Efficacy and Safety of Lumateperone for Treatment of Schizophrenia
A Randomized Clinical Trial

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IMPORTANCE Individuals living with schizophrenia are affected by cardiometabolic, endocrine, and motor adverse effects of current antipsychotic medications. Lumateperone is a serotonin, dopamine, and glutamate modulator with the potential to treat schizophrenia with few adverse effects.

OBJECTIVE To examine the efficacy and safety of lumateperone for the short-term treatment of schizophrenia.

DESIGN, SETTING, AND PARTICIPANTS This randomized, double-blind, placebo-controlled, phase 3 clinical trial was conducted from November 13, 2014, to July 20, 2015, with data analyses performed from August 13 to September 15, 2015. Patients with schizophrenia who were aged 18 to 60 years and were experiencing an acute exacerbation of psychosis were enrolled from 12 clinical sites in the United States.

INTERVENTIONS Patients were randomized 1:1:1 (150 patients in each arm) to receive lumateperone tosylate, 60 mg; lumateperone tosylate, 40 mg (equivalent to 42 or 28 mg, respectively, of the active moiety lumateperone); or placebo once daily for 4 weeks.

MAIN OUTCOMES AND MEASURES The prespecified primary efficacy end point was mean change from baseline to day 28 in the Positive and Negative Syndrome Scale (PANSS) total score vs placebo. The key secondary efficacy measure was the Clinical Global Impression–Severity of Illness (CGI-S) score. The PANSS subscale scores, social function, safety, and tolerability were also assessed.

RESULTS The study comprised 450 patients (mean [SD] age, 42.4 [10.2] years; 346 [77.1%] male; mean [SD] baseline PANSS score, 89.8 [10.3]; mean [SD] baseline CGI-S score, 4.8 [0.6]). In the prespecified modified intent-to-treat efficacy analysis (n = 435), 42 mg of lumateperone met the primary and key secondary efficacy objectives, demonstrating a statistically significant improvement vs placebo from baseline to day 28 on the PANSS total score (least-squares mean difference [LSMD], −4.2; 95% CI, −7.8 to −0.6; P = .02; effect size [ES], −0.3) and the CGI-S (LSMD, −0.3; 95% CI, −0.5 to −0.1; P = .003; ES, −0.4). For 28 mg of lumateperone, the LSMD from baseline to day 28 was −2.6 (95% CI, −6.2 to 1.1; P = .16; ES, −0.2) on the PANSS total score and −0.2 (95% CI, −0.5 to 0.0; P = .02; ES, −0.3) on the CGI-S. Both lumateperone doses were well tolerated without clinically significant treatment-emergent motor adverse effects or changes in cardiometabolic or endocrine factors vs placebo.

CONCLUSIONS AND RELEVANCE Lumateperone demonstrated efficacy for improving the symptoms of schizophrenia and had a favorable safety profile.

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S
cizophrenia is a frequently chronic and debilitating dis-
order that affects approximately 1% of the general 
population. According to the recent Global Burden of 
Disease study, which used disability-adjusted life-years, 
schizophrenia had the highest functional burden among 235 
physical and mental health states. Although current antipsy-
chotic therapy is often effective for improving positive symp-
toms associated with schizophrenia (eg, hallucinations and delu-
sions), efficacy is limited for negative symptoms, cognitive 
impairment, and social functioning. In addition, current treat-
ments are associated with substantial adverse effects, includ-
ing motor impairments, prolactin abnormalities, weight gain, 
metabolic disturbances, and cardiovascular risk factors; these 
effects add to the already increased morbidity and morta-
ility associated with schizophrenia.

Lumateperone (lumateperone tosylate, ITI-007) is a 
mechanistically novel investigational agent for schizophrenia. The 
mechanism of action of lumateperone is unique because it 
simultaneously modulates serotonin, dopamine, and glu-
tamate neurotransmission, the key neurotransmitters impli-
cated in serious mental illness. Specifically, lumateperone acts 
as a potent serotonin 5-HT2A receptor antagonist, a dopa-
mine D2 receptor presynaptic partial agonist and postsynap-
tic antagonist, a D1 receptor–dependent modulator of gluta-
mate, and a serotonin reuptake inhibitor. In addition, 
lumateperone lacks interaction with off-target receptors 
that may contribute to the adverse effects of other antipsychotic 
drugs. Lumateperone is rapidly absorbed, with an effective 
half-life of 13 to 21 hours for lumateperone and metabo-
lites, supporting once-daily administration. This random-
ized, double-blind, placebo-controlled, phase 3 clinical trial 
evaluated the efficacy and safety of lumateperone therapy af-
after 4 weeks of treatment in patients experiencing an acute ex-
acerbation of schizophrenia.

Methods

Patients
This randomized clinical trial was conducted from November 
13, 2014, to July 20, 2015. Data analysis was performed from 
August 13 to September 15, 2015. Patients were recruited at 12 
US clinical sites and admitted to an inpatient research unit for 
a screening period of 2 to 7 days before randomization (trial 
protocol Supplement 1). The trial was conducted in compli-
ance with the principles of the Good Clinical Practice guide-
line and was approved by the Copernicus Group institutional 
review board. All participating patients provided written in-
formed consent, and data were deidentified. The trial fol-
lowed the Consolidated Standards of Reporting Trials 
(CONSORT) reporting guideline.

Eligible participants were aged 18 to 60 years and had a 
clinical diagnosis of schizophrenia according to the DSM-5, 
confirmed by the Structured Clinical Interview for DSM-
IV-TR Axis I disorders, clinical trials version (modified for use 
in this study). Patients were included if they were experi-
cing an acute exacerbation of psychosis, defined as a total 
score on the Brief Psychiatric Rating Scale of 40 or higher,

Key Points

**Question** Does 60 mg of lumateperone tosylate (42 mg of 
lumateperone) significantly reduce symptoms of schizophrenia 
compared with placebo without relevant motor, cardiometabolic, 
or endocrine adverse effects?

**Findings** In this randomized clinical trial of 450 patients with 
acute exacerbation of schizophrenia, 42 mg of lumateperone 
demonstrated statistically significant differences in reducing 
symptoms of schizophrenia without treatment-emergent motor, 
cardiometabolic, or endocrine adverse effects compared with 
placebo.

**Meaning** Lumateperone is a potential treatment for 
schizophrenia and has a favorable safety profile.
secondary efficacy endpoint was the CGI-S score. Other secondary efficacy measures included the PANSS positive, negative, and general psychopathology subscales, the Personal and Social Performance (PSP) scale,20 the PANSS-derived prosocial factor (P3, P6, N2, N4, N7, and G16),21 and the Calgary Depression Scale for Schizophrenia.22

Safety was assessed by treatment-emergent adverse events (TEAEs), modified physical examinations, 12-lead electrocardiograms (ECGs), vital signs, and clinical laboratory tests (eMethods in Supplement 2). Motor tolerability and safety were assessed by the Simpson-Angus Scale,23 Barnes Akathisia Rating Scale,24 and Abnormal Involuntary Movement Scale.16 Suicidality was evaluated by the Columbia Suicide Severity Rating Scale.25

Statistical Analysis
In each treatment arm, 132 patients were expected to have evaluable data. The study was designed to have 90% power to demonstrate an effect size of 0.4, corresponding to a 6-point difference in change from baseline to day 28 in PANSS total score between active treatment and placebo, at a 2-sided significance level of .05.

The treatment effect on the primary efficacy end point was evaluated using a mixed-effects model for repeated measures (MMRM). A mixture-based gatekeeping procedure26–28 was implemented to preserve the type I error rate at the 2-sided .05 level for the multiple-dose group comparisons of the primary and key secondary efficacy end points. All prespecified efficacy analyses were performed for a prespecified modified intent-to-treat analysis set, which includes all randomized patients who received at least 1 dose of study medication and had a valid baseline and at least 1 valid postdose assessment. See additional statistical analysis information in the eMethods in Supplement 2.

Safety results were summarized descriptively by treatment group and visit (when applicable). The incidences of clinical laboratory tests, vital signs, and ECG results that met predefined markedly abnormal criteria were summarized. Selected safety end points (fasting total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, insulin, triglycerides, and prolactin levels) for treatment groups were compared with placebo using MMRM whenever applicable and analysis of covariance for variables that were measured only twice during the study (once at screening or baseline and once after baseline). SAS statistical software, version 9.4 or higher (SAS Institute Inc) was used for the statistical analyses.

Results

Patients
Of 630 patients screened, 450 (71.4%) were randomized to treatment (mean [SD] age, 42.4 [10.2] years; 346 [77.1%] male; mean [SD] baseline PANSS score, 89.8 [10.3]; mean [SD] baseline CGI-S score, 4.8 [0.6]); 150 patients were randomized to each treatment arm. A total of 449 were included in the safety population, and 435 were included in the efficacy intent-to-treat population (Figure 1 and eTable 1 in Supplement 2). Altogether, 366 patients (81.3%) completed the 4-week treatment, and 359 (79.8%) completed the study (Figure 1). Study completion rates were 85.3% in the 42 mg of lumateperone group, 80.0% in the 28 mg of lumateperone group, and 74.0% in the placebo group. Overall, withdrawal of consent and lack of efficacy were the most
common reasons for study discontinuation, which was higher in the placebo group (16 withdrew consent and 17 discontinued because of lack of efficacy) than in the 42 mg of lumateperone group (10 withdrew consent and 6 discontinued because of lack of efficacy) and 28 mg of lumateperone group (8 withdrew consent and 11 discontinued because of lack of efficacy). The median time to discontinuation for any reason was 15 days (range, 1-23 days) for the 42 mg of lumateperone group, 13 days (range, 2-26 days) for the 28 mg of lumateperone group, and 13 days (range, 2-24 days) for placebo, with the difference between the 42 mg of lumateperone and placebo groups being statistically significant (P = .006).

Baseline demographic and clinical characteristics were similar across groups (Table 1). The median time since diagnosis of schizophrenia was 15.0 years (range, <1 to 46 years). There were no meaningful between-group differences in prior medication use at study entry (eTable 2 in Supplement 2).

### Efficacy

Treatment with 42 mg of lumateperone demonstrated a statistically significant improvement in change from baseline to day 28 in PANSS total score vs placebo (least-squares mean difference [LSMD], −4.2; 95% CI, −7.8 to −0.6; effect size, −0.3; unadjusted P = .02; multiplicity-adjusted P = .04) (Table 2 and Figure 2A). The LSMD observed with 28 mg of lumateperone vs placebo was −2.6 (95% CI, −6.2 to 1.1; effect size, −0.2; nominal P = .16; multiplicity-adjusted P = .18). Sensitivity analyses using a pattern-mixture model and an analysis of covariance last observation carried forward confirmed the robustness of the result from the MMRM analysis for the change from baseline to day 28 in PANSS total score in the 42 mg of lumateperone group vs the placebo group (LSMD, −3.9 95% CI, −7.4 to −0.4; effect size, −0.3; nominal P = .03; and LSMD, −5.0; 95% CI, −8.5 to −1.5; effect size, −0.3; nominal P = .006, respectively) (eTable 3 in Supplement 2). Statistically significant differences from placebo in the PANSS total score were observed at the day 8 assessment and continued through the day 28 assessment with 42 mg of lumateperone (Figure 2A). Interaction analyses suggested consistent treatment effects for demographic subgroups of race (black vs not black), ethnicity (Hispanic/Latino vs not Hispanic/Latino), age (≤40 vs >40 years), and sex for the comparison of 42 mg of lumateperone vs placebo in PANSS total score. A responder analysis indicated that 54 patients (36.5%) treated with 42 mg of lumateperone, 53 (36.3%) treated with 28 mg of lumateperone, and 36 placebo-treated patients (25.5%) had 30% or greater improvement in PANSS total score (eTable 4 in Supplement 2).

In individuals in the 42 mg of lumateperone group who met the key secondary end point with a statistically significant change in CGI-S score from baseline to day 28 vs placebo (LSMD, −0.3; 95% CI, −0.5 to −0.1; effect size, −0.4; unadjusted P = .003; multiplicity-adjusted P = .04); although there was no significant difference between the 28 mg of lumateperone group and the placebo group for the primary end point, the groups significantly differed on CGI-S (LSMD, −0.2; 95% CI, −0.5 to 0.0; effect size; −0.3; nominal P = .02) (Table 2 and Figure 2B). Treatment

### Table 1. Demographic and Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lumateperone, 42 mg (n = 150)</th>
<th>Lumateperone, 28 mg (n = 150)</th>
<th>Placebo (n = 149)</th>
<th>Total (N = 449)</th>
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</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics of safety population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>110 (73.3)</td>
<td>113 (75.3)</td>
<td>123 (82.6)</td>
<td>346 (77.1)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>42.4 (10.3)</td>
<td>43.5 (10.1)</td>
<td>41.4 (10.3)</td>
<td>42.4 (10.2)</td>
</tr>
<tr>
<td>Age ≤40 y</td>
<td>62 (41.3)</td>
<td>56 (37.3)</td>
<td>71 (47.7)</td>
<td>189 (42.1)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>108 (72.0)</td>
<td>94 (62.7)</td>
<td>96 (64.4)</td>
<td>298 (66.4)</td>
</tr>
<tr>
<td>White</td>
<td>33 (22.0)</td>
<td>42 (28.0)</td>
<td>42 (28.2)</td>
<td>117 (26.1)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (6.0)</td>
<td>14 (9.3)</td>
<td>11 (7.4)</td>
<td>34 (7.6)</td>
</tr>
<tr>
<td>Non-Hispanic/Latino</td>
<td>137 (91.3)</td>
<td>133 (88.7)</td>
<td>135 (90.6)</td>
<td>405 (90.2)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>86.3 (17.0)</td>
<td>85.8 (16.7)</td>
<td>85.9 (17.0)</td>
<td>86.0 (16.9)</td>
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<tr>
<td>BMI, mean (SD)</td>
<td>28.7 (5.4)</td>
<td>28.4 (5.1)</td>
<td>28.2 (5.3)</td>
<td>28.4 (5.3)</td>
</tr>
<tr>
<td><strong>Baseline efficacy characteristics in the ITT population</strong></td>
<td>148</td>
<td>146</td>
<td>141</td>
<td>435</td>
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<tr>
<td>Time since initial schizophrenia diagnosis, mean (SD), y</td>
<td>16.5 (10.4)</td>
<td>17.0 (10.6)</td>
<td>17.4 (10.6)</td>
<td>17.0 (10.5)</td>
</tr>
<tr>
<td>PANSS total score, mean (SD)</td>
<td>90.1 (9.5)</td>
<td>89.3 (10.2)</td>
<td>90.1 (11.1)</td>
<td>89.8 (10.3)</td>
</tr>
<tr>
<td>PANSS positive symptom subscale score, mean (SD)</td>
<td>26.0 (3.5)</td>
<td>25.8 (3.9)</td>
<td>25.8 (3.9)</td>
<td>25.9 (3.8)</td>
</tr>
<tr>
<td>PANSS negative symptom subscale score, mean (SD)</td>
<td>20.6 (3.8)</td>
<td>20.4 (4.2)</td>
<td>21.0 (4.4)</td>
<td>20.7 (4.1)</td>
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<tr>
<td>PANSS general psychopathology subscale score, mean (SD)</td>
<td>43.5 (6.1)</td>
<td>43.1 (6.0)</td>
<td>43.2 (6.3)</td>
<td>43.3 (6.1)</td>
</tr>
<tr>
<td>PANSS prosocial subscale score, mean (SD)</td>
<td>25.0 (3.4)</td>
<td>24.5 (3.5)</td>
<td>24.3 (3.3)</td>
<td>24.6 (3.4)</td>
</tr>
<tr>
<td>Central CGI-S score, mean (SD)</td>
<td>4.8 (0.5)</td>
<td>4.7 (0.6)</td>
<td>4.8 (0.6)</td>
<td>4.8 (0.6)</td>
</tr>
<tr>
<td>Site CGI-S score, mean (SD)</td>
<td>4.8 (0.6)</td>
<td>4.8 (0.6)</td>
<td>4.8 (0.6)</td>
<td>4.8 (0.6)</td>
</tr>
<tr>
<td>BPRS score, mean (SD)</td>
<td>53.7 (7.4)</td>
<td>53.3 (7.2)</td>
<td>54.2 (7.7)</td>
<td>53.7 (7.4)</td>
</tr>
<tr>
<td>PSP scale score, mean (SD)</td>
<td>47.8 (11.9)</td>
<td>48.2 (12.2)</td>
<td>47.7 (12.4)</td>
<td>47.9 (12.2)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression–Severity of illness; ITT, intent-to-treat; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance.

* Data are presented as number (percentage) of study participants unless otherwise indicated.
with 42 and 28 mg of lumateperone significantly improved the PANSS positive subscale score from baseline to day 28 compared with placebo (42 mg: LSMD, −1.7; 95% CI, −2.9 to −0.5; effect size, −0.3; nominal \( P = .006 \); and 28 mg: LSMD, −1.2; 95% CI, −2.4 to −0.1; effect size, −0.2; nominal \( P = .04 \)) (Figure 2C); the changes in the PANSS negative subscale score from baseline to day 28 compared with placebo were not significant (Figure 2D). Statistically significant improvements vs placebo were observed with 42 mg of lumateperone in the general psychopathology subscale score and in psychosocial function (mea-
sured by the PANSS-derived prosocial factor and PSP scale) (general psychopathology subscale: LSMD, −2.4; 95% CI, −4.3 to −0.5; effect size, −0.3; nominal \( P < .01 \); PANSS-derived prosocial factor: LSMD, −1.1; 95% CI, −2.2 to 0.0; effect size, −0.2; nominal \( P = .04 \); and PSP scale: LSMD, 3.3; 95% CI, 0.1 to 6.6; effect size, −0.3; nominal \( P = .05 \)) (Table 2). Change in Calgary Depression Scale for Schizophrenia score from baseline to day 28 was not significantly different from that in the placebo group after treatment with 42 mg of lumateperone (LSMD, 0.4; 95% CI, −0.2 to 0.96; nominal \( P = .24 \)) or 28 mg of lumateperone (LSMD, 0.2; 95% CI, −0.43 to 0.79; nominal \( P = .57 \)).

Safety

Treatment-emergent adverse events occurred in 97 patients (64.7%) in the 42 mg of lumateperone group, 85 (56.7%) in the 28 mg of lumateperone group, and 75 (50.3%) in the placebo group (eTable 5 in Supplement 2). The TEAEs occurring in either lumateperone group in 5% or more of patients and more than 2 times the rate in the placebo group were somnolence (42 mg of lumateperone group, 26 [17.3%]; 28 mg of lumateperone group, 17 [11.3%]; and placebo, 6 [4.0%]); sedation (19 [12.7%] in the 42 mg of lumateperone group, 14 [9.3%] in the 28 mg of lumateperone group, and 8 [5.4%] in the placebo group), fatigue (8 [5.3%] in the 42 mg of lumateperone group, 7 [4.7%] in the 28 mg of lumateperone group, and 2 [1.3%] in the placebo group), and constipation (10 [6.7%] in the 42 mg of lumateperone group, 6 [4.0%] in the 28 mg of lumateperone group, and 4 [2.7%] in the placebo group) (eTable 5 in Supplement 2). Two patients experienced severe-intensity TEAEs and discontinued treatment: orthostatic hypotension (1 patient [0.7%] in the 42 mg of lumateperone group) and convulsions (1 patient [0.7%] in the 28 mg of lumateperone group; this patient had preexisting risk factors and relevant medical history regarding seizures; this TEAE was deemed serious). All other TEAEs were mild or moderate in intensity. One patient in the placebo group experienced a serious TEAE of asthma. Additional TEAEs leading to discontinuation by treatment arm were as follows: headache (2 [1.3%]) in the 42 mg of lumateperone group and schizophrenia (1 [0.7%]) in the placebo group. One placebo-treated patient (0.7%) died of an unknown cause 13 days after discontinuing the study.

Figure 2. Least-Squares Mean Change in Positive and Negative Syndrome Scale (PANSS) Total Score and Clinical Global Impression–Severity of Illness (CGI-S) and Mean Change in PANSS Positive and Negative Symptom Subscales

![Figure 2](https://example.com/figure2.png)
No serious and unexpected drug reactions were reported during the study. There was no increase in suicidal ideation or behavior with lumateperone at either dose as measured by TE- AEIs or the Columbia Suicide Severity Rating Scale (eTable 6 in Supplement 2). No extrapyramidal symptoms (EPS)-related TE-AEs occurred in 5% or more of patients in any treatment arm (eTable 5 in Supplement 2); EPS-related TE-AEs were rare (eTable 7 in Supplement 2). Treatment with 42 or 28 mg of lumateperone was not associated with increased EPS as measured by the Simpson-Angus Scale, Barnes Akathisia Rating Scale, or Abnormal Involuntary Movement Scale (eTable 8 in Supplement 2). Three patients (2.0%) treated with 42 mg of lumateperone, 1 patient (0.7%) treated with 28 mg of lumateperone, and 4 patients (2.7%) in the placebo group used benztrapine as a rescue medication for EPS during the 28-day treatment period (eTable 9 in Supplement 2).

Mean change in weight from baseline to day 28 was similar in all treatment arms (Figure 3). Median change in weight from baseline to day 28 was 0.9 kg (range, –36 to 11 kg) for 42 mg of lumateperone, 0.6 kg (range, –12 to 13 kg) for 28 mg of lumateperone, and 0.7 kg (range, –12 to 16) for placebo. Weight changes of 7% or greater and shifts in body mass index from overweight to obese were infrequent and similar among groups (eFigure in Supplement 2). There were no significant mean changes in metabolic parameters from baseline to day 28 compared with placebo (Figure 3).

No clinically meaningful changes from baseline or differences observed in physical examination results, vital signs, or ECG findings were found between the lumateperone and placebo groups. One patient in the placebo group (before treatment) and 1 patient in the 28 mg of lumateperone group (before and after treatment) had a corrected QT interval by Fredericia greater than 450 milliseconds. No patients had a corrected QT interval by Fredericia greater than 500 milliseconds or a change greater than 60 milliseconds from baseline.

Discussion

Treatment with 42 mg of lumateperone compared with placebo significantly improved symptoms in patients with acute exacerbation of schizophrenia without causing many of the adverse effects commonly observed with currently available antipsychotics.3-4 These findings support the results of a previous 4-week study that found that treatment with 42 mg of lumateperone (60 mg of lumateperone tosylate) was effective in treating schizophrenia symptoms compared with placebo and had an effect size (0.4) for reduction in PANSS total symptoms similar to that of 4 mg of risperidone.29 The effect sizes for PANSS total (0.30) and CGI-S (0.39) reduction in this study are broadly comparable with standard of care and, especially, newly approved antipsychotic effect sizes for overall reduction in symptoms (PANSS total), including brexpiprazole (0.26), cariprazine (0.34), and lurasidone (0.36).4,30,31 Treatment with 42 mg of lumateperone significantly improved symptoms, with significant reductions beginning at the first week and maintained throughout treatment. A responder analysis indicated that 54 patients (36.5%) who received 42 mg of lumateperone improved on the PANSS total score by 30% or more compared with 36 patients (25.5%) who received placebo (number needed to treat of 9.1). Furthermore, patients treated with 42 mg of lumateperone had significant improvement across a broad range of PANSS subscales and on the CGI-S, consistent with clinical meaningfulness of the improvement.

A higher dose (84 mg) of lumateperone (equivalent to 120 mg of lumateperone tosylate) was not effective in a previous study29; therefore, a lower dose of lumateperone (28 mg) was explored in this study. Although patients treated with 28 mg of lumateperone did not have a statistically significant decrease in the PANSS total score, decreases on the PANSS positive symptom subscale and on the CGI-S outperformed placebo, establishing a dose-response curve for the efficacy of lumateperone.29

The improvement in psychosocial function is a highly desired yet often unrealized outcome in patients with schizophrenia.1 Improvements in psychosocial function were suggested by significant improvements assessed by the site-rated PSP and the centrally rated PANSS-derived prosocial factor, which was previously identified via factor analysis in patients with schizophrenia and mood disorders23 and has been used to assess other antipsychotics.32,33 The 6-item PANSS-derived prosocial factor includes PANSS items of active social avoidance, passive social withdrawal, and emotional withdrawal, 3 symptoms reported to be highly indicative of interpersonal functioning.34

Prior research35 indicates that improvement in schizophrenia symptoms after treatment with lumateperone is associated with approximately 40% striatal D2 receptor occupancy (D2RO) at peak plasma concentrations, which is a substantially lower occupancy at an efficacious dose than most currently available antipsychotics that exhibit 60% to 80% D2RO. The ability to treat schizophrenia at low postsynaptic D2RO and with low EPS and low hyperprolactinemia liability may be attributed to the following characteristics of lumateperone: (1) substantially greater affinity for 5-HT2A receptor than D2-receptor modulation, greater than that of clozapine (60-fold greater affinity for 5-HT2A receptors in vitro and confirmed high cortical 5-HT2A-receptor occupancy and relatively lower striatal D2RO)10; (2) unique interaction with D2 receptors as a presynaptic partial agonist and postsynaptic antagonist with functional mesolimbic and mesocortical selectivity46; (3) inhibition of serotonin reuptake15; and (4) indirect enhancement of glutamate neurotransmission downstream from activation of D2 receptors9 (with 3 and 4 predicting antidepressant effects in addition to antipsychotic effects).10 The observed safety profile may also be associated with lumateperone’s minimal binding at histaminergic or muscarinic receptors,10 which have been traditionally associated with cardiometabolic effects and other tolerability issues of existing antipsychotics.11

Given the high burden of schizophrenia,2 an unmet medical need still exists to treat the broad range of symptoms without increasing adverse effects of antipsychotics, including risk of EPS, parkinsonism and akathisia, hyperprolactinemia, weight gain, dyslipidemia, diabetes, and cardiovascular disease.3,36-41 Furthermore, tolerability and safety issues asso-
Efficacy and Safety of Lumateperone for Treatment of Schizophrenia

Figure 3. Change in Cholesterol, Glucose, Triglycerides, Prolactin, and Insulin Levels and Weight From Baseline

Error bars indicate SE. SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; triglycerides to millimoles per liter, multiply by 0.0113; prolactin to nanograms per liter, multiply by 0.0435; and insulin to picomoles per liter, multiply by 6.945.

Associated with many antipsychotics lead to nonadherence. In this study, treatment with lumateperone demonstrated a safety profile similar to placebo, confirming results observed in a previous clinical trial. The high completion rates and low discontinuation rates attributable to adverse events support the favorable safety profile of lumateperone. There was 1 event of convulsion that was severe and deemed serious; this patient had preexisting risk factors and relevant medical history regarding seizures but was inappropriately randomized because of incomplete medical history and inaccurate self-reporting at screening. Antipsychotics are, in general, associated with risk of seizure; however, the specific risks associated with lumateperone could not be determined from this study because patients with a history of seizure disorder were excluded. The
adverse events in the lumateperone groups that occurred at a clinically meaningful rate were sedation, somnolence, fatigue, and constipation, which all were predominantly mild. Of note, lumateperone was administered in the morning to capture important safety measures during the day around the time of peak plasma levels. In clinical practice, lumateperone will likely be administered in the evening with maintenance of sleep as a potential benefit of the mild sedative effects in some patients. Additional safety studies are being conducted to evaluate lumateperone administered in the evening.

Limitations
The following limitations should be noted. First, patients had to meet specific inclusion criteria, which may limit generalizability of these data to broader populations. Second, the 4-week treatment duration may not elucidate the safety profile associated with longer-term treatment or address maintenance of effectiveness; however, an open-label trial of long-term treatment with lumateperone in patients with schizophrenia is currently in progress, which may extend the generalizability of the current results. Third, the prosocial factor, which improved with lumateperone, includes negative symptoms and positive symptoms. The improvements in the prosocial factor may have been secondary to improvements in positive symptoms in this acutely ill population. Additional studies are warranted to examine the benefit of lumateperone treatment for social function and negative symptoms.

Conclusions
The unique pharmacologic mechanisms of lumateperone seem to confer antipsychotic efficacy with favorable safety and tolerability. The efficacy and safety profiles of lumateperone may differ in important ways from existing treatments for patients with schizophrenia. 

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REFERENCES

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