Adjunctive Lumateperone in Patients With Major Depressive Disorder and Anxious Distress

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Background

- Comorbid anxiety is common in patients with major depressive disorder (MDD), with studies reporting that 54%-78% of patients meet the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) criteria for anxious distress[1]
  - Anxious distress is defined in the DSM-5 as ≥2 anxiety symptoms during a depressive episode (feeling tense, feeling unusually restless, difficulty concentrating, fear that something awful may happen, or a sense of losing control)[2]
- Patients with MDD and anxious distress have poorer quality of life and clinical outcomes, including lower response rates to standard antidepressant therapy (ADT), compared with patients without anxious distress[1,3]
- 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 ADT[4]
  - 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 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), lumateperone 42 mg + ADT met the primary endpoint, with significant improvement in depressive symptoms compared with placebo + ADT, and was generally well tolerated in patients with MDD with inadequate ADT response[6]
- This post hoc analysis of Study 502 investigated adjunctive lumateperone 42 mg efficacy in patients with MDD with inadequate response to ADT who also met DSM-5 criteria for anxious distress

Methods

- Eligible adults (aged 18-65 years, inclusive) met DSM-5 criteria for MDD with inadequate response to 1-2 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–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 ≥6 weeks of ADT monotherapy 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 (defined as all randomized patients who received ≥1 dose of study drug and had a baseline and ≥1 postbaseline MADRS Total score), analyzed using a mixed-effects model for repeated measures (MMRM)
  - Additional measures included change in MADRS inner tension item score based on an MMRM, response (≥50% MADRS Total score decrease) and remission (MADRS Total score ≤10) based on a logistic regression model, and patient-reported outcomes (change from baseline in QIDS-SR-16 Total score) examined using analysis of covariance
- This post hoc analysis evaluated patients based on the presence or absence of DSM-5–defined anxious distress at screening[2]

Results

Patient Population

- Of 469 patients in the mITT population, 179 patients (38.2%) had anxious distress at screening (lumateperone + ADT, n=88; placebo + ADT, n=91)
  - Demographic and baseline characteristics were similar between groups in patients with anxious distress (**Table 1**)

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

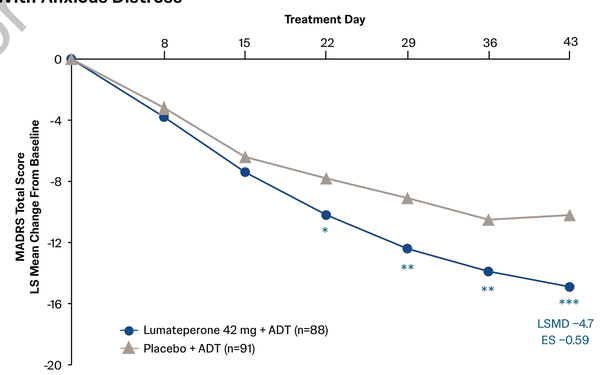
	Lumateperone 42 mg + ADT (n=88)	Placebo + ADT (n=91)
Demographic and Clinical Parameters		
Age, mean (range), years	45.6 (19-65)	44.4 (19-65)
Sex, n (%)		
Female	61 (69.3)	65 (71.4)
Male	27 (30.7)	26 (28.6)
Race, n (%)		
White	85 (96.6)	86 (94.5)
Black	3 (3.4)	4 (4.4)
Other	0	1 (1.1)
Hispanic or Latino ethnicity, n (%)	7 (8.0)	3 (3.3)
Number of lifetime depressive episodes, mean (range)	4.0 (1-11)	5.2 (1-20)
Current MDE also met criteria for anxious distress, n (%)	88 (100.0)	91 (100.0)
Lifetime history of treatment failures including the current episode, n (%)		
1	63 (71.6)	66 (72.5)
2	25 (28.4)	25 (27.5)
Baseline Efficacy Parameters		
MADRS Total score, mean (SD)	30.9 (4.16)	31.9 (4.03)
CGI-S score, mean (SD)	4.6 (0.59)	4.6 (0.64)
QIDS-SR-16 Total score, mean (SD)[a]	17.9 (2.66)	18.2 (2.40)

[a]ITT population (lumateperone 42 mg + ADT, n=92; placebo + ADT, n=91).
ADT, antidepressant therapy; CGI-S, Clinical Global Impression-Severity; ITT, intent-to-treat; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; mITT, modified intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

Efficacy

- 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 population (least squares mean difference vs placebo [LSMD], −4.5; effect size [ES], −0.56; *P*<.0001)
- A significant improvement in MADRS Total score change from baseline at Day 43 was observed with lumateperone 42 mg + ADT compared with placebo + ADT in patients with anxious distress (**Figure 1**)
  - A statistically significant improvement with lumateperone + ADT was achieved beginning at Day 22 in patients with anxious distress and continued through Day 43

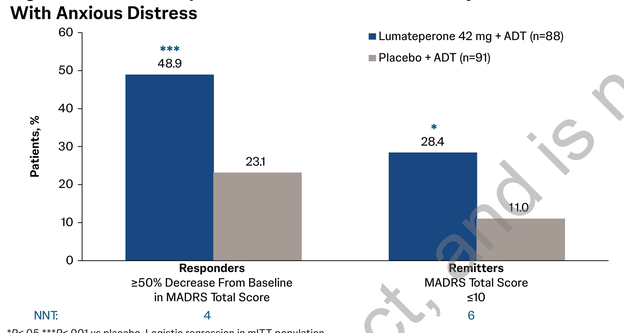
Figure 1. LS Mean Change From Baseline in MADRS Total Score in Patients With Anxious Distress



*P<.05 **P<.01 ***P<.001. 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.

- Lumateperone significantly improved MADRS inner tension single item score from baseline to Day 43 compared with placebo (*P*<.05) in patients with anxious distress
- MADRS response and remission rates at Day 43 were significantly greater with lumateperone + ADT compared with placebo + ADT in patients with anxious distress **(Figure 2**)

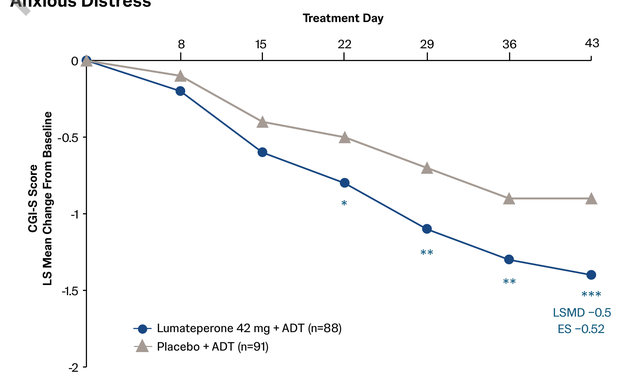
Figure 2. MADRS Response and Remission Rates at Day 43 in Patients With Anxious Distress



*P<.05 ***P<.001 vs placebo. Logistic regression in mITT population.
ADT, antidepressant therapy; 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 score improvement from baseline to Day 43 compared with placebo + ADT in the mITT population (LSMD, −0.5; ES, −0.51; *P*<.0001)
- In patients with anxious distress, a significant improvement in CGI-S score at Day 43 was also observed with lumateperone 42 mg + ADT compared with placebo + ADT (**Figure 3**)
  - CGI-S score significantly improved by Day 22 with lumateperone + ADT and persisted throughout the study in patients with anxious distress

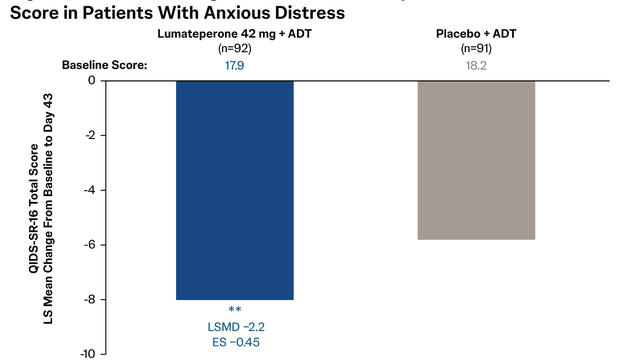
Figure 3. LS Mean Change From Baseline in CGI-S Score in Patients With Anxious Distress



*P<.05 **P<.01 ***P<.001. 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.

- Lumateperone + ADT significantly improved self-reported depressive symptoms from baseline to Day 43, as measured by the QIDS-SR-16 Total score, compared with placebo + ADT in patients with anxious distress (**Figure 4**)

Figure 4. LS Mean Change From Baseline to Day 43 in QIDS-SR-16 Total Score in Patients With Anxious Distress



**P<.01. LSMD vs placebo. ANCOVA in ITT population.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; ES, effect size; 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 the subgroup of patients without anxious distress (mITT population, lumateperone + ADT, n=144; placebo + ADT, n=146), lumateperone + ADT significantly improved MADRS Total score (LSMD, −4.4; ES, −0.55; P<.0001) and CGI-S score (LSMD, −0.50; ES, −0.50; P<.0001) from baseline to Day 43
  - Lumateperone + ADT also demonstrated significant improvement at Day 43 in the QIDS-SR-16 Total score (ITT population, lumateperone + ADT, n=150; placebo + ADT, n=147; LSMD, −2.2; ES, −0.46; P<.001) vs placebo + ADT in patients without anxious distress

Conclusions

- In patients with MDD with anxious distress, lumateperone 42 mg + ADT demonstrated significant and clinically meaningful improvements in depressive symptoms and disease severity compared with placebo + ADT
- Lumateperone 42 mg + ADT significantly improved depression symptoms according to both clinician-rated (MADRS Total score, CGI-S score) and patient-reported outcomes (QIDS-SR-16 Total score)
- MADRS response (NNT, 4) and remission (NNT, 6) rates were significantly greater with lumateperone + ADT vs placebo + ADT in patients with anxious distress
- These results suggest lumateperone 42 mg as a promising adjunctive treatment option for patients with MDD with an inadequate response to ADT who met DSM-5 anxious distress criteria

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Disclosures
WR Earley, S Durgam, Y Mo, and M Chen 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.

R Jain has served as a consultant to Addrenex, Allergan (now AbbVie), Avanir, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Supernus, Takeda, and Teva; paid speaker for Addrenex, Alkermes, Allergan (now AbbVie), Lilly, Lundbeck, Merck, Neos Therapeutics, Otsuka, Pamlab, Pfizer, Rhodes, Shionogi, Shire, Sunovion, Takeda, and Tris Pharmaceuticals; received research support from Allergan (now AbbVie), AstraZeneca, Lilly, Lundbeck, Otsuka, Pfizer, Shire, and Takeda; and served on advisory board for Addrenex, Alkermes, Avanir, Forum, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Supernus, Takeda, and Teva.

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1. Hopwood M. *Neurol Ther*. 2023;12:S5-S12; 2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC. 2013; 3. Brown TM, et al. *J Depress Anxiety*. 2016;5:237; 4. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc.;2025; 5. Titulaer J, et al. *Eur Neuropsychopharmacol*. 2022;62:22-35; 6. Durgam S, et al. *Am J Psychiatry*. 2025;182(12):1072-1082.

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