Lumateperone Treatment for Major Depressive Episodes With Mixed Features in Major Depressive Disorder and Bipolar I or Bipolar II Disorder: A Post Hoc Analysis of Anhedonia

Suresh Durgam, MD[1]; Susan G. Kozauer, MD[1]*; Willie R. Earley, MD[1]; Jason Huo, PhD[1]; Ian D'Souza, PhD[1]; Lakshmi N. Yatham, MBBS, FRCPC, MRCPsych, EMBA[2]

[1] Intra-Cellular Therapies, a Johnson & Johnson Company, Bedminster, NJ, USA; [2] Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada; * Former employee

BACKGROUND

- Anhedonia, diminished interest or pleasure, occurs in ≈70% of patients with major depressive disorder (MDD) and ≈50% of patients with bipolar depression[1,2]
- Heightened levels of anhedonia in mood disorders are associated with more severe and recurrent depressive illness, a greater risk for suicidal ideation, and poorer treatment response compared with lower levels of anhedonia[1]
- Anhedonia is a common residual symptom in patients treated for depression,[3] and treatments that improve a wide range of anhedonia-related symptoms, including sadness and detachment, may improve outcomes
- Lumateperone 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[4,5]
  - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission[5]
  - 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[5]
  - 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 trial (Study 403; NCT04285515) demonstrated the efficacy and safety of lumateperone 42 mg in patients with DSM-5–diagnosed MDD with mixed features or bipolar I or bipolar II depression with mixed features[6]
- This post hoc analysis of Study 403 investigated the efficacy of lumateperone 42 mg in improving anhedonia, assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) anhedonia factor score, in patients with MDD or bipolar depression with mixed features

METHODS

- Eligible males and females (aged 18-75 years inclusive) met DSM-5 criteria for MDD with mixed features or bipolar I or bipolar II disorder with mixed features, were experiencing a current major depressive episode (MDE; MADRS Total score ≥24 and Clinical Global Impression-Severity Scale score ≥4), and had a Young Mania Rating Scale (YMRS) score 4-16 (inclusive) at screening and baseline
- 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
- This post hoc analysis evaluated anhedonia in all 3 populations by change from baseline in MADRS anhedonia factor score and its individual MADRS item component scores (apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel)
  - Anhedonia measures were 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 postbaseline MADRS Total score assessment, and were enrolled after protocol amendment 2.0 (which revised eligibility criteria to include patients with mixed features for MDD and bipolar depression)
- Safety included adverse events (AEs), mania as measured by YMRS Total score, and suicidality as assessed by the Columbia-Suicide Severity Rating Scale (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**)
- At baseline, the most prominent individual items comprising the MADRS anhedonia factor score were reported sadness and apparent sadness in all 3 populations (**Figure 1B**, **2B**, **3B**)

Table 1. Baseline Demographics and Disease Characteristics

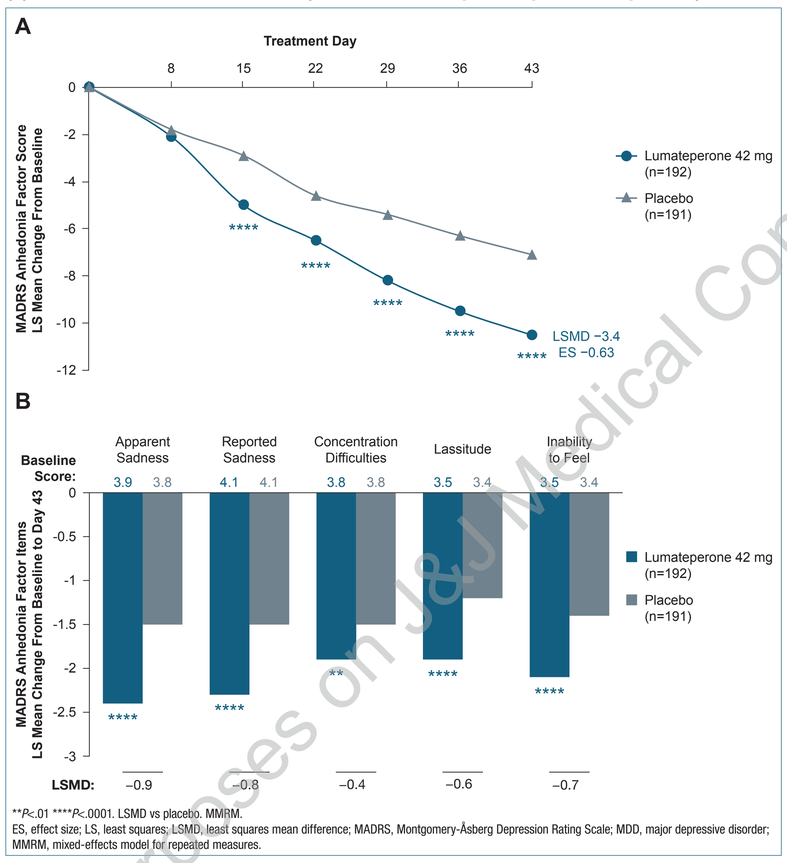
	Combined MDD/Bipolar Depression Population		MDD Population		Bipolar Depression Population	
	Lumateperone 42 mg	Placebo	Lumateperone 42 mg	Placebo	Lumateperone 42 mg	Placebo
Demographic/Clinical Characteristics, Safety Population	**(n=192)**	**(n=193)**	**(n=92)**	**(n=93)**	**(n=100)**	**(n=100)**
Age,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

CGI-S, Clinical Global Impression-Severity Scale; 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 vs placebo in the combined MDD/bipolar depression population (least squares mean difference vs placebo [LSMD], –5.7; 95% CI, –7.6 to –3.84; effect size [ES], –0.64; *P*<.0001)
  - Lumateperone also significantly reduced MADRS Total score at Day 43 vs placebo in the individual MDD population (LSMD, –5.9; 95% CI, –8.61 to –3.29; ES, –0.67; *P*<.0001) and individual bipolar depression population (LSMD, –5.7; 95% CI, –8.29 to –3.05; ES, –0.64; *P*<.0001)
- Lumateperone significantly improved MADRS anhedonia factor score from baseline to Day 43 compared with placebo in the combined MDD/bipolar depression population (**Figure 1A**)
- Lumateperone significantly improved all individual items comprising the MADRS anhedonia factor score at Day 43 vs placebo in the combined MDD/bipolar depression population (**Figure 1B**)
  - The earliest significant (*P*<.05) reductions from baseline occurred at Day 8 for apparent sadness; Day 15 for reported sadness, lassitude, and inability to feel; and Day 29 for concentration difficulties, with significant improvements continuing throughout the study
- Lumateperone significantly improved YMRS Total score from baseline to Day 43 compared with placebo (LSMD, –1.9; 95% CI, –2.49 to –1.22; ES, –0.62; *P*<.0001)

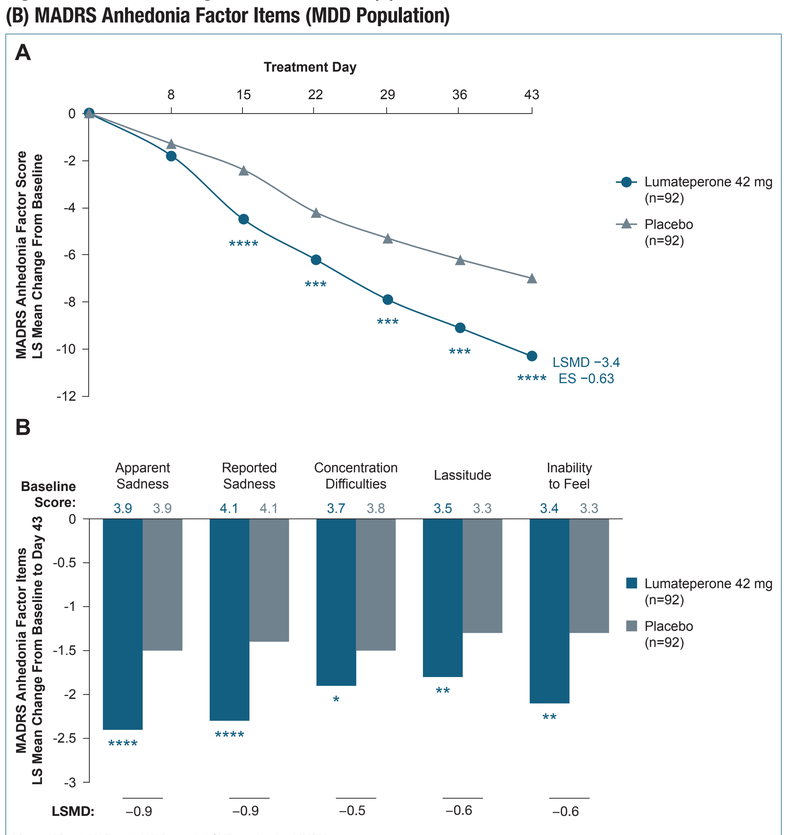
Figure 1. LS Mean Change From Baseline in (A) MADRS Anhedonia Factor Score and (B) MADRS Anhedonia Factor Items (Combined MDD/Bipolar Depression Population)



**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 anhedonia factor score from baseline to Day 43 compared with placebo (**Figure 2A**)
- Lumateperone significantly improved all individual items comprising the MADRS anhedonia factor score in the individual MDD population at Day 43 vs placebo (**Figure 2B**)
  - There were significant (*P*<.05) reductions from baseline that continued through the end of the study starting at Day 15 for apparent sadness, reported sadness, and lassitude, and at Day 29 for concentration difficulties and inability to feel

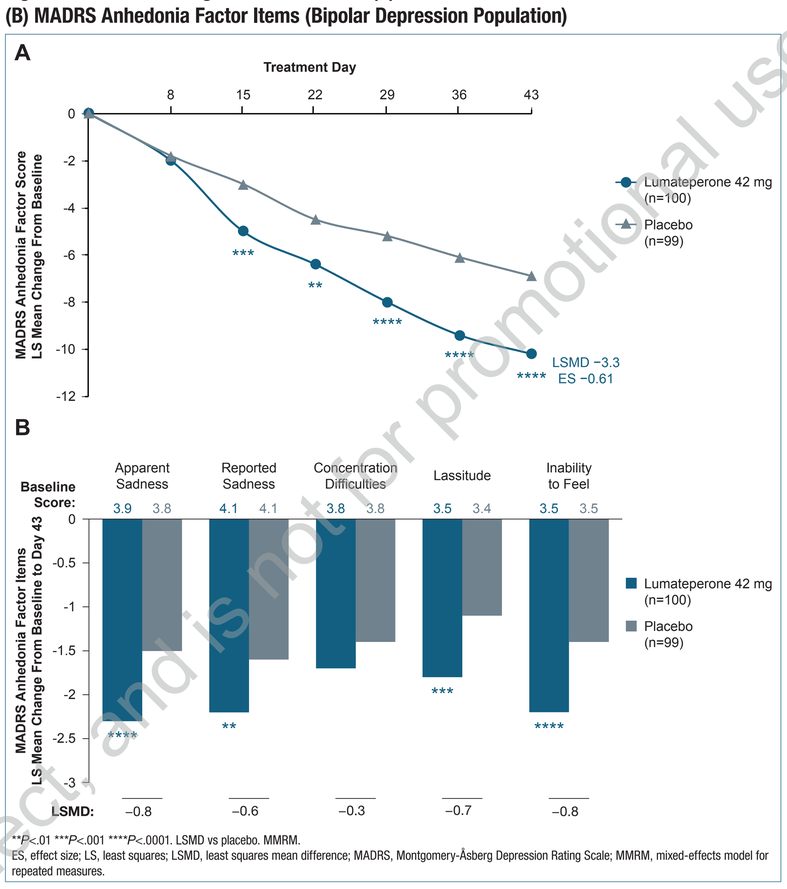
Figure 2. LS Mean Change From Baseline in (A) MADRS Anhedonia Factor Score and (B) MADRS Anhedonia Factor Items (MDD Population)



*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.

- Lumateperone significantly improved MADRS anhedonia factor score vs placebo from baseline to Day 43 in the individual bipolar depression population (**Figure 3A**)
- Lumateperone significantly improved 4 of 5 items comprising the MADRS anhedonia factor score from baseline to Day 43 vs placebo in the individual bipolar depression population (**Figure 3B**)
  - There were significant (*P*<.05) reductions from baseline at Day 15 that continued through the end of the study for apparent sadness, reported sadness, lassitude, and inability to feel

Figure 3. LS Mean Change From Baseline in (A) MADRS Anhedonia Factor Score and (B) MADRS Anhedonia Factor Items (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; MMRM, mixed-effects model for repeated measures.

Safety

- In the combined MDD/bipolar depression population, 54.2% of patients in the lumateperone group compared with 37.3% of patients in the placebo group experienced treatment-emergent AEs (TEAEs)
  - TEAEs occurring in ≥5% of the lumateperone group at more than twice the rate of placebo were somnolence, dizziness, and nausea
  - The majority of TEAEs were mild to moderate in severity, with only 1 patient experiencing severe TEAEs (nausea and vomiting in the lumateperone group)
  - No TEAEs of mania or hypomania were reported in either the lumateperone or placebo groups
- C-SSRS–measured emergence of suicidal ideation was similar between treatment groups (lumateperone, 3.1%; placebo, 4.2%)

CONCLUSIONS

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

REFERENCES

1. Whitton AE and Pizzagalli DA. *Curr Top Behav Neurosci.* 2022;58:111-127.
2. Nierenberg AA. *J Clin Psychiatry.* 2015;76(11):e1480.
3. Whiston A, et al. *Front Psychiatry.* 2022;13:746678.
4. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc.;2023.
5. Titulaer J, et al. *Eur Neuropsychopharmacol.* 2022;62:22-35.
6. Durgam S, et al. *J Clin Psychopharmacol.* 2025;45(2):67-75.

DISCLOSURES AND ACKNOWLEDGMENTS

S Durgam, WR Earley, J Huo, and I D'Souza are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson Company. SG Kozauer is a former employee of Intra-Cellular Therapies, a Johnson & Johnson Company.

LN Yatham has received research support from or served as a consultant or speaker for Allergan (now AbbVie), Alkermes, CANMAT, CIHR, Dainippon Sumitomo Pharma, GlaxoSmithKline, Intra-Cellular Therapies Inc, Lundbeck, Merck, Otsuka, Sanofi, and Sunovion.

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.

Scan the QR code for the full digital poster. The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Presented at the International Society for Bipolar Disorders (ISBD) Annual Conference, September 17-19, 2025, Chiba, Japan

Email questions to John B. Edwards at jedwards@itci-inc.com