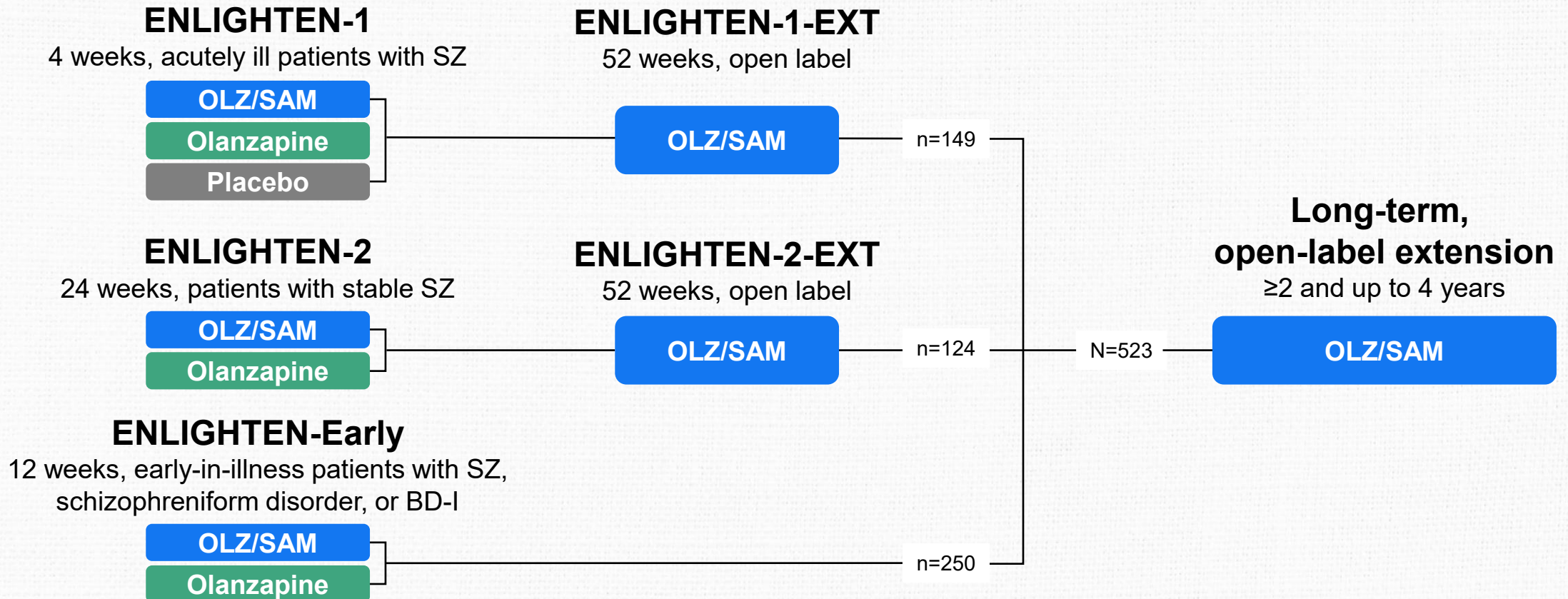


^aPredominant: Marder Negative Factor score ≥ 24 , score ≥ 4 on 2 PANSS negative symptom items, and PANSS Mohr Positive Factor score ≤ 19 . ^bProminent: Marder Negative Factor score ≥ 24 .

ENL-1, ENLIGHTEN-1; OLZ/SAM, combination olanzapine and samidorphan; PANSS, Positive and Negative Syndrome Scale.

McIntyre RS, et al. *J Clin Psychiatry*. 2026;87(2):25m16170.

The ENLIGHTEN Development Program Culminated in a 4-Year Open-Label Safety Study

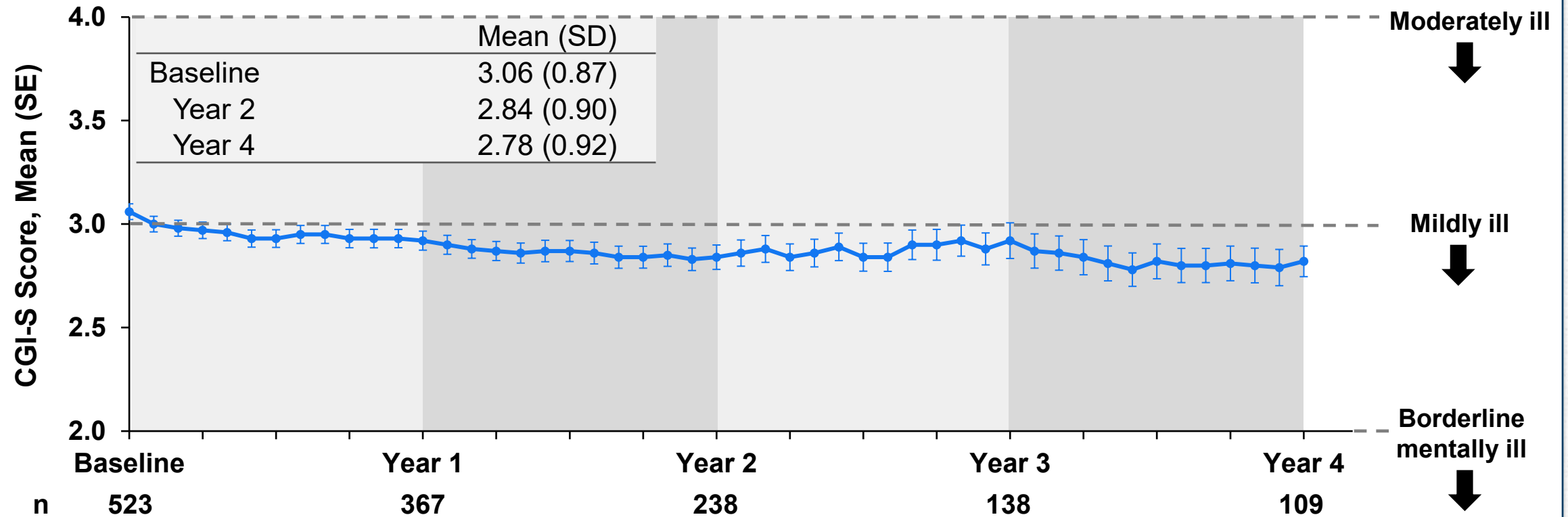


BD-I, bipolar I disorder; EXT, extension; OLZ/SAM, combination olanzapine and samidorphan; SZ, schizophrenia.

1. Potkin SG, et al. *J Clin Psychiatry*. 2020;81(2):19m112769. 2. Yagoda S, et al. *CNS Spectr*. 2020;26(4):383-392. 3. Correll CU, et al. *Am J Psychiatry*. 2020;177(12):1168-1178. 4. Kahn RS, et al. *Schizophr Res*. 2021;232:45-53. 5. Kahn RS, et al. *J Clin Psychiatry*. 2023;84(2):22m14608. 6. Ballon JS, et al. *J Clin Psychiatry*. 2024;86(1):24m15511.

OLZ/SAM Maintained Long-term Symptom Control for up to 4 Years of Treatment

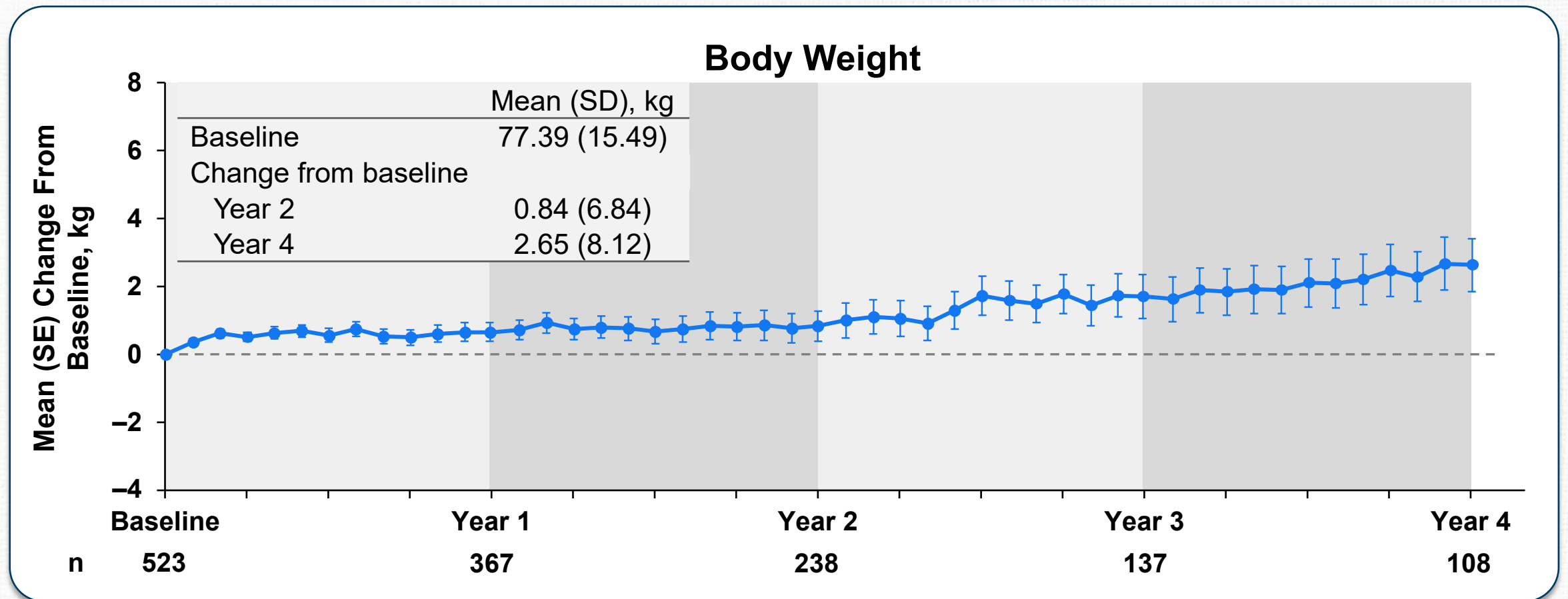
CGI-S



CGI-S, Clinical Global Impression–Severity; OLZ/SAM, combination olanzapine and samidorphan.
Ballon JS, et al. *J Clin Psychiatry*. 2024;86(1):24m15511.

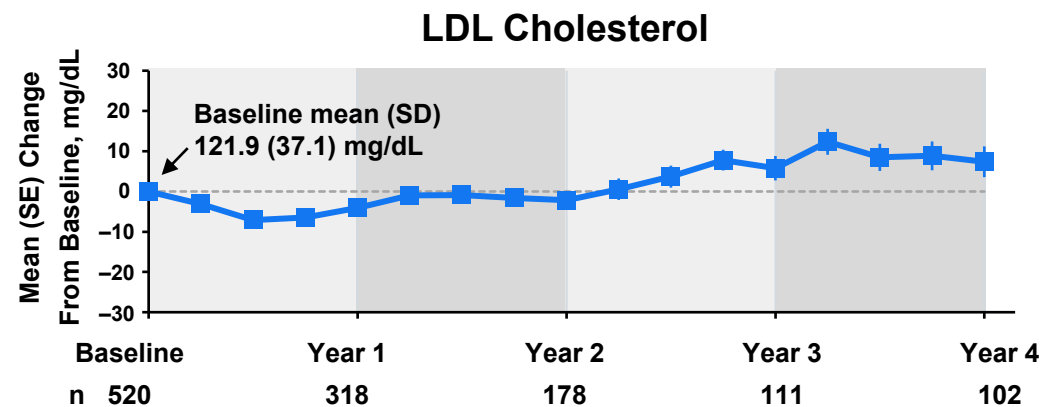
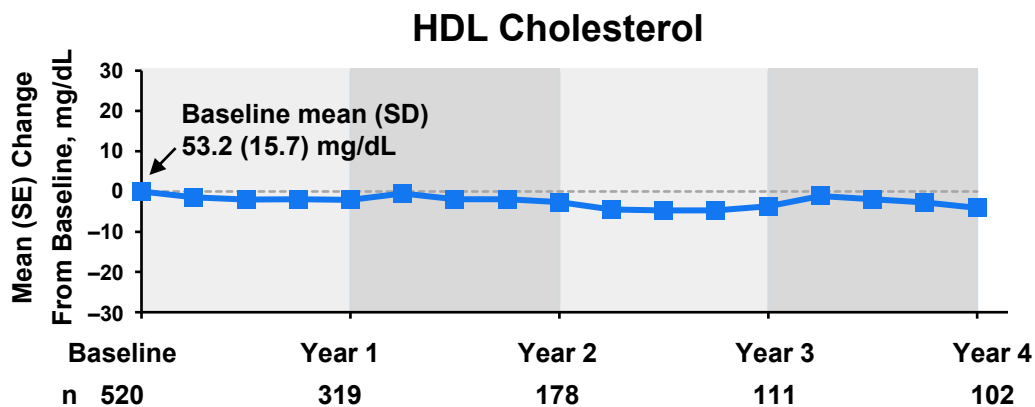
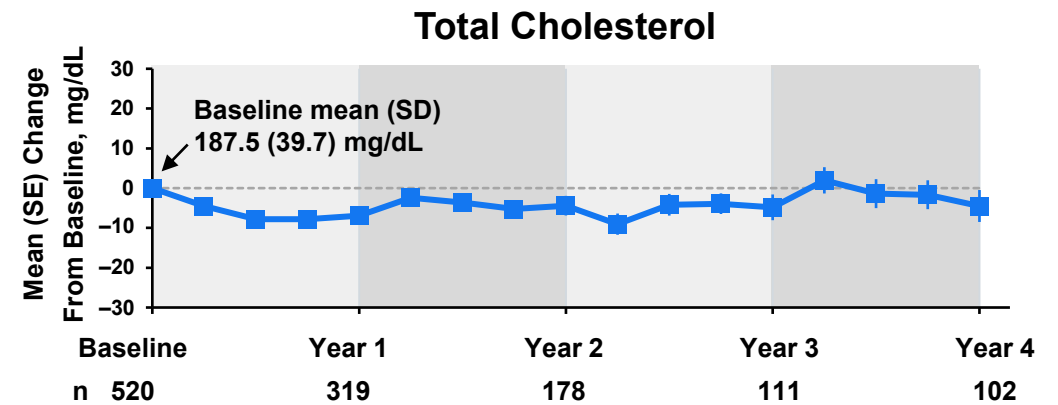
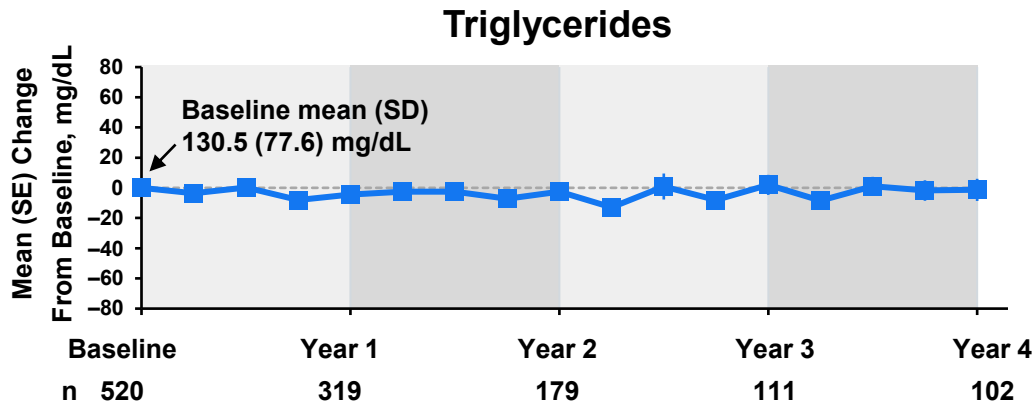


OLZ/SAM Was Associated With Small Changes in Body Weight for up to 4 Years of Treatment



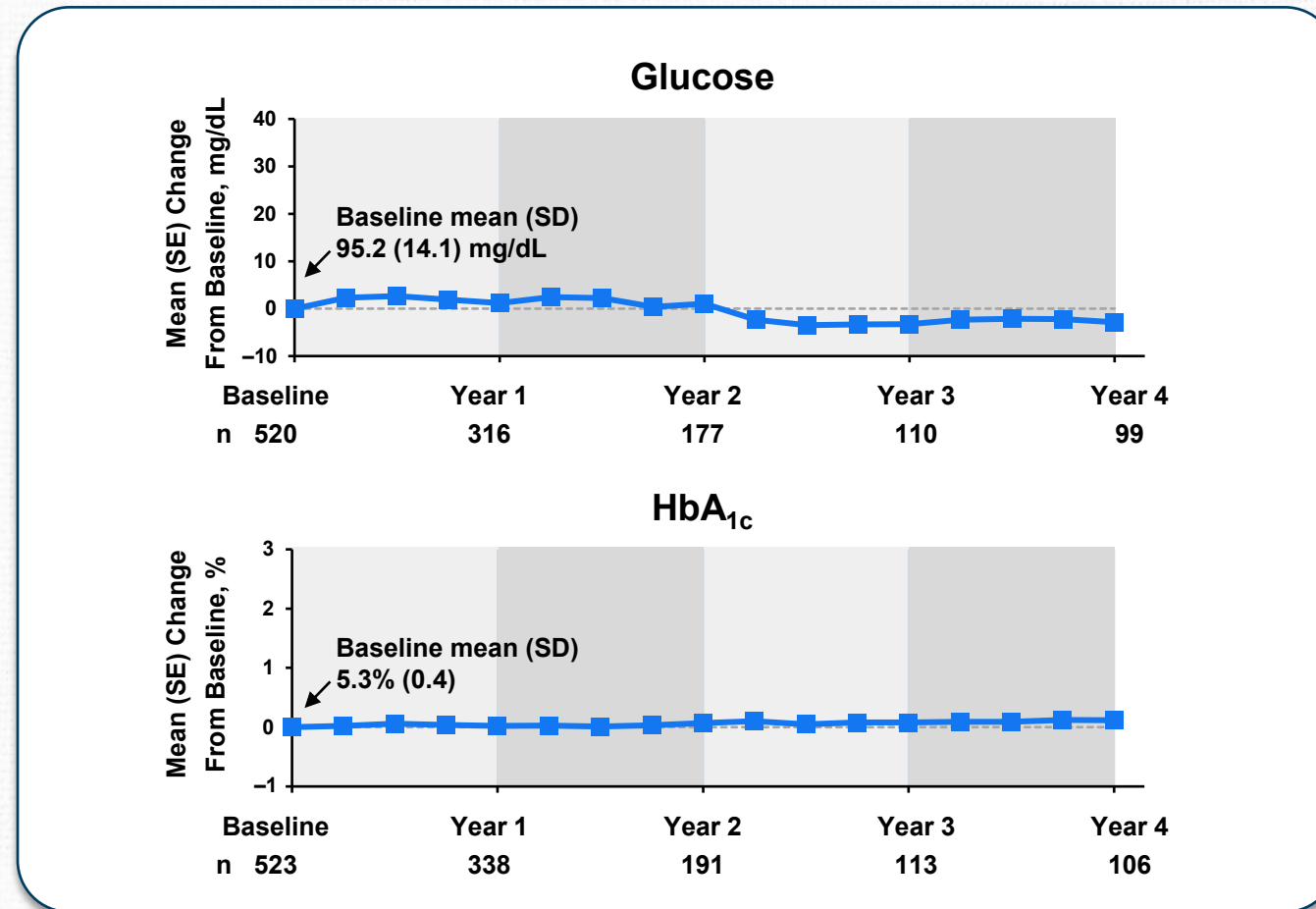
OLZ/SAM, combination olanzapine and samidorphan.
Ballon JS, et al. *J Clin Psychiatry*. 2024;86(1):24m15511.

Minimal Changes in Lipid Parameters Were Observed With up to 4 Years of OLZ/SAM Treatment



HDL, high-density lipoprotein; LDL, low-density lipoprotein; OLZ/SAM, combination olanzapine and samidorphan.
Ballon JS, et al. *J Clin Psychiatry*. 2024;86(1):24m15511.

Minimal Changes in Glycemic Parameters Were Observed With up to 4 Years of OLZ/SAM Treatment



HbA_{1c}, glycosylated hemoglobin; OLZ/SAM, combination olanzapine and samidorphan.
Ballon JS, et al. *J Clin Psychiatry*. 2024;86(1):24m15511.



Broadening Clinical Applicability of OLZ/SAM to Patients Earlier in Their Disease Course

Completed

ENLIGHTEN-Early¹

12 weeks

Early-in-illness patients^a with SZ, schizophreniform disorder, or BD-I, age 16 to <40 years (N=426)

OLZ/SAM

Olanzapine

Ongoing^b

ENLIGHTEN-Youth²

52 weeks

Pediatric patients with SZ, age 13–17 years, or BD-I, age 10–17 years (N~220)

OLZ/SAM

Olanzapine

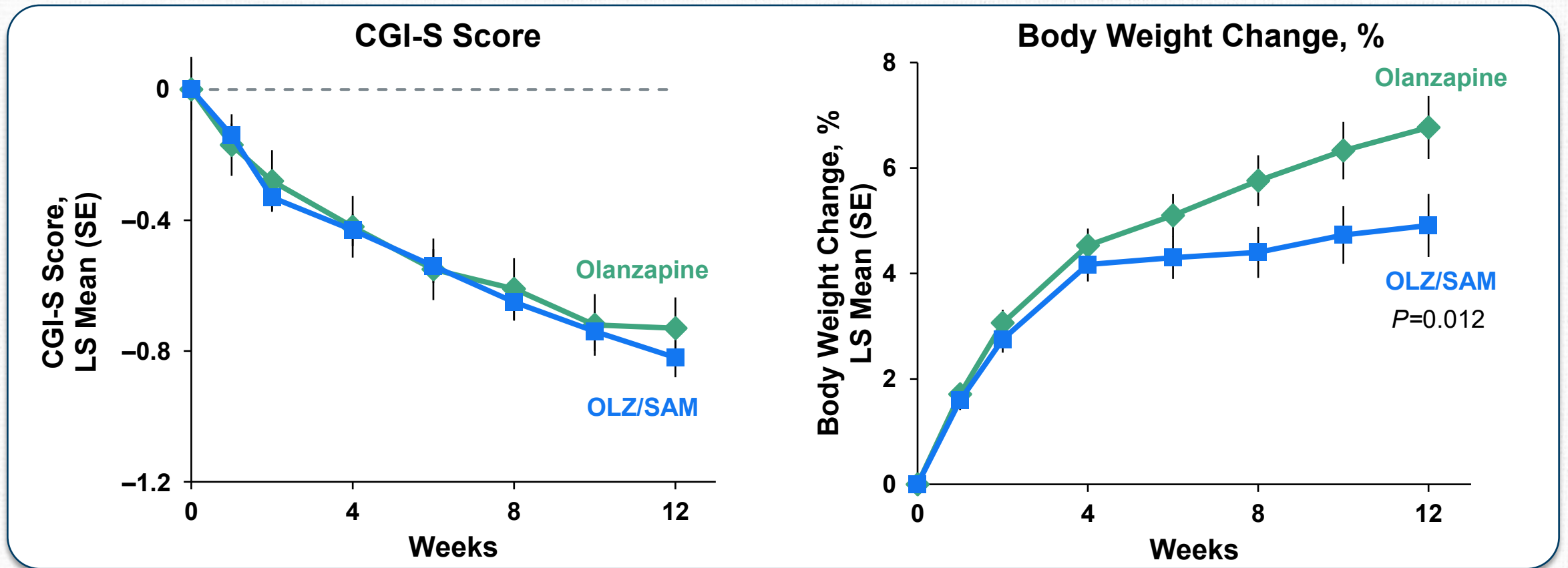
^aEarly in illness defined as <4 years since onset and <24 weeks of antipsychotic exposure. ^bThe use of OLZ/SAM in patients under the age of 18 years is investigational and not approved by any health authority.

BD-I, bipolar I disorder; EXT, extension; OLZ/SAM, combination olanzapine and samidorphan; SZ, schizophrenia.

1. Kahn RS, et al. *J Clin Psychiatry*. 2023;84(2):22m14608. 2. ClinicalTrials.gov identifier NCT05303064.

Efficacy and Weight Mitigation of OLZ/SAM Were Also Demonstrated in Early-in-Illness Patients

ENLIGHTEN-Early



CGI-S, Clinical Global Impression–Severity; LS, least squares; OLZ/SAM, combination olanzapine and samidorphan.
Kahn RS, et al. *J Clin Psychiatry*. 2023;84(2):22m14608.



Safety Profile of OLZ/SAM

- In the pivotal trials, the safety profile of OLZ/SAM was consistent with that of olanzapine, but with less weight gain and lower risk of worsening cardiometabolic risk factors^{1,2}
- In ENLIGHTEN-Early, the overall safety profile of OLZ/SAM was consistent with that of olanzapine, with fewer AEs of weight increase⁴
- In the 4-year open-label study⁵:
 - Small changes in weight
 - Minimal changes to metabolic parameters
 - Most AEs were mild to moderate in severity
 - Serious AEs occurred infrequently
 - AEs leading to treatment discontinuation n (%) = 44 (8.4)

ENLIGHTEN-2 Most Common Adverse Events³

	OLZ/SAM N=274	Olanzapine N=276
SAEs,^a n (%)	10 (3.6)	7 (2.5)
Any AE ≥5%, n (%)	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)

^aThe only SAE in >1 patient was schizophrenia worsening.

AE, adverse event; OLZ/SAM, combination olanzapine and samidorphan; SAE, serious adverse event.

1. Citrome L, et al. *Neuropsychiatr Dis Treat*. 2021;17:2885-2904. 2. Correll CU, et al. *Schizophr Bull*. 2022;49(2):454-463.

3. Correll CU, et al. *Am J Psychiatry*. 2020;177(12):1168-1178. 4. Kahn RS, et al. *J Clin Psychiatry*. 2023;84(2):22m14608.

5. Ballon JS, et al. *J Clin Psychiatry*. 2024;86(1):24m15511.

Expanding the Impact of OLZ/SAM

Evidence for Regulatory Approval



Treats Acute Exacerbations



Maintains Symptom Control



Reduces Acute Weight Gain



Established Safety Profile

Extending the Clinical Evidence Base



Reduces Negative Symptoms



Maintains Long-term Symptom Control



Minimal Long-term Weight Gain and Metabolic Changes



Effectiveness in Early-in-Illness Patients

Real-World Evidence



Expanding the Impact of OLZ/SAM

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Effectiveness in Early-in-Illness Patients

Real-World Evidence

Reduced Risk of Relapse

Better Treatment Adherence

Better Treatment Persistence

Greater Effectiveness in Young Adults

Real-World Evidence Studies Broad Patient Populations to Answer Questions Relevant to Routine Clinical Practice

Research-Grade Administrative Claims Database (Komodo Healthcare Map)

~330 million patients

Schizophrenia or Bipolar I Disorder Diagnosis

~2.5 million patients

Other Eligibility Criteria

(Age, treatment claim)



Treatment Impact on Relapse Rates

- Before and after initiating OLZ/SAM
- Outcomes: Relapse proxies (hospitalizations, ED visits)

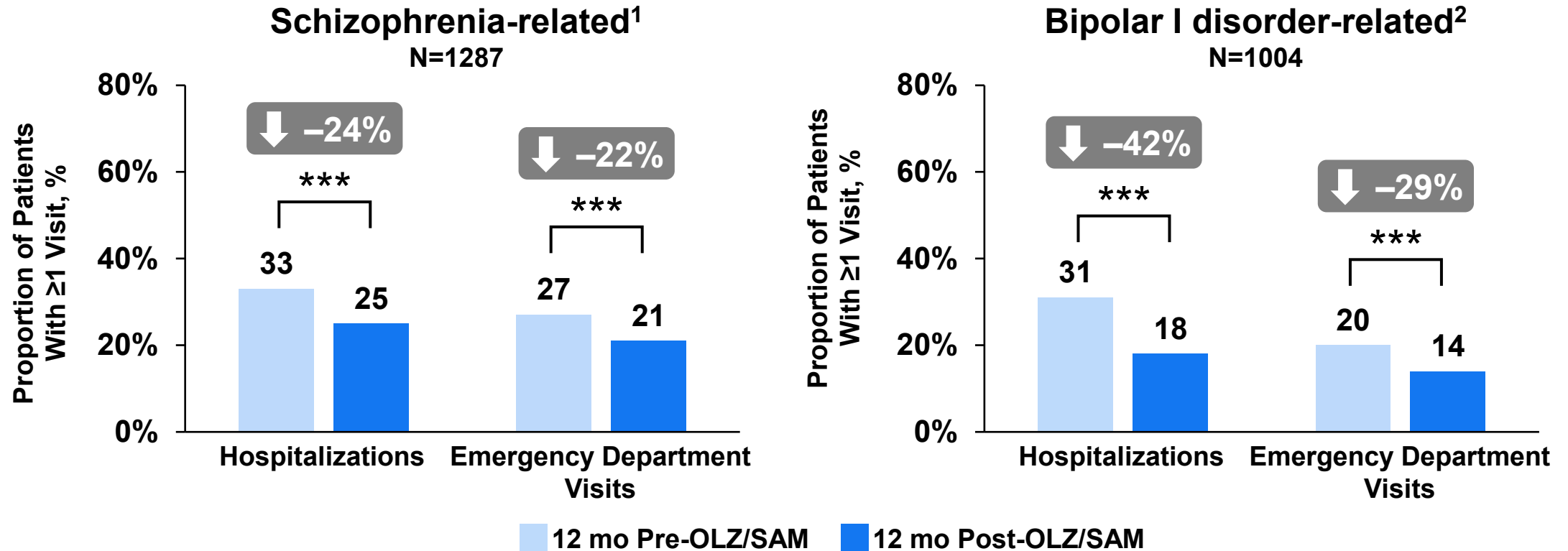
Treatment Comparison with Other Antipsychotics

- OLZ/SAM vs other antipsychotics post-initiation
- Outcomes: Adherence and Persistence

Key limitations: data source not representative of uninsured patients, does not capture disease severity, and may be subject to data omissions; analysis adjusted for known potential confounders, but residual confounding may remain; and no adjustment for multiplicity was performed.

ED, emergency department; OLZ/SAM, combination olanzapine and samidorphan.

OLZ/SAM Initiation Associated With Clinically Meaningful Reductions in Relapse as Evidenced by Fewer Hospitalizations and ED Visits



Outpatient visits were similar before and after OLZ/SAM initiation

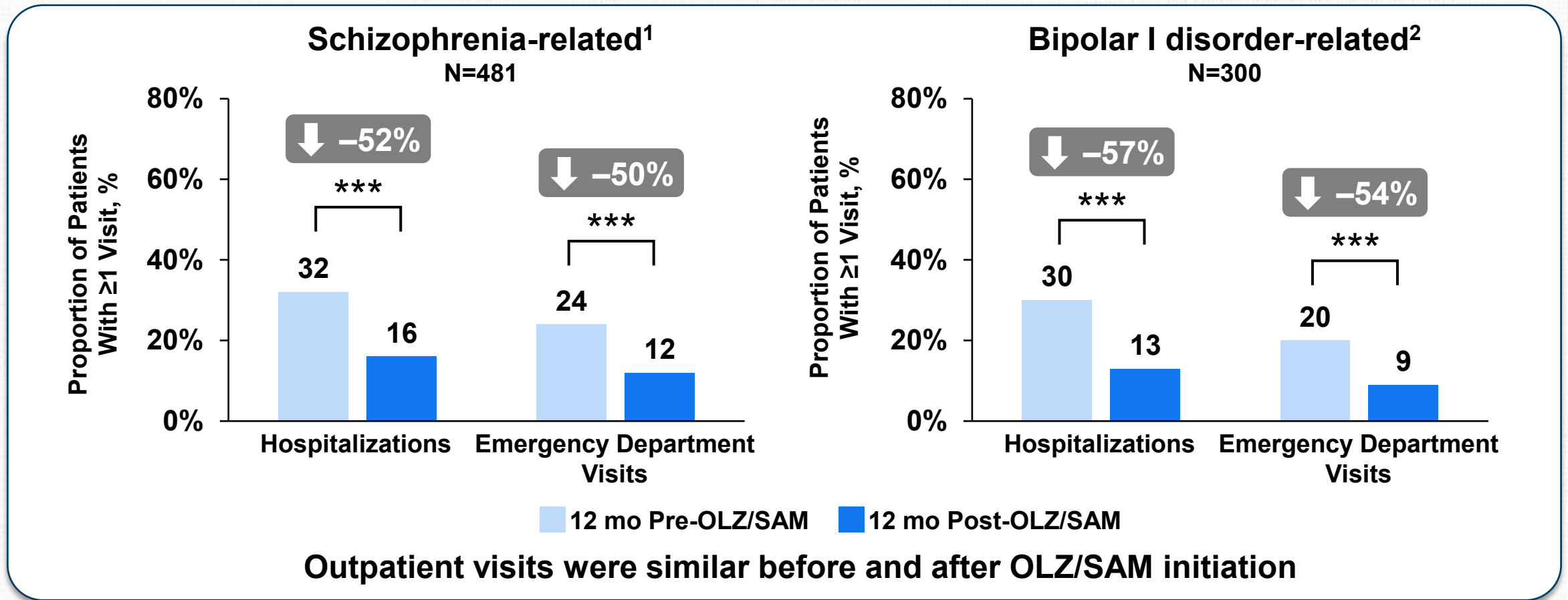
*** $P < 0.001$.

ED, emergency department; OLZ/SAM, combination olanzapine and samidorphan.

1. Cutler AJ, et al. Poster presented at: Psych Congress; October 29-November 2, 2024; Boston, MA. 2. Jain R, et al. Poster presented at: Psych Congress; October 29-November 2, 2024; Boston, MA.



Greater Reductions in Relapse Events in Patients Who Persisted on OLZ/SAM Treatment for 12 Months



***P<0.001.

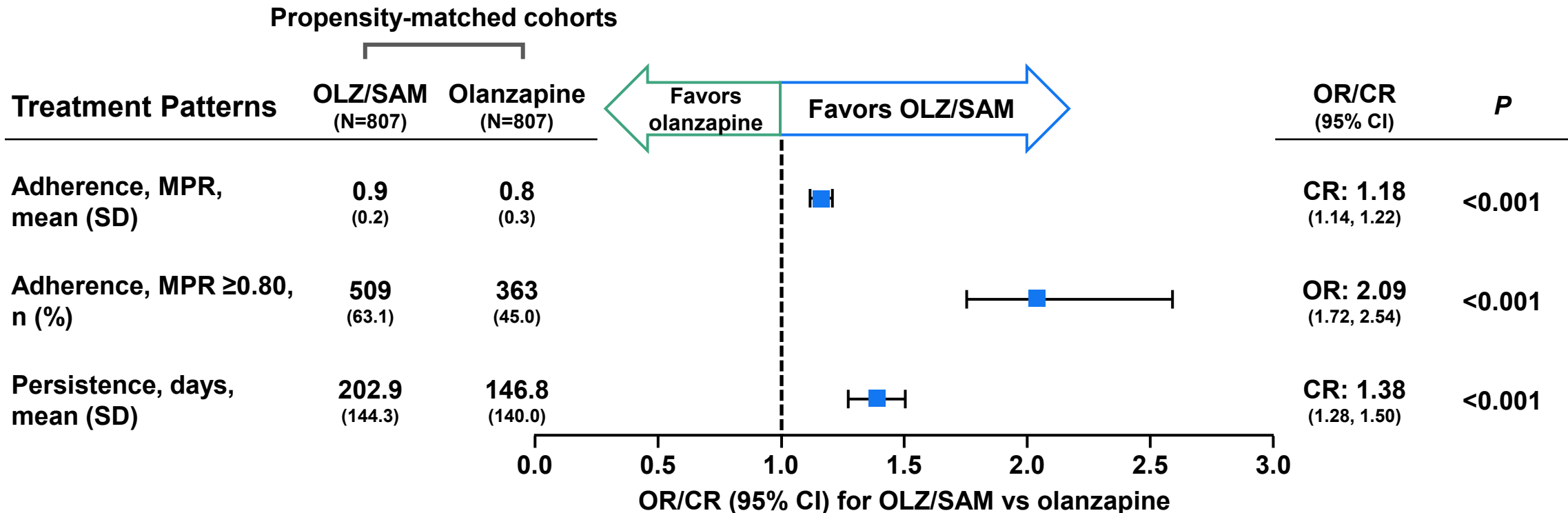
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OLZ/SAM Resulted in Significantly Greater Adherence and Longer Persistence Compared to Olanzapine in Patients With Schizophrenia

OLZ/SAM vs Olanzapine



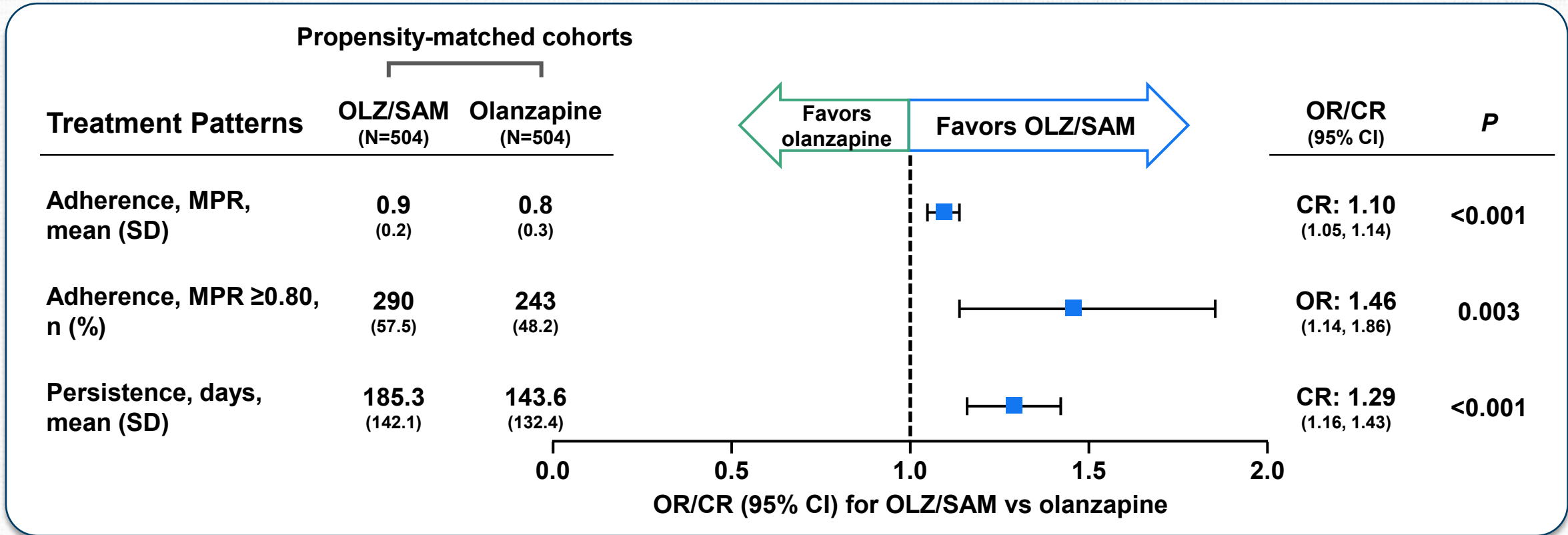
Adherence measured using medication possession ratio, as sum of days' supply/365 (follow-up period); persistence measured as total number of days until discontinuation.

CR, count ratio; MPR, medication possession ratio; OLZ/SAM, combination olanzapine and samidorphan; OR, odds ratio.

Cutler AJ, et al. Poster presented at: Psych Congress; September 19-20, 2025; San Diego, CA.

OLZ/SAM Resulted in Significantly Greater Adherence and Longer Persistence Compared to Olanzapine in Patients With Bipolar I Disorder

OLZ/SAM vs Olanzapine



Adherence measured using medication possession ratio, as sum of days' supply/365 (follow-up period); persistence measured as total number of days until discontinuation.

CR, count ratio; MPR, medication possession ratio; OLZ/SAM, combination olanzapine and samidorphan; OR, odds ratio.

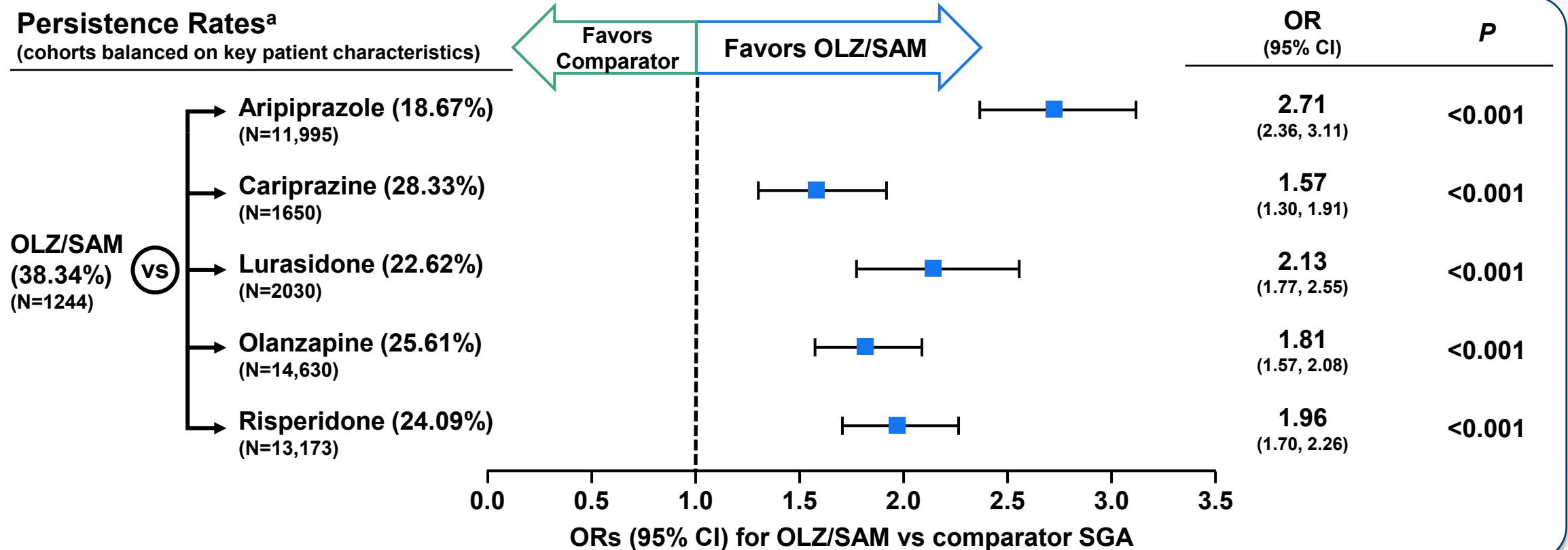
Jain R, et al. Poster presented at: Psych Congress; September 19-20, 2025; San Diego, CA.

OLZ/SAM Resulted in Significantly Higher Persistence Compared to Other Oral SGAs in Patients With Schizophrenia

OLZ/SAM vs Other Oral SGAs

Persistence Rates^a

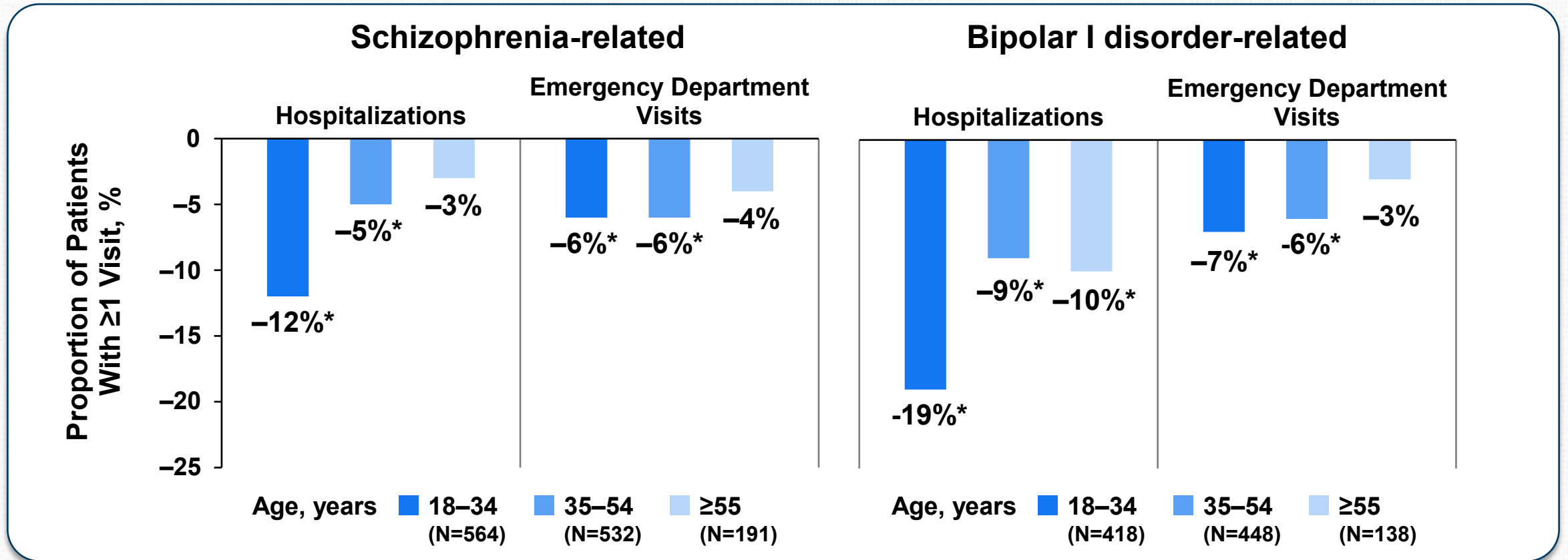
(cohorts balanced on key patient characteristics)



Persistence rate measured as proportion of patients who remain on index treatment for entire 12-month follow-up period. ^aGiven lower sample sizes for brexpiprazole (persistence rate, 28.98%; N=421) and lumateperone (persistence rate, 2.84%; N=423), data are descriptive only and not compared with OLZ/SAM. OLZ/SAM, combination olanzapine and samidorphan; OR, odds ratio; SGA, second-generation antipsychotic. Data on file.

Young Adults Had the Greatest Reductions in Acute Care Events After Initiating OLZ/SAM Treatment

12 Months Before/After Initiating OLZ/SAM: Absolute Changes in Acute Care Events by Age Subgroup Analyses



*P ≤ 0.05.

OLZ/SAM, combination olanzapine and samidorphan.

Cutler AJ, et al. Poster presented at: NEI Congress; November 6-9, 2025; Colorado Springs, CO.

Expanding the Impact of OLZ/SAM

Evidence for Regulatory Approval

- ✔ Treats Acute Exacerbations
- ✔ Maintains Symptom Control
- ✔ Reduces Acute Weight Gain
- ✔ Established Safety Profile

Extending the Clinical Evidence Base

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Real-World Evidence

- ✔ Reduced Risk of Relapse
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Changing the Treatment Paradigm