Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder and Anxious Distress

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BACKGROUND

- Most patients with major depressive disorder (MDD) have comorbid anxiety (54%-78%) according to the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) anxious distress specifier[1]
- Patients with MDD and anxious distress have worse psychosocial functioning and quality of life, increased suicide risk, and poorer treatment response than patients without anxious distress[1]
- Current treatments for MDD are often limited by delayed responses and undesirable side effects (e.g. weight gain, metabolic disturbances, sexual dysfunction, and disturbed sleep)[2,3]
- Lumateperone is a mechanistically novel US FDA–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[4,5]
  - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission[5]
  - 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[5]
  - This novel mechanism of action with multi-modal effects may confer robust efficacy with improved tolerability compared with current treatment options
- In a recent Phase 3, randomized, double-blind, placebo-controlled trial (Study 501; NCT04985942), adjunctive lumateperone 42 mg was efficacious over adjunctive placebo with a favorable safety profile in patients with MDD with inadequate antidepressant therapy (ADT) response
- This post hoc analysis of Study 501 investigated efficacy of adjunctive lumateperone 42 mg in patients who also met DSM-5 criteria for anxious distress

METHODS

- Eligible adults (18-65 years) had DSM-5–diagnosed MDD with inadequate response to 1 or 2 courses of ADT in the current depressive episode, were experiencing a major depressive episode (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥24 and Clinical Global Impression Scale-Severity [CGI-S] score ≥4), and had Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score ≥14 at screening and baseline
  - Inadequate response to ADT was defined as <50% improvement with ADT monotherapy for ≥6 weeks as confirmed by the Antidepressant Treatment Response Questionnaire
- Patients were randomized 1:1 to 6-week oral lumateperone 42 mg + ADT or placebo + ADT
- The primary and key secondary efficacy endpoints were change from baseline to Day 43 in MADRS Total score and CGI-S score, respectively, in the modified intent-to-treat (mITT) population, analyzed using a mixed-effects model for repeated measures (MMRM)
- Patient-reported outcomes included change from baseline in QIDS-SR-16 Total score, examined with an analysis of covariance, and Generalized Anxiety Disorder-7 (GAD-7) Total score, analyzed with an MMRM in the intent-to-treat population (ITT)
- Change in MADRS inner tension item score, response (≥50% MADRS Total score decrease from baseline), and remission (MADRS Total score ≤10) were also assessed
- This post-hoc analysis evaluated patients with DSM-5 anxious distress at screening, defined as the presence of ≥2 anxious symptoms (feeling tense, feeling restless, difficulty concentrating because of worry, fearful something awful may happen, or feeling out of control) during the majority of days during the current major depressive episode

RESULTS

Patient Population

- Of 481 patients in the mITT (lumateperone + ADT, 239; placebo + ADT, 242), 207 (43.0%) had anxious distress at baseline
- Demographics and baseline characteristics were similar between groups (**Table 1**)
  - None of the patients with anxious distress also met criteria for mixed features or psychotic features

Table 1. Baseline Demographics and Clinical Characteristics in Patients With Anxious Distress (mITT Population)

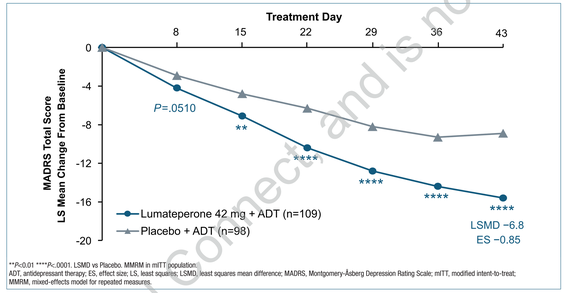
	Lumateperone 42 mg + ADT (n=109)	Placebo + ADT (n=98)
Age, mean (range), years	46.2 (19-65)	44.5 (20-64)
Sex, n (%)		
Women	72 (66.1)	65 (66.3)
Men	37 (33.9)	33 (33.7)
Race, n (%)		
White	94 (86.2)	84 (85.7)
Asian	4 (3.7)	4 (4.1)
Black	10 (9.2)	7 (7.1)
Other	1 (0.9)	3 (3.1)
Hispanic or Latino ethnicity, n (%)	4 (3.7)	8 (8.2)
Number of lifetime depressive episodes, mean (range)	3.7 (1-30)	3.3 (1-15)
Lifetime history of treatment failures including the current MDE, n (%)		
1	82 (75.2)	65 (66.3)
2	27 (24.8)	33 (33.7)
MADRS Total score, mean (SD)	31.0 (3.71)	30.6 (3.61)
CGI-S score, mean (SD)	4.7 (0.55)	4.7 (0.59)
QIDS-SR-16 Total score, mean (SD)[a]	18.8 (2.27)	18.1 (2.26)
GAD-7 Total score, mean (SD)[b]	11.9 (4.36)	11.3 (4.22)

[a] ITT population (lumateperone 42 mg + ADT, n=110; placebo + ADT, n=99). [b] ITT population (lumateperone 42 mg + ADT, n=109; placebo + ADT, n=99).
ADT, antidepressant therapy; CGI-S, Clinical Global Impression Scale-Severity; GAD-7, Generalized Anxiety Disorder-7 item; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; mITT, modified intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptoms-Self Report 16 items.

Efficacy

- In Study 501, the primary endpoint was met for lumateperone + ADT, with significantly greater MADRS Total score improvement from baseline to Day 43 compared with placebo + ADT in the mITT (least squares mean difference vs placebo [LSMD], –4.9; effect size [ES], –0.61; *P*<.0001)
- Lumateperone 42 mg + ADT significantly improved MADRS Total score change from baseline at Day 43 compared with placebo + ADT in patients with anxious distress (**Figure 1**)
  - A statistically significant improvement with lumateperone + ADT was nearly attained at Day 8 (*P*=.0510) and was achieved beginning at Day 15 (*P*=.0044) and maintained through Day 43
- Lumateperone significantly improved change from baseline for the MADRS inner tension single-item score at Day 43 compared with placebo (*P*<.0001) in patients with anxious distress

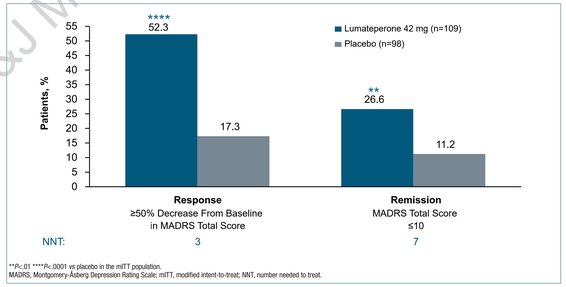
Figure 1. LS Mean Change From Baseline in MADRS Total Score in Patients With Anxious Distress (mITT Population)



**P<.01 ****P<.0001. LSMD vs Placebo. MMRM in mITT population.
ADT, antidepressant therapy; ES, effect size; 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.

- In patients with anxious distress at Day 43, MADRS response and remission rates were significantly greater with lumateperone + ADT vs placebo + ADT (**Figure 2**)

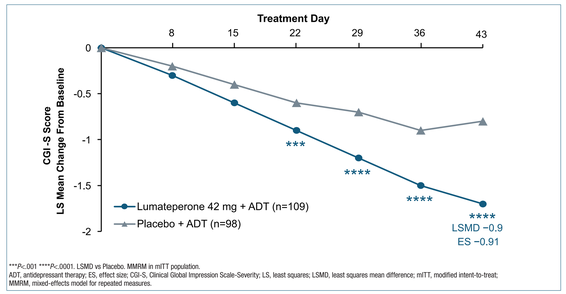
Figure 2. MADRS Response and Remission Rates at Day 43 Patients With Anxious Distress (mITT Population)



**P<.01 ****P<.0001 vs placebo in the mITT population.
MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; NNT, number needed to treat.

- The key secondary endpoint was met for lumateperone + ADT, with significantly greater CGI-S improvement from baseline to Day 43 compared with placebo + ADT in the mITT (LSMD, –0.7; ES, –0.67; *P*<.0001)
- Lumateperone 42 mg + ADT also significantly improved change from baseline for CGI-S score at Day 43 in patients with anxious distress vs placebo + ADT (**Figure 3**)
  - CGI-S score was significantly improved by Day 22 with lumateperone + ADT treatment and continued throughout the study

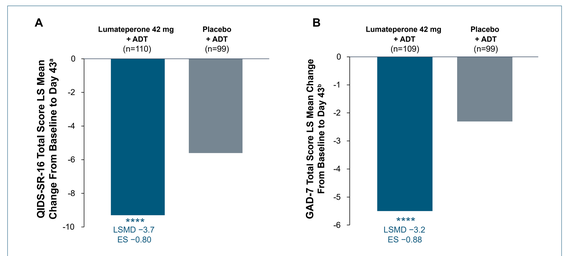
Figure 3. LS Mean Change From Baseline in CGI-S Score in Patients With Anxious Distress (mITT Population)



***P<.001 ****P<.0001. LSMD vs Placebo. MMRM in mITT population.
ADT, antidepressant therapy; ES, effect size; CGI-S, Clinical Global Impression Scale-Severity; LS, least squares; LSMD, least squares mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

- In patients with anxious distress, self-reported depressive symptoms, as measured by QIDS-SR-16 Total score, also significantly improved with lumateperone 42 mg + ADT compared with placebo + ADT from baseline to Day 43 (**Figure 4A**)
- Patient-reported anxiety measured using GAD-7 Total score improved with lumateperone 42 mg + ADT compared with placebo + ADT from baseline to Day 43 in patients with anxious distress (**Figure 4B**)
  - GAD-7 Total score also improved in the overall ITT population including patients with or without anxious distress at Day 43 vs placebo + ADT (baseline mean: lumateperone + ADT, 9.8; placebo + ADT, 9.6; LSMD, –1.6; ES, –0.43; *P*<.0001)

Figure 4. LS Mean Change From Baseline to Day 43 in QIDS-SR-16 Total Score (A) and GAD-7 Total Score (B) in Patients With Anxious Distress (ITT Population)



****P<.0001. LSMD vs Placebo. [a] ANCOVA in ITT population. [b] MMRM in ITT population.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; ES, effect size; GAD-7, Generalized Anxiety Disorder-7 item; ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self-Report-16 item.

CONCLUSIONS

- **In patients with anxious distress, lumateperone 42 mg adjunctive to ADT demonstrated significant, clinically meaningful, efficacy over adjunctive placebo improving depression symptoms and overall disease severity**
- **MADRS response (NNT, 3) and remission (NNT, 7) rates were significantly improved with adjunctive lumateperone 42 mg vs adjunctive placebo in patients with anxious distress**
- **There was also significant improvement in anxiety symptoms in patients with anxious distress treated with adjunctive lumateperone 42 mg compared with adjunctive placebo**
- **These results suggest lumateperone 42 mg adjunctive to ADT is a promising new treatment option for adults with MDD and anxious distress with inadequate response to ADT**

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