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Study ID: ITI-007-403

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of Lumateperone Monotherapy in the Treatment of Patients with Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder (Bipolar Depression) or Major Depressive Disorder

SAP Date: 31 Jan 2023

A Phase 3, Randomized, Double-blind, Placebo-controlled, Multi-Center Study to Assess the Efficacy and Safety of Lumateperone Monotherapy in the Treatment of Patients with Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder (Bipolar Depression) or Major Depressive Disorder

Statistical Analysis Plan

Protocol Number:	ITI-007-403
Version:	Final
Date:	31 Jan 2023
Compound:	Lumateperone
Study Phase:	3
Sponsor:	Intra-Cellular Therapies, Inc. Alexandria Center for Life Science 430 East 29th Street, Suite 900 New York, NY 10016

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1. LIST OF ABBREVIATIONS

AE	adverse event
AIMS	abnormal involuntary movement scale
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ANCOVA	analysis of covariance
BARS	Barnes akathisia rating scale
bITT	bipolar intent-to-treat
BMI	body mass index
BP	blood pressure
BPM	beats per minute
CGI-S	clinical global impression scale-severity
CI	confidence interval
C-SSRS	Columbia-suicide severity rating scale
DBTP	double-blind treatment period
ECG	electrocardiogram, electrocardiographic
ET	early termination
eCRF	electronic case report form
GCP	Good Clinical Practice
ICE	intercurrent event
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	international council on harmonization
ITT	intent-to-treat
LLN	lower limit of normal
LOE	lack of efficacy
MADRS	Montgomery-Åsberg Depression Rating Scale
MAR	missing at random
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model with repeated measure

MNAR	missing not at random
msec	millisecond(s)
PCS	potentially clinically significant
PMM	pattern mixture model
PT	preferred term
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Fridericia formula
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson angus scale
SD	standard deviation
SFUP	safety follow-up period
SOC	system organ class
TEAE	treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	upper limit of normal
WHO	World Health Organization
YMRS	Young Mania Rating Scale

2. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and specified in the Protocol Amendment 4.0 of Study ITI-007-403 (dated 27 Jan 2023). Specifications of tables, figures, and data listings are contained in a separate document.

This study was originally designed as a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of lumateperone as monotherapy in the treatment of patients with Major Depressive Episodes (MDEs) associated with bipolar I or bipolar II disorder. After the study started, Study ITI-007-402 (a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of lumateperone adjunctive to lithium or valproate in the treatment of patients with MDEs associated with bipolar I or bipolar II disorder) reported its results and demonstrated lumateperone successfully reduced MDEs associated symptoms based on treatment difference in change from baseline to Day 43 in MADRS total score for lumateperone vs placebo. As a result, there was no need for an additional pivotal study for the treatment of patients with MDEs associated with bipolar I or bipolar II disorder.

Therefore, Study ITI-007-403 was repositioned for the treatment of patients with MDEs associated with bipolar disorder with mixed features or major depressive disorder (MDD) with mixed features. This change was described in Protocol Amendment 2.0 (dated 02 Nov 2020). A total of 100 patients had been randomized under the original protocol before the implementation of Protocol Amendment 2.0. Protocol Amendment 2.0 plans for an additional enrollment of 350 patients with approximately equal number of patients for bipolar disorder with mixed features and for MDD with mixed features.

For data analysis, the main difference between the original protocol before Protocol Amendment 2.0 and after Protocol Amendment 2.0 is in the patient populations: Original Protocol before Protocol Amendment 2.0 enrolled patients with MDE associated with bipolar I or bipolar II disorder; while after Protocol Amendment 2.0, the study enrolled patients with MDEs associated with bipolar disorder with mixed features or MDD with mixed features.

Both the Original Protocol and Protocol Amendment 2.0 consist of the same study design of a Screening Period, Double-blind Treatment Period (DBTP), and a Safety Follow-up Period (SFUP) with the same planned assessments.

Screening Period (2 Weeks)

Potential patients will be evaluated during a Screening Period lasting up to 2 weeks unless an extension of the Screening Period is approved by the Medical Monitor or Sponsor Designee.

After obtaining written informed consent, diagnostic interviews and physical examinations will be conducted, vital signs and electrocardiogram (ECGs) will be assessed, and blood samples will be collected for laboratory assessments. Patients considered potentially eligible for participation will be required to discontinue their current antidepressant treatment and/or other psychotropic drugs.

At Baseline (Visit 2), patients who continue to meet all eligibility criteria will be randomized to 1 of the 2 treatment arms (lumateperone 42 mg or matching placebo) for a 6-week DBTP.

Double-blind Treatment Period (6 Weeks)

Patients will take their first dose of study drug on the evening of Baseline (Visit 2, Day 1). A single dose will be taken each day in the evening, with or without food, for the duration of the 6-week DBTP.

Following randomization, patients will attend outpatient study visits on Days 8, 15, 22, 29, 36, and 43.

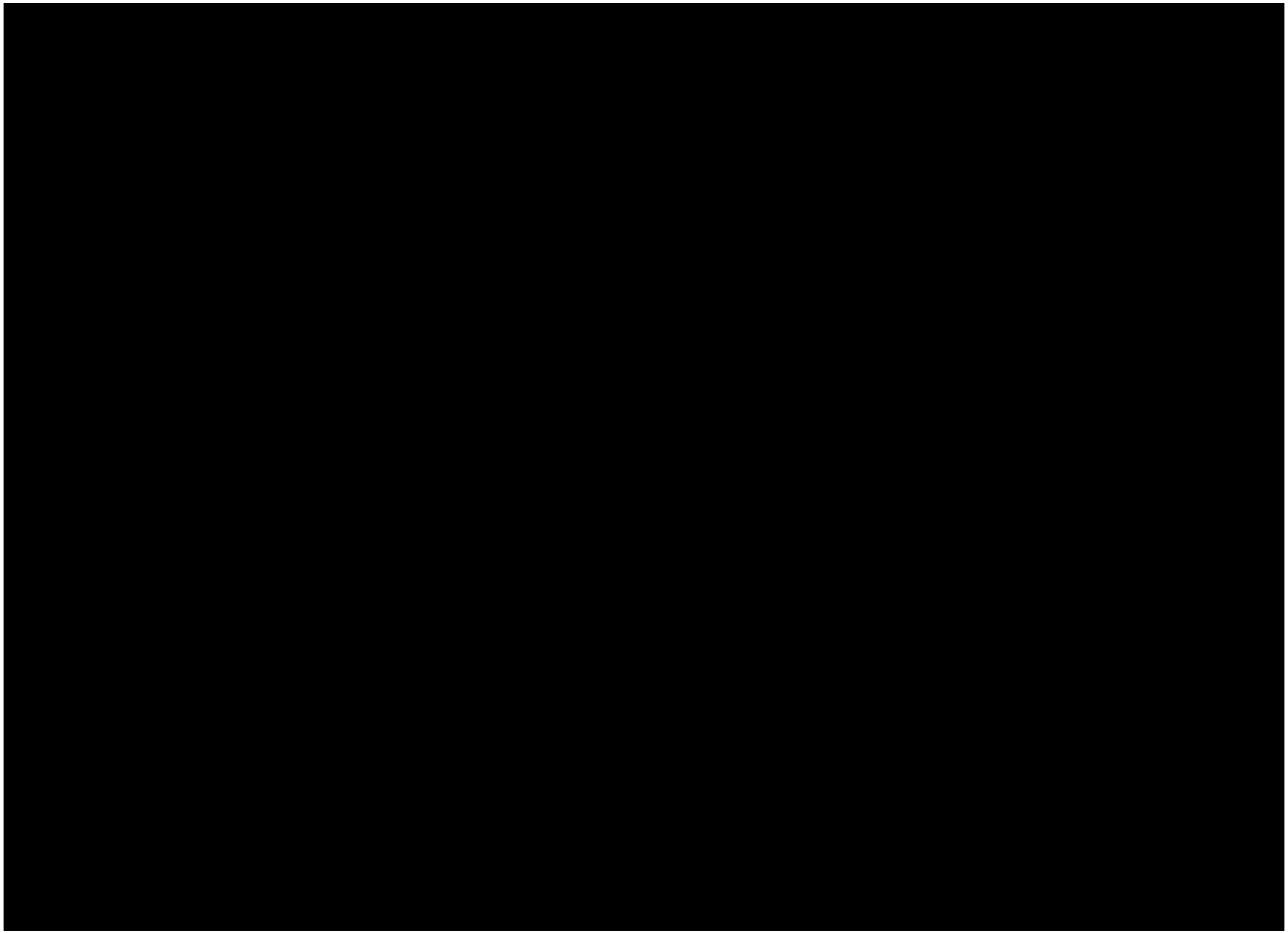
With approval from the Sponsor or Sponsor's representative, sites will be permitted to conduct remote visits if the patient is unable to travel to the site for an in-person visit or if the site is unable to schedule an in-person visit. However, all Screening and Baseline (Visit 2) assessments must be performed in person.

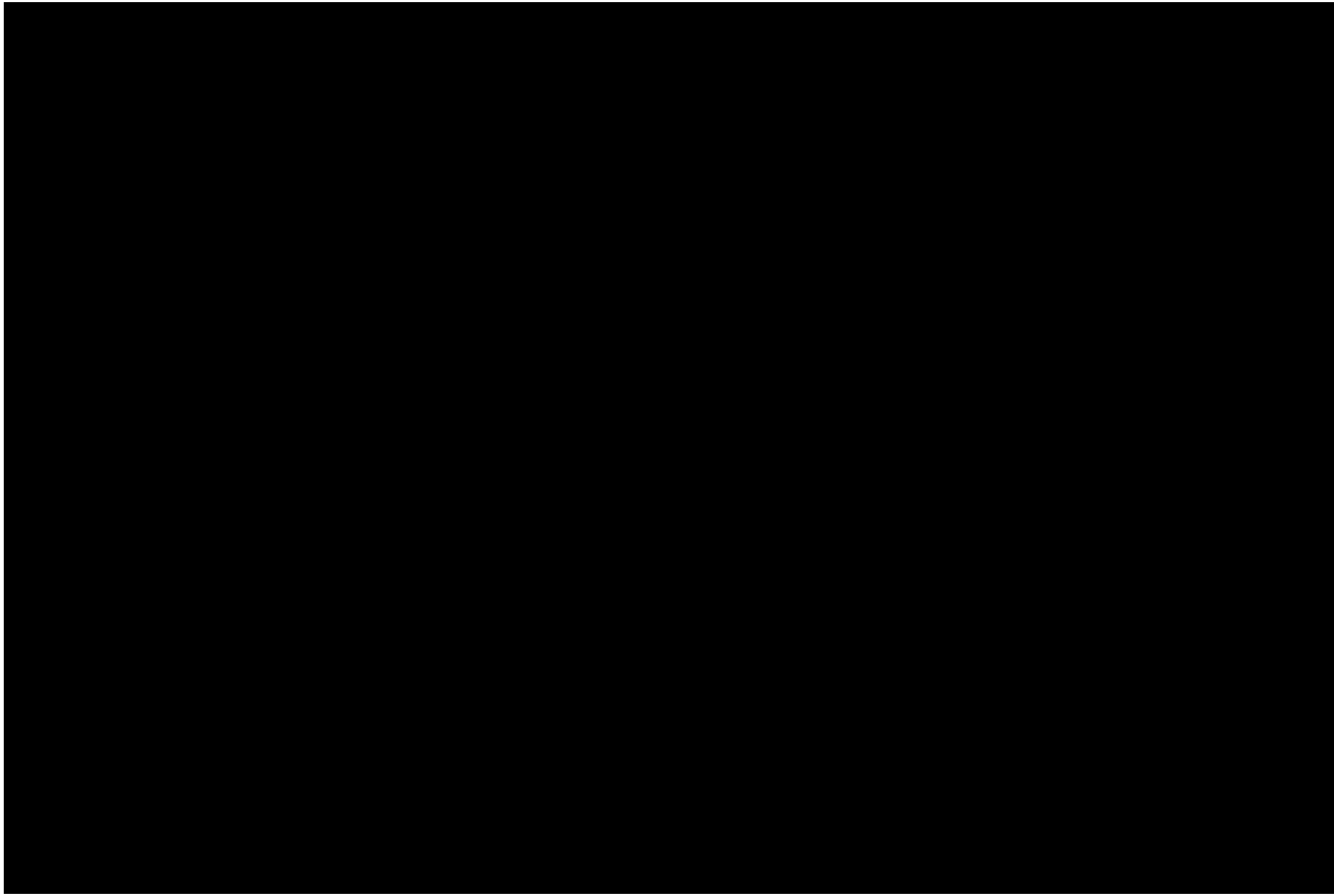
A patient will be defined as a treatment completer if the patient completed the double-blind treatment period (all scheduled visits up to and including Visit 8).

Safety Follow-up Period (2 Weeks)

All patients should return to the clinic for the Safety Follow-up Visit approximately 2 weeks after Visit 8/ET.

The Schedule of Evaluations for this Study is in Table 2-1.





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3. STUDY OBJECTIVES

3.1 Primary Efficacy Objective

Following Protocol Amendment 2.0, the primary objective of this study is to confirm the efficacy of lumateperone 42 mg administered orally once daily compared with that of placebo as measured by mean change from baseline to Day 43 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score in patients with MDEs associated with bipolar depression with mixed features or MDD with mixed features.

Based on the primary efficacy objective, this study will evaluate the efficacy of lumateperone 42 mg based on the following three sets of patients:

1. All patients randomized after Protocol Amendment 2.0, which includes all patients associated with bipolar depression with mixed features and all patients associated with MDD with mixed features;
2. All patients with bipolar disorder (I or II) with mixed features randomized after Protocol Amendment 2.0;
3. All patients with MDD with mixed features.

3.2 Secondary Efficacy Objectives

3.2.1 Key Secondary Efficacy Objective

Following Protocol Amendment 2.0, the key secondary efficacy objective of this study is to confirm the efficacy of lumateperone 42 mg administered orally once daily compared with that of placebo as measured by mean change from baseline to Day 43 in the Clinical Global Impression Scale-Severity (CGI-S) score in patients with MDEs associated with bipolar depression with mixed features or associated with MDD with mixed features.

The key secondary efficacy objective will be assessed using the same three sets of patients defined for the primary efficacy objective.

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4. ANALYSIS SETS

4.1 All Enrolled Set

All Enrolled Set will contain all patients who signed the informed consent form (ICF) for the study.

4.2 All Patients Randomized Set

All Patients Randomized Set will contain all patients who signed the informed consent and were randomized to study drug.

4.3 Safety Analysis Set

Safety Analysis Set will contain all patients who received at least 1 dose of study drug.

4.4 Intent-to-Treat Analysis Set

Intent-to-treat (ITT) Analysis Set will contain all randomized patients who received at least 1 dose of study drug and who had a non-missing (pre-dose) baseline assessment and at least 1 non-missing post-baseline assessment of MADRS total score.

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5. PATIENTS DISPOSITION

The number of patients in the All Patients Randomized Set, Safety Analysis Set, mITT Analysis Set, bITT Analysis Set and ITT Analysis Set will be summarized by treatment group and study site. patients in the All Enrolled Set will only be summarized overall by study site.

Screen failures (ie, patients who are screened but not randomized) and the associated reasons for failure to be randomized will be tabulated overall for all screened patients. The number and percentage of patients who complete the DBTP, patients who prematurely discontinue from the DBTP and patients who enter the SFUP, patients who complete the SFUP, patients who discontinue from the SFUP will be presented by treatment group for the Safety Analysis Set as outlined in Table 2-2. The reasons for premature discontinuation during the DBTP and SFUP as recorded on the disposition pages of the electronic case report forms (eCRFs) will be summarized (number and percentage) by treatment group for the Safety Analysis Set as outlined in Table 2-2.

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7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (eg, age, sex, race, ethnicity, weight, body mass index calculated as weight [kg]/(height [m])^2) and other baseline characteristics will be summarized by treatment group and by overall for the Safety, and ITT Analysis Sets.

Demographic and baseline characteristics will also be summarized separately for patients randomized before Protocol Amendment 2.0 in the Safety and ITT Analysis Sets, for patients randomized after Protocol Amendment 2.0 in the Safety and mITT Analysis Sets, for two subpopulations of bipolar disorder with mixed features and MDD with mixed features in the mITT Analysis Set, and for patients in the bITT Analysis Set.

Medical and surgical history/physical findings will be summarized by treatment group, system organ class (SOC), and preferred term (PT) separately for patients randomized before Protocol Amendment 2.0, and for patients randomized after Protocol Amendment 2.0 separately for the Safety Analysis Set. Bipolar and psychiatric diagnosis and history will be summarized by treatment group and by overall for the Safety Analysis Set and will include current diagnosis, whether the current major depressive episode has psychotic features or whether patient meets criteria for anxious distress, age of patient at first diagnosis of bipolar disorder or MDD, number of lifetime depressive and manic/hypomanic/mixed episodes, number of depressive and manic/hypomanic/mixed episodes within the past year, whether and how many times patient has been hospitalized for any psychiatric related issues.

Baseline efficacy parameters will be summarized by treatment group for patients randomized before Protocol Amendment 2.0 in the ITT Analysis Set, for patients in the mITT Analysis Set and for patients in the bITT Analysis Set. Baseline efficacy parameters will also be summarized by treatment group for patients randomized after Protocol Amendment 2.0, and for two subpopulations of bipolar disorder with mixed features and of MDD with mixed features in the ITT Analysis Set.

Prior medication is defined as any medication which started and stopped before the date of the first dose of double-blind study drug. *Prior Concomitant medication* is defined as any medication which started before the date of the first dose of double-blind study drug and stopped or is ongoing after the date of the first dose of double-blind study drug. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of double-blind study drug and on or before the date of the last dose of double-blind study drug. The *World Health Organization (WHO) Drug Dictionary*, version MAR21 or newer, will be used to code medications.

Prior medication, prior concomitant medication, and concomitant medication will be summarized by treatment group and Anatomical Therapeutic Chemical (ATC) code and preferred term for the Safety Analysis Set as outlined in Table 2-2. Each patient will be counted only once for each ATC code and preferred term.

Any concomitant medication started after the date of the last dose of double-blind study drug will not be included in the summary but will be included in the patient data listings.

Prior medication, prior concomitant medication, concomitant medication, and prior concomitant or concomitant use of Zolpidem and other protocol permitted rescue medication during the study will be summarized by treatment group for patients randomized before Protocol Amendment 2.0, for patients randomized after Protocol Amendment 2.0 and for two subpopulations of bipolar disorder with mixed features and of MDD with mixed features in the Safety Analysis Set.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Extent of Exposure

Exposure to study drug during the DBTP will be based on treatment duration, calculated as the number of days from the date of first dose of double-blind study drug to the date of last dose of double-blind study drug, inclusive. Descriptive statistics (number of patients, mean, standard deviation (SD), median, minimum, and maximum) will be presented by treatment group for the Safety Analysis Set as outlined in Table 2-2.

Patient-years during the DBTP, defined as total exposure to study drug in years, will be summarized by treatment group.

8.2 Treatment Compliance

Dosing compliance for the DBTP is defined as the number of capsules actually taken by a patient during that phase divided by the number of capsules prescribed to be taken during the DBTP multiplied by 100. The total number of capsules actually taken during the DBTP is calculated as the sum of capsules taken during the DBTP as obtained from the study drug record. The number of capsules prescribed to be taken for the DBTP is calculated by multiplying the number of days in the DBTP by the number of capsules prescribed per day.

Descriptive statistics for study drug compliance will be presented by treatment group for the entire DBTP for the Safety Analysis Set as outlined in Table 2-2.

9. EFFICACY ANALYSES

All efficacy analyses will be performed in the following analysis sets: the mITT Analysis Set, the patients with bipolar disorder with mixed features in the mITT Analysis Set, the patients with MDD with mixed feature in the mITT Analysis Set, and the bITT Analysis Set. Baseline for efficacy parameters will be defined as the last non-missing efficacy measurement prior to the first dose of double-blind study drug. All statistical hypothesis tests will be performed at the 2-sided significance level of 5% for main effects. All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

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The efficacy analyses will be performed based on the treatment to which the patient is randomized regardless of the actual treatment received.

The efficacy analyses of MADRS assessments will be based on the rater-administered MADRS.

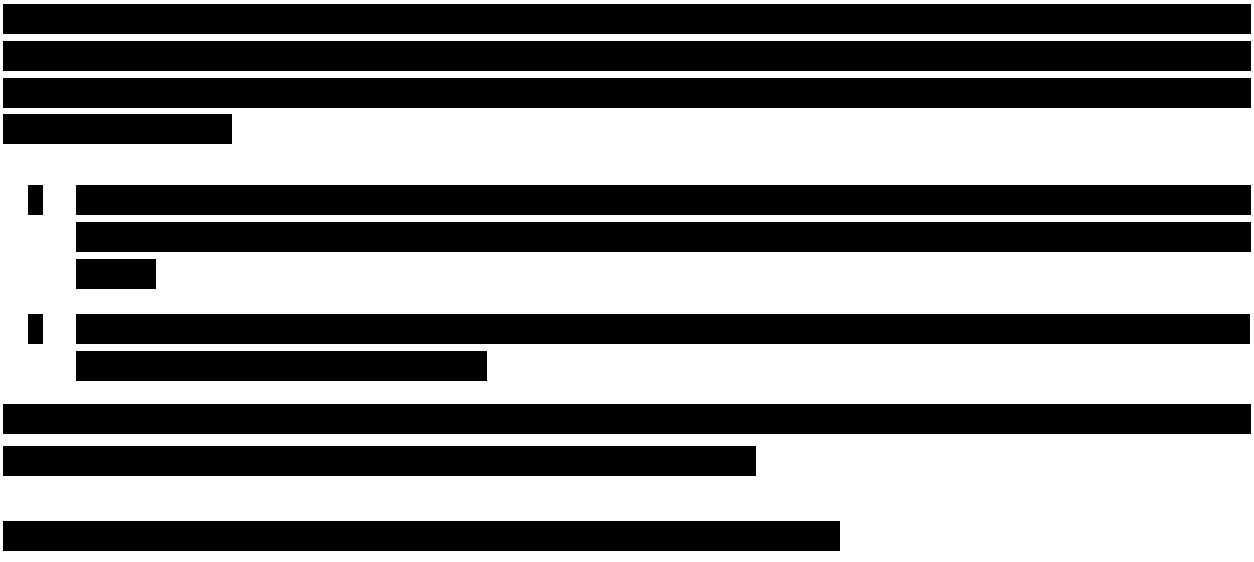
9.1 Primary Efficacy Parameter

The primary efficacy parameter will be the change from baseline in MADRS total score at the end of Week 6 (Day 43). The MADRS contains 10 items that assess depression, with scores for each item ranging from 0 (absence of symptoms) to 6 (symptoms of maximum severity). The MADRS total score is the sum of the 10 individual items.

The primary efficacy analysis will be performed based on the mITT Analysis Set using the mixed model with repeated measures (MMRM) with terms for treatment, pooled study site, stratification variable (bipolar I, bipolar II, or MDD), visit, baseline, and treatment-by-visit and baseline-by-visit interactions. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward et al, 1997). This analysis will only use the observed post-baseline scores without imputation of missing values. The treatment difference for lumateperone 42 mg vs placebo will be estimated and reported along with the corresponding 95% CI and p-value.

In the case that the MMRM with unstructured covariance fails to converge then the Fisher scoring algorithm will be used to provide better initial values of the covariance parameters. In the rare event that model still does not converge after using those initial values, the following alternative structures will be attempted in the specified order until convergence is achieved: heterogeneous Toeplitz structure (TOEPH), heterogeneous autoregressive(1) (ARH(1)), heterogeneous compound symmetry (CSH), No Diagonal Factor Analytic (FA0(q), with q equal to the number of time points), Toeplitz structure (TOEP), autoregressive(1) (AR(1)), and compound symmetry (CS).

The primary efficacy analysis will also be performed based on subpopulation of patients associated with bipolar depression with mixed features and patients associated with MDD with mixed features in the mITT Analysis Set. The same MMRM described above will be applied to subpopulation of bipolar disorder and subpopulation of MDD without the stratification at screening as a factor.



9.2 Secondary Efficacy Parameters

The key secondary efficacy parameter will be the change from baseline to Day 43 in CGI-S score. The key secondary efficacy analysis will be performed based on the mITT Analysis Set using a MMRM similar to those for the primary efficacy parameter. The treatment difference for lumateperone 42 mg vs placebo will be estimated and reported along with the corresponding 95% CI and p-value.

The key secondary efficacy analysis will also be performed based on subpopulation of patients associated with bipolar depression with mixed features and patients associated with MDD with mixed features in the mITT Analysis Set. The same MMRM described above will be applied to the subpopulation of bipolar disorder and the subpopulation of MDD without the stratification at screening as a factor.

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9.3 Additional Efficacy Parameters

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To examine the consistency of the treatment effect of lumateperone vs placebo based on the change from baseline to Day 43 in MADRS total score across demographic and baseline characteristic subgroup categories, subgroup analyses will be performed whenever applicable based on the mITT Analysis Set, the subpopulation of bipolar disorder with mixed features in the mITT Analysis Set, and the subpopulation of MDD with mixed features in the mITT Analysis Set for the following:

- Region (US; Non-US)
- Baseline disease severity (Baseline MADRS total score < 32; Baseline MADRS total score ≥ 32)
- Sex (Male; Female)
- Age group (≤ 40 years; > 40 years)
- Race group (White; Non-White)

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Exploratory analysis of the primary endpoint will be performed in the subgroups of bipolar I and bipolar II of the mITT Analysis Set.

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Descriptive statistics (n, mean, SD, minimum, median, and maximum) and change from baseline value of the MADRS total score and CGI-S score will be presented by treatment group at each assessment point and performed for patients randomized before Protocol Amendment 2.0 in the ITT Analysis Set.

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10. SAFETY ANALYSES

The safety analysis will be performed as outlined in Table 2-2 based on the Safety Analysis Set. Safety variables will include adverse events (AE), clinical laboratory, vital signs, and ECG; suicidality as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS); manic symptoms as assessed by the Young Mania Rating Scale (YMRS); and extrapyramidal symptoms (EPS) as assessed by Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS) scales. For each safety parameter, the last assessment made before the first dose of double-blind study drug will be used as the baseline for all analyses of that safety parameter.

10.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities, version 20.1 or newer.

Treatment emergent AEs (TEAE) are defined as any AEs, regardless of the relationship to study drug, that occur or worsen in severity after the first dose of study drug and on or before the date of last dose of study drug plus one day. An event that occurs is referring to an event that did not occur before, or it started 2 days or more after the end date of the previous event for the same preferred term. Severity increases is referring to an increase in severity for a continuous event during the DBTP.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to study drug. If more than 1 AE is coded to the same PT for the same patient, the patient will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to study drug, respectively.

The incidence of common (≥ 5% of patients in any treatment group) TEAEs will be summarized by PT and treatment group and sorted by decreasing frequency for the lumateperone 42 mg group.

The incidence of serious adverse events (SAEs) and of AEs leading to premature discontinuation of study drug will also be summarized by SOC, PT, and treatment group and will be sorted by decreasing frequency for lumateperone 42 mg group. Listings will be presented for patients with SAEs, patients with AEs leading to premature discontinuation of study drug, patients who died (if any) and patients who died (if any) with AEs.

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10.2 Clinical Laboratory Parameters

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for clinical laboratory values (in SI and conventional units) and change from baseline values will be presented by treatment group at each assessment timepoint (including the end of the DBTP) for the following clinical laboratory parameters:

Hematology: Hematocrit, hemoglobin, HbA1c, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocytes, white blood cell count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophils, neutrophils/leukocytes (%), lymphocytes/leukocytes (%), monocytes/leukocytes (%), eosinophils/leukocytes (%), basophils/leukocytes (%), and platelets,

Chemistry: Albumin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, blood urea nitrogen, gamma-glutamyl transferase, calcium, creatinine, glucose, insulin, cholesterol, triglycerides, phosphate, potassium, Prolactin, lactate dehydrogenase, sodium, chloride, total protein, uric acid, creatine phosphokinase, and Thyroid-stimulating hormone (TSH) (reflex T3 and T4),

Urinalysis: Specific gravity, pH, protein, glucose, ketones, nitrates, blood, red blood cells, white blood cells, casts, epithelial cells, crystals, and granulation.

Clinical laboratory values will be considered to be potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 10-2. The number and percentage of patients who have PCS post-baseline clinical laboratory values will be tabulated by treatment group for the DBTP. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least one post-baseline assessment. The numerator is the total number of patients with available non-PCS baseline values and at least one PCS post-baseline value.

A supportive listing of patients with PCS post-baseline values will be provided including the patient ID, baseline, and post-baseline values (including non-PCS values). A listing of all AEs for patients with PCS clinical laboratory values will also be provided.

Shift tables from baseline to end of the DBTP for clinical laboratory parameters will be presented by treatment group for the following categories: low, normal, and high, which are provided by the laboratory vendor.

Criteria for potential Hy's Law cases is defined by a postbaseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 3 \times$ ULN, along with total bilirubin (TBL) $\geq 2 \times$ ULN and a non-elevated alkaline phosphatase (ALP) $< 2 \times$ ULN, all based on blood draws collected within a 24-hour period. Patients who meet the potential Hy's Law criteria during the DBTP will be summarized. Support listings will also be provided.

Table 10-2: Criteria for Potentially Clinically Significant Clinical Laboratory Tests

Laboratory Parameter	*SI Unit*	*Conversion Factor*[a]	*Conventional Unit*	*PCS Criteria*[b] *Low Values*	*PCS Criteria*[b] *High Values*
Hematology					
Hemoglobin	g/L	0.1	g/dL	≤ 0.9 × LLN	—
Hematocrit	%	1	%	≤ 0.9 × LLN	—
Abs Neutrophils (ANC)	10^9/L	1	10^9/L	< 1.0	—
Platelet count	10^9/L	1	10^9/L	≤ 75	≥ 700
White cell count	10^9/L	1	10^9/L	≤ 2.5	≥ 15
Chemistry					
Albumin	g/L	0.1	g/dL	< 2.5	
Alkaline phosphatase	U/L	1	U/L	—	≥ 2 × ULN
ALT	U/L	1	U/L	—	≥ 3 × ULN
AST	U/L	1	U/L	—	≥ 3 × ULN
Blood urea nitrogen (BUN)	mmol/L	2.8003	mg/dL	—	≥ 30
Calcium	mmol/L	4.008	mg/dL	< 7	> 12
Chloride	mmol/L	1	mg/dL	< 90	> 115
Total Cholesterol (fasting)	mmol/L	38.6698	mg/dL	—	≥ 300
CPK	U/L	1	U/L	—	≥ 5 × ULN
Creatinine	mcmol/L	0.0113	mg/dL	—	> 1.3 × ULN
Glucose (fasting)	mmol/L	18	mg/dL	< 45	> 160
LDL Cholesterol (fasting)	mmol/L	38.6698	mg/dL	—	> 200
Potassium	mmol/L	1	mEq/L	< 3	> 5.5
Prolactin	mIU/L	21.2766	ng/ml		> 200
Sodium	mmol/L	1	mEq/L	< 130	> 150
Total bilirubin	mcmol/L	0.0585	mg/dL	—	≥ 2 × ULN
Triglycerides (fasting)	mmol/L	88.6	mg/dL	—	≥ 300
Urinalysis					
Protein		—	—	—	At least 2 +
Glucose		—	—	—	At least 2 +
Blood		—	—	—	At least 2 +

a Conversion factor from SI units to traditional units.
b Criteria refer to conventional units.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK=creatine phosphokinase; LLN = lower limit of normal of laboratory reference range; PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal of laboratory reference range.

10.3 Vital Signs

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for vital signs assessments (systolic and diastolic blood pressures, pulse rate, weight, temperature, BMI and waist) and changes from baseline values at each assessment visit and at the end of DBTP will be presented by treatment group. For systolic and diastolic blood pressure and pulse rate, measurements will be measured after at least 5 minutes in the supine position and after at least 2 minutes in the standing position. Descriptive statistics for systolic and diastolic blood pressure and pulse rate in the supine position and in the standing position will be presented separately.

Vital sign values will be considered to be PCS if they meet both the observed value criteria and the change from baseline value criteria that are detailed in Table 10-3. The number and percentage of patients who have PCS post-baseline vital sign values will be tabulated by treatment group for the DBTP. The percentages will be calculated relative to the number of patients who have available baseline values and at least 1 post-baseline assessment. The numerator will be the total number of patients with available baseline values and at least 1 PCS post-baseline value.

A listing of all patients with PCS post-baseline values will be provided and will include the patient ID, baseline, all post-baseline (including non-PCS) value and change from baseline. In addition, a listing of all AEs for patients who had PCS vital sign values will be provided.

The number and percentage of patients with orthostatic hypotension will be provided by treatment group. Orthostatic hypotension is defined as a reduction of ≥ 20 mm Hg in systolic BP or a reduction of ≥ 10 mm Hg in diastolic BP measured when the patient changes from the supine position to the standing position. Standing measurements should be taken after sufficient amount of time has been given to allow the blood pressure to equilibrate in the standing state.

A supportive listing of patients with orthostatic hypotension will be provided including the Patient ID, baseline and post-baseline systolic and diastolic BP values (supine and standing).

Table 10-3: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign, unit	*Flag*	*Criterion Value*[a]	*Change From Baseline*[a]
Systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg[b]	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%

a A post-baseline value will be considered potentially clinically significant if it meets both criterion value and change from baseline value.
b Weight change is relative to baseline.
bpm = beats per minute.

10.4 Electrocardiograms

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for 12-lead ECG assessments (eg, heart rate, QRS duration, PR interval, RR interval, uncorrected QT interval, and corrected QT [QTc] intervals) and changes from baseline values at each assessment visit and at the end of DBTP will be presented by treatment group. QTc interval will be calculated using both Bazett (QTcB = QT/(RR)½) and Fridericia (QTcF = QT/(RR)⅓) corrections; if RR is not available, it will be replaced with 60/heart rate in the correction formula.

ECG parameter values will be considered PCS if they meet or exceed the criterion value or the change from baseline value listed in Table 10-4. The number and percentage of patients who have PCS post-baseline ECG values will be tabulated by treatment group for the DBTP. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 post-baseline assessment for PCS criteria based on the actual values and the percentages will be calculated relative to the number of patients who have available baseline values and at least 1 post-baseline assessment for PCS criteria based on changes. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS post-baseline value.

A listing of all patients with PCS post-baseline values will be provided and will include the patient ID, baseline, all post-baseline (including non-PCS) values, and change from baseline. In addition, a listing showing all AEs that occurred in patients who had post-baseline PCS ECG values will be provided.

A shift table from baseline to the end of study in the overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A listing showing patients with post-baseline clinically significant ECG abnormalities according to the overall interpretation will be provided.

Table 10-4: Criteria for Potentially Clinically Significant Electrocardiographic Values

Parameter	*Unit*	*Criterion Value* [a]	*Change from Baseline* [a]
QRS duration	msec	≥ 150	—
PR interval	msec	≥ 250	—
QTcB	msec	≥ 480	—
QTcB	msec	≥ 500	
QTcF	msec	≥ 480	—
QTcF	msec	≥ 500	
QTcB	msec	---	Increase of >30 and ≤60
QTcB	msec	---	Increase of > 60
QTcF	msec	---	Increase of >30 and ≤60
QTcF	msec	---	Increase of > 60

a A post-baseline value will be considered potentially clinically significant if it meets the criterion value or the change from baseline value.

PCS = potentially clinically significant; QTcB = QT interval/(RR)½; QTcF = QT interval/(RR)⅓.

10.5 Other Safety Parameters

Other safety parameters include the C-SSRS, YMRS, AIMS, BARS and SAS.

10.5.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

The number and percentage of patients with suicidal ideation and suicidal behavior as recorded on the C-SSRS will be summarized by treatment group for lifetime history (assessed at the screening visit), during the DBTP and during the post DBTP. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior will be also presented by treatment group for lifetime history, during the DBTP and during the post DBTP. The baseline of suicidal ideation and suicidal behavior is defined as the last non-missing "since last visit" assessment before the first dose of double-blind study drug. The severity of suicidal ideation will be presented in a decreasing order as below:

- Active suicidal ideation with specific plan and intent
- Active suicidal ideation with some intent to act, without specific plan
- Active suicidal ideation with any methods (not plan) without intent to act
- Non-specific active suicidal thoughts
- Wish to be dead

The severity of suicidal behavior will also be presented in a decreasing order as below:

- Completed Suicide
- Actual attempt

- Interrupted attempt
- Aborted attempt
- Preparatory acts or behavior

For the distribution of responses, each patient will be counted only once under the most severe category across all visits during the specific period for suicidal ideation and separately for suicidal behavior.

Supportive listing for patients with suicidal ideation or with suicidal behavior during the study will be provided and will include the Patient ID, treatment group, visit number, lifetime history, and post-baseline values for each patient. A listing of all AEs for patients with suicidal ideation or suicidal behavior will also be provided.

In addition, the number and percentage of patients with the following emergence of suicidal ideation or of suicidal behavior during the DBTP will be summarized by treatment group:

- Emergence of suicidal ideation (no suicidal ideation at Baseline, and any type of suicidal ideation post-Baseline)
- Emergence of serious suicidal ideation (no suicidal ideation at Baseline, and any serious suicidal ideation [Active suicidal ideation with specific plan and intent, or Active suicidal ideation with some intent to act, without specific plan] post-Baseline)
- Worsening of suicidal ideation (most severe suicidal ideation post-Baseline was more severe than it was at Baseline)
- Emergence of suicidal behavior (no suicidal behavior at Baseline, and any type of suicidal behavior post-Baseline)

10.5.2 Young Mania Rating Scale (YMRS)

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for YMRS assessments and changes from baseline values at each assessment visit and at the end of the DBTP will be presented by treatment group.

10.5.3 Abnormal Involuntary Movement Scale (AIMS)

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for AIMS assessments and changes from baseline values at each assessment visit and at the end of the DBTP will be presented by treatment group.

10.5.4 Barnes Akathisia Rating Scale (BARS)

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for BARS assessments and changes from baseline values at each assessment visit and at the end of the DBTP will be presented by treatment group.

10.5.5 Simpson Angus Scale (SAS)

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for SAS assessments and changes from baseline values at each assessment visit and at the end of the DBTP will be presented by treatment group.

11. INTERIM ANALYSIS

No interim analysis is planned for this study.

12. SAMPLE SIZE CONSIDERATION

The sample size for this study is based on assumed effect size (treatment group difference relative to SD) of 0.37. This assumed effect size of 0.37 for lumateperone is based on a treatment difference of 3.3 units with a common pooled SD of 9 for the primary efficacy parameter, change from baseline to Day 43 in MADRS total score. A sample size of 350 patients (175 per treatment group) will be needed to be enrolled after Protocol Amendment 2.0 to provide 90% statistical power for primary analysis based on an MMRM using a simulation method (Lu 2012). The simulation assumed a correlation of 0.7 between the repeated measures and a dropout rate of 10% based on historical data.

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13. STATISTICAL SOFTWARE

Statistical analyses of efficacy and safety parameters will be performed using version 9.4 of SAS.

14. DATA HANDLING CONVENTIONS

14.1 Visit Time Windows

Table 14-1 presents the visits assigned for efficacy and safety analyses and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 14-1: Windows for Analysis Visits

Derived Visit	Scheduled Visit (Day[a])	Window[b]
Baseline	Week 0 (Day 1)	Days ≤ 1
Week 1	Week 1 (Day 8)	Days [2, 11]
Week 2	Week 2 (Day 15)	Days [12, 18]
Week 3	Week 3 (Day 22)	Days [19, 25]
Week 4	Week 4 (Day 29)	Days [26, 32]
Week 5	Week 5 (Day 36)	Days [33, 39]
Week 6	Week 6 (Day 43)	Days ≥ 40 and within double-blind treatment period
End of Double-blind Treatment Period	Final or termination visit during the double-blind treatment period	
Week 8	Week 8 (Day 57)	Within the safety follow-up period

a. Relative to the date of the first dose of double-blind study drug. For example, Day 1 = the date of the first dose of double-blind study drug.
b. Visit day is calculated as visit date − date of the first dose of double-blind study drug + 1 if the visit date is on or after the date of the first dose of double-blind study drug. Otherwise, it is calculated as visit date – date of the first dose of double-blind study drug.

If a patient has 2 or more non-missing assessment within the same window, the assessment closest to the target day will be used for analysis; if the 2 closet assessments are equidistant to the target day, the later one will be used for analysis.

14.2 Derived Efficacy Variables

The MADRS total score at a particular visit will be calculated using (sum of scores from non-missing items) × (total number of items) / (number of non-missing items) only if the number of missing items is ≤ 2. Otherwise, the MADRS total score will be set equal to missing.

14.3 Repeated or Unscheduled Assessments of Safety Parameters

If a patient has repeated assessments before the first dose of double-blind study drug, then the results from the final non-missing assessment made before the first dose of double-blind study drug will be used as baseline. If end-of-treatment assessments are repeated or if unscheduled visits occur, the last non-missing post-baseline assessment will be used as the end-of-treatment assessment for generating summary statistics. However, all post-baseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

14.4 Missing Date of the Last Dose of Study Drug

When the date of the last dose of double-blind study drug in the study is missing for a patient, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts, then the last available dosing date in the DBTP will be used as the last dose date.

14.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE that occurred before the date of the first dose of double-blind study drug, then a severity of *mild* will be assigned. If the severity is missing for an AE that occurred on or after the date of the first dose of double-blind study drug, then a severity of *severe* will be assigned. The imputed values for severity will be used for the incidence summary; the actual values will be presented in data listings.

14.6 Missing Relationship to Study Drug for Adverse Events

If the relationship to study drug is missing for an AE that occurred after the date of the first dose of double-blind study drug, then a causality of Yes will be assigned. The imputed values for relationship to study drug will be used for the incidence summary; the actual values will be presented in data listings.

14.7 Missing Dates Information for Adverse Events

The following imputation rules apply only to cases in which the start date is incomplete (i.e, partially missing) for AEs and prior/concomitant medications.

14.8 Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of double-blind study drug, the month and day of the first dose of double-blind study drug will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the first dose of double-blind study drug, December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of double-blind study drug, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of double-blind study drug, the day of the first dose of double-blind study drug will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the date of the first dose of double-blind study drug or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of double-blind study drug, the last day of the month will be assigned to the missing day
- If either the year of the incomplete start date is after the year of the date of the first dose of double-blind study drug or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of double-blind study drug, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of double-blind study drug, the date of the first dose of double-blind study drug will be assigned to the missing start date
- If the stop date is before the date of the first dose of double-blind study drug, the stop date will be assigned to the missing start date

14.9 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

14.9.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of double-blind study drug, the month and day of the first dose of double-blind study drug will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the first dose of double-blind study drug, *December 31* will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of double-blind study drug, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of double-blind study drug, the day of the first dose of double-blind study drug will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the date of the first dose of double-blind study drug or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of double-blind study drug, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of double-blind study drug or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of double-blind study drug, the first day of the month will be assigned to the missing day

14.9.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of double-blind study drug, the month and day of the last dose of double-blind study drug will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the last dose of double-blind study drug, *December 31* will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the last dose of double-blind study drug, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of double-blind study drug, the day of the last dose of double-blind study drug will be assigned to the missing day
- If either the year of the incomplete stop date is before the year of the date of the last dose of double-blind study drug or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of double-blind study drug, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of double-blind study drug or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of double-blind study drug, the first day of the month will be assigned to the missing day.

15. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

There are no changes to the analyses specified in the protocol.

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