Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder: Results From a Randomized, Double-blind, Phase 3 Trial

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BACKGROUND

- Depression is a leading cause of disability worldwide,[1] and major depressive disorder (MDD) is associated with functional impairment, comorbidities, and reduced quality of life[2]
  - Current treatments for MDD are often limited by delayed responses and undesirable side effects (eg, weight gain, metabolic disturbances, sexual dysfunction, and disturbed sleep)[3,4]
  - Following first-line treatment, the majority of patients fail to achieve remission (≈75%) and the remission rates decrease with each successive treatment,[5] demonstrating the need for novel, effective treatments
- 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[6,7]
  - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission[7]
  - 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[7]
  - This novel mechanism of action with multimodal effects may confer robust efficacy with improved tolerability compared with current treatment options
- This Phase 3, randomized, double-blind, placebo-controlled, multicenter trial (Study 501; NCT04985942) investigated the efficacy and safety of adjunctive lumateperone 42 mg in patients with MDD with inadequate response to antidepressant therapy (ADT)

METHODS

- Eligible males and females (aged 18-65 years) had *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* 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 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 (MMRM)
- Additional measures included response (≥50% MADRS Total score decrease) and remission (MADRS Total score ≤10), analyzed with a logistic regression model
  - Patient-reported outcomes included change from baseline in QIDS-SR-16 Total score, examined with an analysis of covariance-last observation carried forward approach, and Generalized Anxiety Disorder-7 (GAD-7) Total score, analyzed with an MMRM
- Safety assessments included treatment-emergent adverse events (TEAEs), laboratory parameters, extrapyramidal symptoms (EPS), and suicidality via the Columbia-Suicide Severity Rating Scale (C-SSRS)

RESULTS

Patient Population

- Of 485 patients randomized, 484 received treatment adjunctive to ADT (placebo, 243; lumateperone, 241) and 93.4% completed treatment
- Demographics and baseline characteristics were similar between groups (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

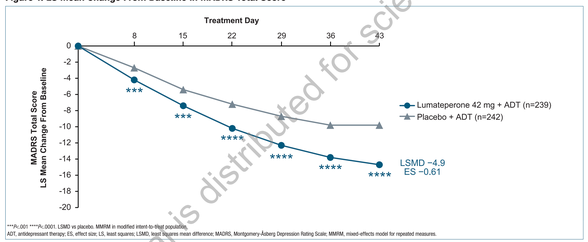
	Lumateperone 42 mg + ADT	Placebo + ADT
Demographic and Clinical Parameters, Safety Population	**(n=241)**	**(n=243)**
Age, mean (range), years	45 (18-65)	45 (19-65)
Sex, n (%)		
Female	158 (65.6)	160 (65.8)
Male	83 (34.4)	83 (34.2)
Race, n (%)		
White	180 (74.7)	191 (78.6)
Asian	40 (16.6)	33 (13.6)
Black	20 (8.3)	16 (6.6)
Other	1 (0.4)	3 (1.2)
Hispanic or Latino ethnicity, n (%)	14 (5.8)	16 (6.6)
No. of lifetime depressive episodes, mean (range)	3.6 (1-30)	3.6 (1-20)
ADT during double-blind treatment, n (%)		
SSRI	168 (69.7)	168 (69.1)
SNRI	59 (24.5)	58 (23.9)
Other (bupropion)	14 (5.8)	17 (7.0)
Baseline Efficacy Parameters, mITT Population	**(n=239)**	**(n=242)**
MADRS Total score, mean (SD)	30.4 (3.75)	30.1 (3.50)
CGI-S score, mean (SD)	4.7 (0.55)	4.6 (0.56)
QIDS-SR-16 Total score, mean (SD)[a]	18.1 (2.31)	17.6 (2.28)
GAD-7 Total score, mean (SD)[a]	9.9 (5.00)	9.6 (5.03)

[a]ITT population. Lumateperone 42 mg + ADT, n=241; placebo + ADT, n=243.
ADT, antidepressant therapy; CGI-S, Clinical Global Impression Scale-Severity; GAD-7, Generalized Anxiety Disorder-7; ITT, intent-to-treat; 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.

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**)
  - MADRS Total score significantly improved by Day 8 and continued throughout the study

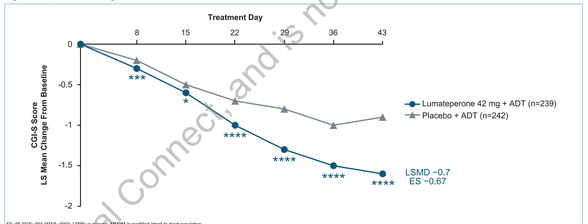
Figure 1. LS Mean Change From Baseline in MADRS Total Score



***P<.001 ****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 8 and persisted throughout the study

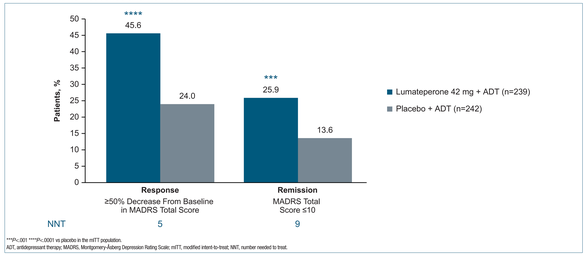
Figure 2. LS Mean Change From Baseline in CGI-S Score



*P<.05 ***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: 5) 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, significantly improved with lumateperone + ADT compared with placebo + ADT from baseline to Day 43 (least squares mean difference vs placebo [LSMD], −2.4; effect size [ES], −0.50; *P*<.0001)
- Lumateperone + ADT also significantly improved self-reported anxiety symptoms, as measured by GAD-7 Total score, compared with placebo + ADT from baseline to Day 43 (LSMD, −1.6; 95% CI, −2.31 to −0.93; ES, −0.43; *P*<.0001)

Figure 3. MADRS Response and Remission Rates at Day 43



***P<.001 ****P<.0001 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 46.5% of the placebo + ADT group and 58.1% of the lumateperone + ADT group; serious adverse events were rare (both groups, 0.4%)
  - TEAEs occurring in the lumateperone + ADT group in ≥5% of patients and at more than twice the rate of the placebo + ADT group were dry mouth, fatigue, and tremor
  - The majority of 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, no clinically relevant increases in prolactin or cardiometabolic parameters occurred at the end of the double-blind treatment period (**Table 2**)

Table 2. Mean Change From Baseline to End of Treatment in Prolactin and Cardiometabolic Parameters

	Lumateperone 42 mg + ADT (n=241)		Placebo + ADT (n=243)	
	Baseline Mean (SD)	Mean Change (SE)	Baseline Mean (SD)	Mean Change (SE)
Prolactin, ng/mL	11.0 (14.57)	1.6 (0.76)	9.6 (8.83)	0.6 (0.48)
Cholesterol, mg/dL				
Total	197.7 (41.38)	−10.3 (2.08)	199.1 (45.89)	−1.3 (2.01)
HDL	54.7 (17.53)	−0.4 (0.77)	57.5 (17.05)	−0.4 (0.64)
LDL	136.0 (39.50)	−9.4 (1.91)	136.2 (46.29)	−0.9 (1.99)
Triglycerides, mg/dL	138.8 (85.89)	−4.7 (5.13)	131.3 (77.24)	1.7 (3.98)
Glucose, mg/dL	91.3 (15.19)	0.9 (0.98)	93.8 (16.45)	0.8 (1.12)
Insulin, mIU/L	15.7 (28.79)	−1.5 (1.98)	13.5 (16.81)	1.4 (1.37)

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 0.8% of the placebo + ADT group and 1.7% of the lumateperone + ADT group per narrow standard Medical Dictionary for Regulatory Activities query (SMQ)
  - According to broad SMQ, EPS-related TEAEs occurred in 2.9% of the placebo + ADT group and 6.2% of the lumateperone + ADT group
- Based on the C-SSRS, no suicidal behavior was reported during treatment, and rates of emergent suicidal ideation were lower in the lumateperone + ADT group (1.4%) compared with the placebo + ADT group (3.5%)

CONCLUSIONS

- **Lumateperone 42 mg adjunctive to ADT demonstrated significant and 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**
- **In an additional, similarly designed trial (Study 502; NCT05061706), lumateperone 42 mg + ADT met primary and key secondary efficacy endpoints and was generally safe and well tolerated in patients with MDD with inadequate ADT response**
- **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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