Predictors of Response With Adjunctive Lumateperone in Patients With Major Depressive Disorder: A Pooled Analysis of 2 Phase 3 Trials

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Background

- Major depressive disorder (MDD) is a leading cause of disability worldwide, and approximately 50% of patients with MDD do not achieve an adequate treatment response[1,2]
  - Historically, many studies have analyzed the contribution of clinical and demographic variables to predict treatment response; however, findings are largely inconsistent[2–4]
  - Identifying specific predictors of beneficial treatment outcomes may guide trial design or influence personalization of treatment[5,6]
- Lumateperone is an atypical antipsychotic indicated in adults for: (1) treatment of MDD as adjunct to antidepressant therapy (ADT); (2) treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate; and (3) treatment of schizophrenia[7]
- Lumateperone simultaneously modulates serotonin, dopamine, and, indirectly through D_1-receptor modulation, glutamatergic NMDA and AMPA receptors[8]
  - Although the mechanism of action is unknown, it could be mediated through a combination of antagonist activity at central serotonin 5-HT_{2A} receptors and partial agonist activity at central dopamine D_2 receptors[2,8]
  - Lumateperone has also moderate binding affinity for D_1 receptors and inhibits uptake of serotonin in cells expressing the human SERT[7,8]
- In two pivotal Phase 3, randomized, double-blind, placebo-controlled, multicenter trials (Study 501, NCT04985942; Study 502, NCT05061706), lumateperone 42 mg/day adjunctive to ADT significantly improved depressive symptoms compared with placebo + ADT, as measured by the change from baseline to Week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total scores, in patients with MDD with an inadequate ADT response[9,10]
  - Lumateperone 42 mg/day + ADT exhibited a consistent safety profile, with no notable changes in cardiometabolic parameters or body weight[9,10]
- We report findings from post hoc analyses of data pooled from two 6-week, double-blind studies, 501 and 502, to investigate patient demographic and disease characteristics associated with a likelihood of achieving response at Day 43 in patients with MDD and an inadequate response to ADT

Methods

- Studies 501 and 502 enrolled adult patients (18–65 years) with *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)–defined MDD with inadequate response to 1 or 2 courses of ADT in the current depressive episode, with a MADRS total score ≥24, Clinical Global Impression–Severity (CGI-S) score ≥4, and Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score ≥14 at screening
- Patients were randomized 1:1 to oral lumateperone 42 mg/day + ADT or placebo + ADT for 6 weeks
- Baseline demographics, clinical characteristics, and other trial parameters in the pooled modified intention-to-treat (mITT) population were evaluated as potential predictors of response, defined as a ≥50% decrease from baseline in MADRS total score at Day 43, using penalized logistic regression models (elastic net and lasso) and multivariable logistic regression with stepwise selection
  - The mITT included all randomized patients who received at least 1 dose of study treatment, had an evaluable baseline MADRS total score, and also had at least one evaluable post-baseline, on-treatment assessment of the MADRS total score
- Additional machine-learning–based approaches, including random forest and Bayesian model averaging, were also performed to assess the consistency of predictors across modelling methods

Results

- Of approximately 30 variables analyzed (baseline demographics and characteristics and other trial parameters) in the pooled population of patients with MDD in trials 501 and 502 (n=950) (**Table 1**), two parameters were identified as predictive of Day 43 response across all statistical models (elastic net regression, lasso regression, and stepwise logistic regression): treatment with lumateperone + ADT and early CGI-S score improvement at Day 8 (**Table 2; Figure 1**)
- Other baseline demographics and clinical characteristics (eg, history of treatment failure, type of concurrent ADT, anxious distress) did not consistently predict a response across all models
- Results were consistent with lumateperone + ADT efficacy across 501 and 502 study populations, with treatment effect remaining the strongest predictor of response regardless of baseline characteristics

Table 1. Variables Evaluated for Response (Not Exhaustive)

Variable	Categories[a]
Baseline Demographics	
Treatment	Lumateperone 42 mg + ADT vs placebo + ADT
Age	Continuous
Pooled age group 1, years	≥40 vs <40
BMI at baseline, kg/m^2	Continuous
Country	Continuous
Ethnicity	Continuous
Race	Continuous
Pooled race group 1	White, non-White
Geographic region 1	US vs non-US
Gender	Male vs Female
Weight at baseline, kg	Continuous
Baseline Psychiatric History	
Age at first diagnosis of MDD, years	≤22 vs >22 / ≤35 vs >35
Number of lifetime MDEs	≤3 vs >3
Duration of current MDE, months	≤6 vs >6
Current MDE also met criteria for anxious distress	Yes vs No
Lifetime history of treatment failure	1 vs 2
Psychiatric hospitalizations	Yes vs No
Baseline Questionnaire	
Baseline C-SSRS	Continuous
Baseline CSFQ-14 total score (only in Study 502)	Continuous
Baseline QIDS-SR-16	Continuous
Baseline CGI-S score	Continuous
Baseline MADRS	Continuous
Baseline GAD-7 (only in Study 501)	Continuous
Prior and Concurrent Medical History	
Prior medication	Sertraline, trazodone, fluoxetine, venlafaxine, escitalopram
Background antidepressant therapy	SNRI, SSRI, other

[a]Where applicable.
ADT, antidepressant therapy; BMI, body mass index; CGI-S, Clinical Global Impression-Severity; CSFQ-14; Changes in Sexual Functioning Questionnaire 14-item scale; C-SSRS, Columbia-Suicide Severity Rating Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; 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; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; US, United States.

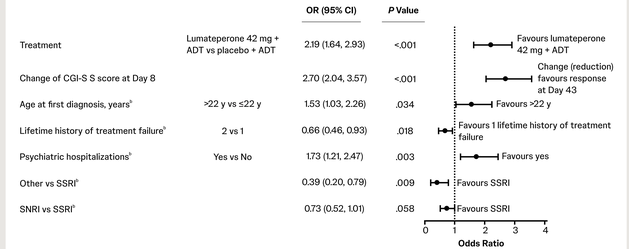
Table 2. Logistical Regression Models of Predictors of Response

	Odds Ratio	95% CI	*P* Value
Elastic Net Regression[a]			
Lumateperone 42 mg + ADT vs placebo + ADT	2.86	1.85, 4.35	<.001
Change in CGI-S score at Day 8	2.78	1.79, 4.35	<.001
Lasso Regression[a]			
Lumateperone 42 mg + ADT vs placebo + ADT	2.87	1.85, 4.35	<.001
Change in CGI-S score at Day 8	2.77	1.79, 4.35	<.001

[a]Variable selection.
ADT, antidepressant therapy; CGI-S, Clinical Global Impression–Severity; CI, confidence interval.

- According to the stepwise logistic regression, treatment with lumateperone + ADT led to a 2.2× greater likelihood of response at Day 43 vs placebo + ADT (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.64, 2.93; *P*<.001) (**Figure 1**)
  - Compared with those who did not have a 1-point improvement in CGI-S score at Day 8, the group with a 1-point improvement in CGI-S score had a 2.7× greater likelihood in achieving a response at Day 43 (OR, 2.7; 95% CI, 2.04, 3.57; *P*<.001)
  - Stepwise multiple regression modelling identified lumateperone + ADT as the strongest and most consistent predictor of response, with early CGI-S score change from baseline as the next strongest predictor
  - Patients receiving lumateperone + ADT showed significantly greater early improvement in CGI-S than those receiving placebo + ADT at Day 8

Figure 1. Stepwise Logistical Regression Model of Predictors of Response[a]



Modified intent-to-treat population.
[a]Response is defined as having ≥50% improvement on Montgomery-Åsberg Depression Rating Scale total score at Day 43. [b]These variables were not consistently identified by the lasso and elastic net regression models.
ADT, antidepressant therapy; CGI-S, Clinical Global Impression–Severity; CI, confidence interval; OR, odds ratio; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; y, years.

Conclusions

- Identifying consistent predictors of response may help inform treatment expectations and support shared clinical decision-making for patients with MDD who have an inadequate response to ADT
- In this pooled post hoc analysis of two Phase 3 trials, adjunctive lumateperone 42 mg and early CGI-S improvement at Day 8 were the two predictors of Day 43 MADRS response that were consistently identified across penalised logistic regression, stepwise logistic regression, and machine-learning-based approaches
- Across the modelling approaches, baseline demographic and clinical characteristics did not consistently predict response, suggesting that adjunctive lumateperone may provide benefit across the range of patient characteristics represented in these trials
- These findings support adjunctive lumateperone 42 mg as an effective treatment option for patients with MDD with an inadequate response to ADT; however, interpretation should consider the post hoc nature of the analyses and the inclusion/exclusion criteria of Studies 501 and 502, which may not fully reflect the broader clinical population

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