# Supplementary Online Content

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**This supplementary material has been provided by the authors to give readers additional information about their work.**

## **eMethods.** Supplemental Methods

**Additional inclusion and exclusion criteria**

Eligible individuals were required to have shown previous treatment response to antipsychotic therapy, and thus were neither treatment-naïve nor treatment-resistant. Accurate diagnosis and appropriate symptom severity at screening were rated by study investigators and confirmed by independent clinicians (Clintara LLC, Boston, Massachusetts) to ensure inclusion of an appropriate patient population. Patients who met any of the following criteria were excluded from the study: unable to provide informed consent; pregnant and/or breast-feeding; dementia, delirium, mental retardation, epilepsy, drug-induced psychosis, brain trauma; schizoaffective disorder, bipolar disorder, major depression with psychotic features; imminent danger to self or others; suicidal ideation or behavior; unstable living environment; use of depot antipsychotic within 1.5 treatment cycles before baseline; use of any antipsychotic within the screening period; use of specific agents with known interaction with 5-$HT_{2A}$ receptors; clinically abnormal laboratory values or medically relevant clinical findings; uncontrolled angina, recent history of myocardial infarction, clinically significant cardiac arrhythmia; hematological, renal, hepatic, endocrinological, neurological, cardiovascular disease; history of neuroleptic malignant syndrome; HIV; hepatitis B or C with evidence of active liver disease; substance abuse or dependence; positive drug or alcohol screen; likely drug allergy/hypersensitivity; prior participation in a study with lumateperone or exposure to any investigational product within 3 months of Day −1; unable to be safely discontinued from current antipsychotic or other psychotropic medications; any patient judged by the investigator to be inappropriate for study participation.

**Additional Measures and Procedures**

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary Version 17.1. Treatment-emergent AEs were defined as AEs that started or worsened in severity on or after the first dose of study medication and on or before the last date of study medication. The incidence of TEAEs was presented by System Organ Class and Preferred Term and also by maximum severity and relationship to study medication.

Blood and urine samples for clinical laboratory analysis were collected from all subjects upon screening and on Days 1, 8, 28, and 33, following overnight fast. A central laboratory was used for evaluation of hematology, clinical chemistry, and urinalysis. Results were analyzed descriptively for glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Summaries of laboratory data included actual and change from baseline, incidence of abnormal values according to normal range criteria, shifts from baseline according to normal range and markedly abnormal criteria, and listing of subjects meeting markedly abnormal criteria. Vital sign measurements including 3-positional blood pressure and pulse rate, respiratory rate, and oral temperature were recorded following electrocardiograms at screening, baseline, and Days 1, 8 and 28. Body weight and waist circumference were recorded on Day -1 and during a modified physical examination performed upon screening and on Day 28. The modified physical examination excluded genital/rectal examination and included neurological examination.

**Additional statistical analyses**

The mixed-effects model for repeated measures (MMRM) included the change from baseline at each pre-specified time point as the response variable and study visit, baseline PANSS total score, baseline PANSS total score-by-study visit interaction, treatment (lumateperone 28 mg, lumateperone 42 mg, and placebo), and treatment-by-study visit interaction. Baseline and baseline-by-visit interactions were included as covariates. An unstructured covariance matrix was used to model the correlation among repeated measurements within a patient. The MMRM approach did not impute missing data but was based on all subjects included in the analysis set using all available longitudinal data, either complete or partial. The Kenward-Rogers approximation was used to estimate the denominator degrees of freedom for the reference distribution. This approach was based on the assumption of data being missing at random. Subjects discontinuing from treatment early were considered to have unobserved values in line with observed outcomes in their treatment arm, taking into account the available data prior to discontinuation. To assess the robustness of this assumption, a sensitivity analysis with a different assumption about unobserved outcomes using multiple imputations was performed.

The mixture-based gatekeeping procedure was proposed by Dmitrienko, Kordzakhia and Brechenmacher[1] as a modification of the standard method introduced by Dmitrienko and Tamhane.[2,3] Briefly, hypotheses associated with

the primary efficacy endpoint (lumateperone vs placebo, change from baseline in PANSS total score at Day 28) were tested first, for both 42 mg and 28 mg dosages, using the truncated Hochberg test. The truncated Hochberg procedure is a convex combination of the Bonferroni procedure and regular Hochberg procedure based on a pre-specified truncation parameter.[4] With $\gamma = 0$, the truncated Hochberg procedure simplifies to the Bonferroni procedure and, with $\gamma = 1$ the truncated Hochberg procedure simplifies to the regular Hochberg procedure. For this study $\gamma = 0.8$. In the mixture-based gatekeeping procedure, hypotheses associated with the key secondary endpoint (lumateperone vs placebo, change from baseline in CGI-S score at Day 28) were only tested if the primary treatment effects were significant, using the regular Hochberg procedure.

A pattern-mixture model (PMM)[1] and analysis of covariance (ANCOVA) with last observation carried forward (LOCF) were performed as a sensitivity analysis. The PANSS total score was used for the responder rate analysis (defined as at least 20%, 30%, or 40% reduction from baseline to Day 28). A patient with missing PANSS assessment on Day 28 was considered a non-responder. Number-needed-to-treat (NNT) was calculated by taking the inverse of the absolute difference of the placebo rate minus the experimental rate then multiplying by 100.

The change from baseline to Day 28 in central CGI-S was the key secondary endpoint and was assessed using similar MMRM methodology as specified for the primary analysis. ANCOVA with LOCF was determined post hoc to be the most appropriate statistical comparison for PANSS subscales and the PANSS-derived prosocial factor. For PSP total score, a multiple imputation model under the assumption of missing at random (MAR) mechanism was used to impute missing data and the observed and imputed data were analyzed using a pre-specified ANCOVA model with effects for baseline score and treatment. Efficacy endpoints were analyzed versus placebo. Efficacy was not compared between the lumateperone 42 mg and 28 mg groups, as the study was not designed with the sample size to detect treatment differences between the two dosages.

**eTable 1.** Patient Randomization by Study Site[a]

| | Lumateperone 42 mg (N=150) | Lumateperone 28 mg (N=150) | Placebo (N=150) |
|---|---|---|---|
| Minimum at single site, n | 2 | 5 | 4 |
| Maximum at single site, n | 27 | 26 | 25 |
| Median randomized at site, n | 12.5 | 13 | 12.5 |

[a] All randomized patients

**eTable 2.** Most Frequently Reported Prior Medications[a] (≥5% in the Safety Set)

| n (%) | **Lumateperone 42 mg (N=150)** | **Lumateperone 28 mg (N=150)** | **Placebo (N=149)** |
|---|---|---|---|
| 1 or more prior medication | 138 (92.0) | 141 (94.0) | 143 (96.0) |
| Lorazepam | 94 (62.7) | 92 (61.3) | 93 (62.4) |
| Quetiapine | 43 (28.7) | 46 (30.7) | 48 (32.2) |
| Risperidone | 42 (28.0) | 43 (28.7) | 49 (32.9) |
| Ibuprofen | 35 (23.3) | 38 (25.3) | 32 (21.5) |
| Haloperidol | 19 (12.7) | 27 (18.0) | 28 (18.8) |
| Tuberculin | 20 (13.3) | 24 (16.0) | 19 (12.8) |
| Trazadone | 9 (6.0) | 18 (12.0) | 12 (8.1) |
| Benztropine | 15 (10.0) | 16 (10.7) | 16 (10.7) |
| Olanzapine | 19 (12.7) | 14 (9.3) | 22 (14.8) |
| Aripiprazole | 14 (9.3) | 12 (8.0) | 18 (12.1) |
| Diphenhydramine | 4 (2.7) | 8 (5.3) | 8 (5.4) |
| Sertraline | 5 (3.3) | 7 (4.7) | 11 (7.4) |
| Zolpidem | 6 (4.0) | 6 (4.0) | 8 (5.4) |
| Valproic acid | 3 (2.0) | 6 (4.0) | 10 (6.7) |

[a] Prior medications are those which started and stopped prior to date and time of first dose of study medication.

**eTable 3.** Sensitivity Analysis for Efficacy Endpoint Measures for Lumateperone Versus Placebo (ITT)

| | Lumateperone 42 mg | Lumateperone 28 mg | Placebo |
|---|---|---|---|
| **PANSS Total Score (PMM)** | **N=148** | **N=146** | **N=141** |
| LS mean change from baseline to day 28 (SE) | −14.4 (1.23) | −12.8 (1.24) | −10.5 (1.28) |
| LS mean difference from placebo (95% CI) | −3.9 (−7.4, −0.4) | −2.3 (−5.8, 1.2) | — |
| Effect size | −0.26 | −0.15 | — |
| *P* value[a] | .03 | .20 | — |
| **PANSS Total Score (ANCOVA-LOCF)** | **N=146** | **N=145** | **N=141** |
| Mean change from baseline to day 28 (SE) | −13.9 (1.26) | −11.6 (1.32) | −9.0 (1.28) |
| LS mean change from baseline to day 28 (SE) | −13.9 (1.26) | −11.7 (1.26) | −8.9 (1.28) |
| LS mean difference from placebo (95% CI) | −5.0 (−8.5, −1.5) | −2.8 (−6.3, 0.7) | — |
| Effect size | −0.33 | −0.18 | — |
| *P* value[a] | .006 | .12 | — |
| **PANSS Positive Symptom subscale score (MMRM)** | **N=130** | **N=123** | **N=109** |
| Mean change from baseline to day 28 (SE) | −5.4 (0.47) | −5.1 (0.44) | −4.4 (0.45) |
| LS mean change from baseline to day 28 (SE) | −5.0 (0.42) | −4.8 (0.43) | −3.6 (0.45) |
| LS mean difference from placebo (95% CI) | −1.4 (−2.57, −0.14) | −1.2 (−2.39, 0.07) | — |
| Effect size | −0.28 | −0.24 | — |
| *P* value[a] | .03 | .07 | — |
| **PANSS Negative Symptom subscale score (MMRM)** | **N=130** | **N=123** | **N=109** |
| Mean change from baseline to day 28 (SE) | −1.8 (0.44) | −1.3 (0.41) | −1.2 (0.48) |
| LS mean change from baseline to day 28 (SE) | −1.6 (0.39) | −1.2 (0.4) | −0.8 (0.42) |
| LS mean difference from placebo (95% CI) | −0.8 (−1.90, 0.33) | −0.4 (−1.50, 0.76) | — |
| Effect size | −0.18 | −0.09 | — |
| *P* value[a] | .17 | .52 | — |
| **PANSS General Psychopathology subscale score (MMRM)** | **N=130** | **N=123** | **N=109** |
| Mean change from baseline to day 28 (SE) | −8.5 (0.74) | −7.3 (0.77) | −6.8 (0.73) |
| LS mean change from baseline to day 28 (SE) | −7.9 (0.67) | −7.0 (0.69) | −6.1 (0.72) |
| LS mean difference from placebo (95% CI) | −1.8 (−3.78, 0.10) | −0.9 (−2.88, 1.03) | — |
| Effect size | −0.24 | −0.12 | — |
| *P* value[a] | .06 | .35 | — |
| **PANSS-derived Prosocial Factor score (MMRM)** | **N=130** | **N=123** | **N=109** |
| Mean change from baseline to day 28 (SE) | −5.4 (0.46) | −5.2 (0.43) | −4.4 (0.47) |
| LS mean change from baseline to day 28 (SE) | −4.9 (0.40) | −4.9 (0.41) | −4.1 (0.43) |
| LS mean difference from placebo (95% CI) | −0.8 (−2.00, 0.31) | −0.9 (−2.03, 0.30) | — |
| Effect size | −0.19 | −0.19 | — |
| *P* value[a] | .15 | .14 | — |

[a] *P* values are nominal and unadjusted for multiplicity unless noted.
ANCOVA-LOCF, analysis of covariance-last observation carried forward; LS mean, least squares mean; MMRM, mixed-effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale; PMM, pattern mixture model; SE, standard error.

**eTable 4.** Responder Analysis for Lumateperone in Patients With Schizophrenia[a] (ITT)

| Reduction in PANSS Total score | Lumateperone 42 mg (N=148) | Lumateperone 28 mg (N=146) | Placebo (N=141) |
|---|---|---|---|
| | n (%) | | |
| ≥20% | 74 (50.0%) NNT=8.5[b] | 71 (48.6%) NNT=9.7[b] | 54 (38.3%) |
| ≥30% | 54 (36.5%) NNT=9.1[b] | 53 (36.3%) NNT=9.3[b] | 36 (25.5%) |
| ≥40% | 38 (25.7%) NNT=10.6[b] | 30 (20.5%) NNT=23.8[b] | 23 (16.3%) |

[a] The PANSS Total score was used for the responder rate analysis. A PANSS response is defined as at least 20%, 30%, or 40% reduction in PANSS Total score from baseline to Day 28. A patient with missing PANSS assessment on Day 28 was considered a non-responder.
[b] Number needed to treat (NNT) was calculated by taking the inverse of the absolute difference of the placebo rate minus the experimental rate then multiplying by 100.

**eTable 5.** Incidence of Treatment-Emergent Adverse Events Occurring in ≥5% of Patients in Any Treatment Group (Safety Set)

| Preferred Term | Lumateperone 42 mg (N=150) | Lumateperone 28 mg (N=150) | Placebo (N=149) |
|---|---|---|---|
| Patients with ≥1 TEAE | 97 (64.7) | 85 (56.7) | 75 (50.3) |
| Headache | 29 (19.3) | 24 (16.0) | 22 (14.8) |
| Somnolence | 26 (17.3) | 17 (11.3) | 6 (4.0) |
| Sedation | 19 (12.7) | 14 (9.3) | 8 (5.4) |
| Nausea | 16 (10.7) | 7 (4.7) | 11 (7.4) |
| Dry mouth | 11 (7.3) | 9 (6.0) | 7 (4.7) |
| Dizziness | 10 (6.7) | 7 (4.7) | 6 (4.0) |
| Constipation | 10 (6.7) | 6 (4.0) | 4 (2.7) |
| Fatigue | 8 (5.3) | 7 (4.7) | 2 (1.3) |

TEAEs are defined as AEs that started or worsened in severity on or after the first dose of study medication and on or before the last date of study medication. TEAEs were coded using MedDRA version 17.1. Although a patient may have had 2 or more AEs, the patient is counted only once in each preferred-term category. The same patient may appear in different preferred-term categories.

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent AE.

**eTable 6.** Lumateperone Was Not Associated With Suicidal Ideation or Behavior as Measured by the Columbia-Suicide Severity Rating Scale (Safety Set)

| | **Lumateperone 42 mg (N=150)** | **Lumateperone 28 mg (N=150)** | **Placebo (N=149)** |
|---|---|---|---|
| | n (%) | | |
| ≥1 suicidal ideation after baseline | 2 (1.4) | 2 (1.4) | 2 (1.4) |
| ≥1 suicidal behavior after baseline | 0 | 0 | 0 |

**eTable 7.** Incidence of Treatment-Emergent Adverse Events Related to Extrapyramidal Symptoms (Safety Set)

| | Lumateperone 42 mg (N=150) | Lumateperone 28 mg (N=150) | Placebo (N=149) |
|---|---|---|---|
| | n (%) | | |
| Patients with ≥1 EPS-related TEAE[a] | 6 (4.0) | 4 (2.7) | 4 (2.7) |
| Akathisia | 6 (4.0) | 2 (1.3) | 4 (2.7) |
| Dyskinesia | 0 | 2 (1.3) | 0 |
| Dystonia | 0 | 0 | 1 (0.7) |

[a]TEAEs related to EPS were determined according to standard MedDRA query narrow criteria by preferred term.
TEAEs are defined as AEs that started or worsened in severity on or after the first dose of study medication and on or before the last date of study medication. TEAEs were coded using MedDRA version 17.1. Although a patient may have had 2 or more AEs, the patient is counted only once in each preferred-term category. The same patient may appear in different preferred-term categories.

AE, adverse event; EPS, extrapyramidal symptoms; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent AE.

**eTable 8.** Extrapyramidal Symptoms as Measured by Objective Clinician-Administered Scales (Mean Change From Baseline to Day 28 on the Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, and Simpson-Angus Scale; Safety Set)

| Change from baseline to Day 28 | Lumateperone 42 mg (N=150) | Lumateperone 28 mg (N=150) | Placebo (N=149) |
|---|---|---|---|
| | Mean (SD) | | |
| BARS Total score | −0.2 (1.02) | −0.1 (0.73) | 0.1 (0.41) |
| BARS Global score | −0.1 (0.54) | 0.0 (0.42) | 0.0 (0.28) |
| AIMS Total score | 0.0 (1.03) | 0.1 (0.96) | 0.1 (0.76) |
| SAS Total score | 0.0 (0.48) | 0.1 (0.95) | 0.0 (0.47) |

AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; SAS, Simpson-Angus Scale; SD, standard deviation.

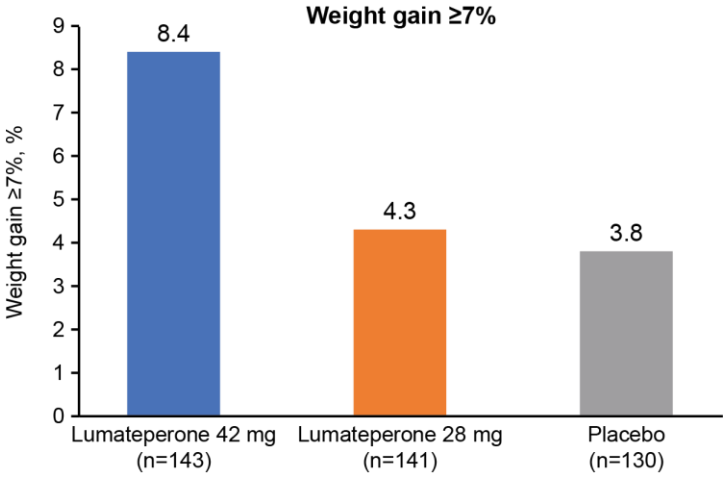
**eTable 9.** Concomitant Psychotropic Medication[a] Use for the Management of Extrapyramidal Symptoms or Agitation (Safety Set)

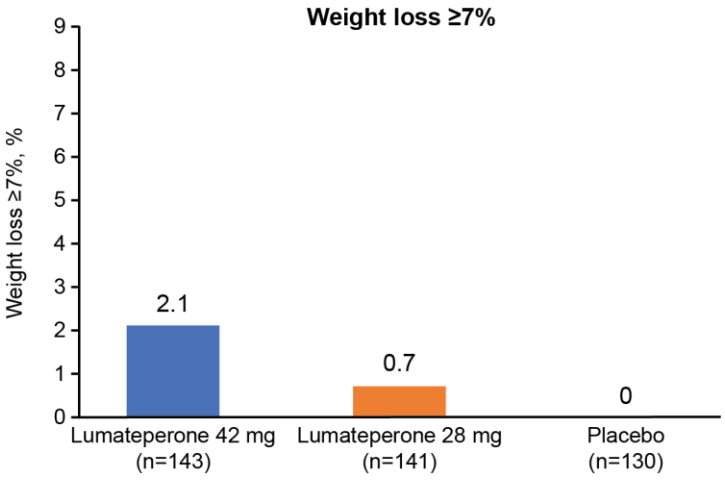
| | Lumateperone 42 mg (N=150) | Lumateperone 28 mg (N=150) | Placebo (N=149) |
|---|---|---|---|
| | n (%) | | |
| Benztropine[b] | 3 (2.0) | 1 (0.7) | 4 (2.7) |
| Lorazepam[c] | 107 (71.3) | 108 (72.0) | 114 (76.5) |
| Propranolol[d] | 7 (4.7) | 5 (3.3) | 4 (2.7) |

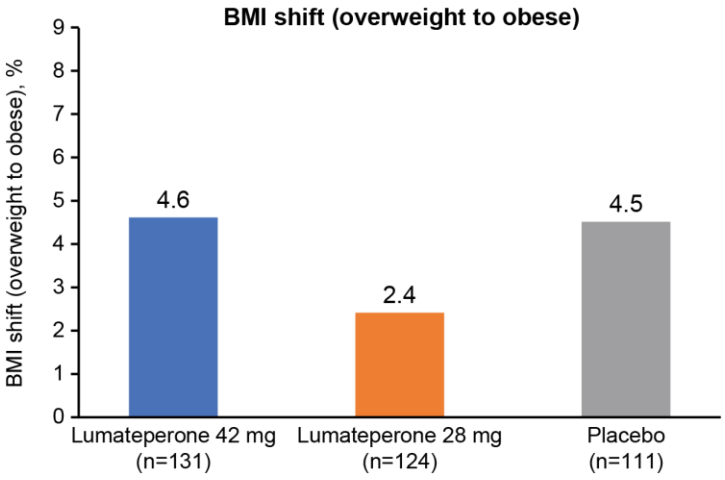
[a]Psychotropic medications were restricted to those listed, within daily limitations, and with approval by the Investigator prior to each administration. One patient in the placebo group had a protocol deviation and took a psychotropic medication other than those listed. [b]Benztropine could be administered for EPS (up to 4 mg/day), but not within 8 hours of a BARS, SAS, or AIMS assessment. [c]Lorazepam could be administered for agitation, anxiety, or to aid sleep (up to 6 mg/day Day 1 to Day 7, up to 4 mg/day Day 8 to Day 14, up to 2 mg/day on no more than 4 days/week Day 15 to Day 28), but not within 8 hours of a PANSS, CGI-S, PSP, or CDSS assessment. [d]Propranolol could be administered for akathisia (up to 40 mg/day), but not within 8 hours of a BARS, SAS, or AIMS assessment.

AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression-Severity of Illness; EPS, extrapyramidal symptoms, PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale; SAS, Simpson Angus Scale.

**eFigure.** Weight Change ≥7% and BMI Shift From Overweight to Obese (Safety Set)




BMI, body mass index.

## eReferences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