Safety and Tolerability of Lumateperone 42 mg for the Treatment of Major Depressive Disorder: A Pooled Analysis of 2 Randomized Placebo-Controlled Trials

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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]
- Current treatment options for MDD have tolerability concerns that affect medication adherence, including weight gain, cardiometabolic disturbances, gastrointestinal symptoms, and sexual dysfunction[2-4]
- Most patients fail to achieve remission (≈75%) or response (≈60%) with first-line treatment, and patients with inadequate antidepressant therapy (ADT) response have increased hospitalization risk and greater impairments in functioning compared with those who respond[5,6]
- 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[7,8]
  - 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
- The efficacy and safety of lumateperone 42 mg adjunctive to ADT were demonstrated in 2 Phase 3, randomized, double-blind, placebo-controlled studies (Study 501 [NCT04985942]; Study 502 [NCT05061706]) in patients with MDD with inadequate ADT response[9,10]
  - In both trials, lumateperone 42 mg + ADT met primary and key secondary efficacy endpoints, significantly improving Montgomery-Åsberg Depression Rating Scale (MADRS) Total score and Clinical Global Impression Scale-Severity (CGI-S) score from baseline to Day 43 compared with placebo + ADT
- This pooled analysis of these trials evaluated the safety and tolerability of lumateperone 42 mg + ADT in patients with MDD who had inadequate response to ADT

METHODS

- Safety and tolerability data were pooled for the lumateperone 42 mg + ADT group and for the placebo + ADT group from Study 501 and Study 502[9,10]
  - Both studies evaluated 6-week oral lumateperone 42 mg + ADT or placebo + ADT
  - Eligible adults (aged 18-65 years, inclusive) had DSM-5–diagnosed MDD with inadequate response to 1 to 2 courses of prior ADT (defined as <50% improvement with ≥6 weeks ADT monotherapy as confirmed by 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 item (QIDS-SR-16) score ≥14 at screening and baseline
- Safety assessments included adverse events (AEs), physical examinations, vital signs, and changes in laboratory parameters, analyzed descriptively
  - Extrapyramidal symptoms (EPS) were assessed using the Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), and by treatment-emergent AEs (TEAEs)
  - Suicidal ideation and behavior were assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS)

RESULTS

Patient Population

- The pooled safety population comprised 964 patients (lumateperone + ADT, 483; placebo + ADT, 481), and 91.4% completed treatment
- Demographics and baseline characteristics were similar between groups (**Table 1**)
  - The majority of patients were female and White

Table 1. Baseline Demographics and Disease Characteristics

	Lumateperone 42 mg + ADT (n=483)	Placebo + ADT (n=481)
Age, mean (range), years	45.3 (18-65)	45.8 (18-65)
Sex, n (%)		
Female	327 (67.7)	325 (67.6)
Male	156 (32.3)	156 (32.4)
Race, n (%)		
White	415 (85.9)	414 (86.1)
Asian	41 (8.5)	36 (7.5)
Black	26 (5.4)	24 (5.0)
Other	1 (0.2)	7 (1.5)
Hispanic or Latino ethnicity, n (%)	51 (10.6)	49 (10.2)
No. of ADT failures in current episode, n (%)		
1	434 (89.9)	420 (87.3)
2	49 (10.1)	61 (12.7)
ADT during double-blind treatment, n (%)		
SSRI	328 (67.9)	312 (64.9)
SNRI	126 (26.1)	138 (28.7)
Other (bupropion)	29 (6.0)	31 (6.4)

ADT, antidepressant therapy; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Adverse Events

- TEAEs were reported in 68.1% of the lumateperone + ADT group and 45.1% of the placebo + ADT group (**Table 2**)
  - TEAEs occurring in the lumateperone + ADT group in ≥5% of patients and at more than twice the rate of placebo + ADT were dizziness, dry mouth, somnolence, nausea, and fatigue
  - Serious TEAEs were rare, occurring in 1 patient per group, and not considered related to treatment (lumateperone + ADT, polypectomy; placebo + ADT, joint dislocation)
  - For most patients experiencing TEAEs, the events were mild or moderate in severity (lumateperone + ADT, 95.1%; placebo + ADT, 98.2%)
- No patients died during the study

Table 2. Adverse Events

n, %	Lumateperone 42 mg + ADT (n=483)	Placebo + ADT (n=481)
≥1 TEAE	329 (68.1)	217 (45.1)
Drug-related TEAE	244 (50.5)	97 (20.2)
SAE	1 (0.2)	1 (0.2)
Drug-related SAE	0	0
Discontinued treatment due to:		
AE	42 (8.7)	4 (0.8)
Drug-related AE	39 (8.1)	4 (0.8)
SAE	0	0
Deaths	0	0
TEAEs in lumateperone + ADT group at ≥5% and twice placebo + ADT		
Dizziness	79 (16.4)	24 (5.0)
Dry mouth	61 (12.6)	16 (3.3)
Somnolence	49 (10.1)	10 (2.1)
Nausea	41 (8.5)	19 (4.0)
Fatigue	35 (7.2)	6 (1.2)

ADT, antidepressant therapy; AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Cardiometabolic Assessments, Prolactin, and Body Morphology

- Mean changes from baseline to the end of the double-blind treatment period in cardiometabolic parameters were similar between lumateperone + ADT and placebo + ADT groups (**Table 3**)
  - The incidence of patients who met potentially clinically significant elevations in cardiometabolic parameters was low and similar between the treatment groups
- No clinically relevant increases occurred in prolactin levels at the end of treatment (**Table 3**)

Table 3. Cardiometabolic and Prolactin Parameters

	Lumateperone 42 mg + ADT (n=483)		Placebo + ADT (n=481)	
	Baseline Mean (SD)	Mean Change to EOT (SD)	Baseline Mean (SD)	Mean Change to EOT (SD)
Cholesterol, mg/dL[a]				
Total	199.7 (41.05)	−9.8 (33.32)	199.2 (43.29)	−2.3 (30.85)
HDL	56.2 (17.26)	−0.6 (11.08)	57.4 (16.45)	−0.6 (9.47)
LDL	138.4 (39.20)	−9.4 (30.21)	137.9 (43.51)	−2.0 (30.43)
Triglycerides, mg/dL[a]	139.7 (89.07)	−3.4 (87.36)	133.5 (75.04)	3.6 (70.15)
Glucose, mg/dL[b]	92.3 (14.66)	0.1 (13.74)	93.7 (15.52)	0.7 (14.99)
Insulin, mIU/L[c]	15.0 (23.30)	−1.4 (23.58)	14.2 (16.34)	0.8 (19.98)
Prolactin, ng/mL[a]	10.0 (9.37)	1.1 (10.20)	9.6 (14.48)	1.0 (8.17)
PCS Criterion	n/N (%)[d]		n/N (%)[d]	
Total cholesterol ≥300 mg/dL	4/434 (0.9)		7/455 (1.5)	
LDL cholesterol >200 mg/dL	8/402 (2.0)		21/424 (5.0)	
Fasting glucose >160 mg/dL	0		3/386 (0.8)	
Fasting triglycerides ≥300 mg/dL	11/367 (3.0)		13/376 (3.5)	

[a] Lumateperone + ADT, n=438; placebo + ADT, n=466. [b] Lumateperone + ADT, n=435; placebo + ADT, n=463. [c] Lumateperone + ADT, n=436; placebo + ADT, 463. [d] Percentage based on patients not meeting PCS criterion at baseline who had ≥1 postbaseline value during treatment.
ADT, antidepressant therapy; EOT, end of treatment; HDL, high density lipoprotein; LDL, low density lipoprotein; PCS, potentially clinically significant.

- Weight, body mass index, and waist circumference remained stable in both groups (**Table 4**)
- Potentially clinically significant increase in weight was low in the lumateperone + ADT (0.4%) group compared with placebo + ADT (1.3%) and potentially clinically significant decrease in weight was similar in lumateperone + ADT and placebo + ADT groups (**Table 4**)

Table 4. Body Morphology

	Lumateperone 42 mg + ADT (n=483)		Placebo + ADT (n=481)	
	Baseline Mean (SD)	Mean Change to EOT (SD)	Baseline Mean (SD)	Mean Change to EOT (SD)
Weight, kg[a]	78.5 (16.71)	−0.1 (1.74)	79.0 (17.24)	0.0 (1.66)
Body mass index, kg/m^2[,a]	27.7 (5.02)	−0.0 (0.61)	27.8 (5.13)	0.0 (0.58)
Waist circumference, cm[b]	92.3 (13.35)	−0.2 (3.98)	93.0 (14.08)	−0.3 (4.42)
PCS Criterion	n/N (%)[c]		n/N (%)[c]	
≥7% increase in weight	2/467 (0.4)		6/479 (1.3)	
≥7% decrease in weight	2/467 (0.4)		2/479 (0.4)	

[a] Lumateperone + ADT, n=467; placebo + ADT, n=479. [b] Lumateperone + ADT, n=422; placebo + ADT, n=445. [c] Percentage based on patients with baseline and ≥1 postbaseline assessment during treatment.
ADT, antidepressant therapy; EOT, end of treatment; PCS, potentially clinically significant.

Extrapyramidal Symptoms and Motor Assessments

- There were no notable changes in EPS as assessed by the BARS, AIMS, or SAS (**Table 5**)
  - EPS-related TEAEs, excluding akathisia and restlessness, occurred in 5.0% of the lumateperone + ADT group and 0.8% of the placebo + ADT group
  - The combined incidence of akathisia or restlessness was 1.0% for the lumateperone + ADT group and 0.8% for the placebo + ADT group

Table 5. Extrapyramidal Symptoms

	Lumateperone 42 mg + ADT (n=483)		Placebo + ADT (n=481)	
	n (%)		n (%)	
≥1 EPS-related TEAE, excluding akathisia and restlessness	24 (5.0)		4 (0.8)	
Akathisia or restlessness TEAEs	5 (1.0)		4 (0.8)	
Clinician-rated scales	**Baseline Mean (SD)**	**Mean Change (SD)[a]**	**Baseline Mean (SD)**	**Mean Change (SD)[a]**
BARS Total score	0.1 (0.46)	−0.0 (0.53)	0.2 (0.59)	−0.1 (0.54)
AIMS Total score	0.1 (0.47)	−0.0 (0.47)	0.0 (0.26)	−0.0 (0.25)
SAS Total score	0.1 (0.41)	0.0 (0.50)	0.1 (0.30)	−0.0 (0.28)

[a] Mean change from baseline to end of treatment.
ADT, antidepressant therapy; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; EPS, extrapyramidal symptoms; SAS, Simpson-Angus Rating Scale; TEAE, treatment-emergent adverse event.

Additional Safety Assessments

- There were no clinically meaningful changes in liver function tests, vital signs, or cardiac electrophysiology
- Based on the C-SSRS, no suicidal behavior was reported during treatment, and rates of emergent suicidal ideation were low and similar between groups (lumateperone + ADT, 1.6%; placebo + ADT, 2.5%)
  - No patients in the lumateperone + ADT group and 1 patient (0.2%) in the placebo + ADT group experienced a TEAE of suicidal ideation

CONCLUSIONS

- **In this pooled analysis, lumateperone 42 mg + ADT had a safety profile similar to placebo + ADT**
- **There were minimal changes in cardiometabolic parameters, prolactin levels, and body morphology with lumateperone 42 mg + ADT, which were similar to placebo + ADT**
- **Risk of EPS and motor symptoms with adjunctive lumateperone 42 mg was low**
- **This pooled analysis suggests that lumateperone 42 mg may be a well-tolerated adjunctive treatment option for patients with MDD with inadequate ADT response**

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