Patterns of response with adjunctive lumateperone in patients with major depressive disorder: a pooled analysis of 2 Phase 3 trials

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Background

- In patients with major depressive disorder (MDD) with inadequate response to ≥1 antidepressant therapy (ADT), adjunctive medication has demonstrated improved response rates[1,2]
- Importantly, early response may be associated with subsequent sustained response[3]
- Lumateperone is a medication indicated for MDD (adjunct to ADT), schizophrenia, and depressive episodes associated with bipolar I or II disorder (bipolar depression; monotherapy and adjunctive therapy)[4]
- In 2 positive, Phase 3, randomized, double-blind, placebo-controlled studies (Study 501 [NCT04985942]; Study 502 [NCT05061706]), lumateperone 42 mg + ADT significantly improved depression symptoms and led to significantly greater response rates vs placebo + ADT at Week 6 in patients with MDD with inadequate ADT response[5,6]
- The objective of this pooled post hoc analysis was to characterize the timing, duration, and sustainability of response to adjunctive lumateperone 42 mg vs placebo in adults with MDD and an inadequate response to prior ADT

Methods

- Data were pooled from 2 studies (Studies 501 and 502)
- Eligible adults (aged 18-65 years) had *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) criteria for MDD with inadequate response to 1 or 2 ADT courses (<50% improvement on the Antidepressant Treatment Response Questionnaire) in the current major depressive episode, Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≥24, Clinical Global Impression–Severity score ≥4, and Quick Inventory of Depressive Symptomatology-Self Report-16 item total score ≥14[5,6]
- Patients were randomized (1:1) to receive 6 weeks of oral lumateperone 42 mg per day or placebo adjunctive to ADT[5,6]
- The modified intent-to-treat (mITT) analysis set included all randomized patients who received ≥1 dose of study drug and had both baseline and ≥1 valid postbaseline MADRS assessments
- Mean changes from baseline in MADRS total score over time were compared between treatment groups using mixed effects model for repeated measures
- The proportion of patients achieving response (≥50% decrease from baseline [randomization] in MADRS total score) between groups was evaluated using logistic regression models over time
  - Odds ratios (ORs) and corresponding 95% CIs were provided
- Mean number of days and the percentage of study time spent in response were summarized, and differences in percentage of study time were compared between groups using the Wilcoxon test
  - Proportion of patients by number of weeks in response was also summarized
- Patients with and without early response were analyzed descriptively according to response achieved at Week 6 and with ORs and corresponding 95% CIs
- The proportion of patients achieving response at continuous visits between groups was evaluated using logistic regression models over time
  - ORs and corresponding 95% CIs were provided

Results

Patient population

- The pooled mITT population comprised 950 patients (lumateperone + ADT, n=471; placebo + ADT, n=479)[7]
- Baseline characteristics were generally similar between treatment arms (**Table 1**)

Table 1. Baseline demographics and clinical characteristics (mITT population)[7]

	Lumateperone 42 mg + ADT (n=471)	Placebo + ADT (n=479)
Age, mean (range), years	45.2 (18-65)	45.8 (18-65)
Female, n (%)	318 (67.5)	325 (67.8)
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)
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)[a]	18.0 (2.42)	17.8 (2.40)

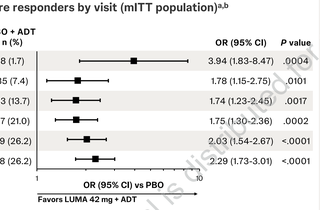
[a]Lumateperone 42 mg + ADT, n=483; placebo + ADT, n=481.
ADT, antidepressant therapy; CGI-S, Clinical Global Impression–Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

MADRS response over time

- Lumateperone + ADT showed greater improvement in MADRS total score from baseline to Week 6 than placebo + ADT (least squares mean difference, −4.7; 95% CI, −5.8 to −3.7; effect size, −0.59; *P*<.0001)
- At Week 6, MADRS response was achieved by 48.2% of patients receiving lumateperone 42 mg + ADT compared with 26.2% of patients receiving placebo + ADT (**Figure 1**)
- The odds of achieving MADRS response at Week 6 were 2.29× greater with lumateperone 42 mg + ADT than with placebo + ADT (OR, 2.29; 95% CI, 1.73-3.01; *P*<.001)
  - Statistically significant differences between the lumateperone 42 mg + ADT and placebo + ADT arms with respect to MADRS response rates were seen by Week 1 and persisted through Week 6

Figure 1. MADRS total score responders by visit (mITT population)[a,b]

Visit	LUMA 42 mg + ADT n (%)	PBO + ADT n (%)	OR (95% CI)	*P* value
Week 1	31 (6.6)	8 (1.7)	3.94 (1.83-8.47)	.0004
Week 2	58 (12.9)	35 (7.4)	1.78 (1.15-2.75)	.0101
Week 3	98 (22.6)	63 (13.7)	1.74 (1.23-2.45)	.0017
Week 4	145 (33.7)	97 (21.0)	1.75 (1.30-2.36)	.0002
Week 5	189 (44.5)	119 (26.2)	2.03 (1.54-2.67)	<.0001
Week 6	202 (48.2)	118 (26.2)	2.29 (1.73-3.01)	<.0001



[a]Response was defined as ≥50% decrease from baseline in MADRS total score.
[b]Visit window allowed for ±4 days around target visit.
ADT, antidepressant therapy; LUMA, lumateperone; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; OR, odds ratio; PBO, placebo.

Time spent in MADRS response

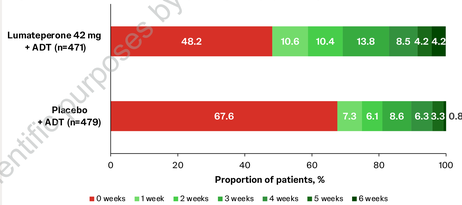
- The mean (SD) days in MADRS total score response was greater for patients receiving lumateperone 42 mg vs placebo (10.8 [13.0] vs 6.4 [10.9] days) (**Table 2**)
  - Lumateperone + ADT treatment resulted in a 67.2% increase in mean percentage of study time spent in response through Week 6 vs placebo + ADT (22.9% vs 13.7%; *P*<.001)
  - A larger percentage of patients receiving lumateperone 42 mg + ADT were in response for 3 to 6 weeks (30.8%) or 1 or 2 weeks (21.0%) than those receiving placebo + ADT (3 to 6 weeks, 19.0%; 1 or 2 weeks, 13.4%) (**Figure 2**)

Table 2. Length of time in response based on MADRS total score (mITT population)[a]

	Lumateperone 42 mg + ADT (n=471)	Placebo + ADT (n=479)
Time in response up to Week 6, mean (range), days[b]	10.8 (0-46)	6.4 (0-44)
Percentage of time in response while on study, mean (range), %[b]	22.9 (0-98)	13.7 (0-94)
P value[c]	<.001	

[a]Response was defined as ≥50% decrease from baseline in MADRS total score.
[b]Visit window allowed for ±4 days around target visit.
[c]Wilcoxon test *P* value.
ADT, antidepressant therapy; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat.

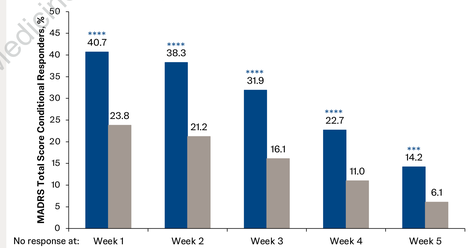
Figure 2. Number of weeks in response (mITT population)[a]



[a]Response was defined as ≥50% decrease from baseline in MADRS total score.
ADT, antidepressant therapy; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat.

- Most patients achieving early response at Week 2 continued to have response at Week 6 (lumateperone + ADT, 44/58 [75.9%] vs placebo + ADT, 24/35 [68.6%]; OR, 1.32; 95% CI, 0.51-3.43; *P*=.5624)
- In patients not in response at a given earlier visit, the odds of ultimately responding at Week 6 were consistently higher among those receiving lumateperone 42 mg + ADT compared with placebo + ADT (OR range, 2.19-2.52) (**Figure 3**)
  - For example, in patients without response at Week 2, 38.3% (158/413) receiving lumateperone 42 mg and 21.2% (94/444) receiving placebo responded at Week 6 (*P*<.0001)

Figure 3. Proportion of patients with Week 6 response among those without response at an earlier visit (mITT population)[a,b]



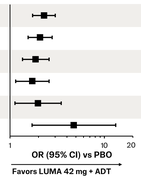
	Week 1	Week 2	Week 3	Week 4	Week 5
n NI	179 440 112 471	158 413 94 444	119 373 67 416	74 326 42 382	40 282 22 360
Odds ratio	2.19	2.30	2.43	2.36	2.52
(95% CI)	(1.65-2.91)	(1.70-3.11)	(1.73-3.41)	(1.57-3.56)	(1.47-4.33)

***P<.001; ****P<.0001.
[a]Response was defined as ≥50% decrease from baseline in MADRS total score.
[b]Visit window allowed for ±4 days around target visit.
ADT, antidepressant therapy; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat.

- The odds of sustaining MADRS total score response through Week 6 were significantly greater for patients receiving lumateperone 42 mg + ADT vs placebo + ADT regardless of week (**Figure 4**)
  - For example, by Week 4, 25.3% of patients receiving lumateperone + ADT and 15.2% receiving placebo + ADT achieved response that was sustained through Week 6 (OR, 1.87; 95% CI, 1.36-2.59; *P*=.0001)

Figure 4. MADRS total score responders by continuous visits (mITT population)[a,b]

Sustained response through	LUMA 42 mg + ADT n (%)	PBO + ADT n (%)	OR (95% CI)	*P* value
Week 6 only	202 (42.9)	118 (24.6)	2.29 (1.73-3.01)	<.0001
Weeks 5 and 6	162 (34.4)	96 (20.0)	2.08 (1.55-2.79)	<.0001
Weeks 4-6	119 (25.3)	73 (15.2)	1.87 (1.36-2.59)	.0001
Weeks 3-6	67 (14.2)	42 (8.8)	1.73 (1.15-2.59)	.0086
Weeks 2-6	36 (7.6)	19 (4.0)	1.98 (1.13-3.49)	.0173
Weeks 1-6	20 (4.2)	4 (0.8)	4.75 (1.71-13.17)	.0028



[a]Response was defined as ≥50% decrease from baseline in MADRS total score.
[b]Visit window allowed for ±4 days around target visit.
ADT, antidepressant therapy; LUMA, lumateperone; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; OR, odds ratio; PBO, placebo.

Conclusions

- In patients with MDD and inadequate ADT response, adjunctive lumateperone + ADT was associated with higher odds of early response, greater time spent in response, and higher Week 6 response rates vs placebo + ADT
- These findings suggest that lumateperone + ADT may provide early and sustained response benefits in this patient population

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AJ Cutler has served as a consultant/on an advisory board for: AbbVie, Acadia, Actinogen, Alfasigma, Alkermes, Anavex Life Sciences, Arrivo BioVentures, Autobahn Therapeutics, Axsome, Aytu Biopharma, Bristol Myers Squibb, Collegium Pharmaceutical, Definium Therapeutics, 4M Therapeutics, Helus Pharma, Incannex Healthcare, Intra-Cellular Therapies, J&J Innovative Medicine, Jazz Pharma, Knight Therapeutics, Kye Pharmaceuticals, Kuvatris Therapeutics, LivaNova, Lundbeck, Luye Pharma, MapLight Therapeutics, Mentavi, Neumora, Neurocrine Biosciences, Noven, Otsuka, Sensorium Therapeutics, Sirtsei Pharmaceuticals, Supernus, Teva, Thynk, Transneural Therapeutics, Tris Pharma, Vanda Pharmaceuticals, and Vistagen; served on a speaker's bureau for: AbbVie, Alfasigma, Alkermes, Axsome, Aytu Biopharma, Bristol Myers Squibb, Collegium Pharmaceutical, Intra-Cellular Therapies, J&J Innovative Medicine, Knight Therapeutics, Kye Pharmaceuticals, Lundbeck, Luye Pharma, Neurocrine Biosciences, Noven, Otsuka, Supernus, Teva, Tris Pharma, and Vanda Pharmaceuticals; served on a data safety monitoring board for COMPASS Pathways; has stock options/equity in EMA Wellness, Evolution Research Group, 4M Therapeutics, Sensorium Therapeutics, and Transneural Therapeutics.

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L Citrome has served as a consultant for AbbVie, Acadia, AdhereTech, Altus, Alumis, Axsome, Alkermes, Arc, Auritec, Autobahn, Avant Healthcare Solutions, Biogen, BioXcel, BMS/Karuna, Boehringer Ingelheim, Cadent, Cerevel, Clario/Medavante/Prophase, Clinilabs, Compass, Corcept, Definium, Delpor, Eisai, Enteris BioPharma, Health Wellness Partners, HLS, Idorsia, Immune Bio, Intra-Cellular Therapies, Janssen/Johnson & Johnson, Little Bear, Lundbeck, Luye, Lyndra, MapLight, Marvin, MindMed, Neurelis, Neushen, Neumora, Neurocrine, Noema, Novartis, Noven, Orexo, Otsuka, Ovid, Pontifax/Draig, Praxis, PSL, Real Chemistry, Relmada, Renew Research, Response, Reviva, Sage, Seaport, Sumitomo/Sunovion, Supernus, Teva, University of Arizona, Vanda, Wells Fargo, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; speaker for AbbVie, Acadia, Alkermes, Bristol Myers Squibb, Eisai, Idorsia, Intra-Cellular Therapies, Janssen/Johnson & Johnson, Lundbeck, Luye, Neopharm, Neurocrine, Noven, Otsuka, Recordati, Takeda, Teva, Vanda, and CME activities organized by medical education companies such as Decera Clinical Education/Clinical Education Alliance/Clinical Care Options, CME Institute, CMEology, HMP/Psych Congress, Medscape/WebMD, MultiMedia Medical LLC, Neuroscience Education Institute, NEI, Paradigm, Real Psychiatry/Efficient, Real World CE, Rockpointe, Total CME, Vindico, and universities, professional organizations/societies and advocacy associations (MHA); owns small amounts of health-related shares of common stock in multiple companies in a portfolio managed externally, and stock options in Reviva; and earns royalties/publishing income from Taylor & Francis (Editor-in-Chief, *Current Medical Research and Opinion*, 2022-date), UpToDate (reviewer), Springer Healthcare (book), and Elsevier (Topic Editor, *Psychiatry, Clinical Therapeutics*, through Spring 2025).

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