# Efficacy of Adjunctive Lumateperone 42 mg Treatment Across Patient-Reported Depression Symptoms in Major Depressive Disorder

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## Background

- Assessing symptom severity of major depressive disorder (MDD) using patient-reported outcomes is an important component in the research and clinical management of this condition[1,2]
  - The Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) is a validated tool that allows patients to rate the severity of their depression symptoms[2,3]
- Because patients with MDD often experience persistent and heterogeneous depression symptoms, efficacious treatments that improve patient-reported symptom severity across multiple symptom domains are needed[4,5]
- Lumateperone is an atypical antipsychotic indicated for: treatment of schizophrenia in adults; treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate; and treatment of MDD in adults as adjunct to antidepressant therapy (ADT)[6]
  - 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
- In a Phase 3, randomized, double-blind, placebo-controlled trial (Study 502 [NCT05061706]) in patients with MDD with inadequate response to ADT, adjunctive lumateperone 42 mg demonstrated significant improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score vs adjunctive placebo at Day 43, meeting the primary endpoint of the study; adjunctive lumateperone was generally well tolerated[8]
  - Additionally, patients treated with lumateperone + ADT vs placebo + ADT reported significant improvement in QIDS-SR-16 total score at Day 43
- In this post hoc analysis of Study 502, the efficacy of lumateperone 42 mg + ADT vs placebo + ADT was evaluated across the QIDS-SR-16 symptom domains in patients with MDD with inadequate ADT response in the overall population and across clinical subgroups

## Methods

- Eligible adults (aged 18–65 years) met DSM-5 criteria for MDD with inadequate response to 1–2 ADTs in the current depressive episode (<50% improvement on the Antidepressant Treatment Response Questionnaire) and had MADRS total score ≥24, Clinical Global Impression–Severity score ≥4, and QIDS-SR-16 total score ≥14
- Patients were randomized 1:1 to receive 6-week lumateperone 42 mg or placebo adjunctive to ADT
- A prespecified analysis measured change from baseline to Day 43 in QIDS-SR-16 total score using an analysis of covariance (ANCOVA) in the intent-to-treat (ITT) population
- This post hoc analysis measured change from baseline to end of treatment (EOT) in the 9 mutually exclusive QIDS-SR-16 domain scores, also using an ANCOVA in the ITT overall population and within subgroups according to baseline disease characteristics (DSM-5–defined anxious distress [yes vs no] and disease severity [MADRS total score <32 vs ≥32])
- The 16 QIDS-SR-16 items correspond with the 9 DSM-5 symptom domains used as the diagnostic criteria for MDD[2,3,9] (**Figure 1**)
  - For each item, symptom severity was reported on a scale from 0 to 3, with higher scores indicating more severe depression symptoms[3]
  - For the 3 symptom domains comprising >1 QIDS-SR-16 item (ie, sleep disturbance, appetite/weight change, and psychomotor agitation/retardation), the domain score was defined as the highest observed score across all included items[3]

**Figure 1. DSM-5 MDD Symptom Criterion Domains and Corresponding QIDS-SR-16 Items[2,3,9]**

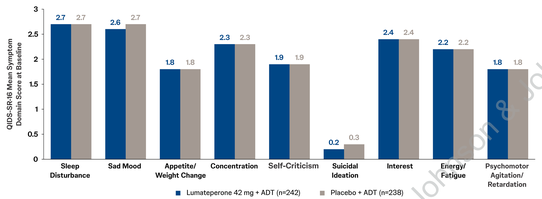
| DSM-5 MDD Symptom Criterion Domains | QIDS-SR-16 Items |
|---|---|
| Sleep disturbance | Highest score among:<br>1. Falling asleep<br>2. Sleep during the night<br>3. Waking up too early<br>4. Sleeping too much |
| Sad mood | 5. Feeling sad |
| Decrease/increase in appetite/weight | Highest score among:<br>6. Decreased appetite<br>7. Increased appetite<br>8. Decreased weight<br>9. Increased weight |
| Concentration | 10. Concentration/ decision-making |
| Self-criticism | 11. View of myself |
| Suicidal ideation | 12. Thoughts of death or suicide |
| Interest | 13. General interest |
| Energy/fatigue | 14. Energy level |
| Psychomotor agitation/retardation | Higher score among:<br>15. Feeling slowed down<br>16. Feeling restless |

DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; MDD, major depressive disorder; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

## Results

- All 480 treated patients were included in the ITT population (lumateperone + ADT, n=242; placebo + ADT, n=238), and 429 (89.4%) completed treatment
- Baseline characteristics were similar between groups[8]
  - Overall, the mean patient age was 46 years; most patients were female (69.6%) and White (95.4%)
- Lumateperone + ADT significantly improved QIDS-SR-16 total score vs placebo + ADT from baseline to Day 43 (least squares mean difference [LSMD] vs placebo, −2.2; effect size, −0.45; *P*<.0001)[8]
- Baseline QIDS-SR-16 symptom domain scores were balanced between treatment groups, with patients reporting the greatest symptom severity in the domains of sleep disturbance, sad mood, interest, concentration, and energy/fatigue (**Figure 2**)

**Figure 2. QIDS-SR-16 Symptom Domain Scores at Baseline (ITT Population)**

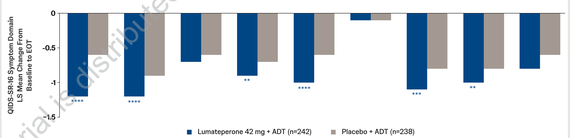



ADT, antidepressant therapy; ITT, intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

- From baseline to EOT, 6 of the 9 QIDS-SR-16 symptom domains significantly improved with lumateperone + ADT vs placebo + ADT (**Figure 3**)
  - Significance was not reached for the change in symptom severity in the domains of appetite/weight change (*P*=.179), suicidal ideation (*P*=.188), or psychomotor agitation/retardation (*P*=.065)

**Figure 3. Change From Baseline to EOT in QIDS-SR-16 Symptom Domain Scores (ITT Population)**

| | Sleep Disturbance | Sad Mood | Appetite/ Weight Change | Concentration | Self-Criticism | Suicidal Ideation | Interest | Energy/Fatigue | Psychomotor Agitation/ Retardation |
|---|---|---|---|---|---|---|---|---|---|
| Effect Size | −0.65 | −0.41 | −0.12 | −0.25 | −0.37 | −0.12 | −0.32 | −0.26 | −0.17 |
| LSMD | −0.61 | −0.35 | −0.11 | −0.20 | −0.33 | −0.04 | −0.29 | −0.21 | −0.12 |
| Mean Baseline Score | 2.7 2.7 | 2.6 2.7 | 1.8 1.8 | 2.3 2.3 | 1.9 1.9 | 0.2 0.3 | 2.4 2.4 | 2.2 2.2 | 1.8 1.8 |




*P<.05 **P<.01 ***P<.001 ****P<.0001. ANCOVA in the ITT population.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; EOT, end of treatment; ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

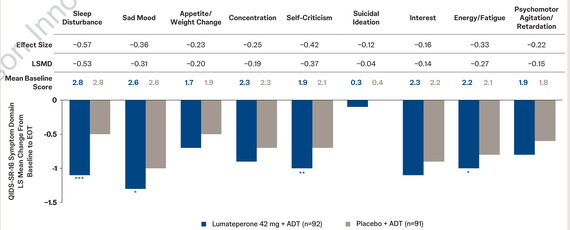
### Subgroup Analyses

- At EOT, lumateperone + ADT significantly improved 4 QIDS-SR-16 symptom domains for patients with DSM-5–defined anxious distress and 5 symptom domains for those without anxious distress (**Figure 4A** and **4B**)
  - The QIDS-SR-16 symptom domain scores for sleep disturbance, sad mood, and self-criticism significantly improved in both subgroups regardless of baseline anxious distress (**Figure 4A** and **4B**)

**Figure 4. Change From Baseline to EOT in QIDS-SR-16 Symptom Domain Scores in Patient Subgroups per Presence/Absence of Baseline Anxious Distress (ITT Population)**

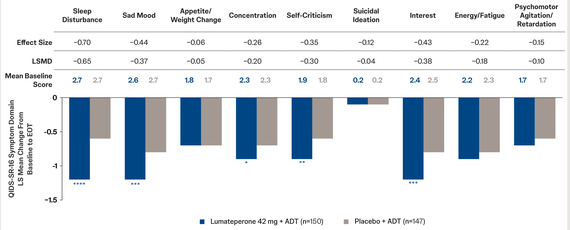
**A. Patients With Anxious Distress**

| | Sleep Disturbance | Sad Mood | Appetite/ Weight Change | Concentration | Self-Criticism | Suicidal Ideation | Interest | Energy/Fatigue | Psychomotor Agitation/ Retardation |
|---|---|---|---|---|---|---|---|---|---|
| Effect Size | −0.57 | −0.36 | −0.23 | −0.25 | −0.42 | −0.12 | −0.16 | −0.33 | −0.22 |
| LSMD | −0.53 | −0.31 | −0.20 | −0.19 | −0.37 | −0.04 | −0.14 | −0.27 | −0.15 |
| Mean Baseline Score | 2.8 2.8 | 2.6 2.6 | 1.7 1.9 | 2.3 2.3 | 1.9 2.1 | 0.3 0.4 | 2.3 2.2 | 2.2 2.1 | 1.9 1.8 |




**B. Patients Without Anxious Distress**

| | Sleep Disturbance | Sad Mood | Appetite/ Weight Change | Concentration | Self-Criticism | Suicidal Ideation | Interest | Energy/Fatigue | Psychomotor Agitation/ Retardation |
|---|---|---|---|---|---|---|---|---|---|
| Effect Size | −0.70 | −0.44 | −0.06 | −0.26 | −0.35 | −0.12 | −0.43 | −0.22 | −0.15 |
| LSMD | −0.65 | −0.37 | −0.05 | −0.20 | −0.30 | −0.04 | −0.38 | −0.18 | −0.10 |
| Mean Baseline Score | 2.7 2.7 | 2.6 2.7 | 1.8 1.7 | 2.3 2.3 | 1.9 1.8 | 0.2 0.2 | 2.4 2.5 | 2.2 2.3 | 1.7 1.7 |




*P<.05 **P<.01 ***P<.001 ****P<.0001. ANCOVA in the ITT population.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; EOT, end of treatment; ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

- In patients with baseline MADRS total score <32, lumateperone + ADT significantly improved 6 QIDS-SR-16 symptom domain scores (sleep disturbance, sad mood, concentration, self-criticism, interest, and energy/fatigue [*P*<.05]) from baseline to EOT
  - Patients with baseline MADRS total score ≥32 had significant improvement (*P*<.05) with lumateperone + ADT at EOT in the QIDS-SR-16 symptom domain scores for sleep disturbance, self-criticism, and suicidal ideation
  - Lumateperone + ADT significantly improved sleep disturbance and self-criticism domains in both MADRS subgroups regardless of baseline disease severity

## Conclusions

- In Study 502, lumateperone 42 mg + ADT significantly improved depression symptom severity across 6 of 9 QIDS-SR-16 symptom domains vs placebo + ADT
- Significant improvements occurred with lumateperone 42 mg + ADT in sleep disturbance and sad mood, which were the most prominent symptom domains at baseline
- Lumateperone 42 mg + ADT significantly improved QIDS-SR-16 symptom domains regardless of baseline anxious distress and disease severity
- These results support the use of adjunctive lumateperone in patients with MDD with inadequate ADT response across a range of symptom domains in MDD

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### Disclosures

**WR Earley**, **R Migliore**, **Y Mo**, and **H Lakkis** are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company. **S Durgam** is a former employee of Intra-Cellular Therapies, a Johnson & Johnson company. **SG Kornstein** receives research support from the National Institutes of Health and the National Science Foundation. She has served as a consultant for Lilly, Sage Therapeutics, Reunion Neuroscience, Relmada, AbbVie, Gerbera, and Arrivo BioVentures. **M Fava** reports the following disclosures related to the last 3 years: Research Support: AbbVie; Acadia Pharmaceuticals; Aditum Bio Management Company, LLC; Allergan, Alkermes, Inc.; Altimate Health Corporation; Alto Neuroscience, Inc.; Ancora Bio, Inc.; Angelini S.p.A; Aptinyx; Arbor Pharmaceuticals LLC; Avanir Pharmaceuticals Inc.; Axsome; Bencisker Pharmaceuticals, Inc.; BioClinica, Inc.; Biogen; BioHaven; BioShin Limited; Cambridge Science Corporation; Centrexion Therapeutics Corporation; Cerecor; Cybin IRL Limited; Damona Pharmaceuticals; EmbarkNeuro; Eliem Therapeutics LTD; Gate Neurosciences, Inc.; GenOmind, LLC; Gentelon, LLC; Gerbera Therapeutics, Inc.; Happify; Johnson & Johnson; Lundbeck Inc.; Marinus Pharmaceuticals; Medpace, Inc.; Methylation Sciences, Inc.; Millennium Pharmaceutics, Inc.; Minerva Neurosciences; Neuralstem; Neurocrine Biosciences, Inc.; NeuroRX Inc.; Novaremed; Novartis; Otsuka; Pfizer; Premiere Research International; Praxis Precision Medicines; Protagenic Therapeutics, Inc.; Relmada Therapeutics Inc.; Reckitt; Shenox Pharmaceuticals; Stanley Medical Research Institute (SMRI); Taisho; Takeda; University of Michigan; Vistagen; WinSanTor, Inc.; Xenon Pharmaceuticals, Inc.; National Institute of Drug Abuse (NIDA); National Institutes of Health (NIH); National Institute of Mental Health (NIMH); and PCORI. **M Fava** has not done any personal consulting. Any consulting he has done has been on behalf of Massachusetts General Hospital, except for Revival Therapeutics and Sensorium Therapeutics. Speaking/Publishing: Lecture given at Global Medical Education, Inc. Mood Disorders Summit, November 2020. Stock/Other Financial Options: Equity Holdings: Compellis; Neuromity; Psy Therapeutics; Revival Therapeutics; Sensorium Therapeutics. Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Patents for pharmacogenomics of Depression Treatment with Folate (US_9546401, US_9540691). Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Belvoir; Lippincott, Williams & Wilkins; Wolters Kluwer; World Scientific Publishing Co. Pte. Ltd.

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