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Title: A Randomized, Double-Blind, Placebo-controlled Multicenter Study to Assess the Efficacy and Safety of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder

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Statistical Analysis Plan

ITI-007-502

A Randomized, Double-Blind, Placebo-controlled Multicenter Study to Assess the Efficacy and Safety of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder

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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

ADT	antidepressant therapy
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATRQ	Antidepressant Treatment Response Questionnaire
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CGI-S	Clinical Global Impression Scale-Severity
CPK	creatine phosphokinase
CSFQ	Changes in Sexual Functioning Questionnaire
ECG	electrocardiogram
eCRF	electronic case report form
ET	Early Termination
HbA1c	hemoglobin A1c
ICE	intercurrent event
LLN	lower limit of normal
MADRS	Montgomery-Åsberg Depression Rating Scale
MAR	Missing at random
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MINI	MINI International Neuropsychiatric Interview
MMRM	mixed-effects model for repeated measures
MNAR	Missing not at random
OH	orthostatic hypotension
PCS	potentially clinically significant
PK	pharmacokinetic
QIDS-SR-16	Quick Inventory of Depressive Symptomatology-Self- Report-16 item
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
SFU	Safety Follow-up
SOC	system organ class
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WHO	World Health Organization

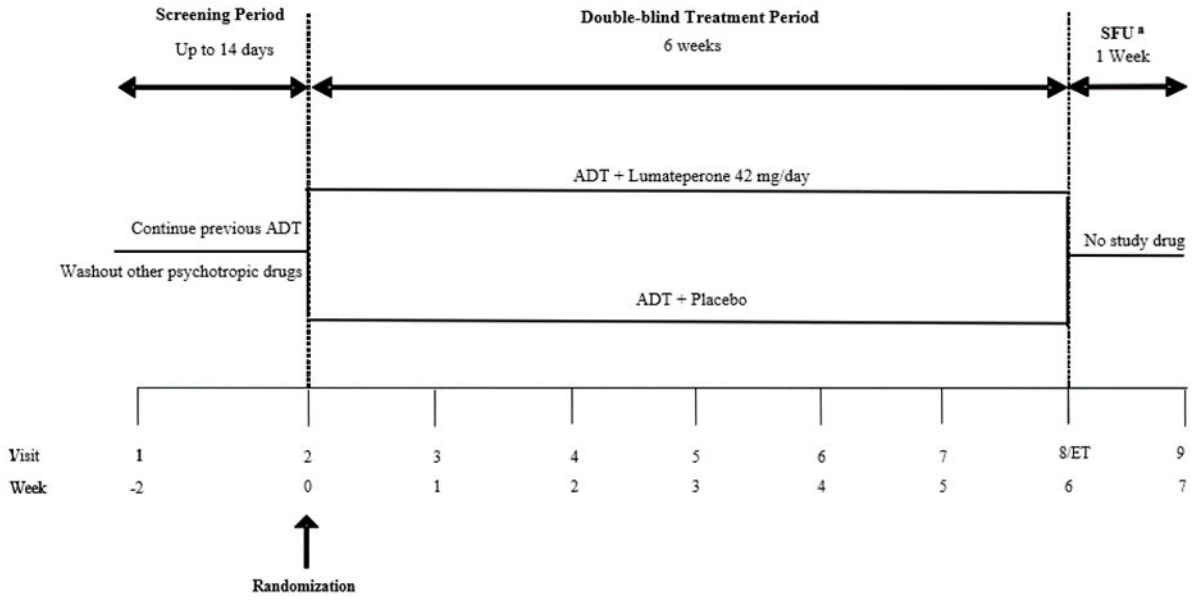
2. INTRODUCTION

This statistical analysis plan (SAP) provides the technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the Original Protocol (dated 18 Aug 2021) for Study ITI-007-502. Specifications of tables, figures, and data listings are contained in a separate document. [redacted]

Study ITI-007-502 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of lumateperone as adjunctive therapy for the treatment of patients with major depressive disorder (MDD). This study will be performed at approximately 60 study centers in the United States and globally.

The study design schematic is provided in Figure 2-1. The Schedule of Evaluations is presented in Table 2-1. Detailed descriptions of the procedures conducted at each study visit are provided in Section 8.5 of the Original Protocol.

Figure 2-1: Schematic of Study Design



ADT = antidepressant treatment; ET = early termination; SFU = Safety Follow-up.
[a] Eligible patients who complete 6 weeks of double-blind treatment and provide informed consent to rollover into the Open-label Safety Study will not enter the SFU Period.

Screening Period (up to 2 Weeks)

Potential patients will be evaluated during a Screening Period lasting up to 14 days. With approval from the Sponsor or designee, short extensions to the Screening Period may be granted in exceptional circumstances. After obtaining written informed consent, diagnostic interviews, determination of inadequate response to current antidepressant therapy (ADT), and physical examinations will be conducted, vital signs and ECGs will be assessed, and blood samples will be

collected for laboratory assessments. Patients considered potentially eligible will be required to continue their current ADT but will be required to discontinue other psychotropic drugs.

Evaluation of diagnostic validity and eligibility of each patient will be undertaken by the Sponsor or designee.

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

Double-blind Treatment Period (6 Weeks)

Patients will self-administer his/her first dose of study treatment on the evening of the Baseline visit (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 Double-blind Treatment Period. Antidepressant treatment will also continue as previously prescribed. The dose and frequency of ADT must not change during the Screening Period or for the duration of the Double-blind Treatment Period.

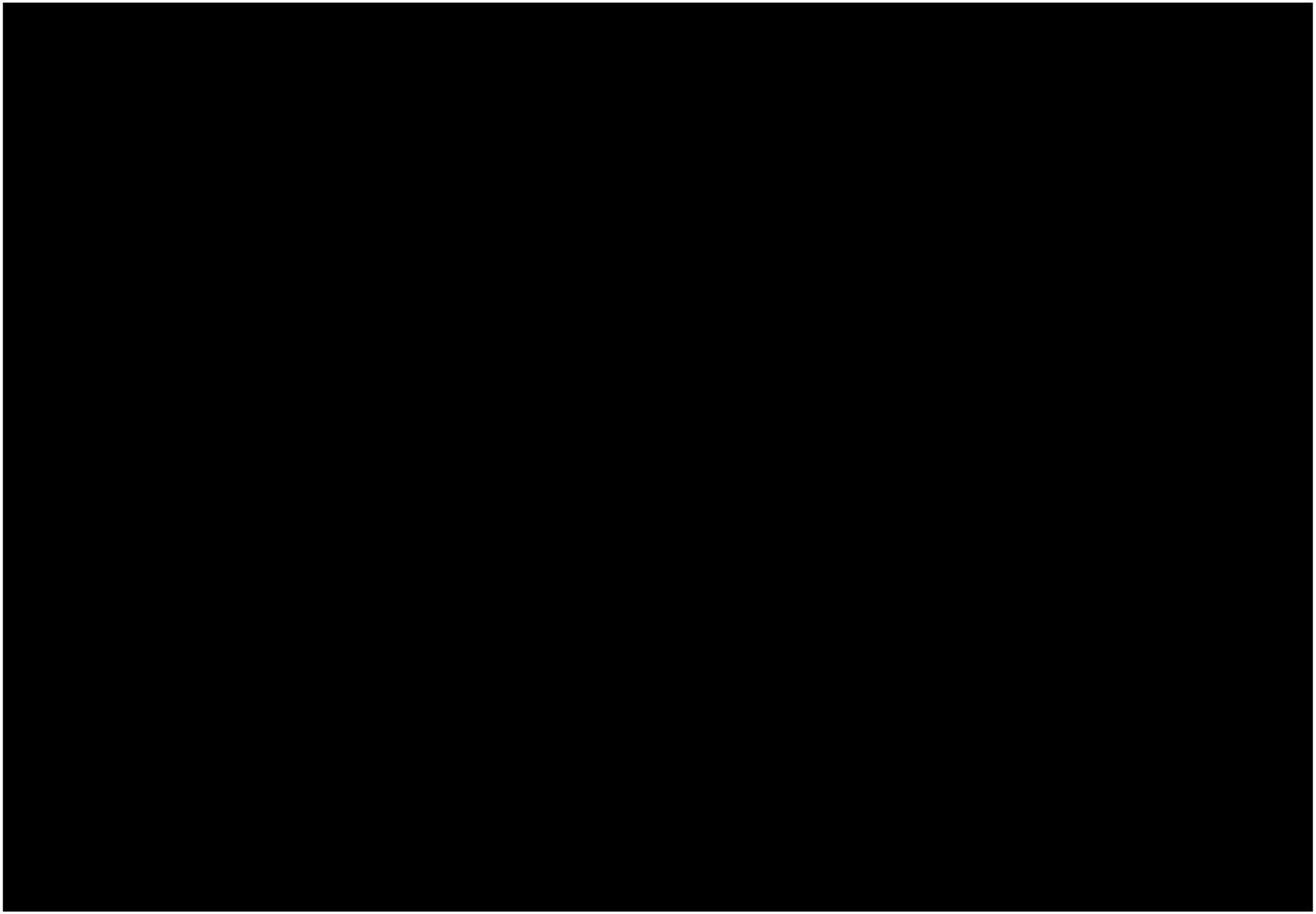
Patients will attend outpatient study visits on Days 8, 15, 22, 29, 36, and 43. With approval from the Sponsor or designee, sites will be permitted to conduct remote visits if a site-based visit is not feasible. However, all Screening (Visit 1) and Baseline (Visit 2) assessments must be performed in person.

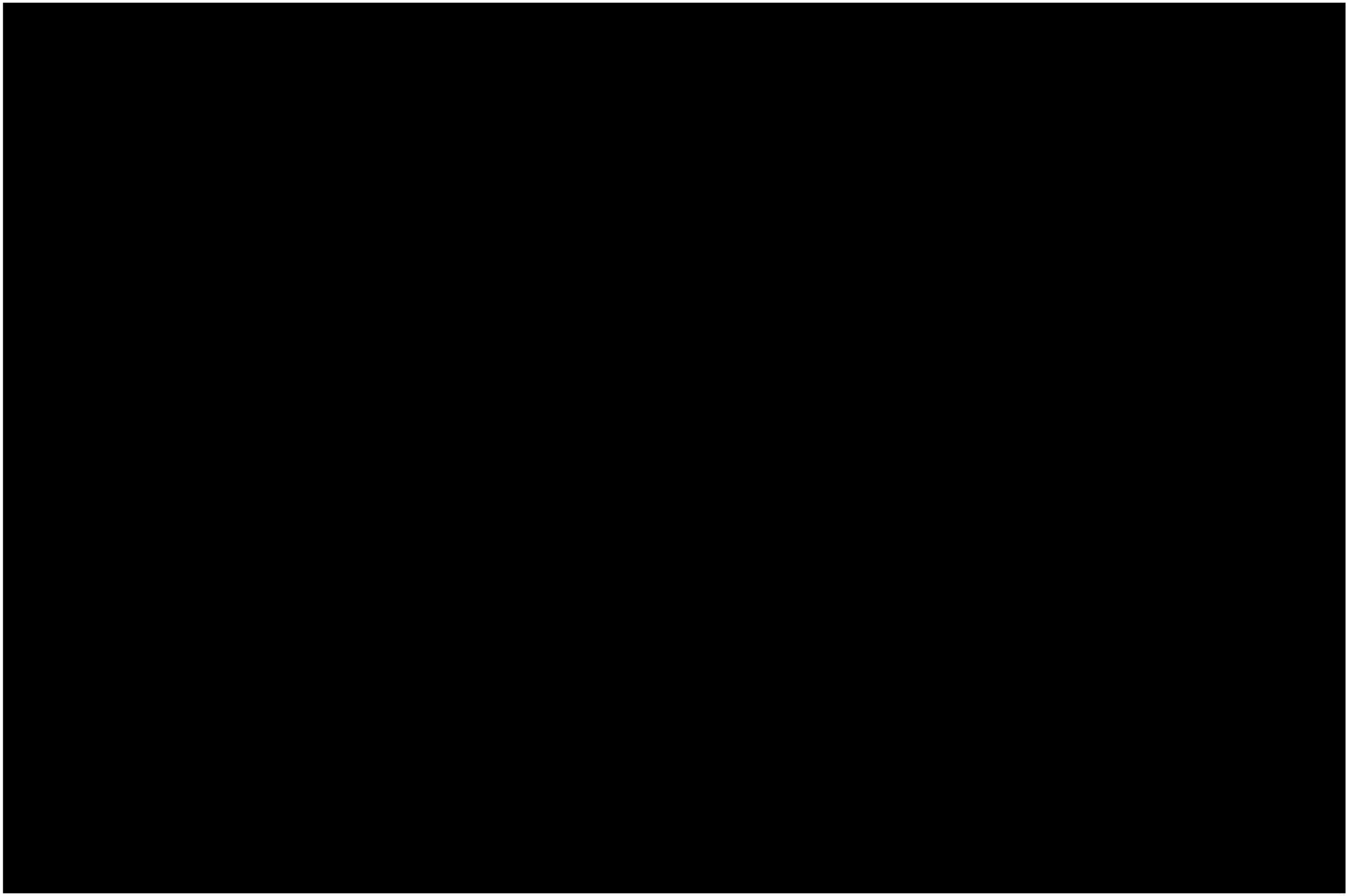
A patient will be defined as a treatment completer if the patient completes the Double-blind Treatment Period (all scheduled visits up to and including Visit 8). Patients who withdraw prematurely should be seen for an Early Termination (ET) visit as soon as possible and will also be asked to return for a Safety Follow-up (SFU) Visit approximately one week after Visit 8/ET.

Safety Follow-up Period (1 Week)

All patients should return to the clinic for the SFU Visit approximately 1 week after Visit 8/ET. Any ongoing AEs at the SFU Visit must be followed until resolution, until the AE stabilizes, until it is determined to be not clinically significant, or until the patient is lost to follow-up.

Patients who complete the 6-week Double-blind Treatment Period, who are considered to be appropriate by the Investigator, and who meet eligibility criteria may enroll in the 6-month Open-label Safety Study at the Visit 8/Week 6 visit. This rollover visit to the Open-label Safety Study at Visit 8/Week 6 must be in person. A patient who enters the Open-label Safety Study will not have a SFU visit (Visit 9/Week 7).





3. STUDY OBJECTIVES

3.1 Efficacy Objectives and Estimands

3.1.1 Primary Objective

The primary efficacy objective of this study is to evaluate the efficacy of lumateperone 42 mg administered once daily compared to placebo as adjunctive treatment to ADT in patients with MDD who have an inadequate response to ongoing ADT as measured by change from baseline to Day 43 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

The hypothetical estimand strategy is considered to address the primary objective and it is described as follows:

- Target Population: Patients with MDD who have an inadequate response to ongoing ADT
- Treatment: Lumateperone 42 mg vs placebo as adjunctive therapy to existing ADT
- Variable (Endpoint): Change from baseline to Day 43 in the MADRS total score
- Intercurrent events (ICE) and corresponding strategies (see Table 3-1)
- Summary measure: Difference in treatment means between lumateperone 42 mg and placebo.

The primary estimand, based on the hypothetical strategy defined by the above 5 attributes, quantifies the efficacy of lumateperone vs placebo with regard to the premature discontinuation of study treatment as adjunctive to existing ADT and in the absence of newly introduced ADT in patients after randomization. This strategy accounts for use of the primary efficacy data based on MADRS assessments while patients who prematurely discontinue are assumed to be on study treatment for the entire 6 weeks treatment period and eliminating potential effect of newly initiated ADT.

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[redacted]

[redacted]

3.1.2 Key Secondary Efficacy Objective

The key secondary efficacy objective of this study is to evaluate the efficacy of lumateperone 42 mg administered once daily compared to placebo as adjunctive treatment to antidepressant therapy in patients with MDD who have an inadequate response to ongoing ADT as measured by change from baseline to day 43 in the Clinical Global Impression Scale-Severity (CGI-S).

The proposed estimand strategy to address the secondary objective will be based on hypothetical strategy and will be similar as the proposed primary estimand based on the 5 attributes described in Section 3.1.1, except the variable and ICE will be based on CGI-S score instead of MADRS total score. [redacted]

4. ANALYSIS POPULATIONS

4.1 Randomized Population

The Randomized Population includes all patients who were randomly assigned to study treatment.

4.2 Safety Population

The Safety Population includes all randomized patients who received at least 1 dose of study treatment.

4.3 Intent-to-Treat (ITT) Population

The ITT Population includes all randomized patients who received at least 1 dose of study treatment and have a baseline MADRS total score.

4.4 Modified Intent-to-Treat (mITT) Population

The mITT Population includes all randomized patients who received at least 1 dose of study treatment, have a baseline MADRS total score, and who have at least one on-treatment, postbaseline MADRS total score. On-treatment MADRS assessments are those performed no later than 3 days after the last dose of study treatment.

5. SUBJECT DISPOSITION

The number of patients in each study analysis population will be summarized by treatment group and study center as follows:

- The number of patients who were screened will be summarized overall by study center.
- The number of patients in the Safety, ITT and mITT Populations will be summarized overall and by treatment group and study center.

In addition, the number and percentage of patients who completed the Double-blind Treatment Period and who prematurely discontinue from the Double-blind Treatment Period will be summarized overall, by treatment group, and by reasons for premature discontinuation for the Safety, ITT, and mITT Populations, respectively. The number and percentage of patients with reasons for premature discontinuation from the Double-blind Treatment Period as recorded on the termination page of the eCRF will be provided by treatment group for the Safety, ITT, and mITT Populations respectively.

[redacted]

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic parameters as allowed by local country legislation (eg, age, sex, race, and ethnicity) and other baseline characteristics (eg, weight and body mass index) will be summarized by treatment group for the Safety, ITT and mITT Populations.

Prior medical and surgical history will be summarized by treatment group for the Safety Population.

Baseline efficacy parameters including MADRS total score, CGI-S score, and CSFQ-14 total score, will be summarized by treatment group for the mITT Populations.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Extent of Treatment Exposure

Exposure to study treatment for the Safety Population will be summarized using treatment duration, calculated as the number of days from the date of the first dose of double-blind study treatment taken to the date of the last dose taken, inclusive. The number and percentage of patients with treatment duration of ≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 35 days, and ≥ 42 days will be also provided by treatment group, respectively.

8.2 Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the total number of capsules of study treatment taken by a patient during the treatment period divided by the number of capsules of study treatment that were expected to be taken during the treatment period multiplied by 100.

The total number of capsules taken during the treatment period will be calculated from the study treatment record. Descriptive statistics for study treatment dosing compliance together with compliance category will be summarized by treatment group for the Safety Population.

8.3 Prior and Concomitant Medication

The latest version of the *World Health Organization Drug Global* (WHODG) will be used to code prior, prior concomitant, and concomitant medications. *Prior medication* is defined as any medication started and stopped before the date of the first dose of double-blind study treatment. A *prior concomitant medication* is any medication that started before the date of the first dose of double-blind study treatment and stopped or is ongoing after the date of the first dose of study treatment. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of double-blind study treatment. Both prior and concomitant medications, including prior concomitant medication use, will be summarized as the number and proportion of patients in each treatment group who received each medication within each therapeutic class (ie, Anatomical Therapeutic Chemical code, Levels 2, 3 and 4) and preferred term for the Safety Population. Multiple medications used by a patient will only be counted once.

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

9. EFFICACY ANALYSES

The primary efficacy analyses and [redacted] will be based on the mITT [redacted] Populations, respectively; other efficacy analyses will be based on the ITT Population, unless stated otherwise. The baseline for each specific efficacy endpoint is defined as the last measurement prior to the first dose of randomized treatment. All statistical hypothesis tests will be performed at the 2-sided 5% significance level for main effects. All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

All investigative sites with fewer than 2 mITT patients per treatment group will be pooled as follows: The largest site with fewer than 2 mITT patients per treatment group will be pooled with the smallest site with fewer than 2 mITT patients per treatment group within the same country. If this results in a pooled site still having fewer than 2 mITT patients per treatment group, this site will be pooled together with the next smallest investigative site within the same country. If a pooled site having all patients enrolled from one country still has less than 2 patients in either treatment group, then this pooled site would be included in the site pooling in the country with the second smallest enrollment. Sites with the same number of mITT patients will be ordered in ascending order of their numerical site identification number. This will serve as a tie-breaker rule in case multiple sites have the same number of mITT patients. Should the primary efficacy analysis model present convergence issues, after testing the sequence of correlation structures, then the site effect will be reconsidered and may be dropped from the model. These pooled investigative sites, as determined based on the primary efficacy response variable, will be used for all analyses that has investigative site as a fixed effect in the model. The actual investigative site numbers will be included in the listings.

[redacted]

9.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Day 43 in the MADRS total score.

9.1.1 Primary Efficacy Analysis

The primary efficacy analysis will be assessed for the hypothetical estimand and the data to be included in this primary analysis will be decided by the intercurrent events as described in Table 3-1.

Based on the primary hypothetical estimand strategy which assumes patients are on study treatment up to the primary time point, efficacy data collected after discontinuing study treatment (ie, performed more than 3 days after last dose of study treatment) or after starting new ADT will be set to missing and will not be included in the primary analysis. Instead, these missing data are assumed as missing at random (MAR).

The hypothetical estimand strategy is being considered to address the primary and key secondary efficacy objectives for the proposed 6-week, double-blind, placebo-controlled study in patients with MDD with mixed features. [redacted]

The primary analysis to estimate and compare the treatment effects of lumateperone vs placebo as defined by the primary estimand will be performed using a mixed-effects model for repeated measures (MMRM) method. The model will include the change from baseline in MADRS total score at each study visit as the response variable, and treatment group, study visit, site (or pooled site) as factors and the baseline MADRS total score as covariate, and interaction terms for baseline MADRS total score-by-study visit and treatment group-by-study visit. An unstructured covariance matrix will be used to estimate the correlation among repeated measurements within patient. The Kenward-Roger approximation (Kenward and Roger, 1997) will be used to estimate the denominator degrees of freedom. The mean treatment difference for lumateperone vs placebo will be estimated via contrast based on treatment group and treatment group-by-study visit factors and will be reported along with the corresponding 95% CI and the p-value for superiority testing.

[redacted]

The MMRM is being considered as the statistical model for the estimation of the primary and key secondary estimands to compare the treatment effect between the lumateperone 42 mg group and the placebo group in combination with the fixed-sequence testing procedure (first test for the primary efficacy endpoint and, if significant, then test for the key secondary efficacy endpoint) for the analyses of the primary and key secondary efficacy endpoints for the proposed 6-week double-blind, placebo-controlled studies in patients with MDD with mixed features.

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9.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the change from baseline to Day 43 in the CGI-S score.

9.2.1 Key Secondary Analysis

The key secondary efficacy endpoint will be tested using the same hypothetical estimand strategy as for the primary efficacy endpoint.

The data to be included in the key secondary efficacy analysis will be decided by the intercurrent events as described in Table 9-3.

[redacted]

Based on the key secondary hypothetical estimand strategy which assumes patients are on treatment up to the Day 43 assessment, efficacy data collected after discontinuing study treatment (ie, performed more than 3 days after last dose of study treatment) or after starting new ADT will be set to missing and will not be included in the key secondary analysis. Instead, the missing data are assumed as missing at random.

The key secondary efficacy endpoint will be analyzed using an MMRM method similar to the one specified for the primary efficacy endpoint while substituting MADRS total-score-related variables in the model with the corresponding CGI-S-related ones, such as baseline score and visit-by-baseline score interaction.

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10. SAFETY ANALYSES

Safety analyses will be performed using the Safety Population. The safety parameters will include AEs, clinical laboratory, vital signs, ECG, and EPS (AIMS, BARS, and SAS) and C-SSRS scales. The baseline for each safety endpoint is defined as the last measurement prior to the first dose of randomized treatment.

10.1 Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

An AE will be considered a treatment-emergent AE (TEAE) if it was not present before the first dose of double-blind study treatment or was present before the first dose of double-blind study treatment but increased in severity after the first dose. An AE that occurs more than 1 day after the date of the last dose of double-blind study treatment will not be counted as a TEAE.

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

The incidence of common (≥ 5% of patients in either treatment group) TEAEs will be summarized by preferred term and treatment group.

The number and percentage of patients reporting serious AEs (SAEs) in each treatment group during double-blind treatment period will be tabulated by SOC and preferred term. Also, the number and percentage of patients reporting AEs leading to drug withdrawal in each treatment group will be tabulated by SOC and preferred term. Listings will be presented for patients with SAEs, patients with AEs leading to drug withdrawal, and patients who died (if any).

The incidence of extrapyramidal symptom (EPS) TEAEs will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for lumateperone 42 mg group. The PTs for EPS will be based on broad and narrow Standardised MedDRA Queries (SMQs) as listed in Table 10-1. The analysis for EPS TEAEs based on Broad SMQs will also include the preferred terms listed under Narrow SMQs.

Table 10-1: Preferred Terms for Extrapyramidal Symptoms

Scope	Preferred Terms
Narrow	Akathisia, Athetosis, Ballismus, Buccoglossal syndrome, Chorea, Choreoathetosis, Dopamine, dysregulation syndrome, Dyskinesia, Dyskinesia neonatal, Dyskinesia oesophageal, Grimacing, Oculogyric crisis, Pharyngeal dyskinesia, Protrusion tongue, Rabbit syndrome, Respiratory dyskinesia, Tardive Dopa-responsive dystonia, Dystonia, Dystonic tremor, Early onset primary dystonia, Emprosthotonus, Meige's syndrome, Oculogyric crisis, Opisthotonus, Oromandibular dystonia, Pharyngeal dystonia, Pleurothotonus, Spasmodic dysphonia, Torticollis, Trismus, Writer's cramp, Akinesia, Bradykinesia, Cogwheel rigidity, Freezing phenomenon, Hypertonia, Hypertonia neonatal, Hypokinetic dysarthria, Muscle rigidity, On and off phenomenon, Parkinsonian crisis, Parkinsonian gait, Parkinsonian rest tremor, Parkinsonism, Parkinsonism hyperpyrexia syndrome, Parkinson's disease, Parkinson's disease psychosis, Propulsive gait, Resting tremor.
Broad	**All preferred terms listed under Narrow (above) plus the following:** Extrapyramidal disorder, Hyperkinesia, Hyperkinesia neonatal, Motor dysfunction, Movement disorder, Psychomotor hyperactivity, Restlessness, Abnormal involuntary movement scale, Chronic tic disorder, Complex tic, Drooling, , Muscle twitching, Provisional tic disorder, Secondary tic, Tic, Blepharospasm, Facial spasm, Gait inability, Laryngospasm,, Muscle contractions involuntary, Muscle spasms, Muscle spasticity, Muscle tightness, Muscle tone disorder, Musculoskeletal stiffness, Oesophageal spasm, Oropharyngeal spasm, Posture abnormal, Posturing, Provisional tic disorder, Risus sardonicus, Tongue spasm, Torticollis psychogenic, Uvular spasm, Action tremor, Bradyphrenia, Dysphonia, Fine motor skill dysfunction, Gait disturbance, Hypokinesia, Hypokinesia neonatal, Laryngeal tremor, Micrographia, Mobility decreased, Postural reflex impairment, Postural tremor, Reduced facial expression, Tremor, Tremor neonatal, Walking disability.

10.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in International System of units [SI] and conventional units) and changes from baseline values at each assessment visit and at the end of double-blind treatment period will be summarized by treatment group for the following clinical laboratory parameters:

- **Hematology:** hematocrit; hemoglobin; red blood cell count with indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration); reticulocytes; white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) reported as percent (%) and absolute values; and platelet count.

- **Chemistry:** albumin; alkaline phosphatase; alanine aminotransferase (ALT); aspartate aminotransferase (AST); bilirubin (total, direct); blood urea nitrogen (BUN); calcium; chloride; cholesterol (high-density lipoprotein [HDL] and low-density lipoprotein [LDL] will be calculated and reported); creatinine; creatine phosphokinase; gamma-glutamyl transferase; glucose; insulin; lactate dehydrogenase; phosphate; potassium; prolactin; sodium; triglycerides; total protein; uric acid; HbA1c; and thyroid-stimulating hormone (TSH) (reflex free T3 and free T4).

- **Urinalysis**: pH and specific gravity.

Clinical laboratory values are considered potentially clinically significant (PCS) values if they meet either the lower or upper criteria listed in Table 10-2. The number and percentage of patients with PCS postbaseline clinical laboratory values during double-blind treatment period will be tabulated by treatment group. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of patients who have PCS values will be provided and will include the PID number and baseline and postbaseline values for each patient. A listing of all AEs for patients with PCS clinical laboratory values will also be provided.

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

Laboratory Parameter	*Conventional Unit*	*PCS Criteria[a] Low Values*	*PCS Criteria[a] High Values*
Hematology			
Hemoglobin	g/dL	< 0.9 × LLN	—
Hematocrit	%	< 0.9 × LLN	—
Absolute neutrophil count (ANC)	$10^3/\mu L$	< 1.0	—
Platelet count	$10^3/\mu L$	≤ 75	≥ 700
White blood cell (WBC) count	$10^3/\mu L$	≤ 2.5	≥ 15
Chemistry			
Albumin	g/dL	< 2.5	—
Alkaline phosphatase	U/L	—	≥ 2 × ULN
ALT	U/L	—	≥ 3 × ULN
AST	U/L	—	≥ 3 × ULN
BUN	mg/dL	—	≥ 30
Calcium	mg/dL	< 7	> 12
Chloride	mEq/L	< 90	> 115
Total Cholesterol	mg/dL	—	≥ 300
CPK	U/L	—	≥ 5 × ULN
Creatinine	mg/dL	—	> 1.3 × ULN
Glucose	mg/dL	< 45	> 160
LDL Cholesterol	mg/dL	—	> 200
Potassium	mEq/L	< 3	> 5.5
Prolactin	ng/ml	—	> 200
Sodium	mEq/L	< 130	> 150
Total bilirubin	mg/dL	—	≥ 2 × ULN
Total protein	—	< 0.9 × LLN	> 1.1 × ULN
Triglycerides	mg/dL	—	≥ 300
Uric Acid	mg/dL	—	> 1.1 × ULN
Urinalysis			
Protein	—	—	At least 2 +
Glucose	—	—	At least 2 +
Blood	—	—	At least 2 +

a Criteria refer to conventional units.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK=creatine phosphokinase; LLN = lower limit of normal of laboratory reference range; PCS = potentially clinically significant; ULN = upper limit of normal of laboratory reference range.

The number and percentage of patients with shifts from baseline at the end of double-blind treatment period according to normal range and PCS criteria (PCS Low, Low, Normal, High, PCS High) will be provided if applicable.

The criteria for elevated liver function-related laboratory values are specified in Table 10-3. The frequency and percentage of subjects with treatment-emergent elevated liver function values during the double-blind treatment period will be summarized for each treatment group for the Safety Population.

Table 10-3: Elevated Liver Function Criteria

Liver Function Parameter	*Criteria*
ALT	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
AST	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
ALT or AST	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Total Bilirubin	≥ 1.5 × ULN
	≥ 2 × ULN
Alkaline phosphatase	≥ 1.5 × ULN
	≥ 2 × ULN
Combined Elevation in ALT or AST, and Total Bilirubin	ALT or AST ≥ 3 × ULN, Total Bilirubin ≥ 1.5 × ULN
	ALT or AST ≥ 3 × ULN, Total Bilirubin ≥ 2 × ULN
Hy's Law	Concurrent evaluation[a]: ALT or AST ≥ 3 × ULN, Total Bilirubin ≥ 2 × ULN, and Alkaline phosphatase < 2 × ULN

a Concurrent assessments: analytes may come from multiple samples taken within a 24-hour period.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal of laboratory reference range.

10.3 Vital Signs

Descriptive statistics for vital signs (eg, supine pulse rate, supine systolic and diastolic BP, body weight) values at baseline and changes from baseline values at each assessment visit, and at the end of the treatment period will be presented by treatment group.

Vital sign values will be considered PCS if they meet the criteria for both the observed value and the change from baseline value listed in Table 10-4. The number and percentage of patients with PCS postbaseline vital sign values during double-blind treatment period will be tabulated by treatment group for the Safety Population. The percentages will be calculated relative to the number of patients with an available baseline value and at least 1 postbaseline assessment. The numerator will be the total number of patients with an available baseline value and at least 1 PCS postbaseline vital sign value. A supportive listing of patients with PCS postbaseline values will be provided and will include the PID number and baseline and postbaseline values for each patient. A listing of all AEs for patients with PCS vital sign values will also be provided.

Table 10-4: Criteria for Potentially Clinically Significant Vital Signs

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

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

The number and percentage of patients with post-baseline orthostatic hypotension (OH) will be provided by treatment group for the Safety Population. OH is defined as a reduction of ≥ 20 mm Hg in SBP or a reduction of ≥ 10 mm Hg in DBP while changing from the supine to standing position. A supportive listing of patients with OH will be provided. A listing of all AEs occurring in patients who experienced OH will also be provided.

10.4 Electrocardiograms

Descriptive statistics for ECG parameters (eg, ventricular heart rate, QTc interval, QRS interval) at baseline and changes from baseline values at each assessment visit, and at the end of the double-blind treatment period will be summarized by treatment group.

ECG parameter values will be considered PCS if they meet the criteria listed in Table 10-5. The number and percentage of patients with PCS postbaseline values during double-blind treatment period will be tabulated by treatment group for the Safety Population. The percentages will be calculated relative to the number of patients with baseline value (for criteria involving change from baseline) or non-PCS baseline value (for criteria not involving change from baseline), and at least 1 assessment during the double-blind treatment period. The numerator will be the total number of

patients out of those included in the denominator and with at least 1 PCS value during the double-blind treatment period. A supportive listing for all patients with PCS values will be provided, which will include the PID number and baseline and postbaseline ECG values for each patient. A listing of all AEs for patients with PCS ECG values will also be provided.

Table 10-5. Criteria for Potentially Clinically Significant Electrocardiographic Values

Parameter, unit	*Criteria*[a]	
	Value	*Change from Baseline*
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; QTc = corrected QT interval; QTcB = QT interval/(RR)½; QTcF = QT interval/(RR)⅓.

10.5 Other Safety Parameters

10.5.1 Abnormal Involuntary Movement Scale (AIMS)

Descriptive statistics for AIMS total score at baseline and changes from baseline at each assessment visit (including the end of the double-blind treatment period) will be presented by treatment group for the Safety Population.

10.5.2 Barnes Akathisia Rating Scale (BARS)

Descriptive statistics for BARS total score at baseline and changes from baseline at each assessment visit (including the end of the double-blind treatment period) will be presented by treatment group for the Safety Population.

10.5.3 Simpson-Angus Rating Scale (SAS)

Descriptive statistics for SAS total score at baseline and changes from baseline at each assessment visit (including the end of the double-blind treatment period) will be presented by treatment group for the Safety Population.

10.5.4 Columbia–Suicide Severity Rating Scale (C–SSRS)

The number and percentage of patients with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be tabulated by treatment group for lifetime history (at the Screening Visit), baseline, double-blind treatment period, and SFU Period for the Safety Population. Baseline of C-SSRS for each patient is defined as the last non-missing pre-treatment 'since last visit' assessment. The distribution of responses for the most severe suicidal ideation and most severe suicidal behavior will be presented by treatment group.

The severity of suicidal ideation will be presented in a decreasing order:

- 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 be presented in a decreasing order:

- Completed Suicide (for double-blind treatment period and for SFU period only)
- Actual attempt
- Interrupted attempt
- Aborted attempt
- Preparatory acts or behavior

For each analysis period (lifetime, baseline, double-blind treatment period, and SFU Period), each patient will be counted only once for suicidal ideation and for suicidal behavior, based on the most severe suicidal ideation and the most severe suicidal behavior reported during each specific period. A listing of patients with suicidal ideation or suicidal behavior will be provided. 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 treatment period will be tabulated by treatment group for the Safety Population:

- 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)

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12. [redacted]

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13. [redacted]

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14. STATISTICAL SOFTWARE

Statistical analyses of efficacy and safety parameters will be performed using version 9.4 (or newer) of SAS®.

15. DATA HANDLING CONVENTIONS

15.1 Visit Time Windows

Table 15-1 presents the visits assigned for the analyses of MADRS (primary efficacy assessment) and CGI-S (key secondary assessment) corresponding to the range of treatment days (window) during which an actual visit may have occurred.

Table 15-1: Visit Time Windows for the Double-blind Treatment Period for MADRS and CGI-S

Derived Visit	*Scheduled Visit (Day[a])*	*Window[b]*	*Target Day*
Baseline	Week 0 (Day 1)	Days ≤ 1	Day 1
Week 1	Week 1 (Day 8)	Days [2, 11]	Day 8
Week 2	Week 2 (Day 15)	Days [12, 18]	Day 15
Week 3	Week 3 (Day 22)	Days [19, 25]	Day 22
Week 4	Week 4 (Day 29)	Days [26, 32]	Day 29
Week 5	Week 5 (Day 36)	Days [33, 39]	Day 36
Week 6	Week 6 (Day 43)	Days ≥ 40	Day 43

a Relative to the date of the first dose of double-blind study treatment.
b Visit day is calculated as visit date − date of the first dose of double-blind study treatment, + 1 day if the visit date is on or after the date of the first dose of double-blind study treatment.

The analysis window will be applied to the MADRS and CGI-S assessments based on the considerations of the ICEs:

- For Primary Efficacy Analysis (Section 9.1.1), [redacted] and Key Secondary Efficacy Analysis (Section 9.2.1), the visit time window will be applied to the assessments made before last dose plus 3 days and before starting new ADT (Table 3-1);
- [redacted]
- [redacted]

If more than one assessment is available in the same analysis window for MADRS or for CGI-S, the assessment closest to the scheduled target day will be selected and assigned to the derived visit. If two or more assessments of MADRS or of CGI-S are available in the same window and are equidistant from the scheduled target day, the earliest assessment will be selected.

[redacted]

[redacted]

Table 15-3 presents the visits assigned for vital signs parameters to the range of treatment days (window) during which an actual visit may have occurred.

Table 15-3: Visit Time Windows for the Double-blind Treatment Period for Vital Sign Parameters

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

a Relative to the date of the first dose of double-blind study treatment.
b Visit day is calculated as visit date − date of the first dose of double-blind study treatment, + 1 day if the visit date is on or after the date of the first dose of double-blind study treatment.

Table 15-4 presents the visits assigned for laboratory and ECG parameters to the range of treatment days (window) during which an actual visit may have occurred.

Table 15-4: Visit Time Windows for the Double-blind Treatment Period for Lab and ECG Parameters

Derived Visit	*Scheduled Visit (Day[a])*	*Window[b]*	*Target Day*
Baseline	Week 0 (Day 1)	Days ≤ 1	Day 1
Week 3	Week 3 (Day 22)	Days [2, 32]	Day 22
Week 6	Week 6 (Day 43)	Days ≥ 33 and within double-blind treatment period	Day 43
End of double-blind treatment period	Final or termination visit during the double-blind treatment period		

a Relative to the date of the first dose of double-blind study treatment.
b Visit day is calculated as visit date − date of the first dose of double-blind study treatment, + 1 day if the visit date is on or after the date of the first dose of double-blind study treatment.

Table 15-5 presents the visits assigned for AIMS, BARS, and SAS parameters to the range of treatment days (window) during which an actual visit may have occurred.

Table 15-5: Visit Time Windows for the Double-blind Treatment Period for AIMS, BARS and SAS Parameters

Derived Visit	*Scheduled Visit (Day[a])*	*Window[b]*	*Target Day*
Baseline	Week 0 (Day 1)	Days ≤ 1	Day 1
Week 2	Week 2 (Day 15)	Days [2, 22]	Day 15
Week 4	Week 4 (Day 29)	Days [23, 36]	Day 29
Week 6	Week 6 (Day 43)	Days ≥ 37 and within double-blind treatment period	Day 43
End of double-blind treatment period	Final or termination visit during the double-blind treatment period		

a Relative to the date of the first dose of double-blind study treatment.
b Visit day is calculated as visit date − date of the first dose of double-blind study treatment, + 1 day if the visit date is on or after the date of the first dose of double-blind study treatment.

Handling of multiple records of safety assessments within the same analysis window is provided in Section 15.2.

15.2 Repeated or Unscheduled Assessments of Safety Parameters

If a patient has repeated assessments on or before the start of double-blind study treatment, then the results from the last assessment made before the start of double-blind study treatment will be used as baseline. For visits with postbaseline repeated or unscheduled assessments of laboratory parameters, the non-missing values of the scheduled assessment will be used for summary statistics. If the scheduled assessments are missing, the last value from repeated or unscheduled assessments within the analysis window will be used. If postbaseline repeated or unscheduled vital signs and/or ECGs occur, apply the time-window rule and select the last non-missing values for each visit or endpoint. All postbaseline assessments will be used for PCS value determination and will be presented in the data listings.

15.3 Missing Date of Double-Blind Study Treatment

When the date of the last dose of double-blind study treatment taken during the double-blind treatment period is missing for a patient in the Safety Population, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts, then the last known dose date will be set as the date of the last dose of double-blind study treatment.

15.4 Missing Severity Assessment for Adverse Events

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

15.5 Missing Relationship to Investigational Product for Adverse Events

If the relationship to double-blind study treatment is missing for an AE that started on or after the first dose date of double-blind study treatment, a causality of *yes* will be assigned. The imputed values for relationship to double-blind study treatment will be used for the incidence summary, while the actual values will be presented in the data listings.

15.6 Missing Date Information for Adverse Events

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

Missing month and day

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

Missing month only

- If only the month of the incomplete start date is missing, the day will also be treated as missing, and both the month and day will be replaced according to the procedure described above.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of double-blind study treatment, then the day of the date of the first dose of double-blind study treatment will be assigned to the missing field;

- If either the year of the incomplete start date is before the year of the date of the first dose of double-blind study treatment or if the 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 treatment, then the last day of the month will be assigned to the missing field;
- If either the year of the incomplete start date is after the year of the date of the first dose of double-blind study treatment or if the 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 treatment, then the first day of the month will be assigned to the missing field.

If the stop date is complete and the imputed start date, when imputed as instructed above, is after the stop date, then the start date will be imputed to equal the stop date.

If the start date is completely missing and the stop date is complete, then use the following algorithm to impute the start date:

- If the stop date is on or after the date of the first dose of double-blind study treatment, the date of the first dose of double-blind study treatment will be assigned to the missing start date;
- If the stop date is before the date of the first dose of double-blind study treatment, the stop date will be assigned to the missing start date.

15.7 Missing Date Information for Prior or Concomitant Medications

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

15.7.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields. If the stop date is complete and the imputed start date is after the stop date, then 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 date of the first dose of double-blind study treatment, then the month and day of the date of the first dose of double-blind study treatment will be assigned to the missing fields;
- If the year of the incomplete start date is before the year of the date of the first dose of double-blind study treatment, then December 31 will be assigned to the missing fields;
- If the year of the incomplete start date is after the year of the date of the first dose of double-blind study treatment, then January 1 will be assigned to the missing fields.

Missing month only

- If only the month of the incomplete start date is missing, the day will also be treated as missing, and both month and day will be replaced according to the procedure described above.

Missing day only

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

15.7.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields. If the date of the last dose of double-blind study treatment is missing, it will be replaced with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed), then 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 date of the last dose of double-blind study treatment, then the month and day of the date of the last dose of study treatment will be assigned to the missing fields;
- If the year of the incomplete stop date is before the year of the date of the last dose of double-blind study treatment, then December 31 will be assigned to the missing fields;
- If the year of the incomplete stop date is after the year of the date of the last dose of double-blind study treatment, then January 1 will be assigned to the missing fields.

Missing month only

- If only the month of the incomplete stop date is missing, the day will also be treated as missing, and both month and day will be replaced according to the procedure described above.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of double-blind study treatment, then the day of the date of the last dose will be assigned to the missing field;

- If either the year of the incomplete stop date is before the year of the date of the last dose of double-blind study treatment or if the 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 treatment, then the last day of the month will be assigned to the missing field;
- If either the year of the incomplete stop date is after the year of the date of the last dose of double-blind study treatment or if the 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 treatment, then the first day of the month will be assigned to the missing field.

15.8 Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, the coded value will need to be appropriately determined for use in the statistical analysis. However, the actual values as reported in the database will be presented in the data listings.

Table 15-6: Example for Coding of Special Character Values for Clinical Laboratory Parameters

Laboratory Test	***Possible Laboratory Results, SI Units***	***Coded Value for Analysis***
Chemistry: ALT	< 5	5
Chemistry: AST	< 5	5
Chemistry: bilirubin, total	< 2	2
Urinalysis: ketones	= OR > 8.0, ≥ 8.0, > 0	Positive
	≤ 0, negative	Negative
Urinalysis: pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Urinalysis: glucose	≤ 50	0
	(50, 100]	1+
	(100, 250]	2+
	(250, 500]	3+
	(500, 1000]	4+
	> 1000	5+
Urinalysis: protein	≤ 0	Negative
	(0, 15]	0
	(15,30]	1+
	(30,100]	2+
	(100,500]	3+
	> 500	4+

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

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