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Lumateperone 42 mg in Patients With Major Depressive Disorder: Analysis of Remission in Short- and Long-Term Trials

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Background

- Major depressive disorder (MDD) is a prevalent and complex psychiatric condition, affecting ≈185 million individuals worldwide[1]
- In patients with MDD, remission rates are low (≈25%) following first-line treatment and decline further with subsequent treatments[2]
- Failure to achieve remission is associated with reduced quality of life and increased relapse rates,[3] underscoring the importance of remission as a key goal of MDD treatment
- Lumateperone is an atypical antipsychotic indicated for the treatment of MDD in adults as adjunct to antidepressant therapy (ADT); the treatment of schizophrenia in adults; and the 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[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, characterized by its multimodal effects, may confer robust efficacy with improved tolerability compared with current treatment options
- The efficacy and safety of lumateperone 42 mg adjunctive to ADT was demonstrated in two Phase 3, randomized, double-blind, placebo-controlled studies (Study 501 [NCT04985942]; Study 502 [NCT05061706]) and an open-label extension study (OLE; Study 503 [NCT05061719]) in patients with MDD with inadequate ADT response[6-8]
 - The primary and key secondary endpoints were met in both short-term studies, with lumateperone 42 mg + ADT significantly improving Montgomery-Åsberg Depression Rating Scale (MADRS) Total score and Clinical Global Impression-Severity (CGI-S) score, respectively, vs placebo + ADT at Day 43; efficacy was maintained throughout the 26-week OLE
 - Lumateperone 42 mg + ADT was generally well tolerated in both short- and long-term studies
- This analysis of Studies 501, 502, and 503 evaluated MADRS Total score remission rates in patients with MDD with inadequate ADT response

Methods

- Efficacy data were pooled for the lumateperone 42 mg + ADT group and the placebo + ADT group from the short-term Studies 501/502; data were presented for the long-term Study 503
- Study 501 and Study 502 enrolled adults (18-65 years old) who met *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for MDD with inadequate response to 1-2 ADTs in the current depressive episode (defined as <50% improvement according to the Antidepressant Treatment Response Questionnaire)
 - Patients were experiencing a major depressive episode (MADRS Total score ≥24, CGI-S score ≥4) and had Quick Inventory of Depressive Symptomatology-Self Report-16 item score ≥14 at screening and baseline
 - Patients were randomized 1:1 to 6-week, double-blind placebo + ADT or lumateperone 42 mg + ADT
- Patients who safely completed double-blind treatment could enroll in Study 503 to receive 26-week, open-label, oral, once-daily lumateperone 42 mg + ADT
 - Screening for the OLE occurred on the last visit of the lead-in study (lead-in study Day 43, OLE Day 1)
- In pooled Studies 501/502 and Study 503, efficacy was evaluated in the overall populations and in patient subgroups (age, type of ADT, and baseline MADRS severity), using logistic regression in the placebo-controlled studies and descriptive statistics in the OLE
- MADRS remission (MADRS Total score ≤10), complete remission (MADRS Total score ≤5), and sustained remission (defined at each visit as MADRS Total score ≤10 at the visit and MADRS Total score ≤10 maintained at all following visits) were assessed

Results

Patient Population

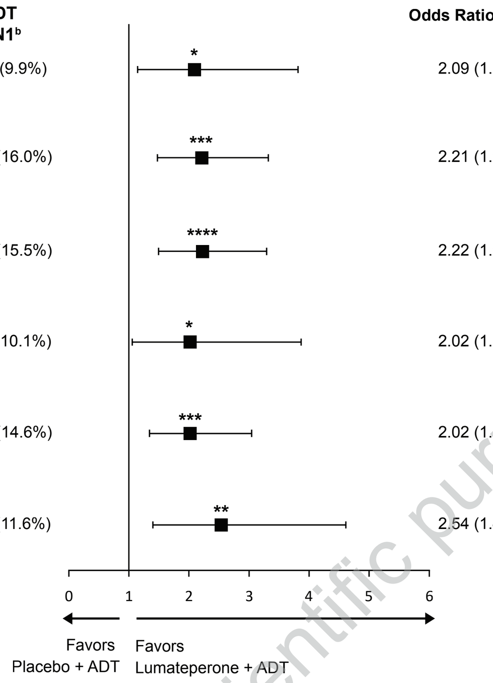
- The modified intent-to-treat (mITT) population comprised 950 patients (lumateperone + ADT, n=471; placebo + ADT, n=479) in the pooled Studies 501/502
- In Study 503, 809 patients were enrolled and treated with lumateperone + ADT
- For Studies 501/502 and Study 503, the majority of patients were female (67.7% and 68.9%, respectively) and White (86.0% and 88.2%, respectively)

Efficacy

- In pooled Studies 501/502, MADRS Total score remission rates were significantly greater (P<.0001) with lumateperone + ADT (25.5%) vs placebo + ADT (13.6%) at Day 43
- Significantly greater MADRS remission rates were observed in patient subgroups with lumateperone + ADT vs placebo + ADT in the pooled population at Day 43 (**Figure 1**)

Figure 1. MADRS Total Score Remission[a] Rates at Day 43 in Patient Subgroups: Pooled Studies 501/502

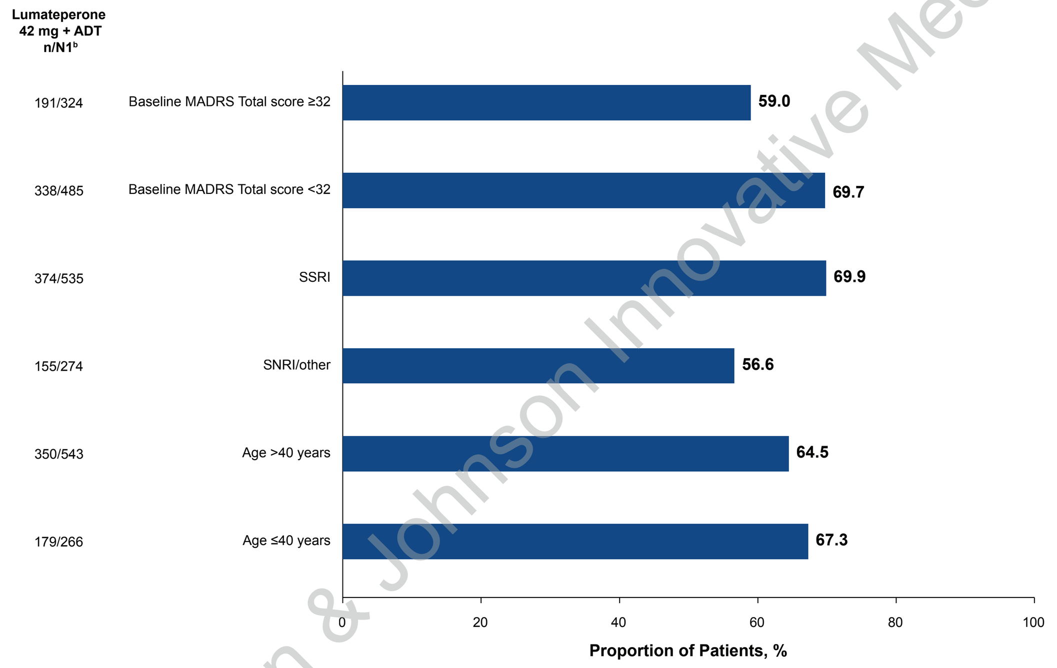
	Lumateperone 42 mg + ADT n/N1[b]	Placebo + ADT n/N1[b]		Odds Ratio (95% CI)
Baseline MADRS Total score ≥32	35/186 (18.8%)	19/191 (9.9%)	*	2.09 (1.1,3.8)
Baseline MADRS Total score <32	85/285 (29.8%)	46/288 (16.0%)	***	2.21 (1.5,3.3)
SSRI	91/320 (28.4%)	48/310 (15.5%)	****	2.22 (1.5,3.3)
SNRI/other	29/151 (19.2%)	17/169 (10.1%)	*	2.02 (1.1,3.9)
Age >40 years	78/304 (25.7%)	46/315 (14.6%)	***	2.02 (1.3,3.0)
Age ≤40 years	42/167 (25.1%)	19/164 (11.6%)	**	2.54 (1.4,4.6)


0
1
2
3
4
5
6
Favors Placebo + ADT
Favors Lumateperone + ADT
Odds Ratio (95% CI) vs Placebo + ADT

*P<.05 **P<.01 ***P<.001 ****P<.0001. Logistic regression model in the mITT population.
[a]Remission was defined as MADRS Total score ≤10 at the visit. [b]N1=Number of patients in each subgroup.
ADT, antidepressant therapy; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

- Remission occurred in 529 (65.4%) patients at end of open-label treatment in Study 503
- In each of the subgroups analyzed in Study 503, MADRS Total score remission occurred in over 55% of patients receiving lumateperone + ADT at end of treatment (**Figure 2**)
 - Remission rates were similar regardless of age, ADT treatment, or baseline disease severity

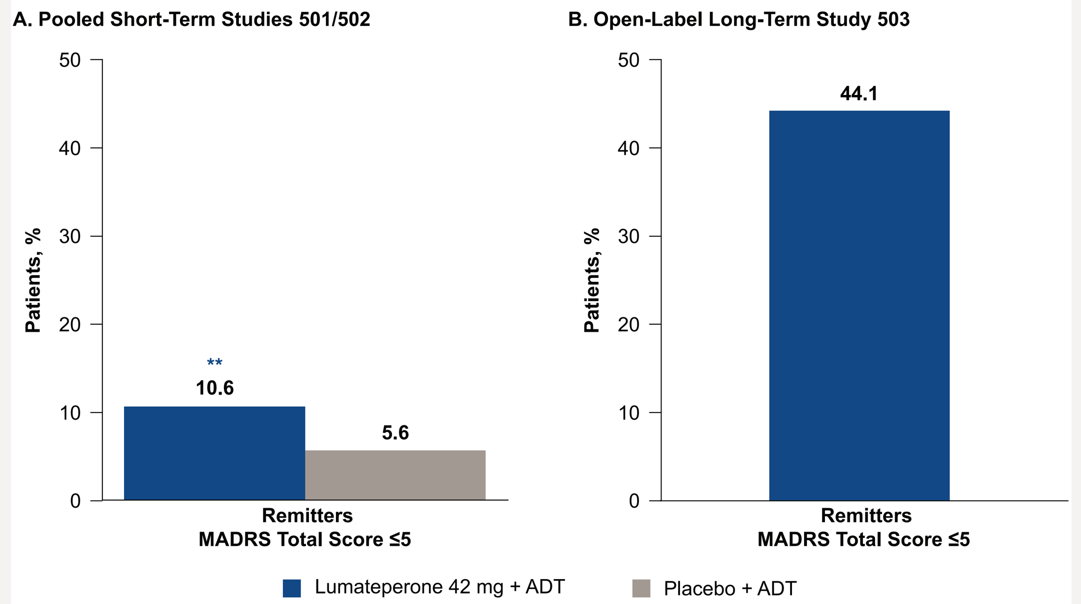
Figure 2. MADRS Total Score Remission[a] Rates at EOT in Patient Subgroups: Study 503


Lumateperone 42 mg + ADT n/N1[b]
191/324 Baseline MADRS Total score ≥32 59.0
338/485 Baseline MADRS Total score <32 69.7
374/535 SSRI 69.9
155/274 SNRI/other 56.6
350/543 Age >40 years 64.5
179/266 Age ≤40 years 67.3
0
20
40
60
80
100
Proportion of Patients, %

[a]Remission was defined as MADRS Total score ≤10 at the visit. [b]N1=Number of patients in each subgroup in the safety population.
ADT, antidepressant therapy; EOT, end of treatment; MADRS, Montgomery-Åsberg Depression Rating Scale; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

- Complete remission was achieved by 50 patients (10.6%) with lumateperone + ADT and 27 patients (5.6%) with placebo + ADT (P<.01) in the pooled mITT population of Studies 501/502 (**Figure 3A**)
- In Study 503, complete remission was achieved by 357 patients (44.1%) (**Figure 3B**)

Figure 3. MADRS Total Score Complete Remission[a]

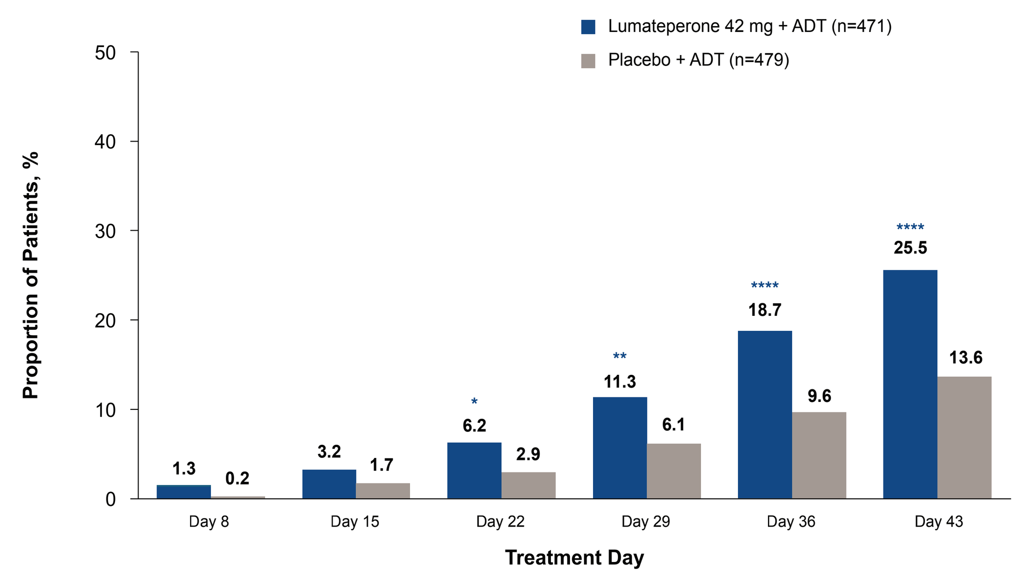

A. Pooled Short-Term Studies 501/502
B. Open-Label Long-Term Study 503
Patients, %
**
10.6
5.6
44.1
Remitters
MADRS Total Score ≤5
Lumateperone 42 mg + ADT
Placebo + ADT

**P<.01. Logistic regression model in Studies 501/502.
[a]Complete remission was defined as MADRS Total score ≤5 at Day 43 in Studies 501/502 and end of open-label treatment in Study 503.
ADT, antidepressant therapy; MADRS, Montgomery-Åsberg Depression Rating Scale.

- Sustained remission rates were significantly greater with lumateperone + ADT vs placebo + ADT beginning at Day 22 in the pooled mITT population of Studies 501/502 (**Figure 4A**)
- In Study 503, sustained remission rates ranged from 13.2% at Week 1 to 60.4% at Week 26 (**Figure 4B**)

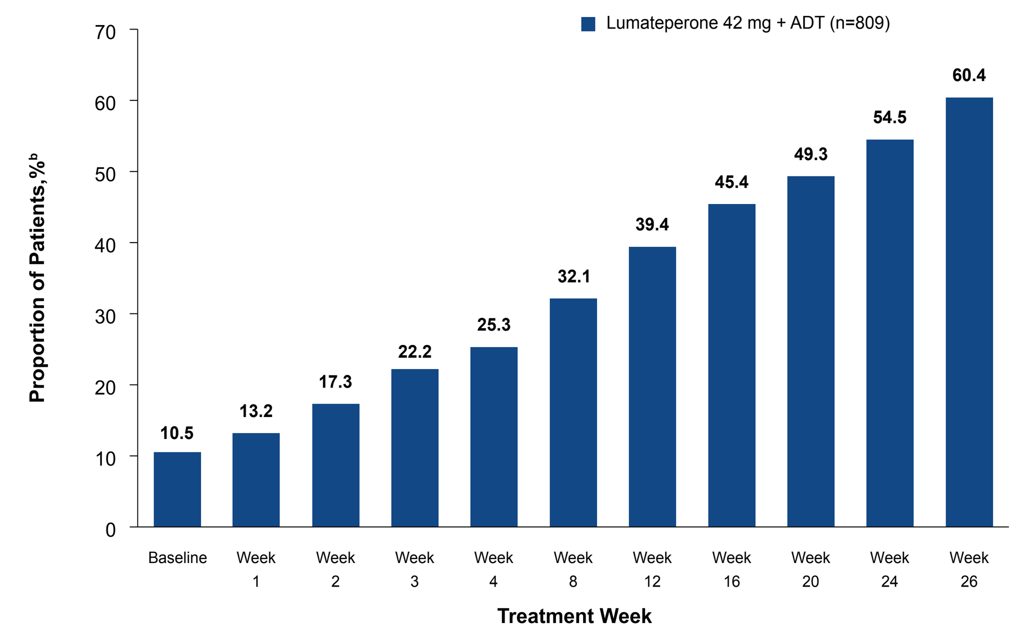
Figure 4. MADRS Total Score Sustained Remission[a] Rates

A. Pooled Short-Term Studies 501/502


Lumateperone 42 mg + ADT (n=471)
Placebo + ADT (n=479)
Proportion of Patients, %
1.3 0.2
3.2 1.7
* 6.2 2.9
** 11.3 6.1
**** 18.7 9.6
**** 25.5 13.6
Day 8
Day 15
Day 22
Day 29
Day 36
Day 43
Treatment Day

	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
Odds ratio	4.44	1.87	2.12	1.93	2.14	2.16
(95% CI)	(0.8, 25.0)	(0.8, 4.3)	(1.1, 4.0)	(1.2, 3.1)	(1.5, 3.1)	(1.5, 3.0)

B. Open-Label Long-Term Study 503


Lumateperone 42 mg + ADT (n=809)
Proportion of Patients,%[b]
Baseline 10.5
Week 1 13.2
Week 2 17.3
Week 3 22.2
Week 4 25.3
Week 8 32.1
Week 12 39.4
Week 16 45.4
Week 20 49.3
Week 24 54.5
Week 26 60.4
Treatment Week

*P<.05 **P<.01 ****P<.0001. Logistic regression model in the mITT population of pooled Studies 501/502.
[a]Sustained remission was defined at each visit as MADRS Total score ≤10 at the visit and MADRS Total score ≤10 maintained at all following visits.
[b]Percentage based on the safety population consisting of patients who safely completed the double-blind lead-in studies 501 or 502.
ADT, antidepressant therapy; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat.

Conclusions

- Lumateperone 42 mg + ADT demonstrated significantly greater MADRS Total score remission rates over placebo + ADT in pooled short-term studies in patients with MDD with inadequate ADT response
- Efficacy was maintained with long-term lumateperone 42 mg + ADT treatment, with ≈2 of every 3 patients achieving remission with 6-month treatment
- These results indicate lumateperone as a promising adjunctive treatment option for patients with MDD with inadequate ADT response

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Disclosures

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S Durgam is a former employee of Intra-Cellular Therapies, a Johnson & Johnson company.

WR Earley, C Chen, and T Escher are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company.

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