Efficacy of Lumateperone 42 mg for the Treatment of Adults With Schizophrenia and Clinically Relevant Depressive Symptoms: Results of a Post Hoc Pooled Analysis

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Background

- Depression is common among adults with schizophrenia and is associated with poorer quality of life, impaired functioning, and higher rates of relapse and hospitalization[1,2]
- Approximately 60% of patients with schizophrenia will experience at least one episode of major depression in their lifetime, while 40–50% of both inpatients and outpatients experience mild to moderate depressive symptoms[1,2]
  - Depression develops in the premorbid period of schizophrenia before onset of psychotic symptoms in 50% of patients[1]
- Most antipsychotic trials in schizophrenia do not include a validated assessment for depression and improvement in depression is generally not an efficacy endpoint[1]
  - This limits the ability for clinicians to fully evaluate treatment effects on clinically relevant depressive symptoms in this patient population[1-3]
- 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[5]
- The efficacy and safety of lumateperone 42 mg in patients with acute exacerbation of schizophrenia have been established in two short-term, 4-week, randomized, double-blind, placebo-controlled trials (NCT01499563 and NCT02282761)[3,6]
- Short-term trials of lumateperone in patients with schizophrenia have included the Calgary Depression Scale for Schizophrenia (CDSS), a validated scale that assesses depression symptomatology in patients with schizophrenia[1-3,6]
- This pooled, post hoc analysis evaluated the efficacy and safety of lumateperone 42 mg in patients with schizophrenia and baseline clinically relevant depressive symptoms (CDSS score >6)

Methods

- The patient population included a subgroup of patients with clinically relevant baseline depressive symptoms (CDSS >6) from two 4-week, randomized, double-blind, placebo-controlled lumateperone trials
- Analyses were conducted based on the intent-to-treat (ITT) set, which included all randomized patients who received at least one dose of study medication and had data recorded for at least one valid baseline and at least one valid postbaseline Positive and Negative Syndrome Scale (PANSS) measurement
- Efficacy endpoints included the change from baseline to Day 28 in PANSS total score and proportion of patients achieving ≥20% reduction in PANSS total score
- Additional efficacy endpoints included PANSS subscale scores (Positive, Negative, and General Psychopathology), Clinical Global Impression–Severity (CGI-S) score, Personal Social Performance (PSP) score, and PANSS Marder Factor scores
- Mean changes from baseline between lumateperone 42 mg and placebo were examined using either a mixed-effects model for repeated measures (MMRM) or analysis of covariance (ANCOVA) models
- Safety outcomes included treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and TEAEs leading to discontinuation

Results

- Baseline demographics in the CDSS >6 subgroup were consistent with those in the overall ITT population across both 4-week trials (**Table 1**)

Table 1. Demographics and Baseline Characteristics

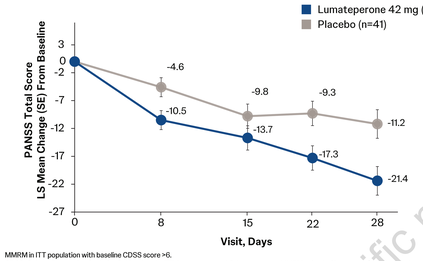
	Lumateperone 42 mg (n=34)	Placebo (n=41)
Age, mean (range), years	42.1 (22-55)	42.7 (19-58)
Sex, n (%)		
Female	10 (29.4)	8 (19.5)
Male	24 (70.6)	33 (80.5)
Race, n (%)		
White	5 (14.7)	6 (14.6)
Asian	1 (2.9)	1 (2.4)
Black	26 (76.5)	32 (78.0)
Other	2 (5.9)	2 (4.9)
Hispanic or Latino ethnicity, n (%)	3 (8.8)	3 (7.3)
Time since first diagnosis of schizophrenia, years, mean (SD)	16.5 (9.8)	16.8 (10.9)

ITT population with baseline CDSS>6.
CDSS, Calgary Depression Scale for Schizophrenia; ITT, intent-to-treat.

PANSS total score

- In the ITT population with CDSS >6 (lumateperone 42 mg, n=34; placebo, n=41), lumateperone 42 mg significantly reduced PANSS total score from baseline to Day 28 versus placebo (least squares mean difference [LSMD]=−10.1 [95% CI −17.2, −3.1], *P*=0.005) (**Figure 1**)

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



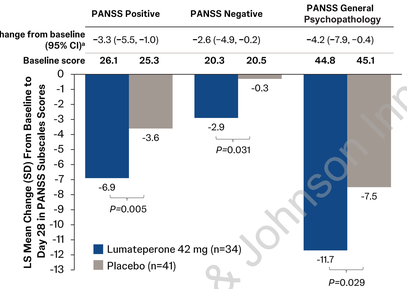
MMRM in ITT population with baseline CDSS score >6.
CDSS, Calgary Depression Scale for Schizophrenia; ITT, intent-to-treat; LS, least squares; MMRM, mixed-effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale.

- At Day 28, 56.7% of patients receiving lumateperone achieved ≥20% improvement in PANSS total score from baseline compared to 35.3% of patients receiving placebo

PANSS subscale scores

- Lumateperone significantly improved all PANSS subscale scores versus placebo (PANSS Positive: −3.3 [95% CI −5.5, −1.0], *P*=0.005; PANSS Negative: −2.6 [95% CI −4.9, −0.2], *P*=0.031; PANSS General Psychopathology: −4.2 [95% CI −7.9, −0.4], *P*=0.029) versus placebo (**Figure 2**)

Figure 2. LS Mean Change From Baseline to Day 28 in PANSS Subscales Scores



MMRM in ITT population with baseline CDSS score >6.
[a]Based on MMRM with treatment group, visit and treatment group-by-visit interaction and baseline score as a covariate.
CDSS, Calgary Depression Scale for Schizophrenia; ITT, intent-to-treat; MMRM, mixed-effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale.

Table 2. Change From Baseline to Day 28 in PANSS Marder Factor Scores

	Lumateperone 42 mg (n=34)	Placebo (n=41)
PANSS Marder, Positive		
Baseline mean (SD)	30.6 (4.21)	29.8 (3.84)
Change from baseline (SD)	−7.4 (6.30)	−2.5 (5.29)
LSMD (lumateperone vs placebo [95% CI])[a]	−4.0 (−6.5, −1.4)	
P value	0.003	
PANSS Marder, Negative		
Baseline mean (SD)	20.6 (3.65)	21.0 (5.03)
Change from baseline (SD)	−3.6 (4.94)	−2.4 (5.14)
LSMD (lumateperone vs placebo [95% CI])[a]	−1.7 (−4.1, 0.7)	
P value	0.163	
PANSS Marder, Disorganized Thought		
Baseline mean (SD)	15.0 (3.59)	15.8 (4.57)
Change from baseline (SD)	−3.5 (3.64)	−1.6 (3.79)
LSMD (lumateperone vs placebo [95% CI])[a]	−2.2 (−3.9, −0.6)	
P value	0.008	
PANSS Marder, Anxiety/Depression		
Baseline mean (SD)	13.4 (2.52)	13.6 (3.05)
Change from baseline (SD)	−4.5 (3.85)	−4.1 (4.41)
LSMD (lumateperone vs placebo [95% CI])[a]	−0.4 (−2.2, 1.4)	
P value	0.646	
PANSS Marder, Excitement/Hostility		
Baseline mean (SD)	10.4 (3.12)	9.4 (3.34)
Change from baseline (SD)	−2.9 (4.23)	−1.4 (3.17)
LSMD (lumateperone vs placebo [95% CI])[a]	−1.0 (−2.3, 0.4)	
P value	0.157	

MMRM in ITT population with baseline CDSS score >6.
[a]Based on MMRM model with treatment group, visit and treatment group-by-visit interaction and baseline score as a covariate.
CDSS, Calgary Depression Scale for Schizophrenia; ITT, intent-to-treat; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale.

PANSS Marder Factor scores

- Lumateperone significantly improved PANSS Positive (LSMD=−4.0 [95% CI −6.5, −1.4], *P*=0.003) and Disorganized Thought (LSMD=−2.2 [95% CI −3.9, −0.6], *P*=0.008) Marder Factor scores versus placebo (**Table 2**)
  - Improvements in additional PANSS Marder scores, including Anxiety/Depression, were observed across both treatment groups, though the small sample sizes in this pooled analysis may have been insufficient to detect statistically significant between-group differences

CGI-S score

- Lumateperone significantly improved CGI-S score from baseline to Day 28 versus placebo (LSMD= −0.5 [95% CI −0.9, −0.1], *P*=0.008), with a least squares mean change from baseline of −1.3 vs −0.7 with lumateperone vs placebo

PSP score

- At Day 28, change from baseline in PSP score did not differ significantly between lumateperone and placebo (LSMD=−1.8 [95% CI −12.3, 8.7], *P*=0.729), with a least squares mean change from baseline of 9.9 vs 11.7 with lumateperone vs placebo
  - PSP assessment were collected in Study 301 only (baseline: lumateperone, n=26 and placebo, n=25; Day 28: lumateperone, n=23 and placebo, n=20)

Safety

- No new safety signals were detected with lumateperone in this patient subgroup
  - The most common AEs occurring in ≥5% of patients were headache, somnolence, dizziness, nausea, dry mouth, and upper respiratory tract infections
- No serious AEs or AEs leading to permanent treatment discontinuation were reported, and no deaths occurred in either treatment group (**Table 3**)

Table 3. Summary of Adverse Events

n (%)	Lumateperone 42 mg (n=34)	Placebo (n=41)
TEAE ≥1	22 (64.7)	19 (46.3)
Related AE[a]	17 (50.0)	11 (26.8)
AEs leading to death	0	0
SAEs	0	0
TEAEs in either treatment group at ≥5%		
Headache	8 (23.5)	6 (14.6)
Somnolence	7 (20.6)	3 (7.3)
Dizziness	3 (8.8)	1 (2.4)
Nausea	5 (14.7)	1 (2.4)
Dry mouth	4 (11.8)	0
Constipation	3 (8.8)	1 (2.4)
Diarrhea	3 (8.8)	0
Abdominal pain	2 (5.9)	1 (2.4)
Dyspepsia	2 (5.9)	1 (2.4)
Upper respiratory tract infection	2 (5.9)	0

ITT population with baseline CDSS score >6.
[a]An AE assessed by the investigator as related to study drug.
AE, adverse event; CDSS, Calgary Depression Scale for Schizophrenia; ITT, intent-to-treat; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

- Lumateperone 42 mg significantly improved a broad range of schizophrenia-related symptoms in adults with schizophrenia and baseline clinically relevant depressive symptoms
- Significant improvements from baseline in clinically relevant symptoms were observed at Day 28 across PANSS total, PANSS subscale, PANSS Positive and Disorganized Thought Marder Factor scores, and CGI-S score versus placebo
- Improvements in additional PANSS Marder scores, including Anxiety/Depression, were observed across both treatment groups, though the small sample sizes in this pooled analysis may have been insufficient to detect statistically significant between-group differences
- Lumateperone 42 mg was well tolerated, with no new safety signals identified

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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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