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Efficacy and Safety of Adjunctive Lumateperone 42 mg in Major Depressive Disorder: A Pooled Analysis of Demographic and Clinical Subgroups From Two Phase 3 Randomized Placebo-Controlled Trials

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Background

- Major depressive disorder (MDD) is a common mental illness associated with functional impairment, comorbidities, reduced quality of life, and impaired work productivity[1,2]
- Despite available treatments, many patients with MDD experience inadequate response to antidepressant therapy (ADT)[3]
- The clinical heterogeneity of MDD may influence treatment response, highlighting the need to establish consistency of treatment effect across patient subgroups according to demographic and clinical characteristics[4,5]
- 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 ADT[6]
  - Evidence supports that lumateperone is a modulator of serotonin, dopamine, and glutamate neurotransmission[7]
  - Specifically, lumateperone is a potent serotonin 5-HT_{2A} receptor antagonist, a serotonin reuptake inhibitor, a dopamine D_2 receptor presynaptic partial agonist and postsynaptic antagonist, and a D_1 receptor-dependent indirect modulator of glutamatergic AMPA and NMDA currents[7]
  - 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 demonstrated in 2 Phase 3, double-blind, placebo-controlled studies (Study 501 [NCT04985942]; Study 502 [NCT05061706]) in patients with MDD with inadequate ADT response[8,9]
  - The primary and key secondary efficacy endpoints were met in both studies, with lumateperone 42 mg + ADT significantly improving Montgomery-Åsberg Depression Rating Scale (MADRS) Total score and Clinical Global Impression–Severity (CGI-S) score from baseline to Day 43 compared with placebo + ADT, and was generally well tolerated[8,9]
- This pooled analysis of Studies 501 and 502 evaluated lumateperone 42 mg adjunctive to ADT across demographic and clinical subgroups of patients with MDD with inadequate response to ADT

Methods

- Data were pooled from Studies 501 and 502, which enrolled eligible adults (aged 18-65 years) who met DSM-5 criteria for MDD with inadequate response to 1-2 courses of ADT in the current depressive episode (MADRS Total score ≥24 and CGI-S score ≥4) and had Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score ≥14 at screening and baseline[8,9]
  - Inadequate response to ADT was defined as <50% improvement with ≥6 weeks ADT monotherapy, as confirmed by the Antidepressant Treatment Response Questionnaire
- 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
  - Change from baseline to Day 43 in patient-rated scales for depression (QIDS-SR-16 Total score, range from 0 to 27; higher scores indicate more severe depression[10]) was also assessed
- Efficacy was evaluated in the overall population and across patient subgroups defined by demographic and baseline disease characteristics using a mixed-effects model for repeated measures (MMRM) or analysis of covariance (**Table 1**)
- Safety assessments included adverse events (AEs), physical examinations, vital signs, and changes in laboratory parameters

Table 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 pooled modified intent-to-treat (mITT) population comprised 950 patients (lumateperone + ADT, n=471; placebo + ADT, n=479) from Studies 501 and 502
- Demographics and baseline characteristics were similar between treatment groups
  - The mean age of patients was 45.2 years for the lumateperone + ADT group and 45.8 years for the placebo + ADT group
  - Most patients were White (86.0%) and female (67.7%)

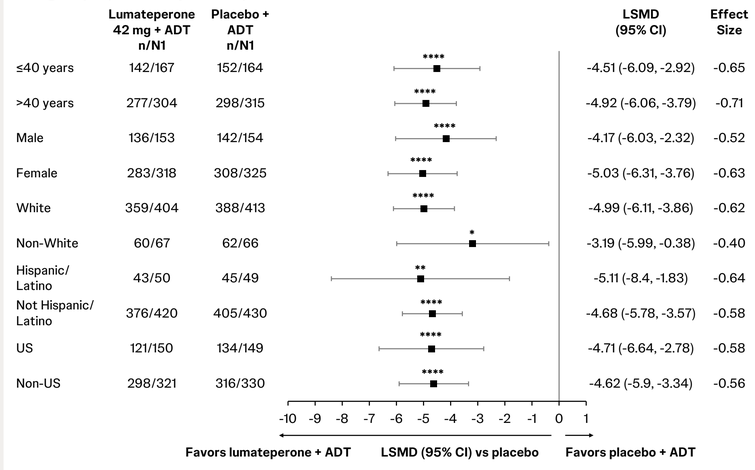
Efficacy

- Lumateperone + ADT met the primary endpoint, showing 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]=-4.7; effect size [ES]=-0.59; *P*<.0001)
- Significant improvement in the CGI-S score from baseline to Day 43 was observed with lumateperone + ADT vs placebo + ADT in the mITT population (LSMD=-0.6; ES=-0.59; *P*<.0001)
- Lumateperone + ADT demonstrated significantly greater improvement in QIDS-SR-16 Total score at Day 43 compared with placebo in the ITT population (LSMD=-2.2; ES=-0.4; *P*<.0001)

Subgroup Analysis

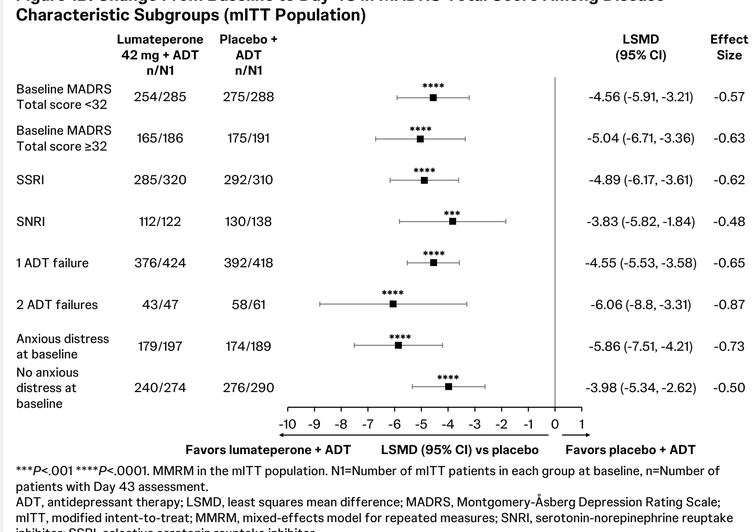
- Significant improvement in MADRS Total score at Day 43 with lumateperone + ADT vs placebo + ADT was observed across all demographic subgroups (age, sex, race, ethnicity, and region) (**Figure 1A**)
- Lumateperone + ADT significantly improved MADRS Total score from baseline to Day 43 across all baseline disease characteristics, including 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<.0001. MMRM in the mITT population. N1=Number of mITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

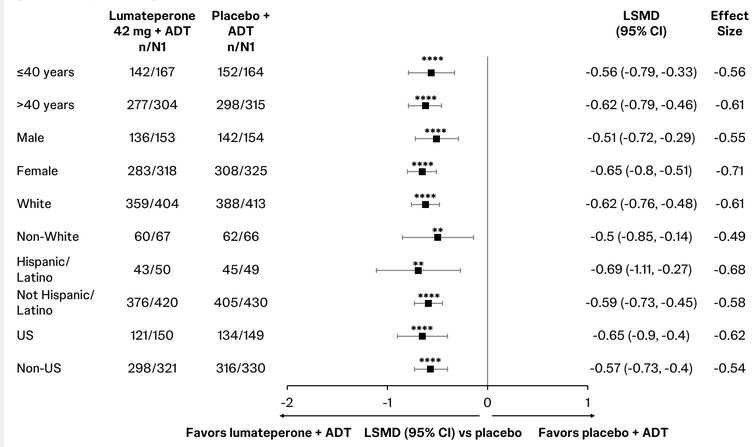
Figure 1B. Change From Baseline to Day 43 in MADRS Total Score Among Disease Characteristic Subgroups (mITT Population)



***P<.001 ****P<.0001. MMRM in the mITT population. N1=Number of mITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

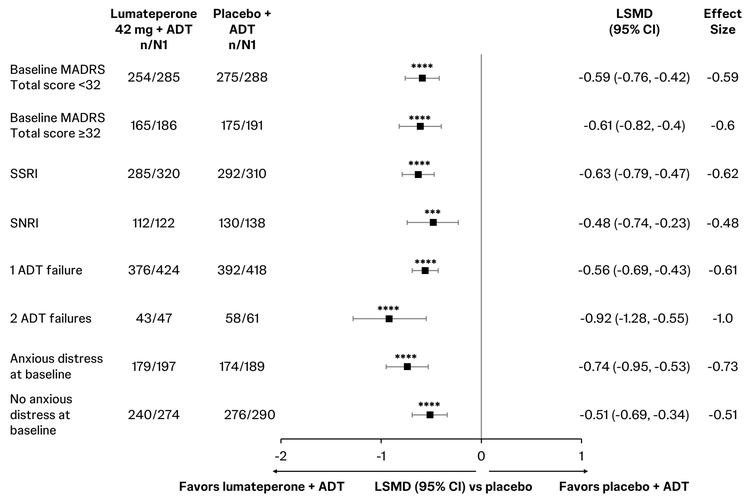
- Treatment with lumateperone + ADT led to significant CGI-S score improvements (*P*<.01) at Day 43 compared with placebo + ADT in all subgroups (age, sex, race, ethnicity, region, baseline disease severity, type of ADT, number of ADT failures, baseline anxious distress) (**Figures 2A and 2B**)

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



**P<.01 ****P<.0001. MMRM in the mITT population. N1=Number of mITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; CGI-S, Clinical Global Impression–Severity; LSMD, least squares mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

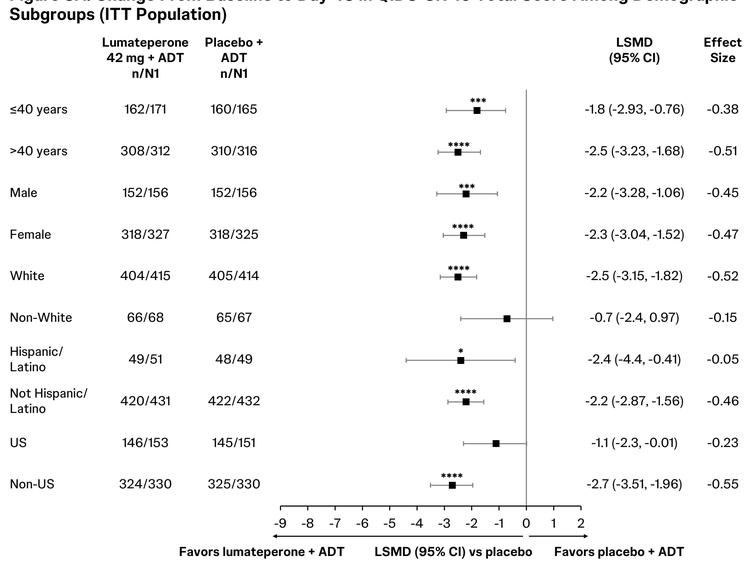
Figure 2B. Change From Baseline to Day 43 in CGI-S Score Among Disease Characteristic Subgroups (mITT Population)



***P<.001 ****P<.0001. MMRM in the mITT population. N1=Number of mITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; CGI-S, Clinical Global Impression–Severity; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

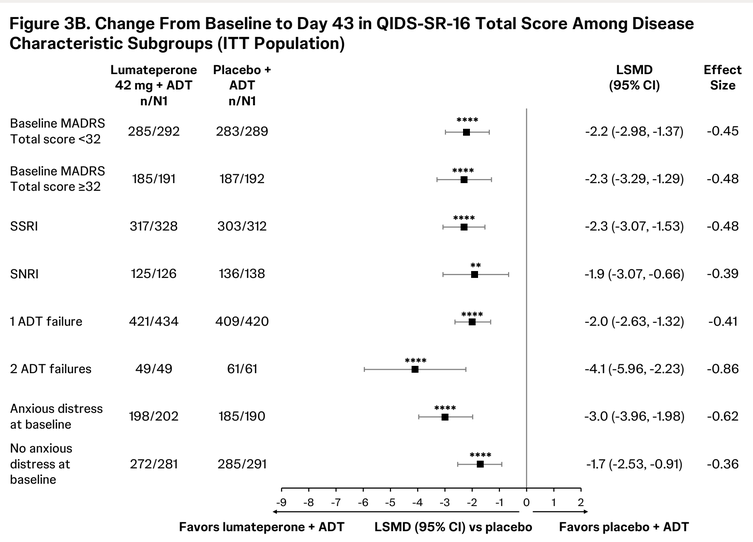
- Significant improvements in QIDS-SR-16 Total score (*P*<.05) at Day 43 were observed with lumateperone + ADT vs placebo + ADT in all patient subgroups, except for race (White, *P*<.0001; non-White, *P*=.4062) and region (non-US, *P*<.0001; US, *P*=.0522) (**Figure 3A and 3B**)

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



*P<.05 ***P<.001 ****P<.0001. ANCOVA in the ITT population. N1=Number of ITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; LSMD, least squares mean difference; ITT, 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 (ITT Population)



**P<.01 ****P<.0001. ANCOVA in the ITT population. N1=Number of ITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; ITT, 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.

Safety

- Treatment-emergent AEs (TEAEs) occurred in 68.1% of patients in the lumateperone + ADT group, compared with 45.1% in the placebo + ADT group
- In the lumateperone + ADT group, dizziness, dry mouth, somnolence, nausea, fatigue, and diarrhea were reported in ≥5% of patients and at more than twice the rate in the placebo + ADT group
- Weight, body mass index, and waist circumference remained stable in both groups (mean [SD] change from baseline to end of treatment: lumateperone + ADT, -0.1 [1.7], -0.0 [0.6], and -0.2 [4.0]; placebo + ADT, 0.0 [1.7], 0.0 [0.6], and -0.3 [4.4], respectively)
- Mean changes from baseline to the end of treatment in cardiometabolic parameters (cholesterol, glucose, and insulin levels) were comparable between lumateperone + ADT and placebo + ADT groups, with no clinically relevant prolactin increases at end of treatment
- There were no notable changes in extrapyramidal symptoms (EPS) scales (Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, and Simpson-Angus Scale) and low rates of EPS-related TEAEs with lumateperone + ADT treatment

Conclusions

In this pooled analysis, lumateperone 42 mg adjunctive to ADT demonstrated consistent and clinically meaningful improvements compared with placebo adjunctive to ADT across demographic and baseline disease subgroups of patients with MDD enrolled in Studies 501 and 502

Lumateperone + ADT was generally well tolerated, supporting its use as an adjunctive treatment option for patients with MDD with inadequate response to ADT

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Disclosures

WR Earley, C Chen, and R Migliore are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company.

S Durgam is a former employee of Intra-Cellular Therapies, a Johnson & Johnson company.

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