Lumateperone in the Treatment of Major Depressive Disorder and Bipolar Depression With Mixed Features: Efficacy Across Symptoms

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BACKGROUND

- Mixed features are common in major depressive disorder (MDD) and bipolar depression (25%-35%), and patients with mixed features have greater depression severity and poorer treatment response than patients without mixed features[1,2]
- There are no approved treatments specifically indicated for MDD with mixed features or bipolar depression with mixed features[3]
- Treatments that improve a wide range of symptoms, like those measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) items, may lead to reduced depressive symptoms, which is an important predictor of quality of life[4]
- Lumateperone (lumateperone tosylate, ITI-007) is a mechanistically novel FDA-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 AMPA and NMDA currents, and a serotonin reuptake inhibitor[6]
  - This novel mechanism of action with multi-modal effects may confer robust efficacy with improved tolerability compared with current treatment options
- In a recent randomized, double-blind, placebo-controlled trial (Study 403; NCT04285515) lumateperone 42 mg demonstrated efficacy and safety in patients with a major depressive episode (MDE) that was a part of MDD or bipolar depression with mixed features[7]
- This prospectively defined analysis of Study 403 investigated the efficacy of lumateperone on individual depressive symptoms as assessed by MADRS single item scores

METHODS

- Eligible adults (18-75 years) had DSM-5 diagnosed MDD with mixed features or bipolar I or bipolar II disorder with mixed features, were experiencing a current MDE (MADRS Total score ≥24 and Clinical Global Impression Scale-Severity [CGI-S] score ≥4), and had a Young Mania Rating Scale (YMRS) score between 4-16 (inclusive) at screening and baseline
  - According to the DSM-5, the definition of mixed features with respect to a depressive episode is the presence of ≥3 manic or hypomanic symptoms during the majority of days of an MDE without meeting the criteria for mania/hypomania[8]
  - Patients were excluded if they had significant risk for suicidal behavior (score of ≥4 on MADRS item 10 [suicidal thoughts] at screening or baseline, suicidal ideation within 6 months prior to screening according to the Columbia Suicide Severity Rating Scale [C-SSRS], or suicidal behavior in the last 2 years)
- Patients were stratified by MDD or bipolar disorder diagnosis and randomized 1:1 to 6-week treatment with lumateperone 42 mg or placebo, administered orally once-daily in the evening
- The primary endpoint was change in MADRS Total score from baseline to Day 43 in 3 populations: combined MDD/bipolar depression population, individual MDD population, and individual bipolar depression population
  - Efficacy was analyzed via a mixed-effects model for repeated measures (MMRM) in the modified intent-to-treat (mITT) populations, 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 and bipolar depression patients)
- This analysis included change from baseline in MADRS single item scores, assessed by visit using an MMRM in the mITT populations
- Safety included adverse events, mania as measured by YMRS Total score, and suicidality as assessed by the C-SSRS

RESULTS

Patient Population

- During the study, 388 patients were randomized, 385 received treatment, and 344 (89.4%) completed treatment
  - The mITT population (n=383) was evenly split between patients with MDD (48%) and bipolar depression (52%)
- Demographics and baseline characteristics were similar between groups (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

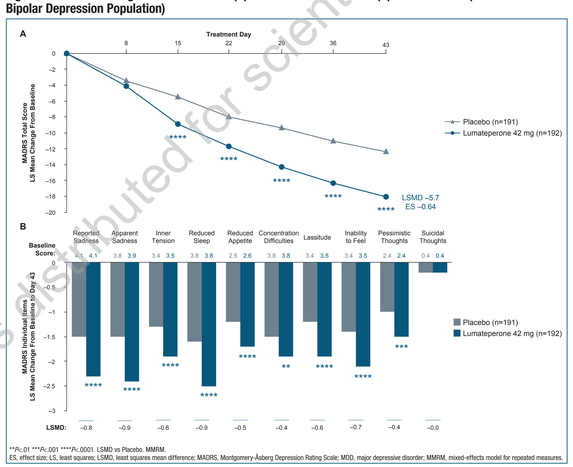
	Combined MDD/ Bipolar Depression Population		MDD Population		Bipolar Depression Population	
	Placebo	Lumateperone 42 mg	Placebo	Lumateperone 42 mg	Placebo	Lumateperone 42 mg
Demographic Parameters, Safety Population	**(n=193)**	**(n=192)**	**(n=93)**	**(n=92)**	**(n=100)**	**(n=100)**
Age, mean (range), years	43 (18-70)	43 (18-73)	45 (18-69)	44 (18-73)	41 (18-70)	42 (18-72)
Sex, n (%)						
Women	119 (61.7)	119 (62.0)	55 (59.1)	55 (59.8)	64 (64.0)	64 (64.0)
Men	74 (38.3)	73 (38.0)	38 (40.9)	37 (40.2)	36 (36.0)	36 (36.0)
Race, n (%)						
White	156 (80.8)	168 (87.5)	76 (81.7)	82 (89.1)	80 (80.0)	86 (86.0)
Black	33 (17.1)	22 (11.5)	14 (15.1)	8 (8.7)	19 (19.0)	14 (14.0)
Other	4 (2.1)	2 (1.0)	3 (3.2)	2 (2.2)	1 (1.0)	0
Hispanic or Latino ethnicity, n (%)	18 (9.3)	18 (9.4)	14 (15.1)	11 (12.0)	4 (4.0)	7 (7.0)
Diagnosis, n (%)						
Bipolar I disorder	79 (40.9)	78 (40.6)	0	0	79 (79.0)	78 (78.0)
Bipolar II disorder	21 (10.9)	22 (11.5)	0	0	21 (21.0)	22 (22.0)
MDD	93 (48.2)	92 (47.9)	93 (100.0)	92 (100.0)	0	0
Baseline Efficacy Parameters, mITT Population	**(n=191)**	**(n=192)**	**(n=92)**	**(n=92)**	**(n=99)**	**(n=100)**
MADRS Total score, mean (SD)	31.1 (4.07)	31.3 (4.05)	31.2 (4.16)	30.8 (3.59)	31.1 (4.01)	31.8 (4.40)
CGI-S score, mean (SD)	4.5 (0.52)	4.5 (0.54)	4.4 (0.48)	4.4 (0.52)	4.6 (0.54)	4.6 (0.55)
YMRS Total score, mean (SD)	9.2 (2.46)	9.0 (2.40)	9.3 (2.09)	9.3 (2.24)	9.1 (2.76)	8.7 (2.52)

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

Efficacy

- The primary endpoint was met for lumateperone, with significant improvement in MADRS Total score from baseline to Day 43 compared with placebo in the combined MDD/bipolar depression population (**Figure 1A**)
- At baseline, the most prominent MADRS individual items were reported sadness and apparent sadness (**Figure 1B**)
- Lumateperone significantly improved all MADRS items, except suicidal thoughts, at Day 43 compared with placebo (**Figure 1B**)
- The earliest significant (P<.05) reductions from baseline occurred at Day 8 for apparent sadness and reduced sleep, with an additional 5 items significantly improving at Day 15 and persisting throughout the study (reported sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts)

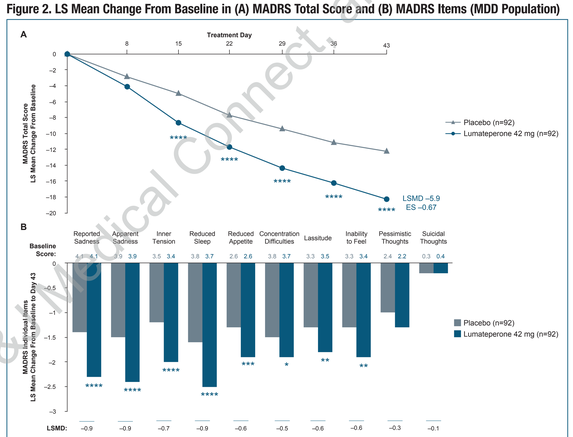
Figure 1. LS Mean Change From Baseline in (A) MADRS Total Score and (B) MADRS Items (Combined MDD/ Bipolar Depression Population)



***P*<.01 ****P*<.001 *****P*<.0001. LSMD vs Placebo. MMRM.
ES, effect size; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MMRM, mixed-effects model for repeated measures.

- In the individual MDD population, lumateperone significantly improved MADRS Total score at Day 43 compared with placebo (**Figure 2A**)
- The most prominent MADRS individual items at baseline were reported sadness and apparent sadness (**Figure 2B**)
- With lumateperone treatment, 8 of 10 MADRS items significantly improved at Day 43 compared with placebo in patients with MDD (**Figure 2B**)
- The earliest significant (P<.01) reduction from baseline occurred at Day 8 for reduced sleep, with an additional 4 items significantly improving at Day 15 and persisting throughout the study (apparent sadness, reported sadness, inner tension, and lassitude)

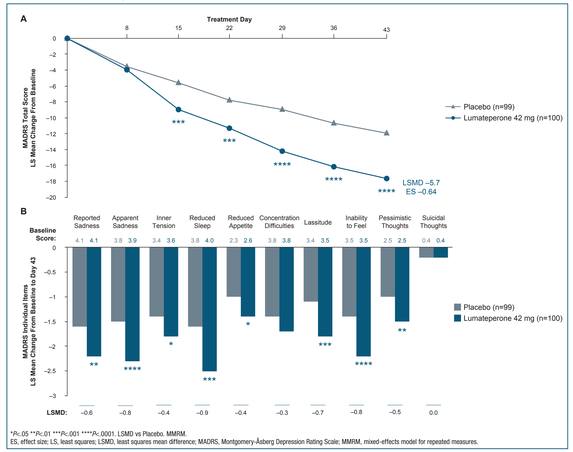
Figure 2. LS Mean Change From Baseline in (A) MADRS Total Score and (B) MADRS Items (MDD Population)



**P*<.05 ***P*<.01 ****P*<.001 *****P*<.0001. LSMD vs Placebo. MMRM.
ES, effect size; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MMRM, mixed-effects model for repeated measures.

- In the individual bipolar depression population, lumateperone significantly improved MADRS Total score at Day 43 compared with placebo (**Figure 3A**)
- The most prominent MADRS items at baseline were reported sadness and reduced sleep (**Figure 3B**)
- Lumateperone significantly improved 8 of 10 MADRS individual items at Day 43 compared with placebo in patients with bipolar depression (**Figure 3B**)
- The earliest significant (P<.05) reductions from baseline occurred at Day 15 and persisted throughout the study for apparent sadness, reported sadness, reduced sleep, lassitude, and inability to feel

Figure 3. LS Mean Change From Baseline in (A) MADRS Total Score and (B) MADRS Items (Bipolar Depression Population)



**P*<.05 ***P*<.01 ****P*<.001 *****P*<.0001. LSMD vs Placebo. MMRM.
ES, effect size; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

Safety

- In the combined MDD/bipolar depression population, 37.3% of patients in the placebo group compared with 54.2% of patients in the lumateperone group experienced treatment-emergent adverse events (TEAEs)
  - TEAEs occurring in the lumateperone group in ≥5% of patients and at more than twice the rate of placebo were somnolence (placebo, 1.6%; lumateperone, 12.5%), dizziness (placebo, 2.1%; lumateperone, 12.0%), and nausea (placebo, 1.6%; lumateperone, 9.9%)
  - The majority of TEAEs were mild-to-moderate in severity, with only 1 patient experiencing severe TEAEs (nausea and vomiting in the lumateperone group)
- Lumateperone significantly improved YMRS Total score from baseline to Day 43 compared with placebo (least squares mean difference vs placebo, –1.9; 95% CI, –2.49 to –1.22; effect size, –0.62; P<.0001)
- Emergence of C-SSRS suicidal ideation was similar between treatment groups (placebo, 4.2%; lumateperone, 3.1%)

CONCLUSIONS

- **Lumateperone 42 mg significantly improved depression symptoms compared with placebo as measured by MADRS Total score in:**
  - **The combined population of patients with MDD or bipolar depression with mixed features**
  - **The individual population of patients with MDD with mixed features**
  - **The individual population of patients with bipolar depression with mixed features**
- **Treatment with lumateperone significantly improved a broad range of depression symptoms across individual MADRS items in all 3 populations, with the greatest improvements in reported sadness, apparent sadness, and reduced sleep**
- **Lumateperone was generally well tolerated and had a favorable safety profile**
- **These results support lumateperone 42 mg to treat the broad range of symptoms of an MDE in MDD with mixed features or bipolar I or bipolar II disorder with mixed features**

REFERENCES

1. McIntyre RS, et al. *J Affect Disord*. 2015;172:259-264.
2. McIntyre RS, et al. *Ther Adv Psychopharmacol*. 2018;8(15):1-16.
3. Stahl SM, et al. *CNS Spect*. 2017;22:203-219.
4. Michalak EE, et al. *CNS Drugs*. 2008;22(5):389-406.
5. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc.;2023.
6. Titulaer J, et al. *Eur Neuropsychopharmacol*. 2022;62:22-35.
7. Durgam S, et al. "Lumateperone Treatment for Major Depressive Episodes With Mixed Features in Major Depressive Disorder and Bipolar I or Bipolar II Disorder." Poster presented at: Psych Congress Annual Meeting. September 6-10, 2023; Nashville, TN.
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association; 2013.

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