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

**Willie R. Earley, MD[1]; Suresh Durgam, MD[1]; Susan G. Kozauer, MD[1*]; Changzheng Chen, PhD[1]; Hassan Lakkis, PhD[1]; Alvin B. Oung, PharmD[1]; Christoph U. Correll, MD[2-5]**

[1] Intra-Cellular Therapies, a Johnson & Johnson Company, Bedminster, NJ, USA; [2] Department of Psychiatry, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA; [3] Department of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; [4] Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin Berlin, Berlin, Germany; [5] German Center for Mental Health (DZPG), partner site Berlin, Berlin, Germany; *Former employee

This material is distributed for scientific purposes on J&J Medical Connect, and is not for promotional use

## 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]
  - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission[8]
  - 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[8]
  - 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 ADT in the current depressive episode (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=433; 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/m²[,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**

## REFERENCES

1. Proudman D, et al. *PharmacoEconomics*. 2021;39(6):619–625.
2. Alva G. *CNS Spectr*. 2023;28(5):521–525.
3. Marx W, et al. *Nat Rev Dis Primers*. 2023;9(1):44.
4. Hiles SA, et al. *Depress Anxiety*. 2016;33(8):754–764.
5. Pigott HE, et al. *BMJ Open*. 2023;13(7):e063095.
6. Knoth RL, et al. *Am J Manag Care*. 2010;16(8):e188–e196.
7. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc.;2023.
8. Titulaer J, et al. *Eur Neuropsychopharmacol*. 2022;62:22–35.
9. Durgam S, et al. *J Clin Psychiatry*. 2025;86(4):25m15848.
10. Durgam S, et al. *Am J Psychiatry*. In Press.

## DISCLOSURES AND ACKNOWLEDGMENTS

WR Earley, S Durgam, C Chen, H Lakkis, and AB Oung 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.

CU Correll has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Damitsa, Delpor, Denovo, Eli Lilly, Gedeon Richter, Hikma, Holmusk, Intra-Cellular Therapies, Jamjoom Pharma, JanssenJ&J, Karuna, LB Pharma, Lundbeck, MedInCell, MedLink, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Saladax, Sanofi, Segirus, SK Life Science, Sumitomo Pharma America, Sunovion, SUN Pharma, Supernus, Tabuk, Takeda, Teva, Terran, Tolmar, Vertex, Viatris, and Xenon Pharmaceuticals. He provided expert testimony for Janssen, Lundbeck, and Otsuka. He served on a data safety monitoring board for Compass Pathways, Denovo, Intra-Cellular Therapies, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Boehringer-Ingelheim, Janssen, and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Medlink, Mindpax, Quantic, and Terran.

The authors thank all study investigators, research staff, and patients for their participation. Medical writing support was provided by Sarah Engelberth, PhD, and 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.



**Email questions to Alvin B. Oung at aoung@itci-inc.com**