Linking Montgomery-Åsberg Depression Rating Scale and Patient Health Questionnaire Total Scores: Evidence From Adjunctive Lumateperone Trial Data

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Background

- Lumateperone is an atypical antipsychotic indicated in adults for: (1) treatment of major depressive disorder (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[1]
- Lumateperone simultaneously modulates serotonin, dopamine, and, indirectly through D_1-receptor modulation, glutamatergic NMDA and AMPA receptors[2]
  - Although the mechanism of action is unknown, 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[1,2]
  - This novel mechanism of action with multimodal effects may confer robust efficacy with improved safety and tolerability
- In two pivotal Phase 3, randomised, double-blind, placebo-controlled, multicentre trials (Study 501, NCT04985942; Study 502, NCT05061706), lumateperone 42 mg/day adjunctive to ADT significantly improved depressive symptoms compared with placebo adjunctive to ADT in patients with MDD with inadequate response to ADT, as measured by both clinician-rated and patient-rated outcomes[3,4]
  - The primary endpoint in these trials was change from baseline to Day 43 in the Montgomery-Åsberg Depression Rating Scale (MADRS) Total score, a 10-item clinician-rated scale used to measure the severity of depressive episodes[3–5]
  - While change in MADRS score is a common endpoint in clinical trials of MDD, the Patient Health Questionnaire-9 (PHQ-9) is widely used in clinical practice to diagnose and measure depression severity[6]
  - The PHQ-9 is a reliable and validated 9-item patient self-reported questionnaire, although it can also be administered by healthcare professionals[6,7]
  - As both lumateperone trials did not utilise the PHQ-9, estimating the PHQ-9–equivalent change from MADRS scores may help clinicians interpret trial results and inform real-world practice[3,4]
- In the Phase 3, randomised TRANSFORM-1&2 studies (NCT02417064, NCT02418585), which assessed efficacy of intranasal esketamine with an oral antidepressant in patients with treatment-resistant depression, both MADRS and PHQ-9 measures were utilised[8,9]
  - Patient-level data from these trials were used to develop a MADRS-to-PHQ-9 mapping model
  - Here, we applied this mapping model to pooled adjunctive lumateperone trial data to translate MADRS Total score change into a PHQ-9–equivalent change

Methods

- Studies 501 and 502 were Phase 3, randomised, double-blind, placebo-controlled trials that evaluated adjunctive lumateperone 42 mg/day plus antidepressant therapy (ADT) versus placebo plus ADT in adults aged 18–65 years with MDD and inadequate response to 1–2 prior ADT courses during the current depressive episode, defined as <50% improvement in depressive symptoms after ≥6 weeks of ADT monotherapy and confirmed using the Antidepressant Treatment Response Questionnaire (ATRQ)
  - Eligible patients were experiencing a major depressive episode at screening and baseline, 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
  - Patients were randomised 1:1 to receive either oral lumateperone 42 mg/day plus ADT or placebo plus ADT for 6 weeks
  - The primary endpoint in each study was change from baseline to Day 43 in MADRS Total score, analysed using a mixed-effects model for repeated measures (MMRM)
- A MADRS-to-PHQ-9 mapping model was developed using patient-level data from the pooled TRANSFORM-1&2 esketamine studies (NCT02417064 and NCT02418585), in which both MADRS and PHQ-9 assessments were collected
- Several statistical approaches were evaluated to characterise the relationship between MADRS and PHQ-9 Total scores, including simple and multiple regression, local regression, equipercentile linking, repeated-measures regression models to account for within-patient correlation across visits, and ordinal logistic regression model to evaluate alignment of clinically relevant score cutoff points across the 2 scales
- The final mapping approach was based on a local regression model using paired MADRS and PHQ-9 endpoint observations from the esketamine studies
- This model was applied to pooled MADRS Total scores from Studies 501 and 502 in the modified intent-to-treat (mITT) population to generate predicted PHQ-9 Total scores in the lumateperone and placebo treatment groups
  - The mITT included all randomised patients who received at least 1 dose of study treatment, had an evaluable baseline MADRS Total score, and also had at least 1 evaluable post-baseline, on-treatment assessment of the MADRS Total score
  - The predicted PHQ-9 Total scores were then analysed as PHQ-9–equivalent outcomes in the pooled studies, although PHQ-9 was not directly collected in Studies 501 and 502
- Mapped outcomes included predicted PHQ-9 score by treatment over time, response (≥50% improvement from baseline in predicted PHQ-9 score), and remission (predicted PHQ-9 score <5)
  - Differences in mean changes from baseline in predicted PHQ-9 scores were analysed using an MMRM; response and remission rates were analysed using χ^2 tests with corresponding odds ratios (ORs) and 95% CIs
- Treatment differences in predicted PHQ-9 Total scores, response, and remission were evaluated to describe the benefit of lumateperone + ADT versus placebo + ADT on a clinically familiar PHQ-9 scale

Results

MADRS to PHQ-9 Conversion Model Using Esketamine Trials

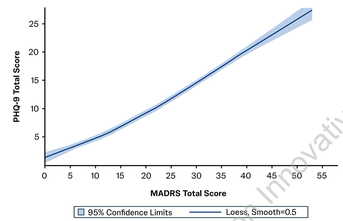
- An initial exploratory assessment of the association between MADRS Total and PHQ-9 Total scores over time in the esketamine trials using simple linear regression is shown in **Table 1**
  - These analyses demonstrate that the 2 scales were positively associated, with the strength of association increasing across study visits
  - However, because simple regression assumes a single linear relationship across the full MADRS score range, it may not fully capture potential nonlinearity in the relationship between clinician-rated MADRS and patient-reported PHQ-9 scores
  - Therefore, the simple regression results were used descriptively to characterise the overall association between the 2 scales, while the final MADRS-to-PHQ-9 mapping model was based on local regression to allow for a more flexible, data-driven relationship
- A local regression model based on paired endpoint MADRS and PHQ-9 Total scores was selected to estimate the relationship between the 2 scales (**Figure 1**)
  - Local regression provides a flexible, data-driven approach for MADRS-to-PHQ-9 mapping because it does not impose a single fixed linear relationship across the full MADRS score range. This approach can better accommodate potential variation in the MADRS–PHQ-9 relationship at different depression severity levels and may therefore be more appropriate
  - The endpoint-based model was chosen because endpoint assessments captured data from all treated patients, including those who discontinued the esketamine studies before the final scheduled visit
  - Correlations at earlier visits may have been attenuated because eligibility for the esketamine trials required a minimum MADRS score but did not require a corresponding minimum PHQ-9 score

Table 1. Simple Regression of PHQ-9 Total Score on MADRS Total Score Over Time During the Double-Blind Induction Phase in the Esketamine Trials[a]

Time/Effect	Observations n	Estimate (95% CI)	*P* Value	R-Squared
Baseline				
Intercept	565	8.44 (6.59, 10.29)	<.001	.228
MADRS Total		0.322 (0.27, 0.37)	<.001	
Day 15				
Intercept	517	−1.25 (−4.03, 1.53)	.376	.557
Baseline MADRS Total		0.04 (−0.04, 0.11)	.314	
MADRS Total		0.47 (0.43, 0.50)	<.001	
Day 28				
Intercept	507	1.13 (−1.25, 3.51)	.351	.733
Baseline MADRS Total		−0.03 (−0.10, 0.03)	.288	
MADRS Total		0.50 (0.47, 0.52)	<.001	
Endpoint				
Intercept	554	1.50 (−0.81, 3.81)	.202	.725
Baseline MADRS Total		−0.04 (−0.10, 0.02)	.228	
MADRS Total		0.49 (0.46, 0.51)	<.001	

[a]NCT02417064 and NCT02418585. MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-9, Patient Health Questionnaire-9. Simple regression assumes a linear relationship between the 2 scales and may not fully capture potential nonlinearity across the MADRS severity range.

Figure 1. Relationship Between PHQ-9 Total and MADRS Total Scores at Endpoint Using Local Regression (Esketamine Trials[a])

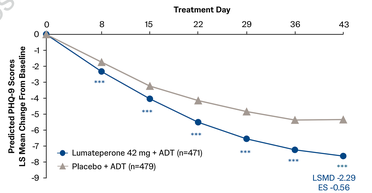


[a]NCT02417064 and NCT02418585. MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-9, Patient Health Questionnaire-9.

Application of Conversion Model to Lumateperone Trial Data

- When applying the MADRS-to-PHQ-9 esketamine-derived mapping model to predict PHQ-9 scores based on MADRS Total scores in the lumateperone 501/502 studies, lumateperone + ADT (n=471) significantly improved predicted PHQ-9 scores versus placebo + ADT (n=479) beginning at Day 8 (least squares mean difference vs placebo [LSMD] + ADT: −0.59 [standard error (SE), 0.16]; 95% CI, −0.91, −0.28; effect size [ES], −0.24; *P*<.001), with significant improvements maintained through Day 43 (LSMD [SE], −2.29 [0.27]; 95% CI, −2.82, −1.75; ES, −0.56; *P*<.001) (**Figure 2**)
  - Patients receiving lumateperone + ADT showed significantly greater improvements in predicted PHQ-9 scores than those receiving placebo + ADT

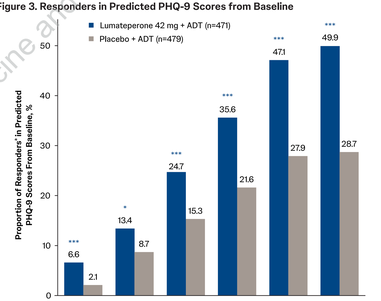
Figure 2. Predicted PHQ-9 Score by Treatment Over Time



***P<.001. LSMD versus placebo. LS-Mean changes and *P* values were obtained from MMRM model. mITT population. Baseline mean (SD) predicted PHQ-9 value was 15.8 (2.2) for lumateperone 42 mg + ADT and 15.7 (2.2) for placebo + ADT. Day 43 mean (SD) predicted PHQ-9 value was 7.9 (4.1) for lumateperone 42 mg + ADT and 10.2 (4.2) for placebo + ADT. ADT, antidepressant therapy; ES, effect size; LS, least squares; LSMD, least squares mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; PHQ-9, Patient Health Questionnaire-9.

- PHQ-9 response rates (≥50% improvement from baseline in predicted PHQ-9 score) were significantly greater with lumateperone + ADT versus placebo + ADT at Day 8 (6.6% vs 2.1%; OR, 3.3; 95% CI, 1.58, 6.73; *P*<.001) and at each visit through Day 43 (49.9% vs 28.7%; OR, 2.5; 95% CI, 1.87, 3.28; *P*<.001) (**Figure 3**)
  - Lumateperone + ADT was associated with a 3.7 times greater likelihood of achieving a sustained response for ≥36 days versus placebo + ADT (OR, 3.7; 95% CI, 1.47, 9.19; *P*<.01)

Figure 3. Responders in Predicted PHQ-9 Scores from Baseline

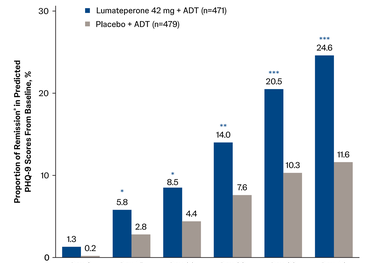


Odds Ratio (95% CI)	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
	3.26 (1.58, 6.73)	1.62 (1.07, 2.47)	1.82 (1.30, 2.54)	2.00 (1.49, 2.70)	2.30 (1.74, 3.04)	2.48 (1.87, 3.28)

*P<.05 ***P<.001. mITT population. [a]A responder is defined as a ≥50% improvement from baseline. ADT, antidepressant therapy; mITT, modified intent-to-treat; PHQ-9, Patient Health Questionnaire-9.

- PHQ-9 remission rates (predicted PHQ-9 score <5) were significantly greater with lumateperone + ADT vs placebo + ADT from Day 15 (5.8% vs 2.8%; OR, 2.2; 95% CI, 1.10, 4.28; *P*<.05) through Day 43 (24.6% vs 11.6%; OR, 2.5; 95% CI, 1.73, 3.59; *P*<.001) (**Figure 4**)
  - The likelihood of sustained remission for ≥22 days was 2.3 times greater with lumateperone + ADT than with placebo + ADT (OR, 2.3; 95% CI, 1.18, 4.32; *P*<.05)

Figure 4. Remission in Predicted PHQ-9 Scores from Baseline



Odds Ratio (95% CI)	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
	6.09 (0.73, 50.79)	2.17 (1.10, 4.28)	2.05 (1.17, 3.58)	1.98 (1.28, 3.08)	2.23 (1.52, 3.28)	2.49 (1.73, 3.59)

*P<.05 **P<.01 ***P<.001. mITT population. [a]Remission is defined as a predicted PHQ-9 <5. ADT, antidepressant therapy; mITT, modified intent-to-treat; PHQ-9, Patient Health Questionnaire-9.

Conclusions

- A MADRS-to-PHQ-9 mapping model derived from TRANSFORM-1 & 2 esketamine trial data enabled translation of clinician-rated MADRS Total scores into predicted PHQ-9 Total scores, providing a clinically familiar scale for interpreting outcomes from the pooled lumateperone + ADT trials
- Using this mapping approach, lumateperone + ADT demonstrated significantly greater improvements in predicted PHQ-9–equivalent scores than placebo + ADT, with treatment separation observed early and maintained through Day 43
- Lumateperone + ADT was also associated with significantly higher predicted PHQ-9 response and remission rates compared with placebo + ADT, supporting a consistent treatment benefit across mapped symptom-severity outcomes
- Because PHQ-9 was not directly collected in Studies 501 and 502, these findings should be interpreted as model-derived PHQ-9–equivalent estimates; however, they may help clinicians contextualise the observed MADRS benefits of lumateperone + ADT in terms of a patient-reported depression severity scale commonly used in real-world practice

Limitations

- Limitations of this analysis include differences between the treatment-resistant depression population used to develop the mapping model and the MDD population to which it was applied, as well as the relatively limited sample sizes available for model development and validation
- These factors may affect generalisability, robustness, and predictive accuracy; therefore, predicted PHQ-9 scores should be interpreted cautiously, particularly at the individual-patient level, and should not be used in isolation for clinical decision-making

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Disclosures

TG Rhee has nothing to disclose. **S Durgam** is a former employee of Intra-Cellular Therapies, a Johnson & Johnson company. **WR Earley** is a full-time employee of Intra-Cellular Therapies, a Johnson & Johnson company. **I Turkoz** is an employee of Johnson & Johnson. **JJ Sheehan** is an employee of Johnson & Johnson.

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