# Adjunctive Lumateperone in Patients With Major Depressive Disorder: Results From an Additional Randomized, Double-Blind, Phase 3 Trial

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# **BACKGROUND**

- Major depressive disorder (MDD) is a highly burdensome illness and is associated with functional impairment, comorbidities, and reduced quality of life<sup>1</sup>
- Available treatments are limited by adverse effects and low remission and response rates, with the majority of patients failing to achieve remission (≈75%) or response (≈60%) following first-line treatment<sup>2,3</sup>
- Patients with MDD who have inadequate antidepressant therapy (ADT) response have increased hospitalization risk and greater impairments in functioning compared with those who respond,<sup>4</sup> highlighting the need for novel, safe, and effective treatments for this patient population
- Lumateperone is a mechanistically novel US Food and Drug Administration–approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate<sup>5,6</sup>
- Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission<sup>6</sup>
- Specifically, lumateperone is a potent serotonin 5-HT<sub>2A</sub> receptor antagonist, a dopamine D<sub>2</sub> receptor presynaptic partial agonist and postsynaptic antagonist, a D<sub>1</sub> receptor–dependent indirect modulator of glutamatergic AMPA and NMDA currents, and a serotonin reuptake inhibitor<sup>6</sup>
- This novel mechanism of action with multimodal effects may confer robust efficacy with improved tolerability compared with current treatment options
- In a recent Phase 3, randomized, double-blind, placebo-controlled, multicenter trial (Study 501; NCT04985942), lumateperone 42 mg + ADT met primary and key secondary efficacy endpoints and was generally safe and well tolerated in patients with *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5)–defined MDD and inadequate ADT response<sup>7</sup>
- This similarly designed Phase 3, randomized, double-blind, placebo-controlled, multicenter trial (Study 502; NCT05061706) also investigated the efficacy and safety of adjunctive lumateperone 42 mg in patients with MDD and inadequate response to ADT

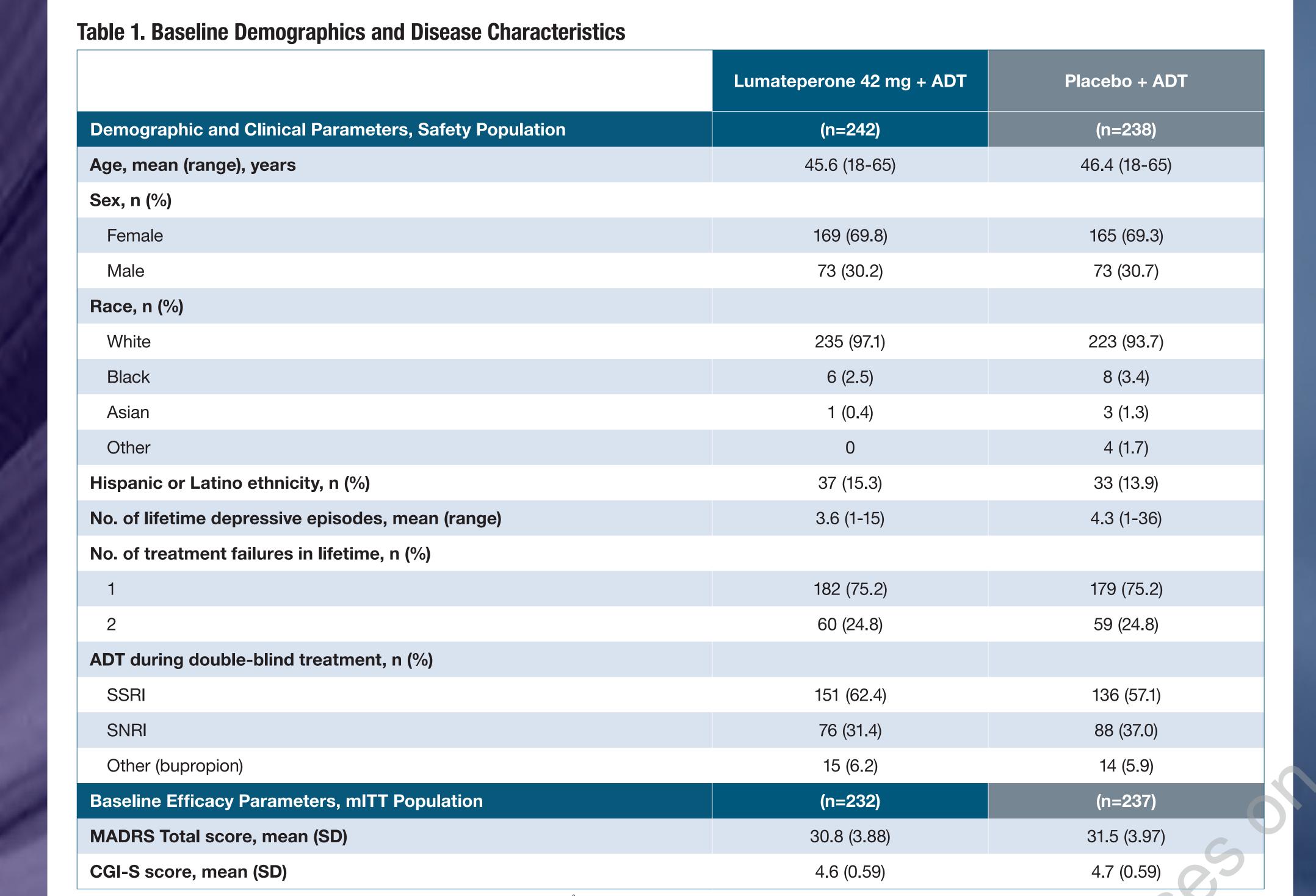
# **METHODS**

- Eligible adults (aged 18-65 years, inclusive) had DSM-5-diagnosed MDD with inadequate response to 1 to 2 courses
  of prior ADT, were experiencing a major depressive episode (Montgomery-Åsberg Depression Rating Scale [MADRS]
  Total score ≥24 and Clinical Global Impression Scale-Severity [CGI-S] score ≥4), and had Quick Inventory of Depressive
  Symptomatology-Self Report-16 item (QIDS-SR-16) score ≥14 at screening and baseline
- Inadequate response to ADT was defined as <50% improvement with ≥6 weeks of ADT monotherapy as confirmed by the Antidepressant Treatment Response Questionnaire
- Patients were randomized 1:1 to 6-week oral placebo + ADT or lumateperone 42 mg + ADT
- The primary and key secondary efficacy endpoints were change from baseline to Day 43 in MADRS Total score and CGI-S score, respectively, analyzed using a mixed-effects model for repeated measures
- Change from baseline in QIDS-SR-16 Total score was examined with an analysis of covariance-last observation carried forward approach
- Safety assessments included treatment-emergent adverse events (TEAEs), laboratory parameters, extrapyramidal symptoms (EPS), and suicidality

# **RESULTS**

## **Patient Population**

- All 480 patients who were randomized also received treatment adjunctive to ADT (placebo, 238; lumateperone, 242), and 89.4% completed treatment
- Demographics and baseline characteristics were similar between groups (**Table 1**)
- The majority of patients were female and White

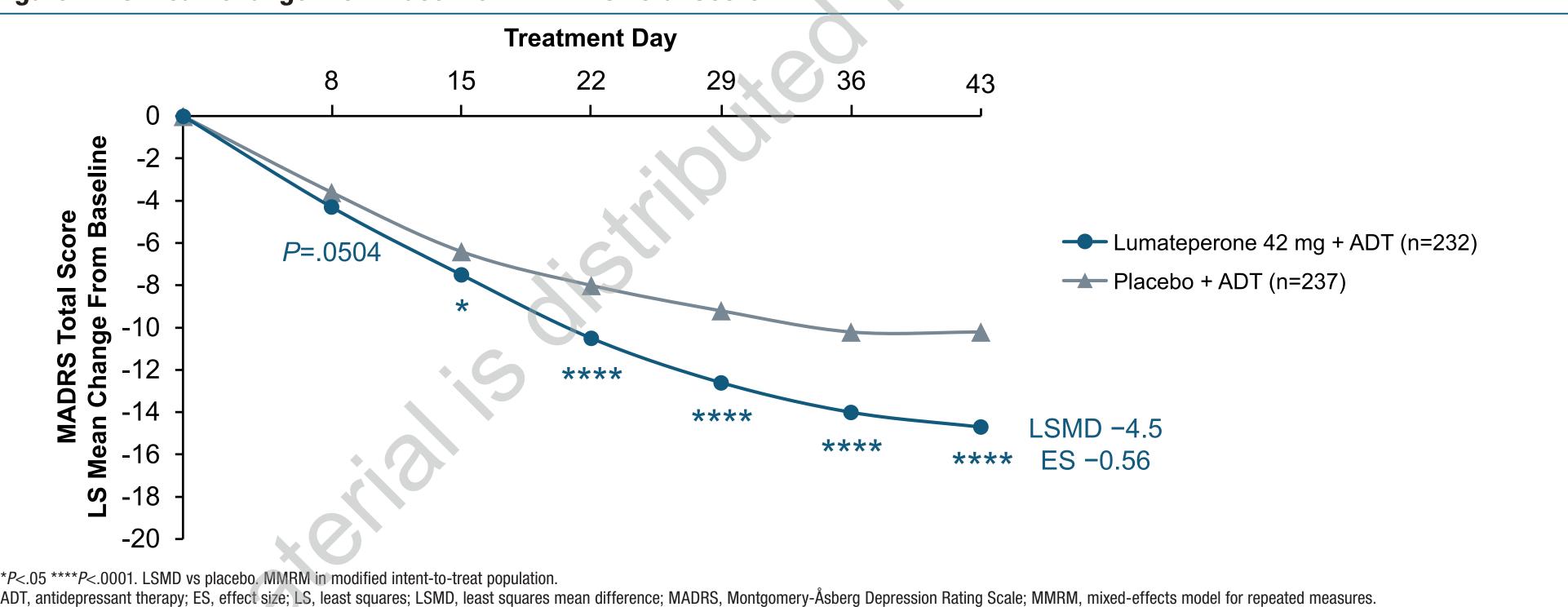


## ADT, antidepressant therapy; CGI-S, Clinical Global Impression Scale-Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

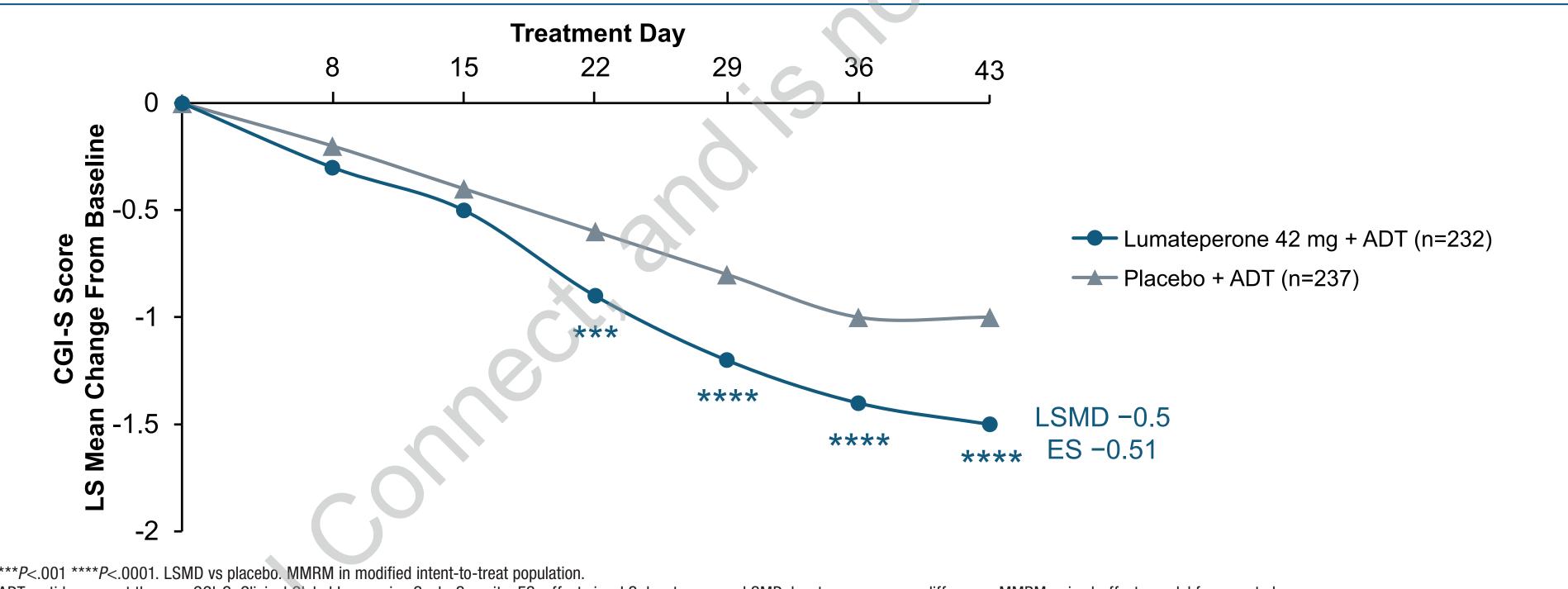
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- The primary endpoint was met for lumateperone + ADT, with significantly greater MADRS Total score improvement from baseline to Day 43 compared with placebo + ADT (**Figure 1**)
- A statistically significant improvement with lumateperone + ADT was nearly attained at Day 8 (P=.0504) and was achieved beginning at Day 15 (P=.0384) and maintained through Day 43
- The key secondary endpoint was also met for lumateperone + ADT, with significantly greater CGI-S improvement from baseline to Day 43 compared with placebo + ADT (**Figure 2**)
- CGI-S score significantly improved by Day 22 and persisted throughout the study
- Self-reported depressive symptoms, as measured by QIDS-SR-16 Total score, also significantly improved with lumateperone + ADT compared with placebo + ADT from baseline to Day 43 (**Figure 3**)

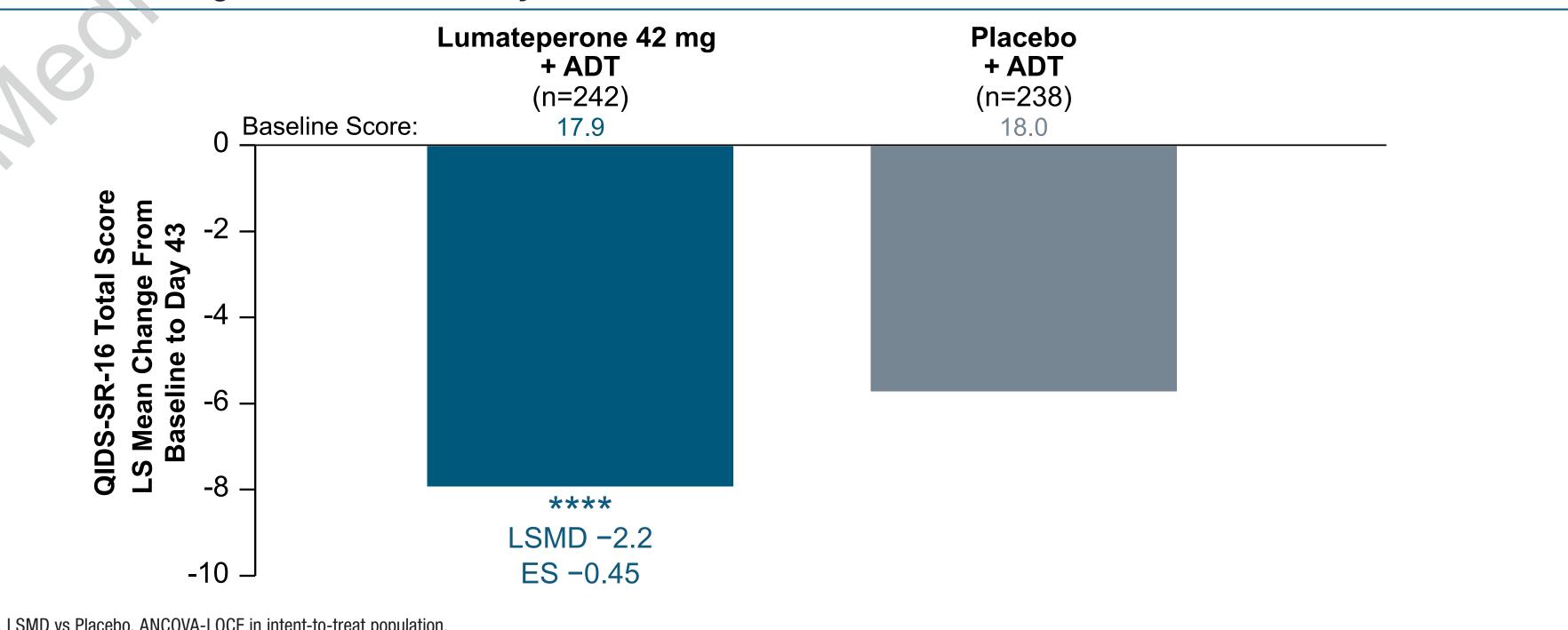
## Figure 1. LS Mean Change From Baseline in MADRS Total Score



# Figure 2. LS Mean Change From Baseline in CGI-S Score



## Figure 3. LS Mean Change From Baseline to Day 43 in QIDS-SR-16 Total Score



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- TEAEs were reported in 43.7% of the placebo + ADT group and 78.1% of the lumateperone + ADT group
- Serious adverse events were rare, occurring in no patients in the placebo + ADT group and 2 patients (0.8%) in the lumateperone + ADT group
- TEAEs occurring in the lumateperone + ADT group in ≥5% of patients and at more than twice the rate of placebo + ADT were dizziness, somnolence, dry mouth, nausea, diarrhea, and fatigue
- For most patients, TEAEs were mild or moderate in severity
- No patients died during the study
- Weight and body mass index remained stable in both groups
- In the lumateperone + ADT group, there were no clinically relevant increases at the end of the double-blind treatment period in prolactin or cardiometabolic parameters (**Table 2**)

## Table 2. Mean Change From Baseline to End of Treatment in Prolactin and Cardiometabolic Parameters

		Lumateperone 42 mg + ADT (n=242)		Placebo + ADT (n=238)	
	Baseline Mean (SD)	Mean Change (SE)	Baseline Mean (SD)	Mean Change (SE)	
Prolactin, ng/mL	9.5 (8.78)	0.6 (0.59)	9.5 (18.25)	1.3 (0.59)	
Cholesterol, mg/dL					
Total	202.7 (40.67)	-9.3 (2.44)	199.3 (39.93)	-3.4 (2.04)	
HDL	58.3 (16.76)	-0.9 (0.73)	57.3 (15.78)	-0.8 (0.60)	
LDL	140.8 (40.07)	-9.4 (2.19)	138.9 (39.93)	-3.2 (2.00)	
Triglycerides, mg/dL	141.1 (90.34)	-2.0 (6.70)	136.8 (74.08)	5.5 (5.17)	
Glucose, mg/dL	92.7 (14.45)	-0.8 (0.86)	93.2 (14.21)	0.6 (0.82)	
Insulin, mIU/L	14.3 (14.79)	-1.3 (0.98)	15.2 (16.24)	0.2 (1.25)	
ADT, antidepressant therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein.					

- There were no notable changes in EPS as assessed by the Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Simpson-Angus Scale
- EPS-related TEAEs occurred in 0.4% of the placebo + ADT group and 1.2% of the lumateperone + ADT group per narrow standard Medical Dictionary for Regulatory Activities query (SMQ)
- According to broad SMQ, EPS-related TEAEs occurred in 0.4% of the placebo + ADT group and 5.4% of the lumateperone + ADT group
- Based on the Columbia-Suicide Severity Rating Scale, no suicidal behavior was reported during treatment, and rates of emergent suicidal ideation were low and similar between groups (placebo + ADT, 1.4%; lumateperone + ADT, 1.9%)

# CONCLUSIONS

- Lumateperone 42 mg adjunctive to ADT demonstrated significant, clinically meaningful efficacy over placebo adjunctive to ADT, improving depressive symptoms and disease severity
- Lumateperone 42 mg + ADT improved depression as measured by both clinician-rated and patient-reported outcomes (MADRS Total score, CGI-S score, and QIDS-SR-16 Total score)
- Lumateperone 42 mg + ADT was generally safe and well tolerated, consistent with prior lumateperone trials
- These results suggest lumateperone 42 mg adjunctive to ADT is a promising new treatment option for adults with MDD with inadequate response to prior ADT

## REFERENCES

- 1. Proudman D, et al. *PharmacoEconomics*. 2021;39(6):619-625.
- Alva G. CNS Spectr. 2023;28(5):521-525.
   Pigott HE, et al. BMJ Open. 2023;13(7):e063095.
- 4. Knoth RL, et al. *Am J Manag Care*. 2010;16(8):e188-e196.
- 5. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc.;2023.
  6. Titulaer J, et al. *Eur Neuropsychopharmacol.* 2022;62:22-35.
- 7. Durgam S, et al. "Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder: Results From a Randomised, Double-blind, Phase 3 Trial."
- Durgam S, et al. "Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder: Results From a Randomised, Double-blind, Poster presented at: European College of Neuropsychopharmacology (ECNP) Annual Congress. September 21-24, 2024; Milan, Italy.

## DISCLOSURES AND ACKNOWLEDGMENTS

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