Efficacy of Adjunctive Lumateperone 42 mg Treatment Across Depression and Anhedonia Symptoms in Major Depressive Disorder

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Background

- Current treatments for major depressive disorder (MDD) may not resolve all symptoms, and the presence of residual symptoms predicts disease relapse, recurrence, and functional impairment[1-3]
- Anhedonia is common (≈70%) in patients with MDD and often persists following treatment[1,4]
  - The DSM-5 defines anhedonia as markedly diminished interest or pleasure[1]
  - Treatments that improve a broad range of the symptoms, including anhedonia, from the Montgomery-Åsberg Depression Rating Scale (MADRS) items, may improve outcomes for patients with MDD
- Lumateperone is a mechanistically novel US Food and Drug Administration–approved antipsychotic to treat adults with schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate, and adjunct to antidepressant therapy (ADT) for MDD[5]
  - 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 glutamatergic AMPA and NMDA currents, and a serotonin reuptake inhibitor[6]
  - This novel mechanism of action with multimodal effects may confer robust efficacy with improved tolerability compared with current treatment options
- In a recent positive Phase 3, randomized, double-blind, placebo-controlled, multicenter trial (Study 502, NCT05061706), lumateperone 42 mg + ADT met primary and key secondary efficacy endpoints and was generally safe and well tolerated in patients with MDD with inadequate ADT response[7]
  - Lumateperone 42 mg + ADT significantly improved symptoms of depression as measured by both clinician-rated and patient-rated outcomes[7]
- This analysis of Study 502 assessed the broad efficacy of lumateperone 42 mg + ADT across depression symptoms measured using MADRS single item scores and the MADRS anhedonia factor

Methods

- Eligible males and females (aged 18-65 years) met DSM-5 criteria for MDD with inadequate response to 1 to 2 courses of ADT in the current depressive episode, were experiencing a major depressive episode (MADRS Total score ≥24 and Clinical Global Impression Scale-Severity score ≥4), and had Quick Inventory of Depressive Symptomatology-Self Report-16 item score ≥14 at screening and baseline
  - Inadequate response to ADT was defined as <50% improvement with ≥6 weeks ADT monotherapy, as confirmed by the Antidepressant Treatment Response Questionnaire
- Patients were randomized 1:1 to 6 weeks of oral lumateperone 42 mg + ADT or placebo + ADT
- Efficacy analyses were performed by-visit using a mixed-effects model for repeated measures in the modified intent-to-treat (mITT) population (defined as all randomized patients who received ≥1 dose of study drug and had a baseline and ≥1 postbaseline MADRS Total score)
  - The primary endpoint was change from baseline to Day 43 in MADRS Total score
  - A prospective analysis measured change from baseline in individual MADRS single item scores
  - A post hoc analysis investigated anhedonia symptoms according to change from baseline in MADRS anhedonia factor (sum of the single items for apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel)
  - MADRS Total score and MADRS anhedonia factor score were analyzed in patients with anhedonia baseline higher than the median, defined as baseline MADRS anhedonia factor score ≥19 (median baseline value for mITT population)
  - Additional measures included MADRS response (≥50% decrease from baseline in MADRS Total score) and remission (MADRS Total score ≤10) based on a logistic regression model

Results

Patient Population

- Of 480 patients treated, 469 were included in the mITT population (lumateperone + ADT, 232; placebo + ADT, 237) and 429 (89.4%) completed treatment
- Demographics and baseline characteristics were similar between groups (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics (mITT Population)

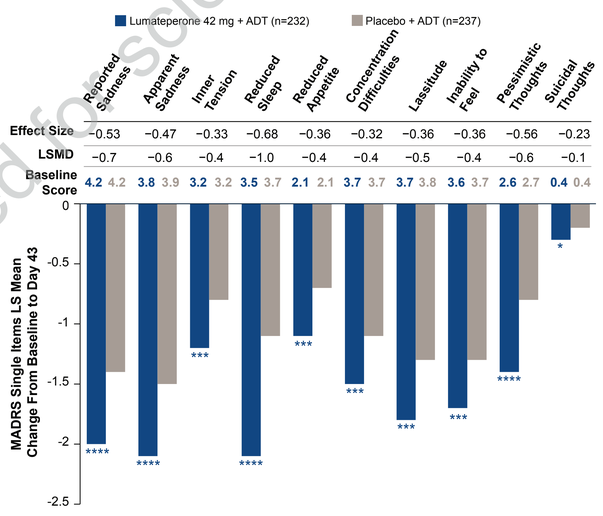
	Lumateperone 42 mg + ADT (n=232)	Placebo + ADT (n=237)
Demographics		
Age, mean (range), years	45.6 (18-65)	46.5 (18-65)
Sex, n (%)		
Female	162 (69.8)	165 (69.6)
Male	70 (30.2)	72 (30.4)
Race, n (%)		
White	226 (97.4)	222 (93.7)
Asian	1 (0.4)	3 (1.3)
Black	5 (2.2)	8 (3.4)
Other	0	3 (1.7)
Hispanic or Latino ethnicity, n (%)	36 (15.5)	33 (13.9)
Disease Characteristics		
MADRS Total score, mean (SD)	30.8 (3.88)	31.5 (3.97)
MADRS anhedonia factor score, mean (SD)	19.0 (2.66)	19.3 (2.69)
CGI-S score, mean (SD)	4.6 (0.59)	4.7 (0.59)

ADT, antidepressant therapy; CGI-S, Clinical Global Impression-Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat.

Efficacy

- Lumateperone + ADT met the primary endpoint, significantly improving depression symptoms compared with placebo + ADT, according to MADRS Total score at Day 43 (least squares mean difference vs placebo + ADT, −4.5; effect size, −0.56; $P<.0001$)
- Reported sadness and apparent sadness were the most prominent MADRS single items at baseline (**Figure 1**)
- All 10 MADRS single items significantly improved with lumateperone + ADT versus placebo + ADT at Day 43 (**Figure 1**)
  - The greatest improvement at Day 43 occurred for reduced sleep, and the improvements with lumateperone + ADT were significant ($P<.05$) at every visit
  - Lumateperone + ADT significantly improved reported sadness and apparent sadness from Day 15 to the end of treatment
  - Single items for lassitude, inability to feel, and pessimistic thoughts significantly improved from Day 22 onwards and items for inner tension and concentration difficulties significantly improved from Day 29 onwards with lumateperone + ADT
  - Significant improvement for reduced appetite occurred at Day 36 and up to the end of treatment, and occurred for suicidal thoughts at Day 43 with lumateperone + ADT

Figure 1. LS Mean Change From Baseline to Day 43 in MADRS Single Items

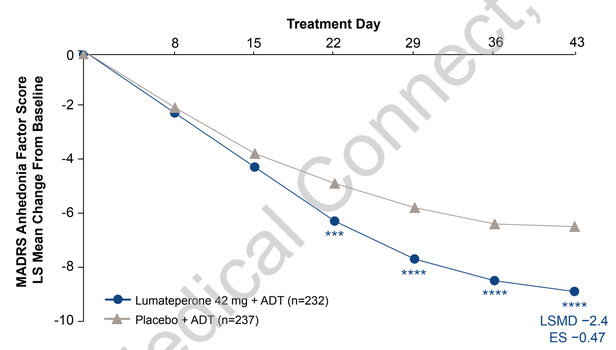


*$P<.05$ **$P<.01$ ***$P<.001$ ****$P<.0001$. LSMD vs placebo. MMRM. mITT population.

ADT, antidepressant therapy; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

- Lumateperone + ADT significantly improved MADRS anhedonia factor score compared with placebo + ADT from Day 22 to the end of treatment (**Figure 2**)
- All 5 items included in the MADRS anhedonia factor score significantly improved with lumateperone + ADT by Day 29, with continued significant improvement throughout the study

Figure 2. LS Mean Change From Baseline in MADRS Anhedonia Factor Score[a]



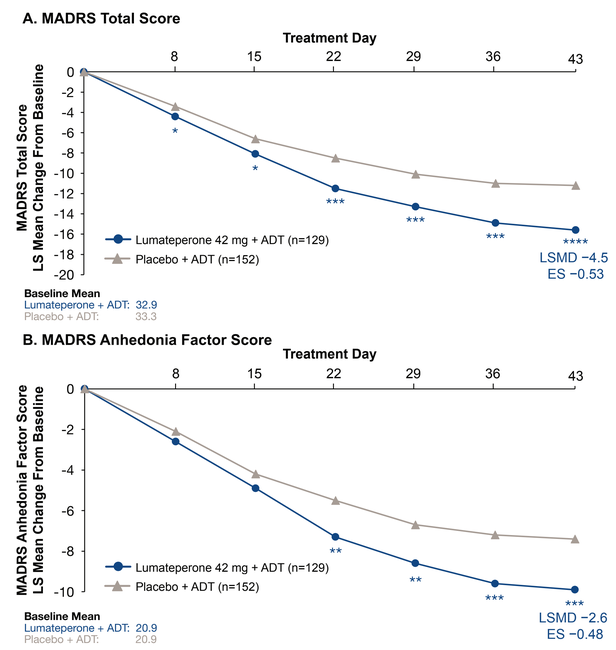
***$P<.001$ ****$P<.0001$. LSMD vs placebo. MMRM. mITT population.

[a]Comprised of 5 individual MADRS item component scores: apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel.

ADT, antidepressant therapy; ES, effect size; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

- In the subgroup of patients with anhedonia baseline higher than the median, lumateperone + ADT significantly improved MADRS Total score at every visit up to Day 43 (**Figure 3A**)
- MADRS anhedonia factor score also significantly improved with lumateperone + ADT in patients with anhedonia baseline higher than the median, with significant reductions beginning at Day 22 and persisting up to Day 43 (**Figure 3B**)

Figure 3. LS Mean Change From Baseline in A) MADRS Total Score and B) MADRS Anhedonia Factor Score[a] in Patients With Anhedonia Baseline Higher Than Median[b]



*$P<.05$ **$P<.01$ ***$P<.001$ ****$P<.0001$. LSMD vs placebo. MMRM. mITT population.

[a]Comprised of 5 individual MADRS item component scores: apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel.

[b]Defined as baseline MADRS anhedonia factor score ≥19 (median baseline value for mITT population).

ADT, antidepressant therapy; ES, effect size; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

- At Day 43, among the subgroup of patients with baseline anhedonia higher than the median, MADRS response rate was significantly greater with lumateperone + ADT versus placebo + ADT (38% vs 24.3%; number needed to treat [NNT], 8; $P<.05$)
- At Day 43, among the subgroup of patients with baseline anhedonia higher than the median, the MADRS remission rate was higher with lumateperone + ADT versus placebo + ADT (19.4% vs 12.5%) but was not statistically significant

Conclusions

- Lumateperone 42 mg + ADT significantly improved a broad range of depression symptoms across all 10 MADRS single items in patients with MDD with inadequate ADT response
- The greatest improvements occurred for reduced sleep, with significant improvements as early as Day 8 that persisted throughout the study
- Symptoms of anhedonia significantly improved with lumateperone + ADT compared with placebo + ADT, as measured by the MADRS anhedonia factor score
- In patients with anhedonia baseline higher than the median, lumateperone + ADT significantly improved symptoms of depression and anhedonia compared with placebo + ADT
- These results support lumateperone 42 mg + ADT to treat the broad range of depression and anhedonia symptoms in patients with MDD with inadequate ADT response

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Disclosures

JF Goldberg is a consultant at Alkermes, Alvogen, Genomind, Luye Pharma, Neuroma, Otsuka, Sunovion, Supernus; serves on speakers bureaus for Alkermes, Axsome, Bristol Myers Squibb, Intracellular Therapies, Inc; receives royalties from American Psychiatric Publishing, Cambridge University Press.

WR Earley, S Durgam, Y Mo, H Lakkis, and W Rowe 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.

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