# Lumateperone Treatment in Patients With Major Depressive Disorder With Mixed Features: Results From a Randomized Controlled Trial

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## BACKGROUND

- Depression is a leading cause of disability worldwide, and major depressive disorder (MDD) is associated with functional impairment, comorbidities, and reduced quality of life[1,2]
- About 1 in 4 people with MDD experience mixed features and have more lifetime depressive episodes, more comorbidities, increased suicide risk, and poorer treatment response than patients without mixed features[3,4]
  - According to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), the definition of mixed features with respect to a depressive episode is the presence of subsyndromal manic or hypomanic symptoms nearly every day during the majority of days of a major depressive episode (MDE)[5]
- 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
- A randomized, double-blind, placebo-controlled, multicenter trial (Study 403, NCT04285515) established the efficacy and safety of lumateperone 42 mg to treat MDEs in patients with DSM-5–diagnosed MDD with mixed features or bipolar depression with mixed features[8]
- This analysis focuses on the efficacy and safety of lumateperone 42 mg in the population of patients with MDD with mixed features

## METHODS

- Eligible adults (18-75 years) had DSM-5–diagnosed MDD with mixed features, were experiencing a current MDE (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥24 and Clinical Global Impression Scale-Severity [CGI-S] score ≥4), and had a Young Mania Rating Scale (YMRS) score of 4-16 (inclusive) at screening and baseline
- Patients were randomized 1:1 to 6-week treatment with lumateperone 42 mg or placebo, administered once daily in the evening
- The primary and key secondary endpoints were change from baseline to Day 43 in MADRS Total score and CGI-S score, respectively
  - Efficacy endpoints were analyzed via a mixed-effects model for repeated measures in the modified intent-to-treat (mITT) population, defined as all randomized patients who received ≥1 dose of study drug, had a baseline and ≥1 post-baseline MADRS Total score assessment, and were enrolled after protocol amendment 2.0 (which revised eligibility criteria to include mixed features for MDD)
- Additional efficacy measures were response (≥50% MADRS Total score decrease from baseline) and remission (MADRS Total score ≤10)
- Safety assessments included treatment-emergent adverse events (TEAEs), suicidality, mania, and changes in vital signs, laboratory parameters, and extrapyramidal symptoms (EPS)

## RESULTS

### Patient Population

- During the study, 186 patients with MDD with mixed features were randomized, 185 received treatment, and 166 (89.7%) completed treatment
- Demographics and baseline characteristics were similar between groups (**Table 1**)

### Efficacy

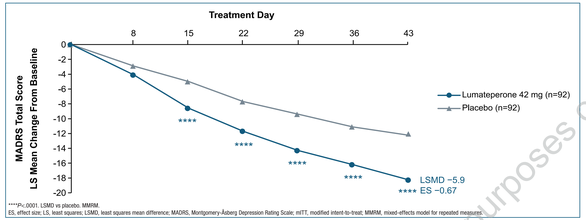
- The primary endpoint was met for lumateperone, with significant improvement in MADRS Total score from baseline to Day 43 compared with placebo (**Figure 1**)
  - MADRS Total score significantly improved by Day 15 and continued throughout the study

**Table 1. Baseline Demographics and Disease Characteristics**

| | Lumateperone 42 mg | Placebo |
|---|---|---|
| **Demographic Parameters, Safety Population** | **(n=92)** | **(n=93)** |
| **Age, mean (SD), years** | 44 (15.0) | 45 (14.8) |
| **Sex, n (%)** | | |
| Female | 55 (59.8) | 55 (59.1) |
| Male | 37 (40.2) | 38 (40.9) |
| **Race, n (%)** | | |
| White | 82 (89.1) | 76 (81.7) |
| Black | 8 (8.7) | 14 (15.1) |
| Other | 2 (2.2) | 3 (3.2) |
| **Hispanic or Latino ethnicity, n (%)** | 11 (12.0) | 14 (15.1) |
| **Age at first diagnosis, mean (SD), years** | 34 (12.7) | 33 (13.2) |
| **No. of lifetime depressive episodes, n (%)** | | |
| 1-9 | 81 (88.0) | 87 (93.5) |
| 10-20 | 10 (10.9) | 4 (4.3) |
| >20 | 1 (1.1) | 2 (2.2) |
| **Baseline Efficacy Parameters, mITT Population** | **(n=92)** | **(n=92)** |
| **MADRS Total score, mean (SD)** | 30.8 (3.59) | 31.2 (4.16) |
| **CGI-S score, mean (SD)** | 4.4 (0.52) | 4.4 (0.48) |
| **YMRS score, mean (SD)** | 9.3 (2.24) | 9.3 (2.09) |

CGI-S, Clinical Global Impression Scale-Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; YMRS, Young Mania Rating Scale.

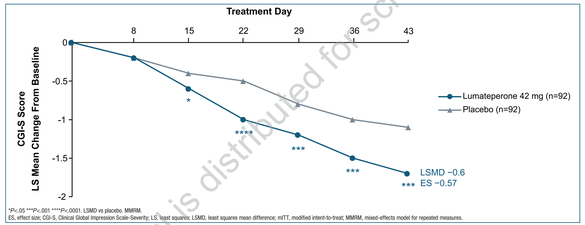
**Figure 1. LS Mean Change From Baseline in MADRS Total Score (mITT Population)**




****$P_c$.0001. LSMD vs placebo. MMRM.
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.

- Lumateperone significantly improved CGI-S score, the key secondary endpoint, from baseline to Day 43 compared with placebo (**Figure 2**)
  - CGI-S score significantly improved by Day 15 and persisted throughout the study

**Figure 2. LS Mean Change From Baseline in CGI-S Score (mITT Population)**




*$P_c$.05, ***$P_c$.001, ****$P_c$.0001. LSMD vs placebo. MMRM.
ES, effect size; CGI-S, Clinical Global Impression Scale-Severity; LS, least squares; LSMD, least squares mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

- MADRS Total response rate was significantly greater at Day 43 with lumateperone compared with placebo (placebo, 39.1%; lumateperone, 63.0%; $P<.01$)
- Similarly, MADRS Total remission rate at Day 43 was also significantly higher with lumateperone vs placebo (placebo, 20.7%; lumateperone, 40.2%; $P<.01$)

### Safety

- In patients with MDD with mixed features, 51.1% of patients in the lumateperone group compared with 32.3% of patients in the placebo group experienced TEAEs (**Table 2**)
  - The most common TEAEs with lumateperone were somnolence, dizziness, and nausea
  - All TEAEs were mild or moderate in severity
- One patient in the placebo group and no patients in the lumateperone group experienced serious adverse events (**Table 2**)
- No patients died during the study

**Table 2. Summary of Adverse Events (Safety Population)**

| n (%) | Lumateperone 42 mg (n=92) | Placebo (n=93) |
|---|---|---|
| **≥1 TEAE** | 47 (51.1) | 30 (32.3) |
| Drug-related TEAE | 38 (41.3) | 16 (17.2) |
| **Discontinued due to AE** | 2 (2.2) | 1 (1.1) |
| **SAE** | 0 | 1 (1.1) |
| **Patients who died** | 0 | 0 |
| **TEAEs occurring in ≥5% of the lumateperone group and more than twice that of placebo** | | |
| Somnolence | 11 (12.0) | 1 (1.1) |
| Dizziness | 11 (12.0) | 4 (4.3) |
| Nausea | 10 (10.9) | 1 (1.1) |

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

### Body Morphology, Metabolic, and Prolactin Assessments

- There were no notable changes in weight, body mass index, or waist circumference during treatment
- No patients in the lumateperone group experienced potentially clinically significant (≥7% change from baseline) weight increase or decrease during treatment
- There were no clinically relevant changes in cardiometabolic parameters (**Table 3**)
- The small increase in prolactin level from baseline to end of treatment in the lumateperone group was not clinically relevant (mean change: placebo, −0.7 µg/L; lumateperone, +3.7 µg/L)

**Table 3. Mean Change From Baseline in Cardiometabolic Parameters at EOT (Safety Population)**

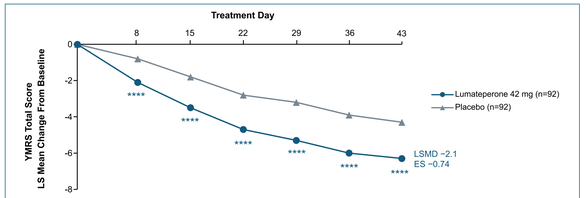
| | Lumateperone 42 mg (n=92) | | Placebo (n=93) | |
|---|---|---|---|---|
| | Baseline Mean (SD) | Mean Change From Baseline (SD) | Baseline Mean (SD) | Mean Change From Baseline (SD) |
| **Cholesterol, mg/dL** | | | | |
| Total | 194.6 (47.40) | −1.4 (32.54) | 196.5 (46.48) | −0.1 (32.34) |
| LDL | 115.3 (40.42) | −1.1 (27.87) | 119.5 (41.24) | 0.3 (29.26) |
| HDL | 56.1 (17.81) | −1.1 (14.12) | 52.3 (15.22) | 0.5 (12.94) |
| **Triglycerides, mg/dL** | 115.7 (68.42) | 12.2 (69.93) | 123.9 (72.57) | −4.4 (58.72) |
| **Glucose, mg/dL** | 94.0 (11.60) | 1.0 (17.28) | 94.4 (16.23) | −1.7 (17.20) |
| **Insulin, mIU/L** | 15.8 (12.94) | 2.6 (25.95) | 16.8 (25.67) | −2.3 (27.05) |

EOT, end of treatment; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

### EPS and Additional Safety Assessments

- There were no notable changes in EPS as assessed by the mean change from baseline at the end of treatment in Abnormal Involuntary Movement Scale (placebo, 0.0; lumateperone, 0.0), Barnes Akathisia Rating Scale (placebo, −0.0; lumateperone, 0.0), and Simpson-Angus Scale (placebo, −0.0; lumateperone, −0.1)
  - The only EPS-related TEAE based on narrow standard Medical Dictionary for Regulatory Activities query (SMQ) was mild akathisia in 1 patient in the lumateperone group
  - According to broad SMQ, 2 patients (0.8%) in the placebo group experienced EPS-related TEAEs and 12 patients (5.0%) in the lumateperone group reported EPS-related TEAEs
- No TEAEs of mania or hypomania were reported in either the lumateperone or placebo groups, and there were significant improvements from baseline in YMRS Total score with lumateperone compared with placebo (**Figure 3**)
- According to the Columbia-Suicide Severity Rating Scale, suicidal behavior and emergence of serious suicidal ideation did not occur during treatment in either group

**Figure 3. LS Mean Change From Baseline in YMRS Total Score (mITT Population)**

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ES, effect size; LS, least squares; LSMD, least squares mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; YMRS, Young Mania Rating Scale.

## CONCLUSIONS

- **Lumateperone 42 mg monotherapy significantly improved depression symptoms and disease severity compared with placebo in patients with MDD with mixed features**
- **Lumateperone 42 mg was generally well tolerated and had a favorable safety profile, which is consistent with prior placebo-controlled studies in schizophrenia and bipolar depression**
- **In 2 recent positive, Phase 3, randomized, double-blind, placebo-controlled trials (Study 501 [NCT04985942], Study 502 [NCT05061706]), lumateperone 42 mg adjunctive to antidepressant treatment in patients with MDD with inadequate response to antidepressant treatment:**
  - **Met primary and key secondary efficacy endpoints**
  - **Was generally safe and well tolerated**
- **These results support lumateperone 42 mg to treat an MDE in MDD with mixed features**

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