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[1]
  - 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[2,3]
  - Patients with MDD who have inadequate antidepressant therapy (ADT) response have increased hospitalization risk and greater impairments in functioning compared with those who respond,[4] 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[5,6]
  - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission[6]
  - 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 glutamatergic AMPA and NMDA currents, and a serotonin reuptake inhibitor[6]
  - 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[7]
- 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 males and females (aged 18-65 years, inclusive) had DSM-5–diagnosed MDD with inadequate response to 1 to 2 courses of ADT in the current depressive episode, 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
- Additional measures included response (≥50% MADRS Total score decrease) and remission (MADRS Total score ≤10), analyzed with a logistic regression model, and change from baseline in QIDS-SR-16 Total score, 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**)

Table 1. Baseline Demographics and Disease Characteristics

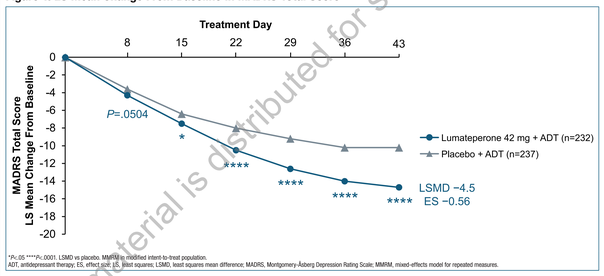
	Lumateperone 42 mg + ADT	Placebo + ADT
Demographic and Clinical Parameters, Safety Population	**(n=242)**	**(n=238)**
Age, mean (range), years	45.6 (18-65)	46.4 (18-65)
Sex, n (%)		
Female	169 (69.8)	165 (69.3)
Male	73 (30.2)	73 (30.7)
Race, n (%)		
White	235 (97.1)	223 (93.7)
Black	6 (2.5)	8 (3.4)
Asian	1 (0.4)	3 (1.3)
Other	0	4 (1.7)
Hispanic or Latino ethnicity, n (%)	37 (15.3)	33 (13.9)
No. of lifetime depressive episodes, mean (range)	3.6 (1-15)	4.3 (1-36)
ADT during double-blind treatment, n (%)		
SSRI	160 (66.1)	144 (60.5)
SNRI	67 (27.7)	80 (33.6)
Other (bupropion)	15 (6.2)	14 (5.9)
Baseline Efficacy Parameters, mITT Population	**(n=232)**	**(n=237)**
MADRS Total score, mean (SD)	30.8 (3.88)	31.5 (3.97)
CGI-S score, mean (SD)	4.6 (0.59)	4.7 (0.59)
QIDS-SR-16 Total score, mean (SD)*	17.9 (2.56)	18.0 (2.48)

*ITT population. Lumateperone 42 mg + ADT, n=242; placebo + ADT, n=238.
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.

Efficacy

- 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

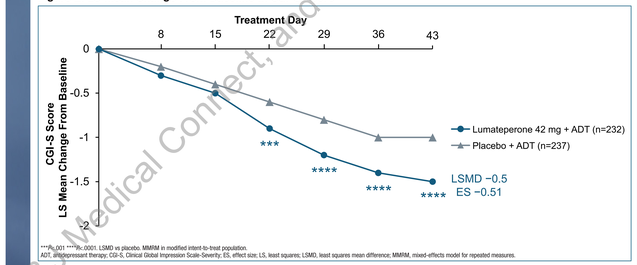
Figure 1. LS Mean Change From Baseline in MADRS Total Score



*P<.05 ****P<.0001. LSMD vs placebo. MMRM in modified intent-to-treat population.
ADT, antidepressant therapy; ES, effect size; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

- 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

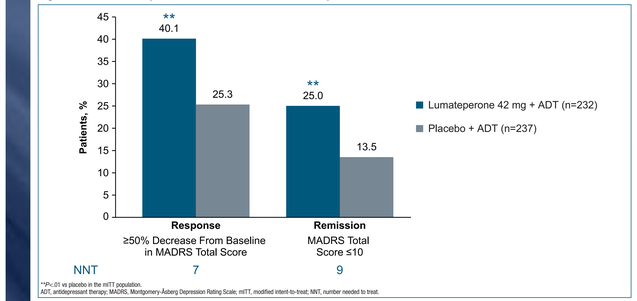
Figure 2. LS Mean Change From Baseline in CGI-S Score



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

- MADRS response (number needed to treat: 7) and remission (number needed to treat: 9) were significantly greater with lumateperone + ADT compared with placebo + ADT at Day 43 (**Figure 3**)
- 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 (least squares mean difference vs placebo, −2.2; effect size, −0.45; P<.0001)

Figure 3. MADRS Response and Remission Rates at Day 43



**P<.01 vs placebo in the mITT population.
ADT, antidepressant therapy; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; NNT, number needed to treat.

Safety

- TEAEs were reported in 43.7% of the placebo + ADT group and 78.1% of the lumateperone + ADT group
  - There were 2 serious adverse events in the lumateperone + ADT group and none in the placebo + 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 ADT**

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DISCLOSURES AND ACKNOWLEDGMENTS

WR Earley, S Durgam, SG Kozauer, Y Mo, H Lakkis, and C Gallardo are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson Company.
SG Kornstein receives research support from the National Institutes of Health and the National Science Foundation. She has served as a consultant for Lilly, Sage Therapeutics, Reunion Neuroscience, Relmada, AbbVie, Gerbera, and Arrivo Biventures.
M Fava reports the following: Research Support: AbbVie; Acadia Pharmaceuticals; Aditum Bio Management Company, LLC; Alergan, Alkermes, Inc.; Altimate Health Corporation; Alto Neuroscience, Inc.; Ancora Bio, Inc.; Angelini S.p.A; Aptinyx; Arbor Pharmaceuticals LLC; Avanir Pharmaceuticals Inc.; Axsome; Beinckiser Pharmaceuticals, Inc.; BioClinica, Inc.; Biogen; BioHaven; BioShin Limited; Cambridge Science Corporation; Centrexion Therapeutics Corporation; Cerecor; Cybin IRL Limited; Damona Pharmaceuticals; EmbarkNeuro; Eliem Therapeutics LTD; Gate Neurosciences, Inc.; GenOmind, LLC; Gentelon, LLC; Gerbera Therapeutics, Inc.; Happify; Johnson & Johnson; Lundbeck Inc.; Marinus Pharmaceuticals; Medpace, Inc.; Methylation Sciences, Inc.; Millennium Pharmaceutics, Inc.; Minerva Neurosciences; Neuralstem; Neurocrine Biosciences, Inc.; NeuroRX Inc.; Novaremed; Novartis; Otsuka; Pfizer; Premiere Research International; Praxis Precision Medicines; Protagenic Therapeutics, Inc.; Relmada Therapeutics Inc.; Reckitt; Shenox Pharmaceuticals; Stanley Medical Research Institute; Taisho; Takeda; University of Michigan; Vistagen; WinSanTor, Inc.; Xenon Pharmaceuticals, Inc.; National Institute of Drug Abuse; National Institutes of Health; National Institute of Mental Health; and PCORI. Consulting: Massachusetts General Hospital, Revival Therapeutics, and Sensorium Therapeutics. Speaking/Publishing: Lecture at Global Medical Education, Inc. Mood Disorders Summit, November 2020. Stock/Other Financial Options: Equity Holdings: Compellis; Neuronity; Psy Therapeutics; Revival Therapeutics; Sensorium Therapeutics. Other income from royalties, patents, and copyrighted scales and questionnaires. List available upon request.
The authors thank all study investigators, research staff, and patients for their participation. Medical writing support was provided by Kendall Foote, PhD, of Nucleus Global, an Inizio company, funded by Intra-Cellular Therapies, a Johnson & Johnson Company.

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