Efficacy of Adjunctive Lumateperone 42 mg Treatment Across a Broad Range of Depression Symptoms in Patients With 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 and recurrence as well as reduced quality of life and functional impairment[1–3]
- Lumateperone is an atypical antipsychotic indicated in adults for: (1) treatment of MDD as adjunct to antidepressant therapy (ADT); (2) treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate; (3) and treatment of schizophrenia[4]
- Lumateperone simultaneously modulates serotonin, dopamine, and indirectly through D_1-receptor modulation, glutamatergic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors[5]
  - Although the mechanism of action is unknown, 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[4,5]
  - This novel mechanism of action with multimodal effects may confer robust efficacy with improved safety and tolerability
- The two pivotal Phase 3, randomized, double-blind, placebo-controlled, multicenter trials (Study 501, NCT04985942; Study 502, NCT05061706) demonstrated that lumateperone 42 mg/day + ADT significantly improved depressive symptoms compared with placebo + ADT, as measured by both clinician-rated and patient-rated outcomes, in patients with MDD with inadequate ADT response[6,7]
  - Lumateperone 42 mg/day + ADT had a favourable safety profile, with no notable changes in cardiometabolic parameters or body weight[6,7]
- This pooled post hoc analysis of Studies 501 and 502 assessed the efficacy of lumateperone 42 mg + ADT on individual Montgomery-Åsberg Depression Rating Scale (MADRS) item scores to determine whether improvements in depressive symptoms were observed across MADRS items or were driven by changes in only a limited number of symptoms

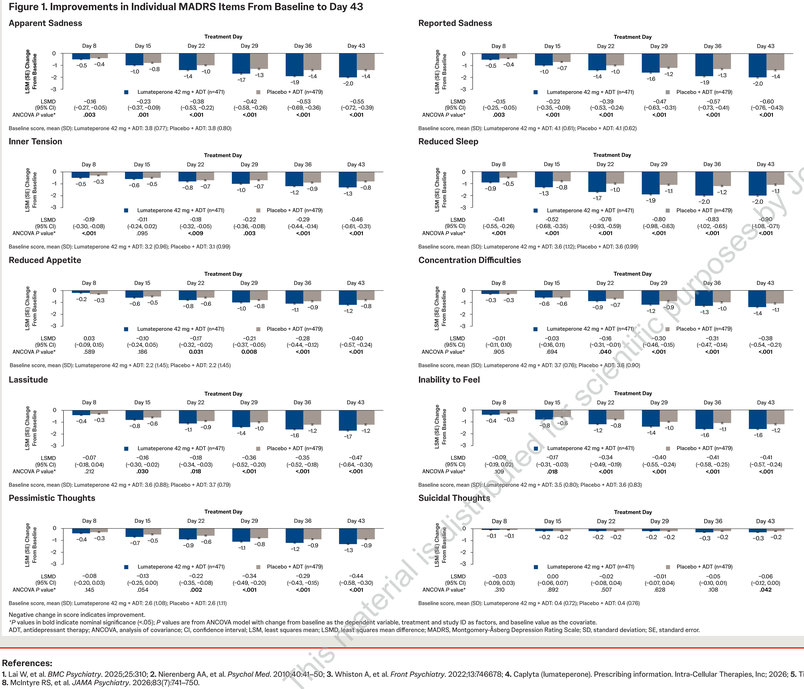
Methods

- Pooled data were analyzed from Studies 501 and 502 involving adults (18–65 years) with Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition–defined MDD with inadequate response to 1 or 2 ADT in the current depressive episode, with a MADRS total score ≥24, Clinical Global Impression–Severity score ≥4, and Quick Inventory of Depressive Symptomatology-Self Report-16 item score ≥14
- Patients with a significant risk of suicidal behaviour were excluded
- Patients were randomized to 6 weeks of lumateperone 42 mg + ADT or placebo + ADT
- The change from baseline to Day 43 in MADRS total score was analyzed using a mixed-effects model for repeated measures in the modified intent-to-treat (mITT) population (all randomized patients who received ≥1 treatment dose, with a baseline and ≥1 postbaseline MADRS total score)
- This post hoc analysis investigated change in individual MADRS items using analysis of covariance models in the mITT population
  - Clinically meaningful change in individual MADRS items was defined as the proportion of patients with an improvement of ≥2 points from baseline
  - The proportion of patients with MADRS item scores ≤1 (minimal or no symptoms) at Day 43 was also assessed

Results

- A total of 950 patients were included in the pooled mITT population (lumateperone 42 mg + ADT, n=471; placebo + ADT, n=479)
- Baseline characteristics were similar for the 2 groups
  - The mean (range) age was 45.2 (18–65) years in the lumateperone 42 mg + ADT group and 45.8 (18–65) years in the placebo + ADT group
  - Most patients were female (67.5% in the lumateperone 42 mg + ADT group and 67.8% in the placebo + ADT group) and White (85.8% in the lumateperone 42 mg + ADT group and 86.2% in the placebo + ADT group)
- At Day 43, lumateperone + ADT significantly improved MADRS total score versus placebo + ADT (least squares mean difference [LSMD] vs placebo + ADT, −4.7 [95% CI, −5.8, −3.7]; effect size, −0.59; $P<.0001$)
  - Mean baseline scores on individual MADRS items ranged from 4.1 (reported sadness; 'pervasive') to 0.4 (suicidal thoughts; 'enjoys life or takes it as it comes') in the lumateperone + ADT group (**Figure 1**)
  - Median baseline scores on individual MADRS items ranged from 4.0 (reported sadness, apparent sadness, reduced sleep, concentration difficulties, lassitude, inability to feel) to 0 (suicidal thoughts) in the lumateperone + ADT group
- At Day 43, there were statistically significant improvements in all 10 MADRS items with lumateperone + ADT versus placebo + ADT (**Figure 1**)
  - The largest improvement was in reduced sleep (LSMD, −0.90; 95% CI, −1.08, −0.71; $P<.001$)
  - The smallest improvement was in suicidal thoughts (LSMD, −0.06; 95% CI, −0.12, 0.00; $P=.042$); this may be explained by the lower baseline values on this item stemming from the exclusion of patients with risk of suicidal behaviour
- Significant improvements with lumateperone + ADT versus placebo + ADT were seen from Day 8 for apparent sadness, reported sadness, inner tension, and reduced sleep and from Day 15 for lassitude and inability to feel; improvements were maintained through end of treatment (**Figure 1**)

Figure 1. Improvements in Individual MADRS Items From Baseline to Day 43



- At Day 43, improvements of ≥2 points were observed across 9 of the 10 MADRS items in patients receiving lumateperone 42 mg + ADT (**Figure 2**)
  - The exclusion of patients with risk of suicidal behaviour explains the low proportion of patients with ≥2 point improvement in suicidal thoughts

Figure 2. (A) Frequency of MADRS Individual Item Scores at Baseline

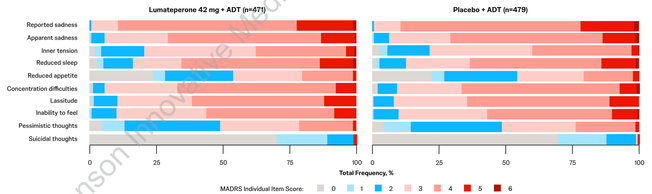
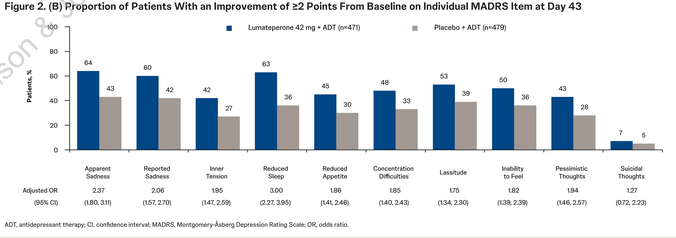


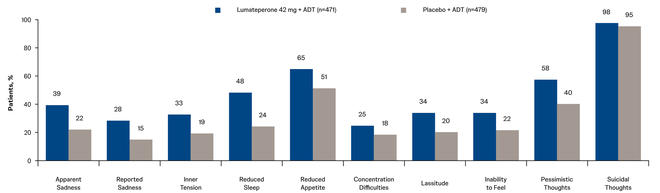
Figure 2. (B) Proportion of Patients With an Improvement of ≥2 Points From Baseline on Individual MADRS Item at Day 43



ADT, antidepressant therapy; CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; OR, odds ratio.

- At Day 43, the proportion of patients with absent or minimal individual symptoms increased across all items in the lumateperone 42 mg + ADT group versus the placebo + ADT group (**Figure 3**)
  - The exclusion of patients with risk of suicidal behaviour explains the higher proportion of patients with a score of ≤1 on the suicidal thoughts item at Day 43

Figure 3. Proportion of Patients With a Score of ≤1 on Each MADRS Item at Day 43 With Lumateperone 42 mg + ADT versus Placebo + ADT



An item score of ≤1 indicates absent or minimal symptoms.
ADT, antidepressant therapy; MADRS, Montgomery-Åsberg Depression Rating Scale.

Conclusions

- Lumateperone 42 mg + ADT demonstrated superior efficacy compared with placebo + ADT in improving a broad range of depression symptoms in patients with MDD with inadequate ADT response
- Early improvement from baseline was seen across key MADRS items with lumateperone 42 mg + ADT versus placebo + ADT and maintained through end of treatment
- More patients achieved ≥2 points improvement in individual MADRS items with lumateperone 42 mg + ADT versus placebo + ADT
- Lumateperone + ADT compared with placebo + ADT was associated with an increased percentage of patients with no or minimal symptoms as assessed using individual MADRS items, which accords with evidence of relatively large effect size improvement in overall depressive symptoms[8]

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