Long-Term Efficacy of Lumateperone 42 mg for the Treatment of Adults With Schizophrenia and Clinically Relevant Depressive Symptoms: A Post Hoc Analysis of a 1-Year Open-Label Study

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Background

- Schizophrenia is a complex and often disabling psychiatric disorder affecting up to 1% of the global population [1,2] and associated with substantial functional impairment, increased morbidity, and premature mortality [1-3]
- Depressive symptoms are common in adults with schizophrenia, with approximately 60% of patients experiencing at least one episode of major depression over their lifetime and 40–50% of both inpatients and outpatients experiencing mild to moderate depressive symptoms in clinical settings [4,5]
- Most antipsychotic trials in schizophrenia do not include a validated assessment for depression [1]
  - This limits clinicians' ability to evaluate treatment effects on clinically relevant depressive symptoms [4-6]
- Lumateperone is an atypical antipsychotic indicated in the US for the treatment of schizophrenia in adults; the treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults; and the treatment of MDD in adults as adjunct to antidepressant therapy [7]
  - Lumateperone is a mechanistically novel, multimodal antipsychotic that modulates serotonergic, dopaminergic, and indirectly glutamatergic neurotransmission [8]
- A 1-year, open-label, Phase 3 safety study (Study 303B) evaluated the long-term safety and efficacy of lumateperone 42 mg in patients with acute exacerbation of schizophrenia [9]
- Long-term trials of lumateperone in patients with schizophrenia have included the Calgary Depression Scale for Schizophrenia (CDSS), a validated scale for assessing depressive symptoms in this population [4,5,9-11]
- In this post hoc analysis of Study 303B, the efficacy and safety of lumateperone 42 mg were evaluated in adults with stable schizophrenia and clinically relevant depressive symptoms at baseline (CDSS >6)

Methods

- The long-term safety and efficacy of lumateperone treatment in patients with stable symptoms of schizophrenia were established in a 1-year, open-label, Phase 3 extension study, Study 303B [9]
  - Eligible adults (aged ≥18 years) had a clinical diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth edition* (DSM-5), stable psychopathology, and were able to be treated on an outpatient basis
  - Stable schizophrenia was defined as no hospitalization for psychiatric illness within 3 months prior to study Day 1, a Clinical Global Impression–Severity (CGI-S) score ≤4 at screening and baseline, and a score ≤4 on each of 4 core items of the Positive and Negative Syndrome Scale (PANSS) at baseline
- All analyses used observed cases from the safety population, which included all patients enrolled who had received at least one dose of study medication
- Efficacy endpoints included change from baseline to Day 368 in PANSS total score and the proportion of patients achieving ≥20% reduction in PANSS total score
- Additional efficacy endpoints included PANSS subscale scores (Positive, Negative, and General Psychopathology), CGI-S score, Personal and Social Performance (PSP) score, and PANSS Marder Factor scores
- Mean changes from baseline were examined using Wilcoxon signed-rank or one-sample t-test, along with 95% confidence intervals (CIs)
- Treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and TEAEs leading to discontinuation were assessed

Results

- Baseline demographics in the CDSS >6 subgroup were consistent with those in the overall safety population (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

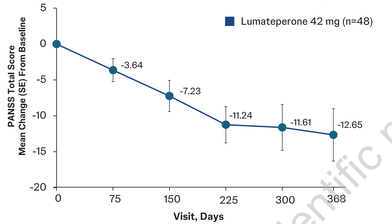
	Lumateperone 42 mg (n=48)
Demographics Parameters	
Gender, n (%)	
Male	33 (68.8)
Female	15 (31.3)
Age, years	
Mean (SD)	47.3 (12.18)
Race	
White	10 (20.8)
Black or African American	35 (72.9)
Other	3 (6.3)
Baseline Efficacy Parameters	
PANSS scores, mean (SD)	
Total	71.9 (10.41)
Positive symptom subscale	18.0 (2.97)
Negative symptom subscale	17.6 (3.92)
General psychopathology subscale	36.2 (6.02)
CGI-S score, mean (SD)	3.7 (0.47)
PSP total score, mean (SD)	57.4 (8.75)
CDSS total score, mean (SD)	8.6 (1.96)

Safety set with baseline CDSS score >6.
CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression Scale–Severity; PANSS, Positive and Negative Syndrome Scale;; PSP, Personal and Social Performance Scale; WHO, World Health Organization.

PANSS total score

- Lumateperone 42 mg significantly reduced PANSS total score from baseline to Day 368 (mean change: −12.65 [95% CI −20.4, −4.9], *P*=0.004) (**Figure 1**)

Figure 1. Mean Change From Baseline in PANSS Total Score by Visit



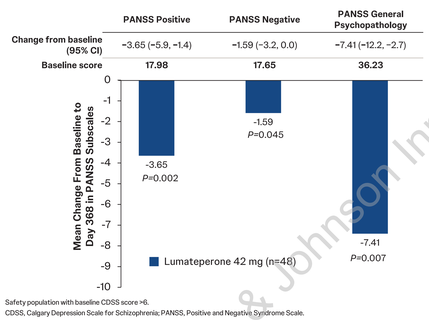
Safety population with baseline CDSS score >6.
CDSS, Calgary Depression Scale for Schizophrenia; PANSS, Positive and Negative Syndrome Scale.

- At Day 368, 41.2% of patients receiving lumateperone achieved ≥20% improvement in PANSS total score from baseline

PANSS subscale scores

- Lumateperone was associated with significant improvements from baseline to Day 368 across all PANSS subscales, including Positive (−3.65 [95% CI −5.9, −1.4], *P*=0.002), Negative (−1.59 [95% CI −3.2, 0.0], *P*=0.045), and General Psychopathology (−7.41 [95% CI −12.2, −2.7], *P*=0.007) (**Figure 2**)

Figure 2. Mean Change From Baseline to Day 368 in PANSS Subscales Scores

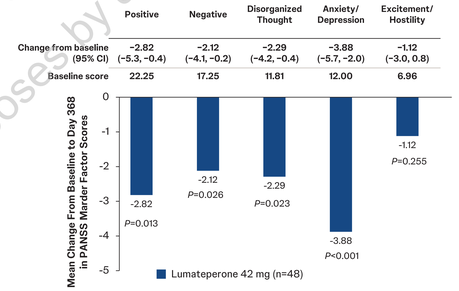


Safety population with baseline CDSS score >6.
CDSS, Calgary Depression Scale for Schizophrenia; PANSS, Positive and Negative Syndrome Scale.

PANSS Marder Factor scores

- From baseline to Day 368, lumateperone was associated with significant improvements (mean change) across PANSS Marder Factor scores: Positive (−2.82 [95% CI −5.3, −0.4], *P*=0.013), Negative (−2.12 [95% CI −4.1, −0.2], *P*=0.026), Disorganized Thought (−2.29 [95% CI −4.2, −0.4], *P*=0.023), and Anxiety/Depression (−3.88 [95% CI −5.7, −2.0], *P*<0.001) (**Figure 3**)

Figure 3. Mean Change From Baseline to Day 368 in PANSS Marder Factor Scores

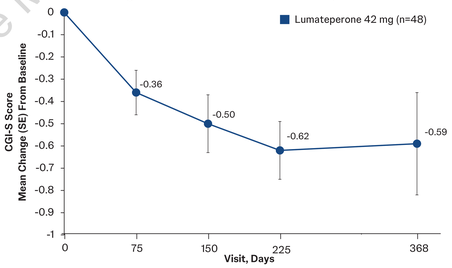


Safety population with baseline CDSS score >6.
CDSS, Calgary Depression Scale for Schizophrenia; PANSS, Positive and Negative Syndrome Scale.

CGI-S score

- Lumateperone was associated with a significant improvement in CGI-score from baseline to Day 368 (mean change: −0.59 [95% CI −1.1, −0.1], *P*=0.036) (**Figure 4**)

Figure 4. Mean Change From Baseline in CGI-S Score by Visit

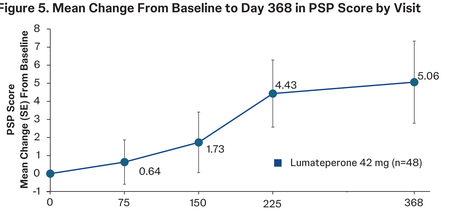


Safety population with baseline CDSS score >6.
CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression–Severity.

PSP score

- Lumateperone showed a significant improvement in PSP from baseline to Day 368 (mean change: 5.06 [95% CI 0.2, 9.9], *P*= 0.041) (**Figure 5**)

Figure 5. Mean Change From Baseline to Day 368 in PSP Score by Visit



Safety population with baseline CDSS score >6.
CDSS, Calgary Depression Scale for Schizophrenia; PSP, Personal and Social Performance.

Safety

- No new safety signals were identified with lumateperone 42 mg
  - The most common AEs occurring in ≥5% of patients were insomnia, dry mouth, headache, dizziness, diarrhea, nausea, cough, hypertension, and pain in extremities
- No related serious AEs were observed, and no deaths occurred; 4 patients (8.3%) experienced AEs leading to permanent treatment discontinuation (**Table 2**)

Table 2. Summary of Adverse Events

n (%)	Lumateperone 42 mg (n=48)
TEAE ≥1	24 (50.0)
Related AE*	15 (31.3)
AE leading to death	0
SAEs	1 (2.1)

*An AE assessed by the investigator as related to study drug.
AE, adverse events; SAE, serious adverse events; TEAE, treatment-emergent adverse event.

Conclusions

- Lumateperone 42 mg demonstrated significant, sustained improvements across a broad range of schizophrenia-related symptoms in adults with stable schizophrenia and baseline clinically relevant depressive symptoms
- Improvements across PANSS total, PANSS subscales, PANSS Marder Factor (except Excitement/Hostility), CGI-S, and PSP scores with lumateperone 42 mg treatment were maintained over the 1-year period
- The small sample size may limit the interpretation of these findings
- No new safety signals were identified with lumateperone

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Disclosures

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K Johnston, I Turkoz, M Doring, KR Dorsey, and P Jalli are employees of Johnson & Johnson.

J Hamilton is a paid ambassador at the Point of Care Network and Senior Medical Science Liaison at Tempus AI.

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