Efficacy of Lumateperone 42 mg in the Treatment of Major Depressive Disorder: A Pooled Analysis of Phase 3 Randomized Controlled Trials

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Faculty Conflict of Interest Disclosure

We have the following potential conflict(s) of interest to report:

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	Rakesh Jain has received research support from Allergan (now AbbVie), AstraZeneca, Lilly, Lundbeck, Otsuka, Pfizer, Shire, and Takeda
Receipt of honoraria or consultation fees	Rakesh 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
Participation in a company sponsored speaker's bureau	Rakesh Jain has served as a paid speaker for Addrenex, Alkermes, Allergan (now AbbVie), Lilly, Lundbeck, Merck, Neos Therapeutics, Otsuka, Pamlab, Pfizer, Rhodes, Shionogi, Shire, Sunovion, Takeda, and Tris Pharmaceuticals
Stock shareholder	None
Spouse/partner	None
Other support (please specify)	Suresh Durgam, Willie R. Earley, Susan G. Kozauer, Changzheng Chen, and John B. Edwards are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company Rakesh Jain has 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

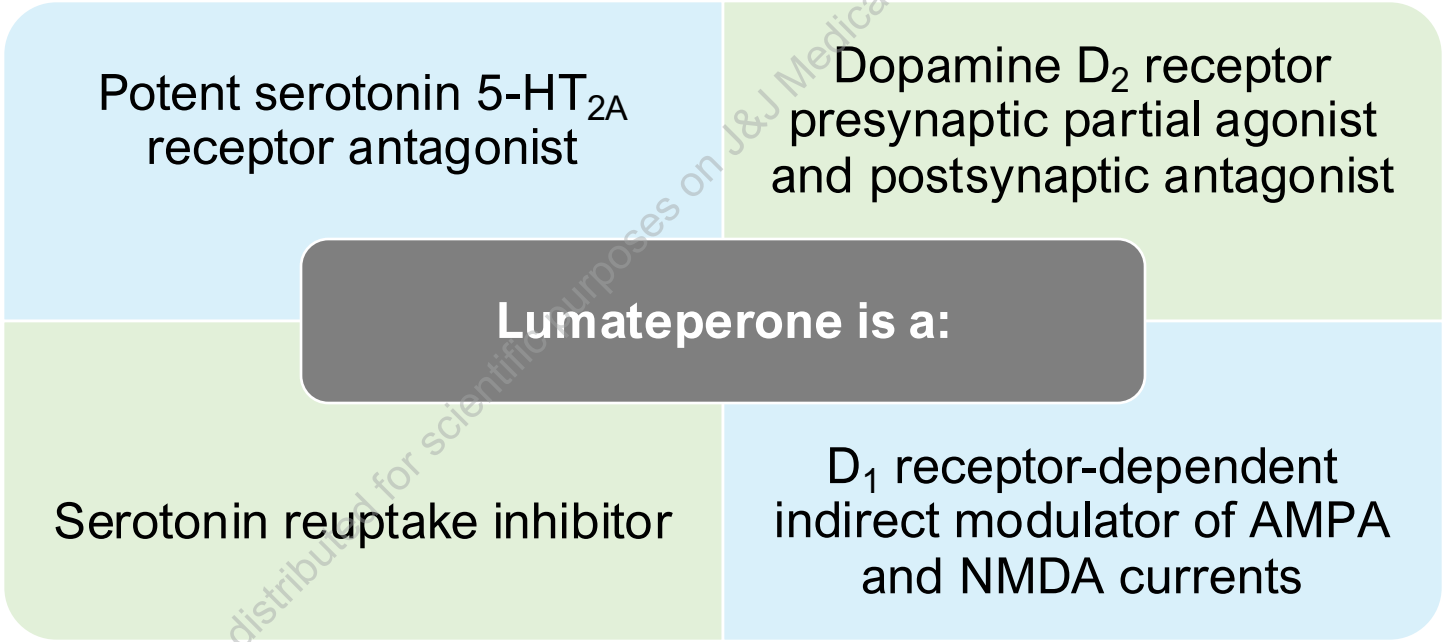
Background: Major Depressive Disorder (MDD)

- MDD is a common and complex mental illness which affects over 185 million people globally[1]
- MDD is associated with[1,2]
  - Functional impairment
  - Comorbidities
  - Reduced quality of life
  - Heightened risk of suicide
- Current treatments for MDD are often limited by delayed responses and undesirable side effects[3]

1. Marx W, et al. *Nat Rev Dis Primers*. 2023;9:. 2. Proudman D, et al. *PharmacoEconomics*. 2021;39:619-625. 3. Alva G. *CNS Spect*. 2023;28(5):521-525.
MDD, major depressive disorder.

Background: Lumateperone

- Lumateperone is a mechanistically novel FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder[1,2]
- Lumateperone simultaneously modulates serotonin, dopamine, and glutamate neurotransmission[2]



1. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc.;2023. 2. Titulaer J, et al. *Eur Neuropsychopharmacol*. 2022;62:22-35.
AMPA, α-amino-3–hydroxy-5-methyl-4-isoxazolepropionic acid; FDA, US Food and Drug Administration; NMDA, *N*-methyl-D-aspartate.

Background: Efficacy and Safety of Lumateperone

- The efficacy and safety of lumateperone adjunctive to ADT was evaluated in 2 Phase 3 studies in patients who had inadequate response to 1-2 ADTs in the current depressive episode

Study 501 NCT04985942	Positive 6-week, randomized, double-blind, placebo-controlled, trial of adjunctive lumateperone in patients with MDD and inadequate response to ADT
Study 502 NCT05061706	Positive 6-week, randomized, double-blind, placebo-controlled, trial of adjunctive lumateperone in patients with MDD and inadequate response to ADT

- In both studies, lumateperone 42 mg + ADT met the primary endpoint, with significant improvement in depressive symptoms compared with placebo + ADT
- Lumateperone was generally well tolerated

This pooled analysis of Studies 501 and 502 was conducted to demonstrate the robustness of the efficacy of lumateperone 42 mg + ADT compared with adjunctive placebo in patients with MDD with inadequate ADT response

ADT, antidepressant therapy; FDA, US Food and Drug Association; MDD, major depressive disorder; sNDA, supplemental new drug application.

501 and 502 Study Design

- Efficacy data were pooled for the lumateperone 42 mg + ADT groups and for the placebo + ADT groups from Study 501 and Study 502

Key Eligibility Criteria

- 18-65 years (inclusive)
- DSM-5–diagnosed MDD
- Current MDE (MADRS Total score ≥24; CGI-S score ≥4; QIDS-SR-16 score ≥14)
- Inadequate response to 1-2 courses of prior ADT (<50% improvement) per ATRQ

Study 501 & 502 Design

Treatment randomized 1:1 to
- Lumateperone 42 mg + ADT
- Placebo + ADT

Screening (≤2 weeks) → Double-blind treatment (6 weeks) → Follow-up (1 week)

Outcomes

Primary:
MADRS Total score

Key Secondary:
CGI-S score

Additional:
MADRS response and remission rates

QIDS-SR-16 score
Safety

ADT, antidepressant therapy; ARTQ, Antidepressant Treatment Response Questionnaire; CGI-S, Clinical Global Impression-Severity; DSM-5, Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

Patient Disposition in the Pooled Safety Population

- A total of 964 patients were screened for Study 501 and Study 502
- 91.4% of patients in the safety population completed the double-blind treatment period
- Discontinuation rates were 12% in the lumateperone group and 5.2% in the placebo group
- The most common reasons for discontinuation from the double-blind treatment period were:
  - Adverse event (4.7%)
  - Withdrawal of consent (2.2%).

	Lumateperone 42 mg + ADT (n=483)	Placebo + ADT (n=481)
Completed double-blind treatment period, n (%)	425 (88.0)	456 (94.8)
Discontinued from double-blind treatment period, n (%)	58 (12.0)	25 (5.2)
Adverse Event	43 (8.9)	3 (0.6)
Death	0	0
Lack of efficacy	0	4 (0.8)
Lost to follow up	3 (0.6)	3 (0.6)
Pregnancy	0	0
Protocol violation	4 (0.8)	2 (0.4)
Site terminated by sponsor	0	0
Study terminated by sponsor	0	0
Subject withdrew consent	8 (1.7)	13 (2.7)
Other	0	0

ADT, antidepressant therapy.

Baseline Demographics and Clinical Characteristics in Pooled mITT Population

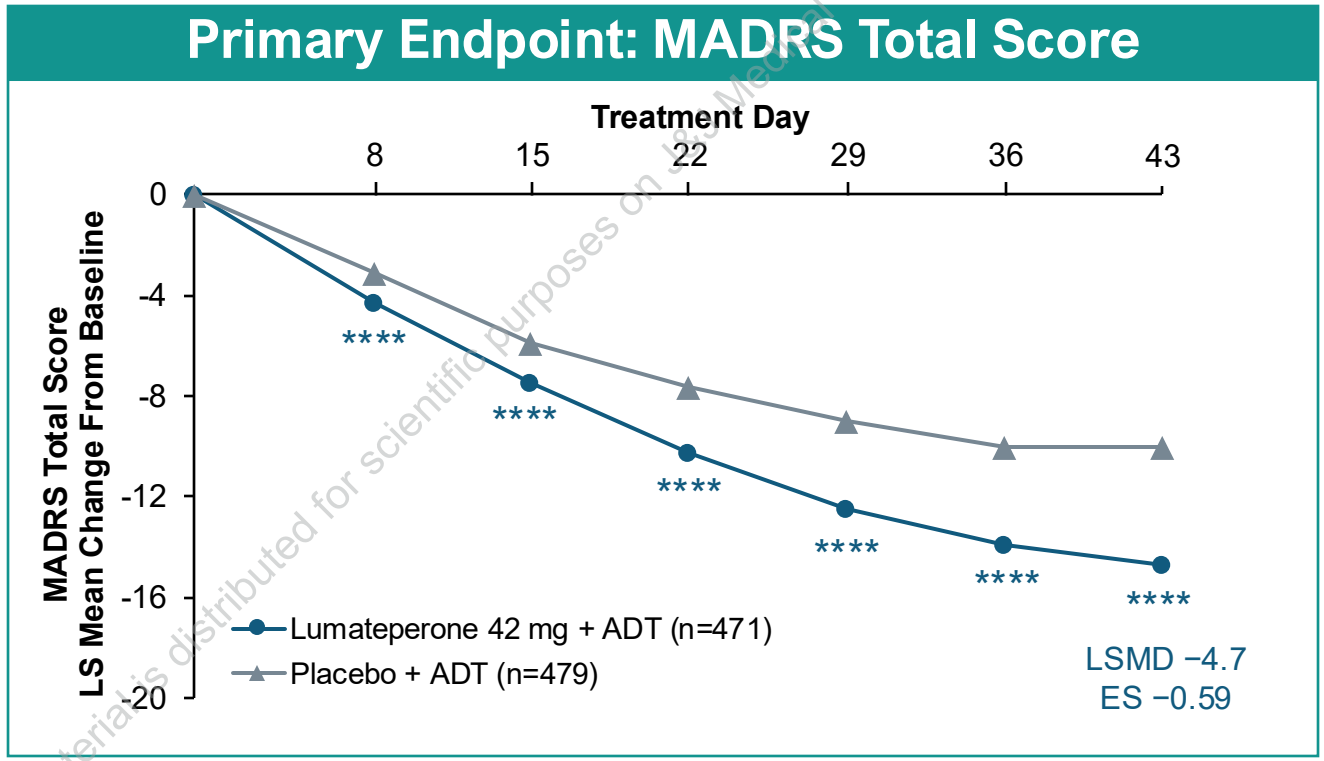
- The mITT population comprised 950 patients
- Baseline demographics and clinical characteristics were similar between groups
- At baseline, patients had moderate-to-severe depression in both studies[a]

	Lumateperone 42 mg + ADT (n=471)	Placebo + ADT (n=479)
Age, mean (range), years	45.2 (18-65)	45.8 (18-65)
Sex, n (%)		
Women	318 (67.5)	325 (67.8)
Men	153 (32.5)	154 (32.2)
Race, n (%)		
White	404 (85.8)	413 (86.2)
Asian	41 (8.7)	35 (7.3)
Black	25 (5.3)	24 (5.0)
Other	1 (0.2)	7 (1.5)
Hispanic or Latino ethnicity, n (%)	50 (10.6)	49 (10.2)
Number of lifetime depressive episodes, mean (range)	3.6 (1-30)	4.0 (1-36)
Lifetime history of treatment failures including the current MDE, n (%)		
1	352 (74.7)	352 (73.5)
2	119 (25.3)	127 (26.5)
MADRS Total score, mean (SD)	30.6 (3.82)	30.8 (3.80)
CGI-S score, mean (SD)	4.7 (0.57)	4.6 (0.57)
QIDS-SR-16 Total score, mean (SD)[b]	18.0 (2.42)	17.8 (2.40)

[a] Baseline mean MADRS Total score (lumateperone 42 mg, 30.6; placebo, 30.8) and CGI-S score (lumateperone, 4.7; placebo 42 mg, 4.6). [b] ITT population (lumateperone 42 mg + ADT n=483, placebo + ADT n=481).
ADT, antidepressant therapy; CGI-S, Clinical Global Impression-Severity; 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.

Pooled Efficacy: MADRS Total Score

- Lumateperone met the primary endpoint:
  - Lumateperone + ADT significantly improved MADRS Total score from baseline to Day 43 vs placebo + ADT in patients with MDD
  - Significantly greater MADRS Total score reductions were observed at the earliest assessment (Day 8) with lumateperone 42 mg + ADT treatment and persisted throughout the study

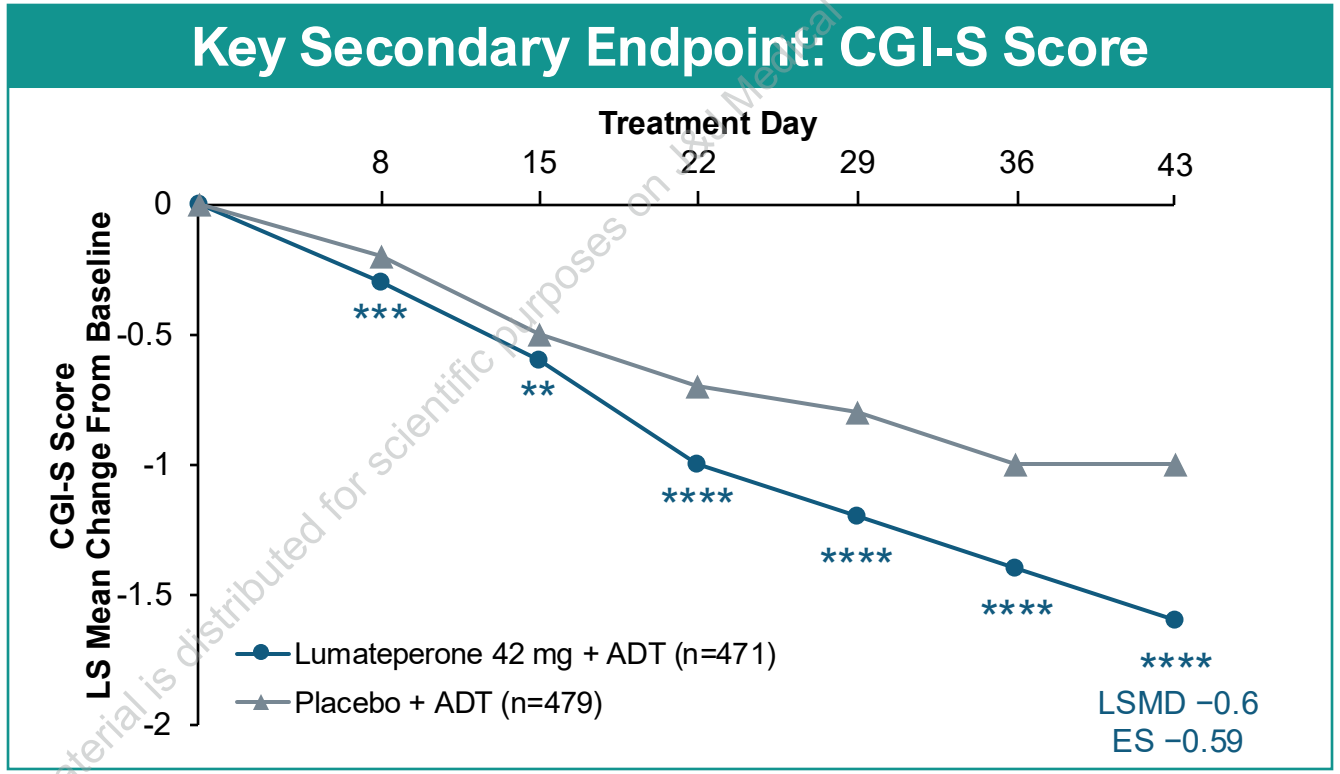


****P<.0001. LSMD vs Placebo. MMRM in mITT population.

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.

Pooled Efficacy: CGI-S Score

- Lumateperone met the key secondary endpoint:
  - Lumateperone + ADT was associated with improvements in overall MDD disease severity compared with placebo + ADT in patients with MDD
  - CGI-S score showed improvements by Day 8 with lumateperone 42 mg + ADT treatment and continued throughout the study

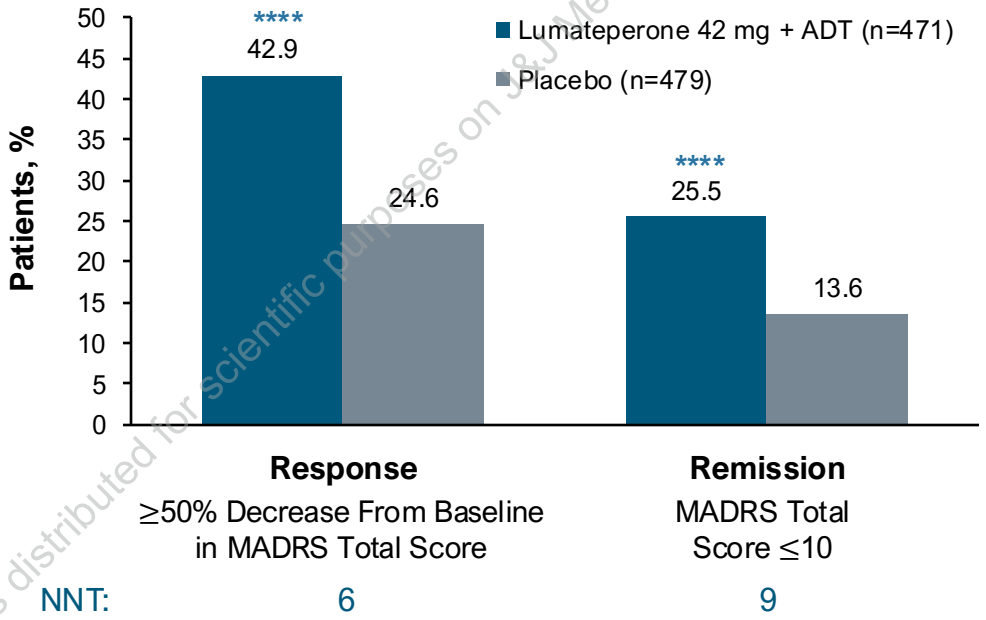


**P<.01 ***P<.001 ****P<.0001. LSMD vs Placebo. MMRM in mITT population.
ADT, antidepressant therapy; ES, effect size; CGI-S, Clinical Global Impression-Severity; LS, least squares; LSMD, least squares mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

Pooled Efficacy: MADRS Response and Remission

- MADRS response rate (NNT 6) and remission rate (NNT 9) were significantly greater with lumateperone + ADT vs placebo + ADT at Day 43
  - Based on the NNT, lumateperone + ADT compared with placebo + ADT was associated with clinically meaningful patient outcomes

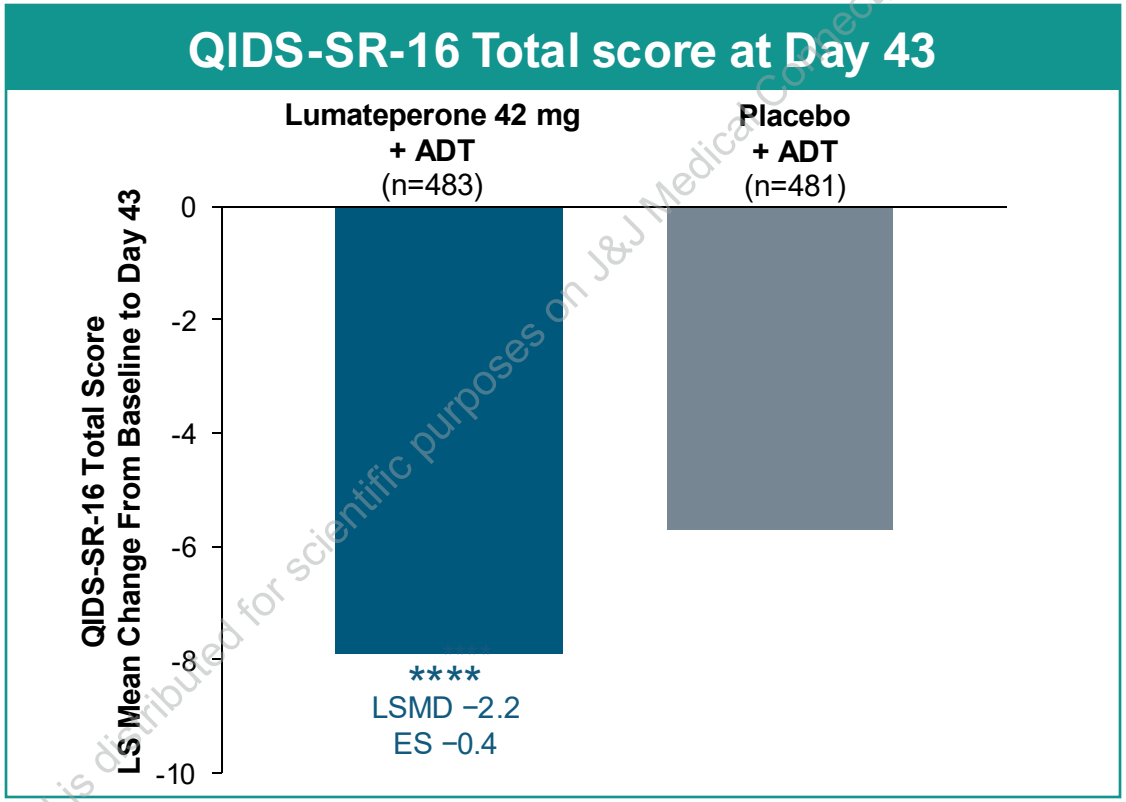
MADRS Response and Remission at Day 43



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

Pooled efficacy: QIDS-SR-16 Total Score

- Lumateperone + ADT significantly improved patient-reported depressive symptoms at Day 43 vs placebo + ADT



****P<.0001. 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.

Conclusions

- Lumateperone 42 mg adjunctive to ADT demonstrated robust, clinically meaningful efficacy over adjunctive placebo to ADT in this pooled analysis of 2 trials in patients with MDD with inadequate ADT response
- Lumateperone 42 mg adjunctive to ADT improved:
  - Depression symptoms (MADRS Total score)
  - Disease severity (CGI-S score)
  - Response and remission rates (MADRS response and remission)
  - Patient-reported depression (QIDS-SR-16 Total score)
- This pooled analysis suggest lumateperone 42 mg adjunctive to ADT is a promising new treatment option for adults with MDD and with inadequate response to 1 to 2 courses of prior ADT

ADT, antidepressant therapy; CGI-S, Clinical Global Impression-Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self-Report-16 item.

Thank you

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