Efficacy of Lumateperone 42 mg for the Treatment of Major Depressive Disorder: Analysis of Demographic and Clinical Subgroups in a Phase 3 Randomized Placebo-Controlled Trial

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Background

- Major depressive disorder (MDD) is a complex mental illness with varying clinical presentations and treatment responses[1–3]
- Demographic and clinical characteristics can influence treatment outcomes in patients with MDD, making it essential to evaluate treatment efficacy in distinct subgroups to establish consistency of treatment effect[1,2]
- Lumateperone is an atypical antipsychotic indicated for: treatment of schizophrenia in adults; treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate; and treatment of MDD in adults as adjunct to antidepressant therapy (ADT)[4]
  - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission[5]
  - Specifically, lumateperone is a potent serotonin 5-HT$_{2A}$ receptor antagonist, a dopamine D$_2$ receptor presynaptic partial agonist and postsynaptic antagonist, a D$_1$ receptor–dependent indirect modulator of AMPA and NMDA currents, and a serotonin reuptake inhibitor[5]
  - This novel mechanism of action with multimodal effects may confer robust efficacy with improved tolerability compared with current treatment options
- The efficacy and safety of lumateperone 42 mg adjunctive to ADT were established in 2 Phase 3 randomized, double-blind, placebo-controlled trials (Study 501 [NCT04985942] and Study 502 [NCT05061706]) in patients with MDD with inadequate ADT response[6–9]
  - In both studies, lumateperone 42 mg + ADT met the primary and key secondary endpoints, showing significant improvement vs placebo + ADT at Day 43 on both the Montgomery–Åsberg Depression Rating Scale (MADRS) Total score and Clinical Global Impression–Severity (CGI-S) score, and was generally well tolerated[6,7]
- This analysis of Study 501 evaluated the efficacy of lumateperone 42 mg adjunctive to ADT across demographic and clinical subgroups of patients with MDD with inadequate ADT response

Methods

- Study 501 enrolled eligible adults (18-65 years) who met DSM-5 criteria for MDD with inadequate response to 1-2 courses of ADT in the current depressive episode, defined as <50% improvement on the Antidepressant Treatment Response Questionnaire
  - Patients were experiencing a major depressive episode (MADRS Total score ≥24 and CGI-S score ≥4) and had Quick Inventory of Depressive Symptomatology-Self Report-16 (QIDS-SR-16) item score ≥14 at screening and baseline
- Patients were randomized 1:1 to 6-week, oral lumateperone 42 mg/day + ADT or placebo + ADT
- The primary and key secondary endpoints were the changes from baseline to Day 43 in MADRS Total score and CGI-S score, respectively
- MADRS response and remission, as well as change from baseline to Day 43 in patient-rated scales for depression (QIDS-SR-16 Total score, range from 0 to 27; higher scores indicating more severe depression[10]), were also assessed
- Efficacy was evaluated in the overall population and in patient subgroups by demographic and baseline disease characteristics using a mixed-effects model for repeated measures (MMRM) or analysis of covariance (**Box 1**)

Box 1. Demographic and Baseline Disease Characteristic Subgroups

Demographic subgroups	Baseline disease characteristic subgroups
• Age: ≤40 or >40 years • Sex: male or female • Race: White or non-White • Ethnicity: Hispanic/Latino or not Hispanic/Latino • Region: US or non-US	• Disease severity • Type of ADT • Number of ADT failures in the current episode • Presence/absence of DSM-5–defined anxious distress

ADT, antidepressant therapy; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

Results

Patient Population

- The modified intent-to-treat (mITT) population comprised 481 patients (lumateperone + ADT, n=239; placebo + ADT, n=242)
- Baseline demographics and clinical characteristics were similar between groups
  - The mean age of patients was 45 years
  - Most patients were White (76.7%) and female (65.7%)

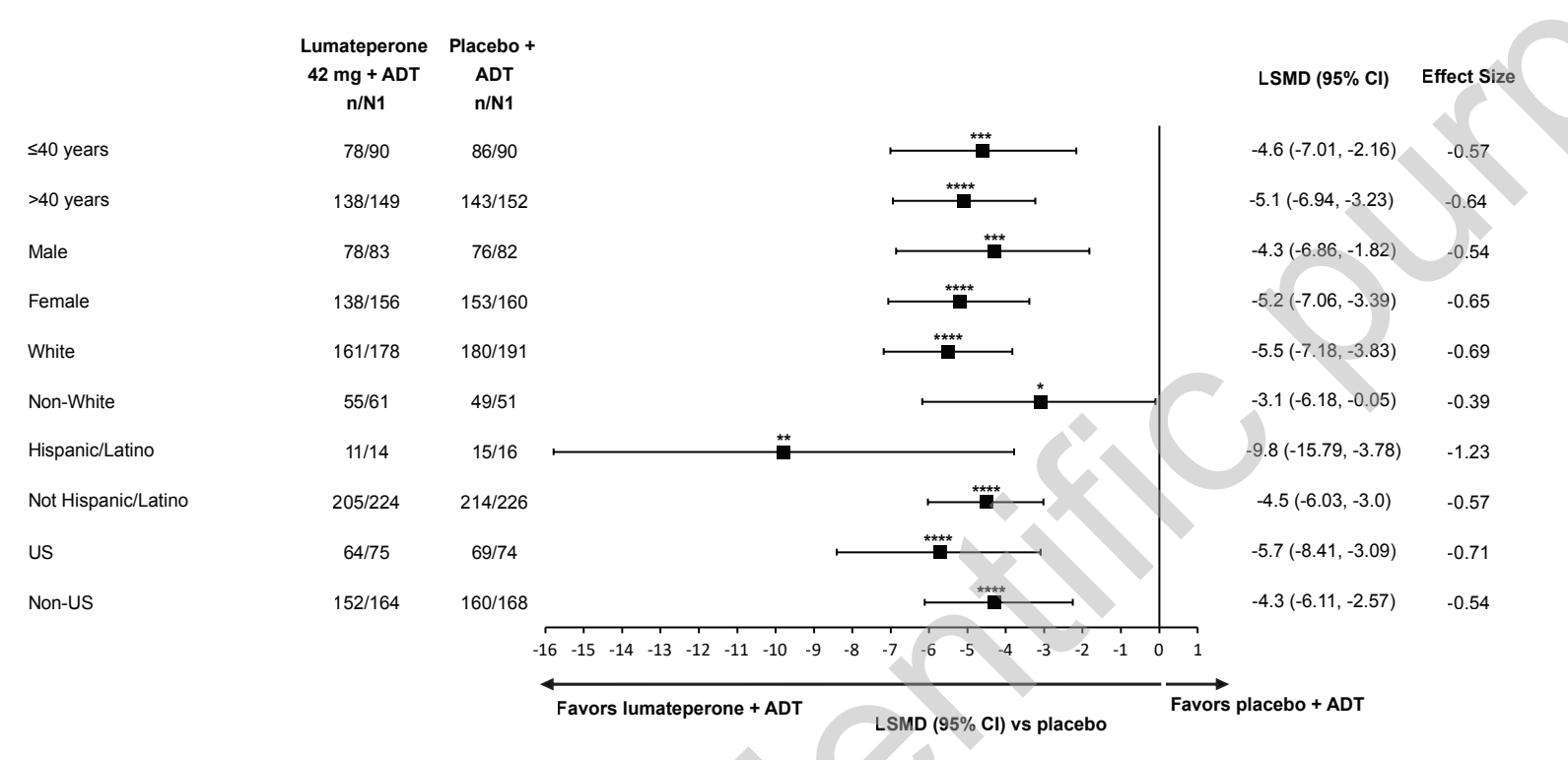
Efficacy

- The primary endpoint was met for lumateperone + ADT, with significantly greater MADRS Total score improvement from baseline to Day 43 vs placebo + ADT in the mITT population (least squares mean difference vs placebo [LSMD], −4.9; effect size [ES], −0.61; *P*<.0001)
- Lumateperone + ADT significantly improved CGI-S score (LSMD, −0.7; ES, −0.67; *P*<.0001) from baseline to Day 43 vs placebo + ADT in the mITT population
- Lumateperone + ADT significantly improved self-reported depressive symptoms at Day 43 vs placebo + ADT, as measured by QIDS-SR-16 Total score (LSMD, −2.4; *P*<.0001) in the ITT population

Subgroup Analysis

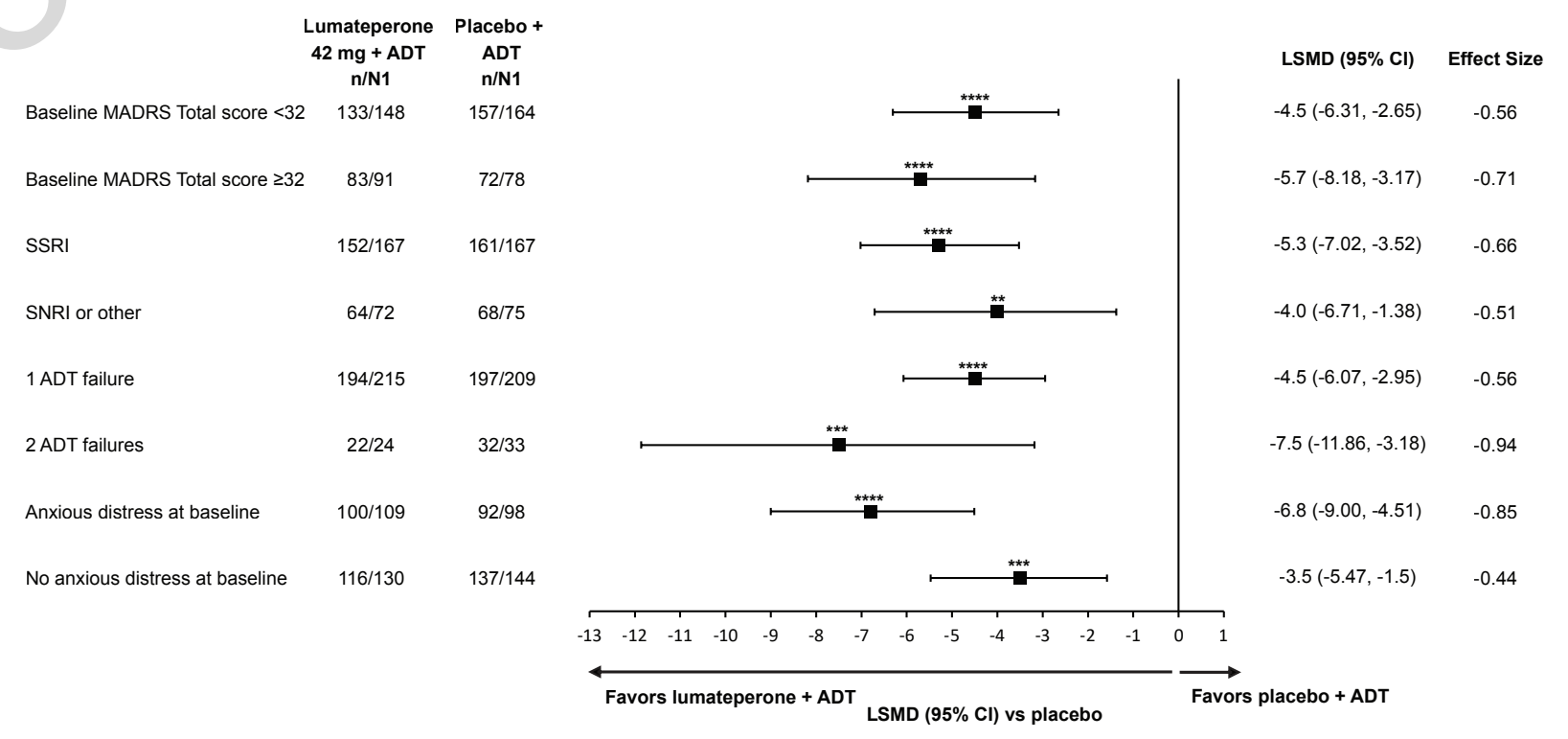
- Consistent improvement in MADRS Total score at Day 43 with lumateperone + ADT vs placebo + ADT was observed in all demographic subgroups assessed (age, sex, race group, ethnicity, and region) (**Figure 1A**)
- Lumateperone + ADT significantly improved MADRS Total score from baseline to Day 43 irrespective of baseline disease characteristics (disease severity, type of ADT, number of ADT failures in the current episode, and presence/absence of anxious distress) (**Figure 1B**)

Figure 1A. Change from Baseline to Day 43 in MADRS Total Score Among Demographic Subgroups (mITT Population)



**P*<.05 ***P*<.01 ****P*<.001 *****P*<.0001.
N1=Number of patients in each group at baseline.
ADT, antidepressant therapy; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat.

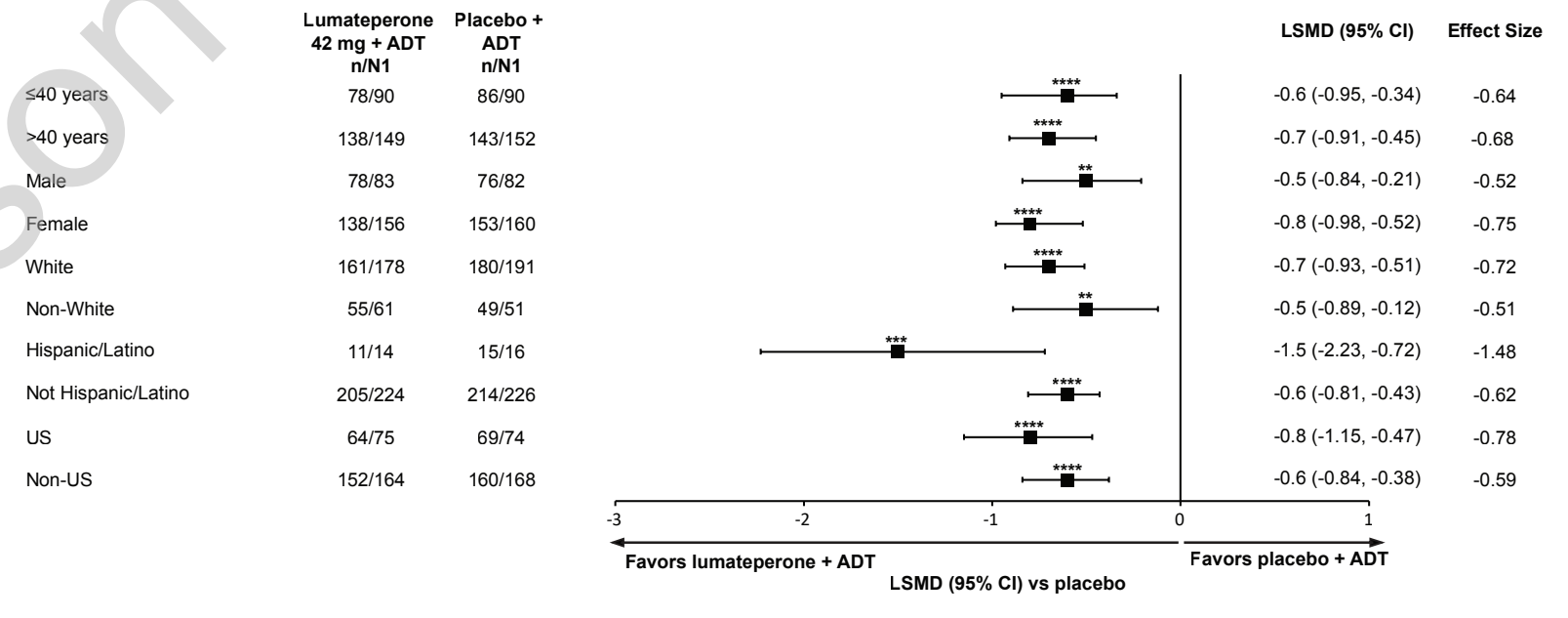
Figure 1B. Change from Baseline to Day 43 in MADRS Total Score Among Disease Characteristic Subgroups (mITT Population)



**P*<.05 ***P*<.01 ****P*<.001 *****P*<.0001.
N1=Number of patients in each group at baseline.
ADT, antidepressant therapy; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

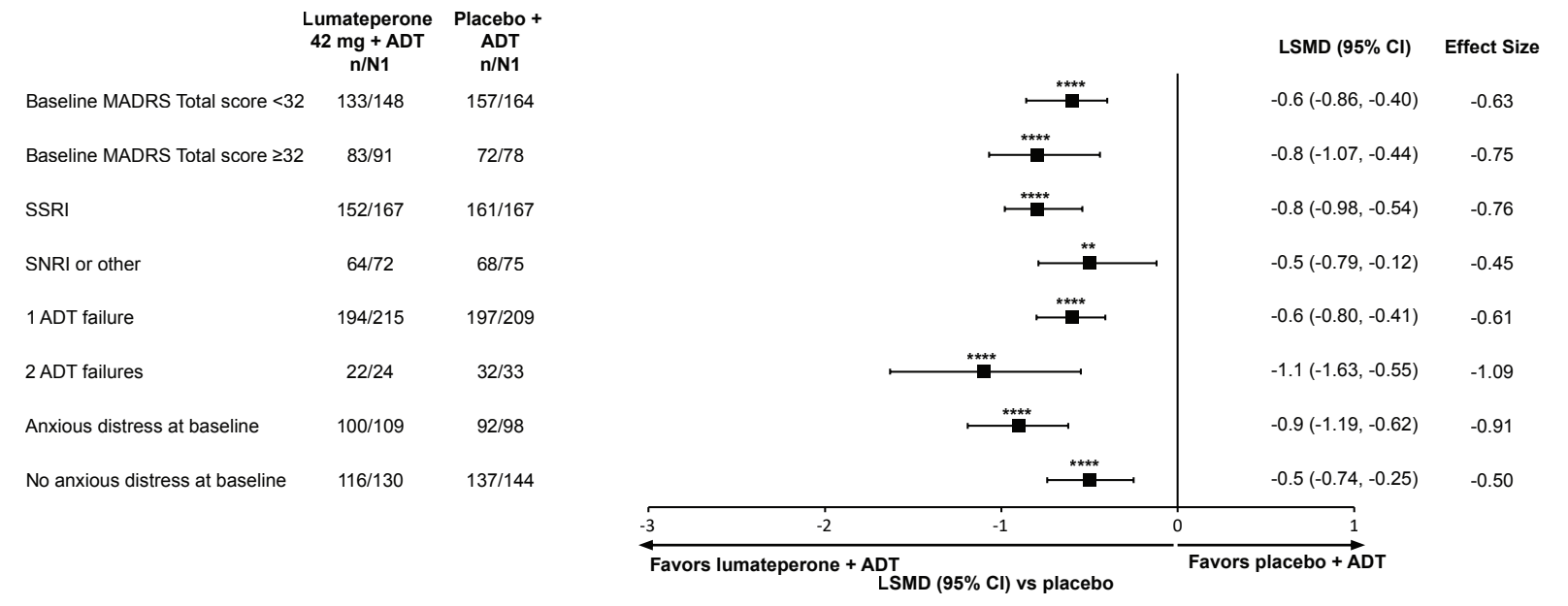
- Treatment with lumateperone + ADT consistently led to statistically significant improvements (*P*<.05) in CGI-S score vs placebo + ADT from baseline to Day 43 across all patient subgroups, independent of age, sex, race, ethnicity, geographic region, baseline severity, ADT type, number of prior ADT failures in the current episode, or baseline anxious distress (**Figures 2A and 2B**)

Figure 2A. Change from Baseline to Day 43 in CGI-S Score Among Demographic Subgroups (mITT Population)



**P*<.05 ***P*<.01 ****P*<.001 *****P*<.0001.
n=Number of patients analyzed; N1=Number of patients in each group at baseline.
ADT, antidepressant therapy; CGI-S, Clinical Global Impression-Severity Scale; LSMD, least squares mean difference; mITT, modified intent-to-treat.

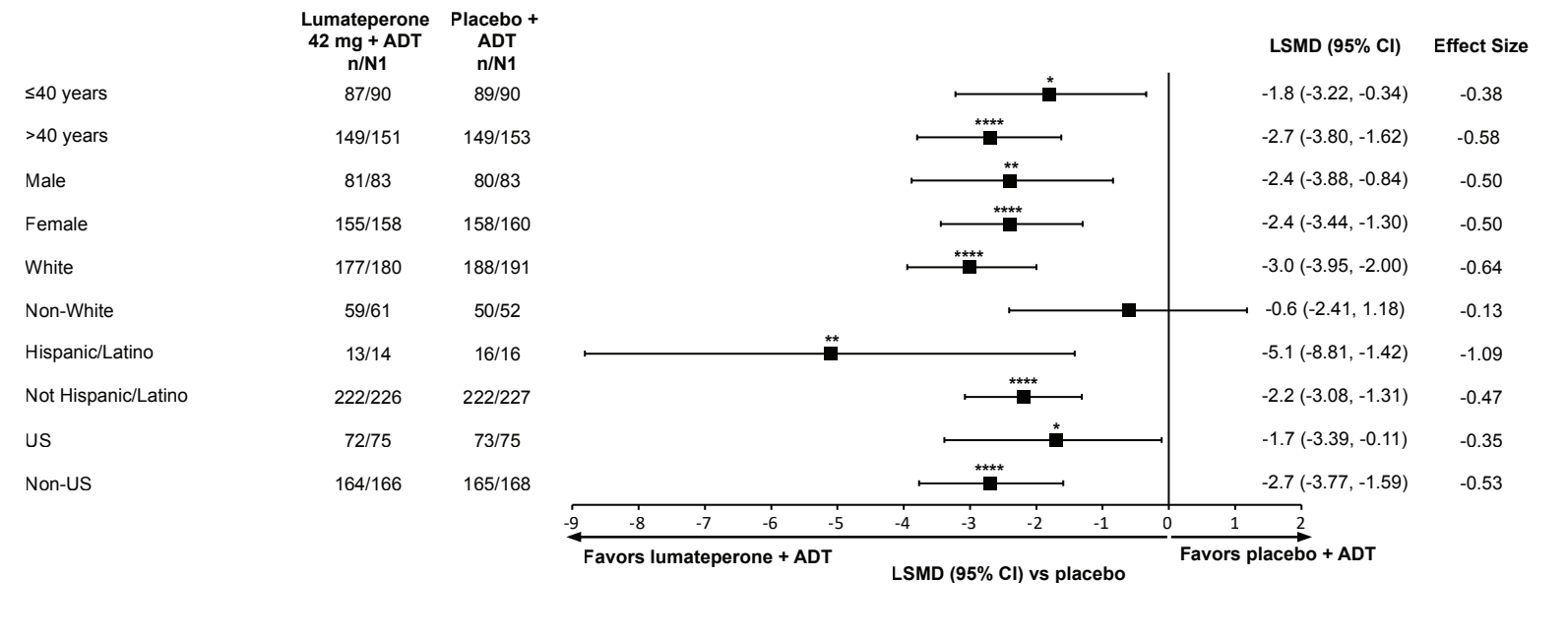
Figure 2B. Change from Baseline to Day 43 in CGI-S Score Among Disease Characteristic Subgroups (mITT Population)



**P*<.05 ***P*<.01 ****P*<.001 *****P*<.0001.
n=Number of patients analyzed; N1=Number of patients in each group at baseline.
ADT, antidepressant therapy; CGI-S, Clinical Global Impression-Severity Scale; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

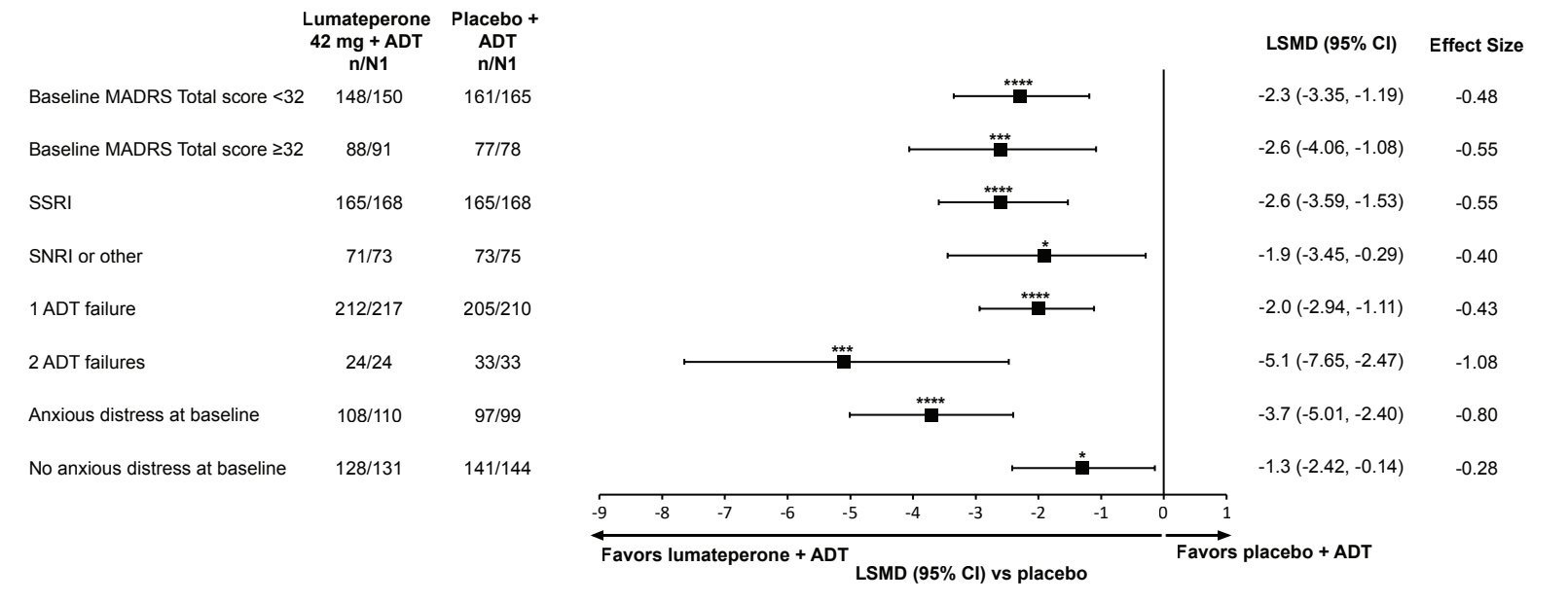
- Lumateperone + ADT significantly improved (*P*<.05) QIDS-SR-16 Total score at Day 43 vs placebo + ADT in all patient subgroups, except for race (White, *P*<.0001; non-White, *P*=.5011) (**Figure 3A and 3B**)

Figure 3A. Change from Baseline to Day 43 in QIDS-SR-16 Total Score Among Demographic Subgroups (mITT Population)



**P*<.05 ***P*<.01 ****P*<.001 *****P*<.0001.
n=Number of patients analyzed; N1=Number of patients in each group at baseline.
ADT, antidepressant therapy; LSMD, least squares mean difference; mITT, modified intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

Figure 3B. Change from Baseline to Day 43 in QIDS-SR-16 Total Score Among Disease Characteristic Subgroups (mITT Population)



**P*<.05 ***P*<.01 ****P*<.001 *****P*<.0001.
n=Number of patients analyzed; N1=Number of patients in each group at baseline.
ADT, antidepressant therapy; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

- Treatment with lumateperone + ADT consistently led to statistically significant improvements (*P*<.05) in MADRS response at Day 43 vs placebo + ADT in all patient subgroups, except for race (White, *P*<.0001; non-White, *P*=.2660) and ethnicity (Hispanic/Latino, *P*=.0938; not Hispanic/Latino, *P*<.0001)
- Treatment with lumateperone + ADT consistently led to statistically significant improvements (*P*<.05) in MADRS remission at Day 43 vs placebo + ADT across subgroups for age, sex, region, disease severity, and presence/absence of anxious distress, but not for race (White, *P*=.0002; non-White, *P*=.7936), ethnicity (Hispanic/Latino, *P*=.1009; not Hispanic/Latino, *P*=.0028), type of ADT (SNRI/other, *P*=.3141; SSRI, *P*=.0010), or number of ADT failures in the current episode (2 failures, *P*=.2127; 1 failure, *P*=.0023)

Conclusions

- ✓ Lumateperone 42 mg adjunctive to ADT demonstrated consistent and clinically meaningful improvements over placebo adjunctive to ADT across demographic and disease characteristic subgroups of patients with MDD enrolled in Study 501
- ✓ These results highlight lumateperone as a promising adjunctive treatment option for patients with MDD with inadequate ADT response

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Disclosures

S Durgam is a former employee of Intra-Cellular Therapies, a Johnson & Johnson company.
WR Earley, N Wagner, and H Lakkis are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company.

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