Adjunctive Lumateperone 42 mg Treatment in Major Depressive Disorder: Efficacy in Anhedonia and Across Broad Range of Depressive Symptoms

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BACKGROUND

- Anhedonia occurs in ≈70% of individuals with major depressive disorder (MDD) and is associated with severe and recurrent illness, reduced quality of life, and impaired functioning¹²
 - Anhedonia is defined by the DSM-5 as markedly diminished interest or pleasure¹
- Currently available MDD treatments may result in residual symptoms, including anhedonia symptoms, which increases the risk for depression relapse and recurrence,³ highlighting the need for effective new treatments
- Lumateperone is a mechanistically novel, US Food and Drug Administration-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 valproate⁴
 - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission⁵
 - Specifically, lumateperone is a potent serotonin 5-HT_{2A} receptor antagonist, a dopamine D₂ receptor presynaptic partial agonist and postsynaptic antagonist, a D₁ receptor-dependent indirect modulator of glutamatergic AMPA and NMDA currents, and a serotonin reuptake inhibitor⁵
 - 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, randomised, double-blind, placebo-controlled, multicentre trial (Study 501, NCT04985942), lumateperone 42 mg adjunctive to antidepressant therapy (ADT) significantly improved depressive symptoms and disease severity in patients with MDD with inadequate response to ADT⁶
 - Lumateperone 42 mg + ADT was generally safe and well tolerated, consistent with prior lumateperone trials⁶
- This analysis of Study 501 evaluated the broad efficacy of lumateperone 42 mg + ADT across depression symptoms assessed by Montgomery-Åsberg Depression Rating Scale (MADRS) single item and anhedonia factor scores

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-Severity Scale 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 randomised 1:1 to 6-week treatment with oral lumateperone 42 mg + ADT or placebo + ADT
- Efficacy analyses were performed by-visit using a mixedeffects model for repeated measures (MMRM) in the
 modified intent-to-treat (mITT) population (defined as all
 randomised patients who received ≥1 dose of study drug
 and had a baseline and ≥1 postbaseline MADRS Total
 score)
 - The primary endpoint was change in MADRS Total score from baseline to Day 43
 - A prospective analysis investigated change from baseline in MADRS single item scores
 - A post hoc analysis evaluated anhedonia symptoms according to change in MADRS anhedonia factor score (sum of the single items for apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel)
 - MADRS Total score and the MADRS anhedonia factor score were analysed in patients with anhedonia baseline higher than the median, defined as baseline MADRS anhedonia ≥18 (median baseline value in mITT population)

RESULTS

Patient Population

- During the study, 484 patients were treated, of which 481 were included in the mITT population (lumateperone + ADT, 239; placebo + ADT, 242) and 452 (93.4%) completed treatment.
- Demographics and baseline characteristics were similar between groups (Table 1)

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

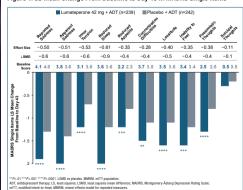
	Lumateperone 42 mg + ADT (n=239)	Placebo + ADT (n=242)
Demographics		
Age, mean (range), years	45 (18-65)	45 (19-65)
Sex, n (%)		
Female	156 (65.3)	160 (66.1)
Male	83 (34.7)	82 (33.9)
Race, n (%)		
White	178 (74.5)	191 (78.9)
Asian	40 (16.7)	32 (13.2)
Black	20 (8.4)	16 (6.6)
Other	1 (0.4)	3 (1.2)
Hispanic or Latino ethnicity, n (%)	14 (5.9)	16 (6.6)
Disease Characteristics		
MADRS Total score, mean (SD)	30.4 (3.75)	30.1 (3.50)
MADRS anhedonia factor score, mean (SD)	18.4 (2.10)	18.2 (2.17)
CGI-S score, mean (SD)	4.7 (0.55)	4.6 (0.56)

DT. antideoressant therapy: CGI-S. Clinical Global Impression-Severity Scale: MADRS. Montpomery-Asberg Depression Rating Scale: mITT. modified intent-to-treat

Efficacy

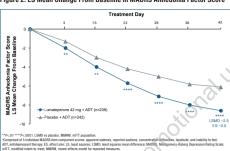
- The primary endpoint was met for lumateperone + ADT, with significant improvement in MADRS Total score at Day 43 compared with placebo + ADT (least-squares mean difference vs placebo + ADT [LSMD], -4.9; ES, -0.61; P< 0001)
- The most prominent MADRS single items at baseline were reported sadness and apparent sadness (Figure 1)
- At Day 43, lumateperone + ADT significantly improved all MADRS single items, except suicidal thoughts, compared with placebo + ADT (Figure 1)
 - The largest improvement at Day 43 occurred for reduced sleep
 - The earliest significant (P<.05) reductions from baseline occurred at Day 8 for reported sadness, apparent sadness, and reduced sleep, and these improvements continued throughout the study
 - Significant improvements for inability to feel and pessimistic thoughts were observed at Day 15 and persisted up to Day 43
 - Consistent significant improvements for inner tension and concentration difficulties were observed beginning at Day 22, and for reduced appetite and lassitude beginning at Day 29

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



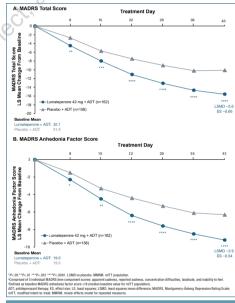
- Lumateperone + ADT significantly improved MADRS anhedonia factor score compared with placebo + ADT at every visit (Figure 2)
 - Each of the 5 items comprising the MADRS anhedonia factor score significantly improved with lumateperone + ADT by Day 29, with persistent improvement throughout the study

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



- In the subgroup of patients with anhedonia baseline higher than the median, significant improvements in MADRS Total score were observed at every visit up to Day 43 with lumateperone + ADT (Figure 3A)
- Lumateperone + ADT also significantly improved MADRS anhedonia factor score in patients with anhedonia baseline higher than the median, with significant reductions beginning at Day 8 and continuing 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



CONCLUSIONS

- Lumateperone 42 mg + ADT significantly improved a broad range of depression symptoms across MADRS single items in patients with MDD with inadequate ADT response
- Improvements with lumateperone 42 mg + ADT were significant at every visit for reported sadness, apparent sadness, and reduced sleep
- Lumateperone 42 mg + ADT significantly improved symptoms of anhedonia compared with placebo + ADT, as measured by MADRS anhedonia factor score
- In patients with anhedonia baseline higher than the median, lumateperone 42 mg + ADT significantly improved both depression and anhedonia symptoms 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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ME Thase has served as an advisor or a consultant for Autobahn Therapeutics, Assome Therapeutics, Inc.; Clexio Bilosciences; Genon Lehran; Gift Therapeutics, M. Lundbeck, A.S., Janssen Pharmaceuticals, Inc.; Chexio Bilosciences; Genon Lehran; Gift Therapeutics, M. Lundbeck, A.S., Janssen Pharmaceuticals, Cohenga, M.E. Older Therapeutics, Device Pharmaceutical Company, ILL; Jensen Casser, M. Lundbeck, A.S., Landbeck, A.S., Land

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