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 globally[1]
  - It is associated with multiple comorbidities, impaired functioning, and a heightened risk of suicide[1]
  - 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 neurotransmission[4]
  - 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[4]
  - 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 42 mg, 4.7; placebo, 4.6) indicate moderate-to-severe depression at baseline

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

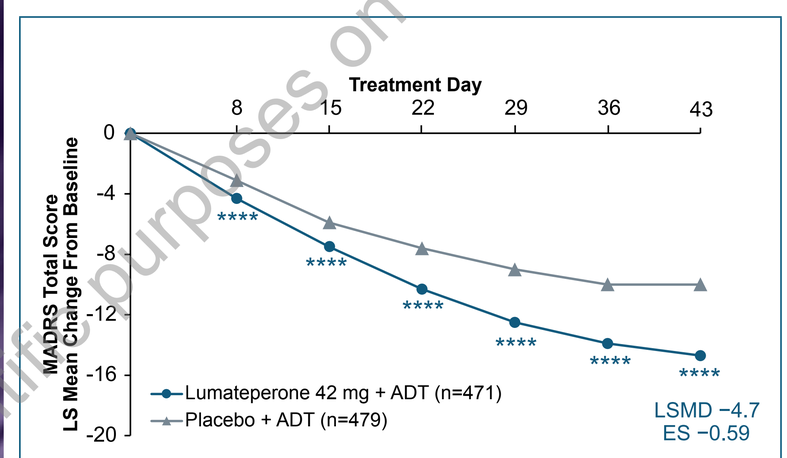
	Lumateperone 42 mg + ADT (n=471)	Placebo + ADT (n=479)
Age, mean (range), years	45.2 (18-65)	45.8 (18-65)
Sex, n (%)		
Women	318 (67.5)	325 (67.8)
Men	153 (32.5)	154 (32.2)
Race, n (%)		
White	404 (85.8)	413 (86.2)
Asian	41 (8.7)	35 (7.3)
Black	25 (5.3)	24 (5.0)
Other	1 (0.2)	7 (1.5)
Hispanic or Latino 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 Symptoms-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

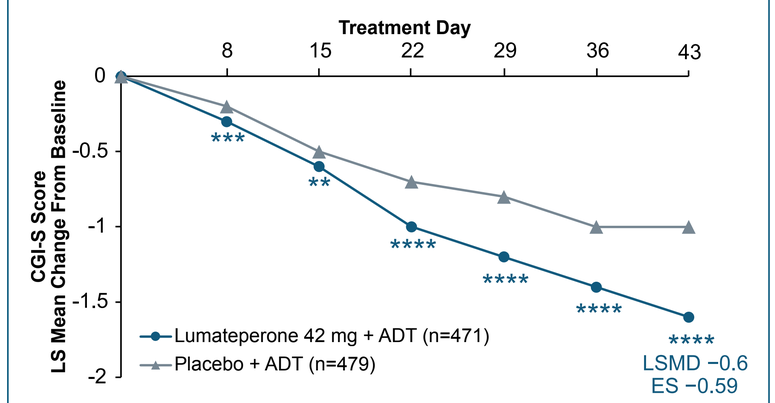
Figure 1. LS Mean Change From Baseline in MADRS Total Score



****P<.0001. LSMD vs Placebo. MMRM in mITT population.
ADT, antidepressant therapy; ES, effect size; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

- 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

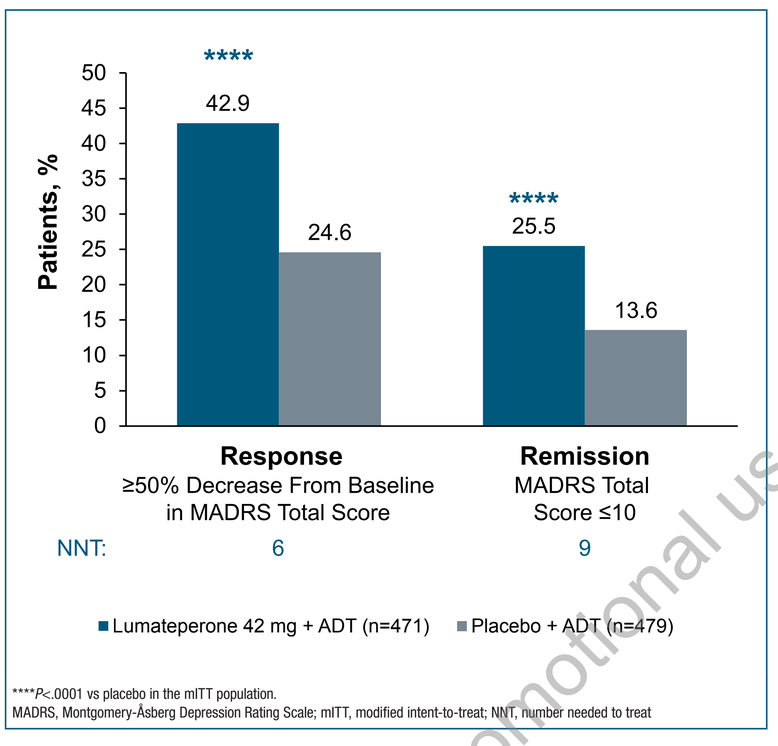
Figure 2. LS Mean Change From Baseline in CGI-S Score



**P<.01 ***P<.001 ****P<.0001. LSMD vs Placebo. MMRM in mITT population.
ADT, antidepressant therapy; ES, effect size; CGI-S, Clinical Global Impression-Severity; LS, least squares; LSMD, least squares mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

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

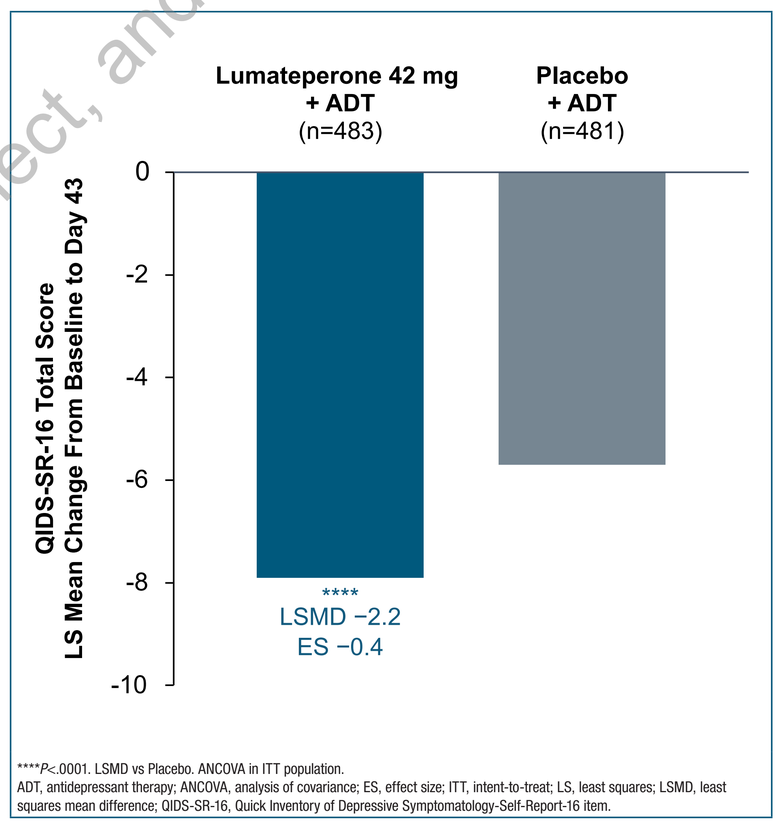
Figure 3. MADRS Response and Remission Rates at Day 43



****P<.0001 vs placebo in the mITT population.
MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; NNT, number needed to treat

- 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



****P<.0001. LSMD vs Placebo. ANCOVA in ITT population.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; ES, effect size; ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self-Report-16 item.

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 ADT**

REFERENCES

1. Marx W, et al. *Nat Rev Dis Primers*. 2023;9.
2. Mago R, et al. *BMC Psychiatry*. 2018;18:33.
3. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc.;2023.
4. Titulaer J, et al. *Eur Neuropsychopharmacol*. 2022;62:22-35.
5. Durgam S, et al. "Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder: Results From a Randomised, Double-blind, Phase 3 Trial." Poster presented at: European College of Neuropsychopharmacology Annual Congress, September 21-24, 2024, Milan, Italy.
6. Durgam S, et al. "Adjunctive Lumateperone in Patients With Major Depressive Disorder: Results From an Additional Randomized, Double-Blind, Phase 3 Trial." Poster presented at: Psych Congress Annual Meeting, October 29- November 2, 2024, Boston, MA.

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S Durgam, WR Earley, C Chen, and JB Edwards are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson Company. SG Kozauer is a former employee of Intra-Cellular Therapies, a Johnson & Johnson Company.

R Jain has served as a consultant to Addrenex, Allergan (now AbbVie), Avanir, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Supernus, Takeda, and Teva; paid speaker for Addrenex, Alkermes, Allergan (now AbbVie), Lilly, Lundbeck, Merck, Neos Therapeutics, Otsuka, Pamlab, Pfizer, Rhodes, Shionogi, Shire, Sunovion, Takeda, and Tris Pharmaceuticals; received research support from Allergan (now AbbVie), AstraZeneca, Lilly, Lundbeck, Otsuka, Pfizer, Shire, and Takeda; and served on advisory board for Addrenex, Alkermes, Avanir, Forum, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Supernus, Takeda, and Teva.

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