

Efficacy of Lumateperone 42 mg in the Treatment of Major Depressive Disorder: A Pooled Analysis of Phase 3 Randomized Controlled Trials

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BACKGROUND

- Major depressive disorder (MDD) is a common and complex mental illness affecting over 185 million people globally¹
 - It is associated with multiple comorbidities, impaired functioning, and a heightened risk of suicide¹
 - Current treatments have limited response and remission rates and ~50% of patients with MDD have inadequate response to antidepressant therapy (ADT)²
- 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^{3,4}
 - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission⁴
 - Specifically, lumateperone is a potent serotonin 5-HT_{2A} receptor antagonist, a dopamine D₂ receptor presynaptic partial agonist and postsynaptic antagonist, a D₁ receptor-dependent indirect modulator of AMPA and NMDA currents, and a serotonin reuptake inhibitor⁴
 - This novel mechanism of action with multi-modal effects may confer robust antidepressant efficacy with improved tolerability compared with current treatment options
- The efficacy and safety of lumateperone adjunctive to ADT was evaluated in 2 Phase 3, randomized, double-blind, placebo-controlled studies (Study 501, NCT04985942; Study 502, NCT05061706) in patients with MDD with inadequate ADT response
 - In both studies, lumateperone 42 mg + ADT met the primary endpoint, with significant improvement in depressive symptoms compared with placebo + ADT, and was generally well tolerated
- This pooled analysis of Study 501 and Study 502 was conducted to demonstrate the robustness of the efficacy of lumateperone 42 mg + ADT compared with adjunctive placebo in patients with MDD with inadequate ADT response

METHODS

- Efficacy data were pooled for the lumateperone 42 mg + ADT group and for the placebo + ADT group from Study 501 and Study 502^{5,6}
- Both studies evaluated 6-week oral lumateperone 42 mg + ADT or placebo + ADT
- Eligible adults (18-65 years) who met DSM-5 criteria for MDD with inadequate response to 1-2 ADT in the current depressive episode (defined as <50% improvement with ≥6 weeks ADT monotherapy as confirmed by the Antidepressant Treatment Response Questionnaire)
- Patients were experiencing a major depressive episode (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥24 and Clinical Global Impression-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
- Primary and key secondary endpoints were the change from baseline to Day 43 in MADRS Total score and CGI-S score, respectively, analyzed using a mixed-effects model for repeated measures
- Additional measures included response (≥50% MADRS Total score decrease) and remission (MADRS Total score ≤10), based on a logistic regression model
- Patient-reported outcomes included change from baseline in QIDS-SR-16 Total score, evaluated using an analysis of covariance

RESULTS

Patient Population

- The modified intent-to-treat population comprised 950 patients (lumateperone + ADT, n=471; placebo + ADT, n=479)
- Baseline demographics and clinical characteristics were similar between groups (**Table 1**)
 - Mean baseline MADRS Total score (lumateperone 42 mg, 30.6; placebo, 30.8) and CGI-S score (lumateperone, 4.7; placebo 42 mg, 4.6) indicate moderate-to-severe depression at baseline (**Table 1**)

Table 1. Baseline Demographics and Clinical Characteristics (mITT Population)

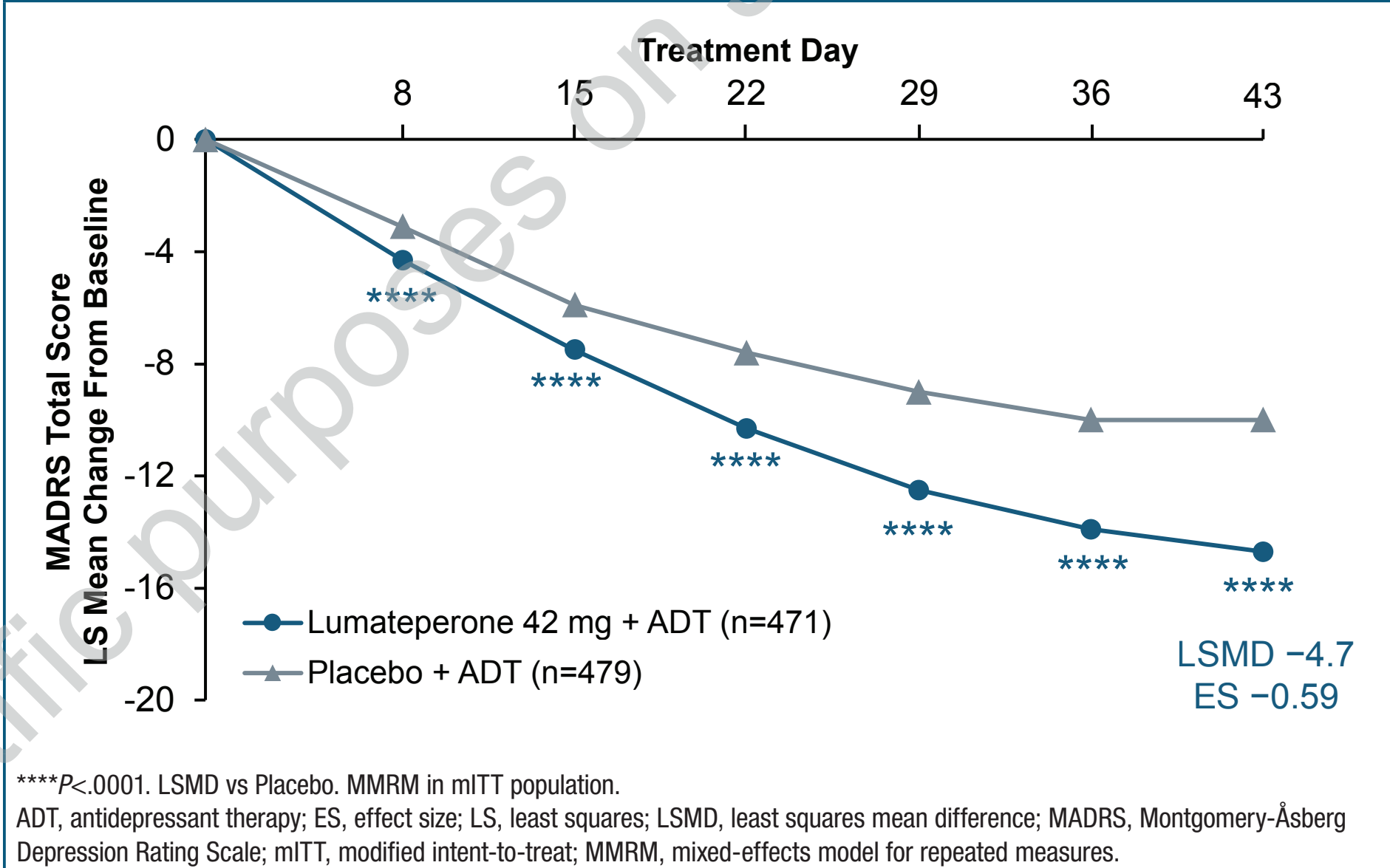
	Lumateperone 42 mg + ADT (n=471)	Placebo + ADT (n=479)
Age, mean (range), years	45.2 (18-65)	45.8 (18-65)
Sex, n (%)		
Women	318 (67.5)	325 (67.8)
Men	153 (32.5)	154 (32.2)
Race, n (%)		
White	404 (85.8)	413 (86.2)
Asian	41 (8.7)	35 (7.3)
Black	25 (5.3)	24 (5.0)
Other	1 (0.2)	7 (1.5)
Hispanic or Latino ethnicity, n (%)	50 (10.6)	49 (10.2)
Number of lifetime depressive episodes, mean (range)	3.6 (1-30)	4.0 (1-36)
Lifetime history of treatment failures including the current MDE, n (%)		
1	352 (74.7)	352 (73.5)
2	119 (25.3)	127 (26.5)

^a ITT population (lumateperone 42 mg + ADT n=483, placebo + ADT n=481).
ADT, antidepressant therapy; CGI-S, Clinical Global Impression-Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; mITT, modified intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report 16 Items

Efficacy

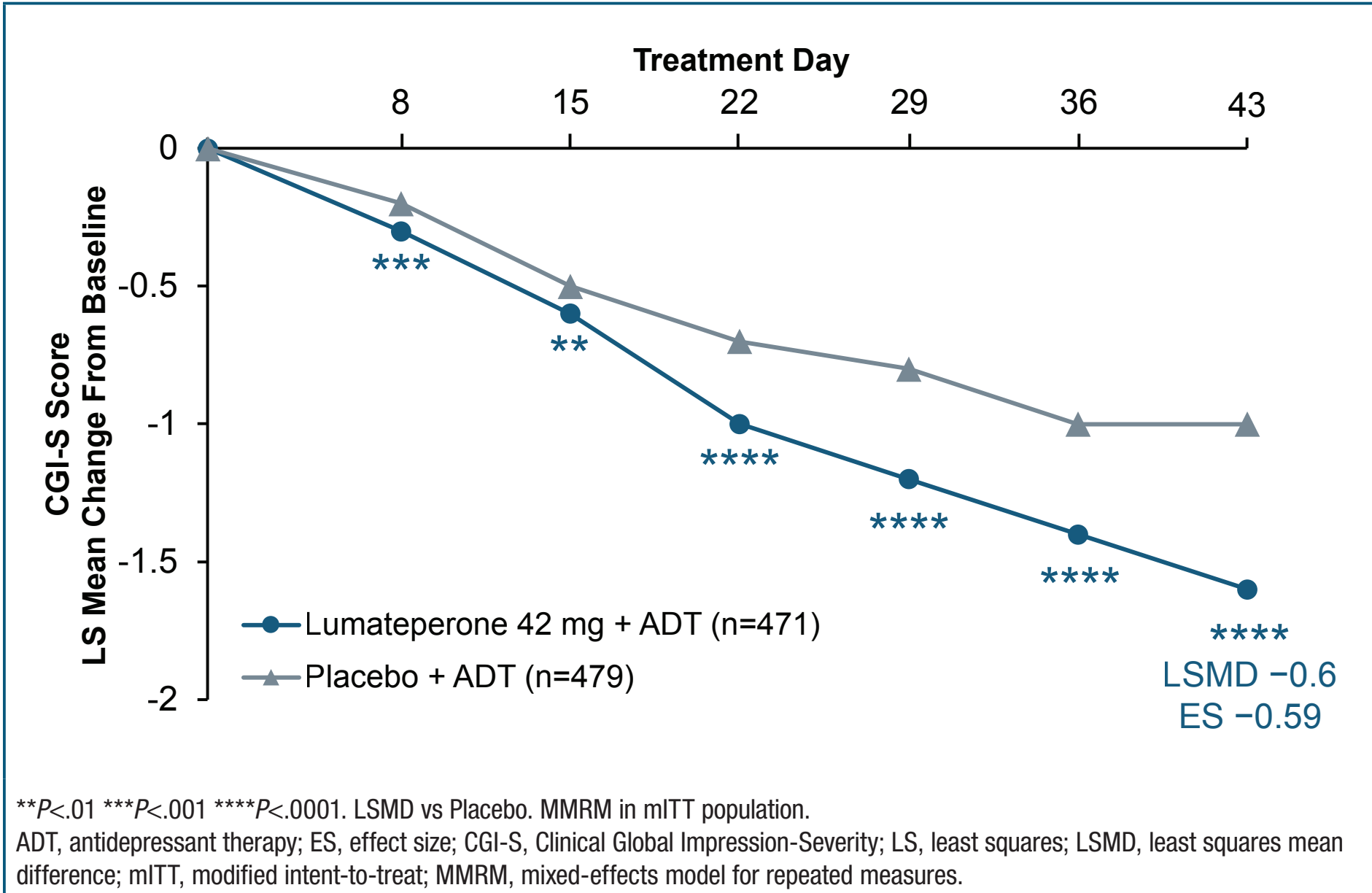
- Lumateperone 42 mg + ADT significantly improved MADRS Total score at Day 43 compared with placebo + ADT in patients with MDD (**Figure 1**)
 - Significantly greater MADRS Total score reductions were observed at the earliest assessment (Day 8) with lumateperone 42 mg + ADT treatment and persisted throughout the study

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



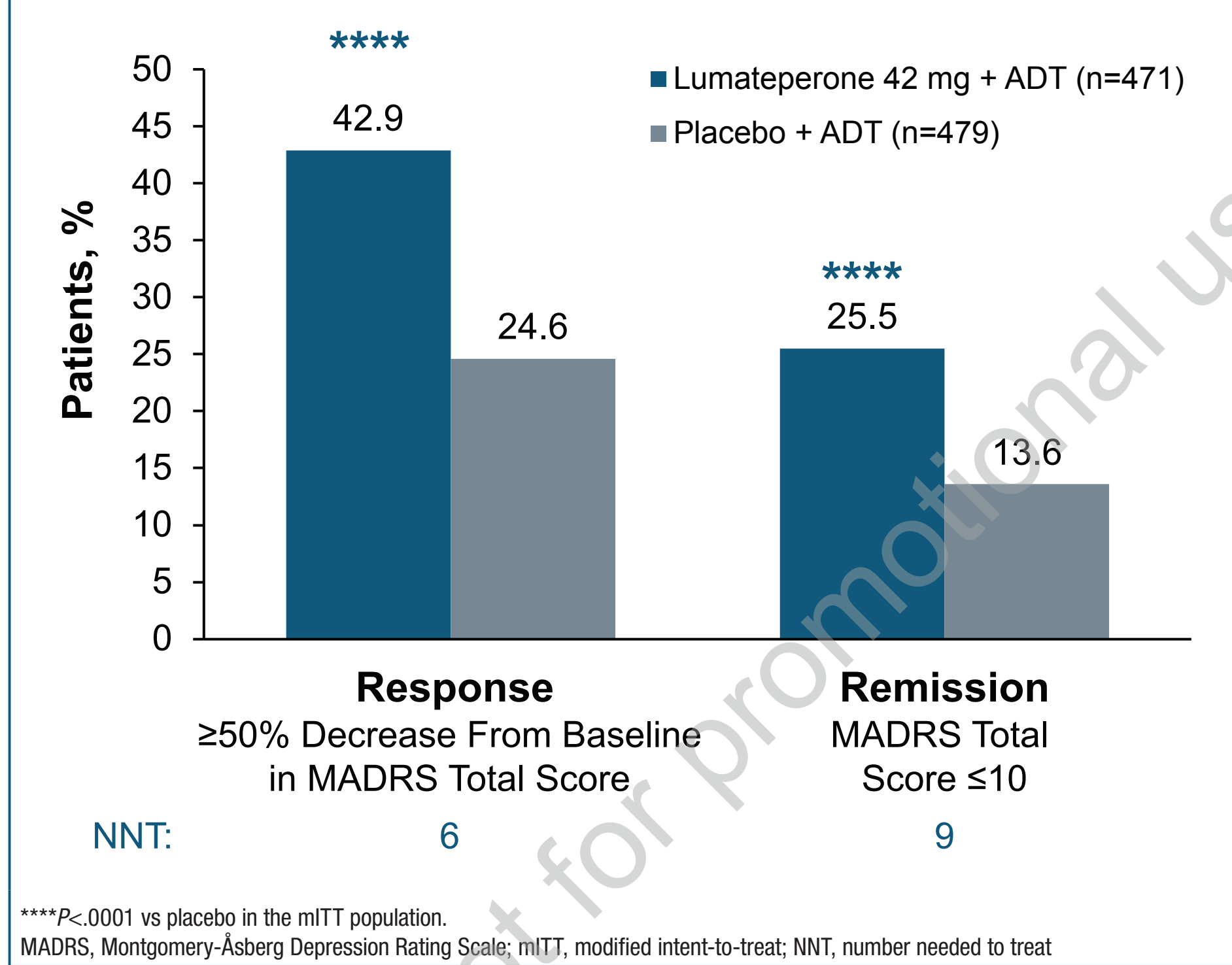
- Similarly, lumateperone 42 mg + ADT was associated with improvements in overall MDD disease severity (**Figure 2**)
 - CGI-S score showed improvements by Day 8 with lumateperone 42 mg + ADT treatment and continued throughout the study

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



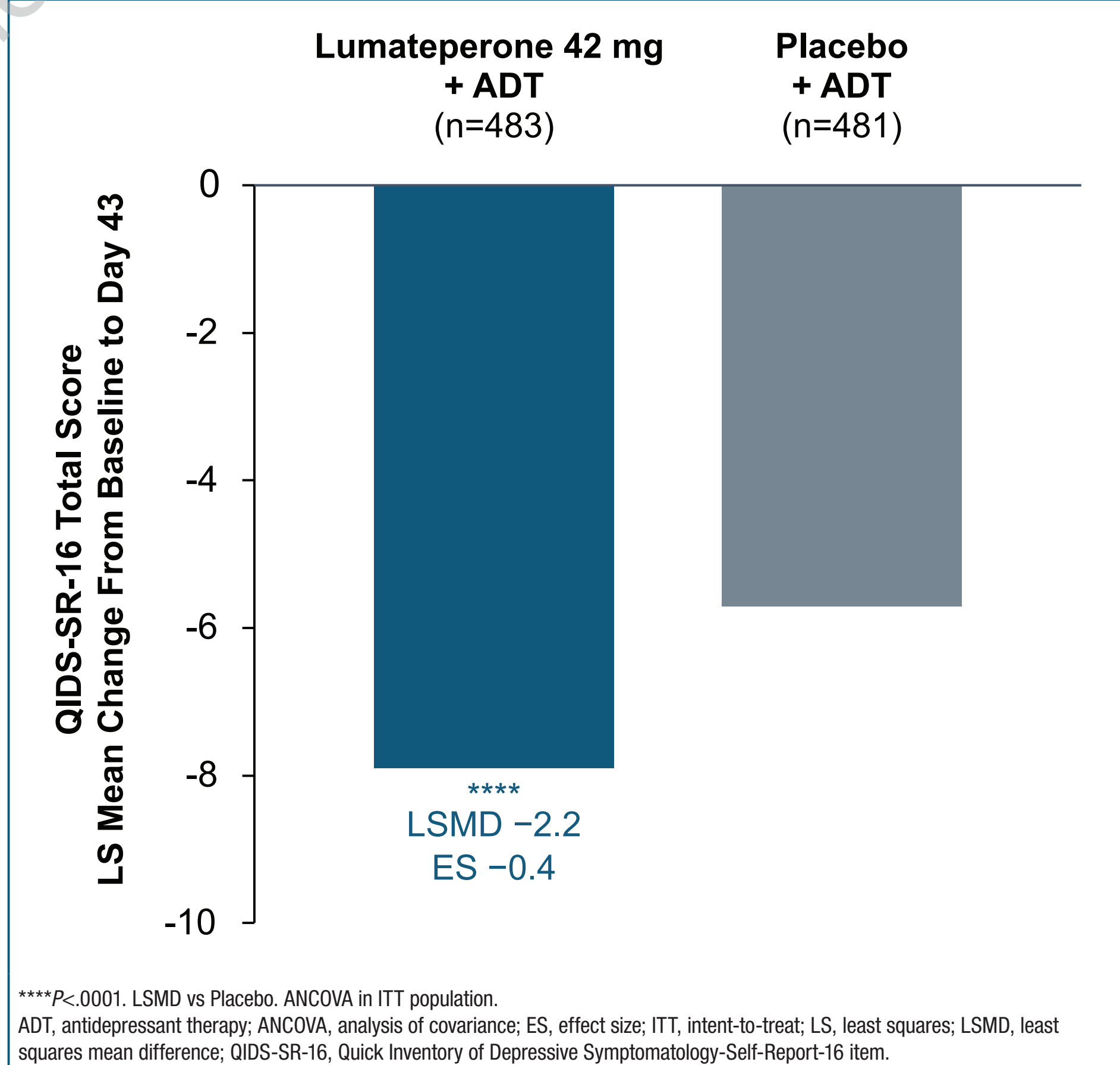
- In the pooled population at Day 43, rates of MADRS Total score response and remission were significantly greater with lumateperone + ADT vs placebo + ADT at Day 43 (**Figure 3**)
 - Based on number needed to treat (NNT), lumateperone + ADT compared with placebo + ADT was associated with clinically meaningful patient outcomes

Figure 3. MADRS Response and Remission Rates at Day 43



- In the pooled population, self-reported depressive symptoms, as measured by QIDS-SR-16 Total score, also significantly improved with lumateperone 42 mg + ADT compared with placebo + ADT from baseline to Day 43 (**Figure 4**)

Figure 4. LS Mean Change From Baseline to Day 43 in QIDS-SR-16 Total Score



CONCLUSIONS

- Lumateperone 42 mg adjunctive to ADT demonstrated robust, clinically meaningful efficacy over adjunctive placebo to ADT in this pooled analysis of 2 trials in patients with MDD with inadequate ADT response**
- Lumateperone 42 mg adjunctive to ADT improved depression symptoms, disease severity, and patient reported outcomes**
- This pooled analysis suggest lumateperone 42 mg adjunctive to ADT is a promising new treatment option for adults with MDD and with inadequate response to 1 to 2 courses of prior ADT**

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