27

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]

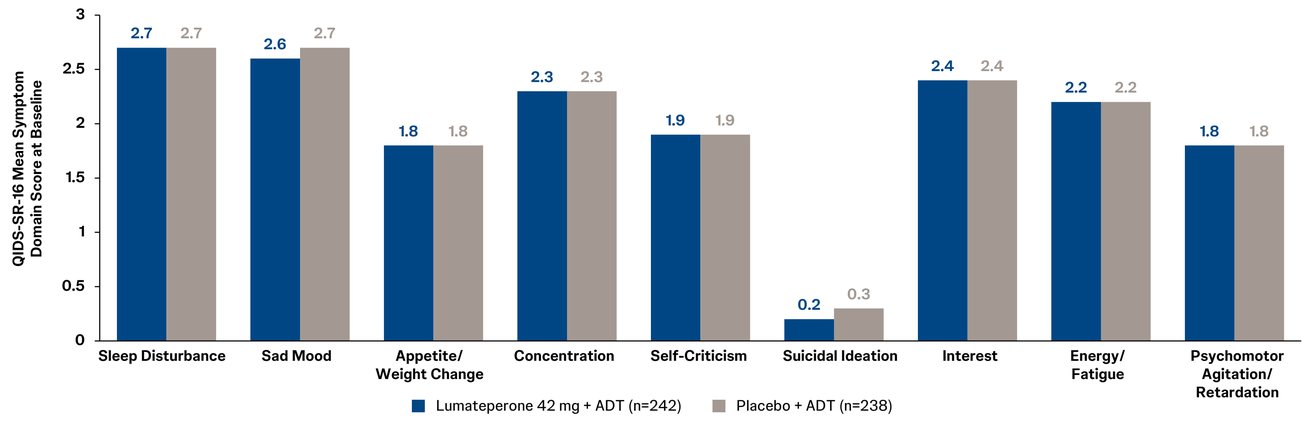
DSM-5 MDD Symptom Criterion Domains	QIDS-SR-16 Items
Sleep disturbance	**Highest score among:** 1. Falling asleep 2. Sleep during the night 3. Waking up too early 4. Sleeping too much
Sad mood	5. Feeling sad
Decrease/increase in appetite/weight	**Highest score among:** 6. Decreased appetite 7. Increased appetite 8. Decreased weight 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:** 15. Feeling slowed down 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 vs placebo [LSMD], −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)

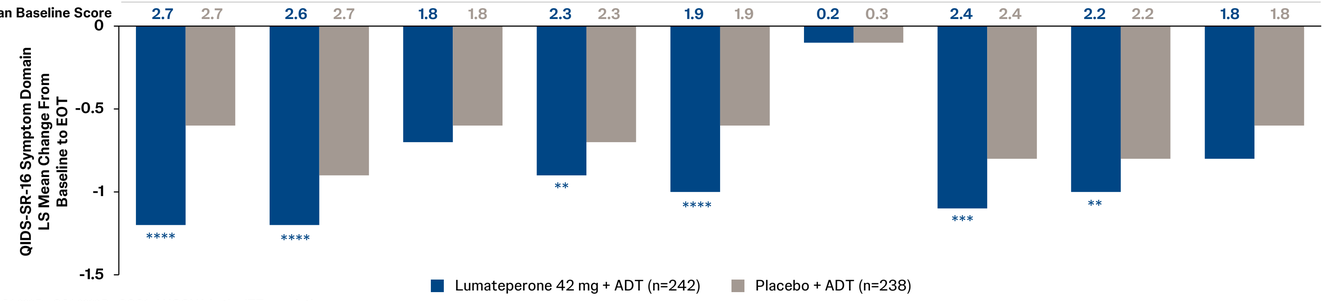


ADT, antidepressant therapy; ITT, intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

- 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*<.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.

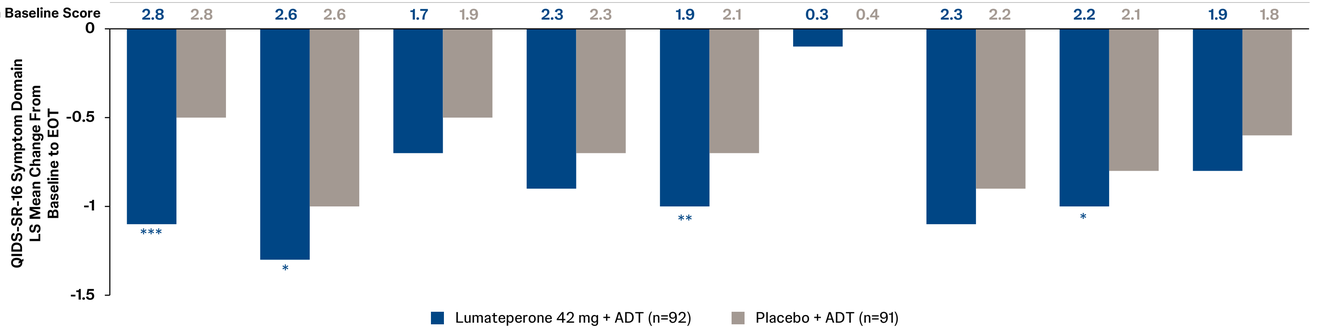
Subgroup Analyses

- 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)

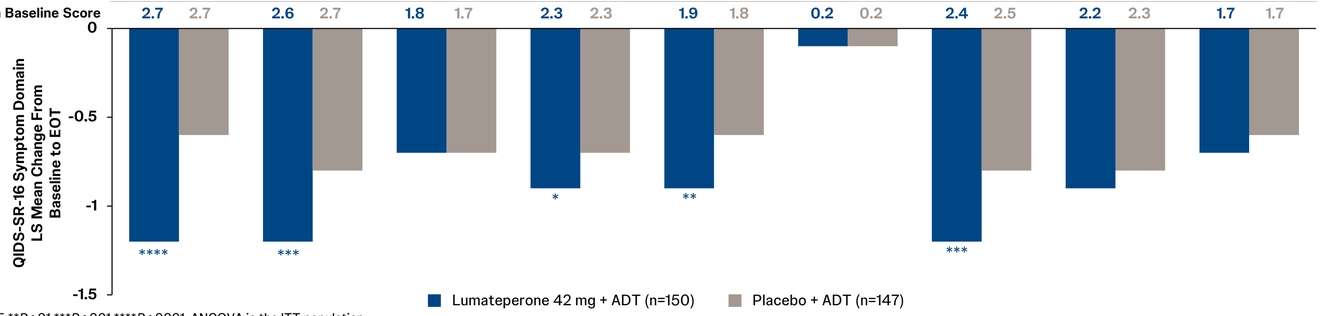
A. Patients With Anxious Distress

	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.

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