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SAP Date: 19 Sep 2024

A Randomized, Double-blind, Placebo-controlled, Parallel-group study of Lumateperone for the Prevention of Relapse in Patients with Schizophrenia

Statistical Analysis Plan

Protocol Number:	ITI-007-304
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Confidentiality Statement

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Intra-Cellular Therapies, Inc., the Sponsor.

STATISTICAL ANALYSIS PLAN AMENDMENT 1: SUMMARY OF CHANGES

Amendment 1 to the Statistical Analysis Plan (SAP) for Study ITI-007-304, dated 19 Sep 2024, provides the following clarifications to the Original SAP (dated 12 Aug 2024).

Major changes include:

- Addition of exploratory subgroup analyses for the primary efficacy endpoint of time to first symptom relapse based on sex, age, region, and race/ethnicity (Section 9.3)
- Clarification that the calculation of efficacy parameter at a particular visit applies to the positive and negative syndrome scale (PANSS) total score only (Section 14.2).

No other changes were implemented.

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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
BARS	Barnes akathisia rating scale
BMI	body mass index
BP	blood pressure
BPM	beats per minute
CDSS	Calgary Depression Scale for Schizophrenia
CGI-S	clinical global impression scale-severity
C-SSRS	Columbia-suicide severity rating scale
DB	double-blind
DBTP	double-blind treatment phase
ECG	electrocardiogram, electrocardiographic
EPS	extrapyramidal symptom
ET	early termination
ICF	informed consent form
ICH	International Council on Harmonization
ITT	intent-to-treat
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond(s)
OL	open-label
OLTP	open-label treatment phase
PANSS	positive and negative syndrome scale
PCS	potentially clinically significant
PSP	Personal and Social Performance
PT	preferred term
OH	orthostatic hypotension
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

RIP	Run-in phase
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson angus scale
SFUP	Safety follow-up phase
SP	Stabilization phase
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World health organization

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 2 for Study ITI-007-304 (dated 23 May 2022). Specifications of tables, figures, and data listings are contained in a separate document.

Study ITI-007-304 is a Phase 3, global, multicenter, randomized, double-blind, placebo controlled, parallel-group, fixed-dose study to evaluate the efficacy, safety, and tolerability of lumateperone as treatment for adult patients with schizophrenia. This study will be performed at approximately 60 study centers in the United States and in countries outside of the United States.

Approximately 800 patients will be enrolled in the open-label Run-in Phase (RIP) of this study, and at least 200 patients are expected to be randomized in a 1:1 ratio (lumateperone: placebo) to the double-blind treatment phase (DBTP). The maximum per-patient study duration will be up to approximately 47 weeks.

The study will be conducted as follows:

- A **Screening Phase** up to 7 days in duration. During this no-drug Screening Phase (Visit 1 and Visit 2), patient eligibility will be determined. In addition, patients will be admitted to an inpatient facility.
- A 6-week, open-label **Run-in Phase** during which patients will receive open-label lumateperone 42 mg/day. Patients will remain in an inpatient facility for up to the first 3 weeks of the RIP. Patients may be discharged earlier and followed as outpatients at the discretion of the Investigator. Patients who are not stable to transition to outpatient care after 21 days of inpatient care must be discontinued.
- A 12-week open-label **Stabilization Phase** (SP) during which patients will receive open label lumateperone 42 mg/day. Patients may continue into the SP only if all of the following criteria are met and must not have been hospitalized after discharge from the inpatient facility during the RIP:
    - Completion of the 6-week RIP through Visit 8 (end of Week 6)
    - PANSS total score ≤ 60 at Visit 8 (end of Week 6)
    - At least 20% decrease in PANSS total score from Baseline (Visit 2) to Visit 8 (end of Week 6)
    - Clinical Global Impression Scale - Severity (CGI-S) score ≤ 4 at Visit 8 (end of Week 6)
    - Score of ≤ 4 on each of the following 7 PANSS items: P1, P2, P3, P6, P7, G8 and G14 at Visit 8 (end of Week 6)
    - No significant tolerability issues as judged by the Investigator at Visit 8 (end of Week 6).

Patients who do not meet the above SP criteria should be discontinued from the study and seen for a final early termination (ET) visit.

Patients who enter the SP will begin the SP by receiving the same dose of open-label lumateperone 42 mg/day that they were receiving in the RIP. However, if there are significant tolerability issues any time prior to randomization in the DBTP, as judged by the Investigator, the patient should be discontinued. An unscheduled visit should be arranged at time points between scheduled visits if necessary.

When at least 200 patients have been randomized into the DBTP, all patients active in the Run-In and Stabilization Phases will have the option to complete the open-label part of the study but will not be enrolled into the DBTP. All patients will have an Early Termination (ET) Visit and enter the Safety Follow-up Phase (SFUP).

- An up to 26-week **Double-blind Treatment Phase** during which patients will be randomized in a 1:1 ratio to receive either placebo or lumateperone 42 mg/day. The DBTP will be variable in duration with a maximum of 26 weeks or until early termination including a relapse event. At Visit 14 (end of Week 18), patients will be randomized to 1 of 2 treatment groups (lumateperone or placebo) if they meet all of the following criteria and have maintained outpatient status for the entire SP:
  - Completion of the 12-week SP through Visit 14 (end of Week 18)
  - PANSS total score ≤ 60 at Visit 14 (end of Week 18)
  - At least 20% decrease in PANSS total score from Baseline (Visit 2) through Visit 14 (end of Week 18)
  - CGI-S score ≤ 4 at Visit 14 (end of Week 18)
  - Score of ≤ 4 on each of the following 7 PANSS items: P1, P2, P3, P6, P7, G8 and G14 at Visit 14 (end of Week 18)
  - No suicidal or homicidal ideation;
  - No significant tolerability issues as judged by the Investigator.

These criteria must be met at every visit in SP, with one excursion from these criteria allowed after the patient enters the SP. This excursion cannot occur at the randomization visit (Visit 14).

The duration of the DBTP will vary for each patient. All randomized patients will continue in the DBTP until they discontinue from the study, or complete 26 weeks of double-blind treatment (through Visit 29/ET), whichever is first. Patients who have not completed 26 weeks of double-blind treatment will be seen for a final ET visit and safety follow-up visit.

- A 2-week **Safety Follow-up** phase: Patients who complete the study or who prematurely discontinue from the study will be followed for 2 more weeks and will have evaluations for safety assessments at Visit 30 during the SFU phase. During the SFU, patients will receive standard-of-care treatment at the discretion of the Investigator or designee. Patients will not receive study drug during the SFU.

The Schedules of Evaluations for this study are provided in Table 2-1 and Table 2-2.

Table 2-1: Schedule of Evaluations: Study ITI-007-304—Screening and Open-Label Phases

Study Period	*Screening*	*Baseline Day*	*Open-label Run In Phase*						*Open-label Stabilization Phase*[a]					
Visit Number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*[b]
End of Study Week	**–1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**
Informed consent	X													
Caregiver consent	X[c]													
Inclusion/exclusion	X	X												
Assess for SP eligibility								X						
Assess randomization eligibility														X
Medical and psychiatric history	X													
Prior medications	X													
Physical examination	X													X
Clinical laboratory tests[d]	X	X			X			X		X		X		X
Urine drug screen[e]	X	X						X						X
Pregnancy test[f]	X	X			X			X		X		X		X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[h]	X	X			X			X		X		X		X
Modified SCID-5-CT	X													
SCI-PANSS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDSS		X						X						X
PSP		X						X						X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BARS/AIMS/SAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensing[i]		X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug return[i]			X	X	X	X	X	X	X	X	X	X	X	X

***NOTE**:* During study conduct, 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, sites will be permitted to conduct remote visits with approval from the Sponsor or Sponsor's representative. If on-site laboratory and ECG assessments are not feasible, local laboratory and ECG testing is permitted if clinically indicated as per Investigator judgement. Remote assessments of PANSS, CGI-S, CDSS, PSP and C-SSRS should be performed if possible with caregiver input if available. However, for any visit that requires specific stability criteria to be met, PANSS, CGI, C-SSRS and AE evaluation must be performed and documented at a minimum. **All Screening (Visit 1), Baseline (Visit 2), and Randomization (Visit 14) assessments must be performed in person**.

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CDSS = Calgary Depression in Schizophrenia Scale; CGI-S = Clinical Global Impressions–Severity; C-SSRS = Columbia–Suicide Severity Rating Scale; DBTP = Double-blind Treatment Phase; ECG = electrocardiogram; FOCBP = females of childbearing potential; h = hour; HbA1c = hemoglobin A1c; ICF = informed consent form; PSP = Personal and Social Performance scale; RIP = Run-in Phase; SAS = Simpson-Angus Scale; SCID-5 = Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders-DSM-5*; SCI-PANSS = Structured Clinical Interview for the Positive and Negative Syndrome Scale; SP = Stabilization Phase; TSH = thyroid-stimulating hormone.

a Patients may continue into the Stabilization Phase only if they meet the following criteria: completion of the 6-week RIP; PANSS total score ≤ 60 at Visit 8; at least 20% decrease in PANSS total score from RIP Baseline (Visit 2) to Visit 8; CGI-S score ≤ 4 at Visit 8; score ≤ 4 on each of the following PANSS items: P1, P2, P3, P6, P7, G8, and G14 at Visit 8; no significant tolerability issues as judged by the Investigator at Visit 8.

b For eligible patients, randomization for the DBTP will occur at Visit 14 (end of Week 18) which will serve as the DBTP baseline.

c Caregiver consent to be obtained at Visit 1 or at any time before the patient is discharged from the inpatient facility during the RIP.

d At all visits after the Screening Visit (Visit 1), patients are required to have fasted for at least 8 hours. Hepatitis screening is performed at Visit 1 only. HbA1c is to be measured at Visits 1, 14, and 29/ET Visit only; fasting insulin is to be measured at Visits 2, 14, and 29/ET Visit only. TSH will be assayed at Screening only; if the result is abnormal, free thyroxine and free triiodothyronine will be assayed. Unscheduled visits for repeat laboratory assessments may be performed at any time for safety reasons or at the discretion of the Investigator.

e An unscheduled visit for urine drug and alcohol screening test can be conducted at any time during the study at the Investigator's discretion.

f At all specified visits, urine and serum pregnancy tests will be administered to FOCBP. Urine pregnancy testing will use a urine dipstick.

g At all visits, vital signs include: respiratory rate, body temperature, pulse rate, blood pressure, and body weight. Blood pressure and pulse rate are to be assessed while the patient is supine and standing. Height and BMI will be measured only at Visit 1. Waist circumference will be measured at Visits 1, 14, and 29/ET Visit.

h Unscheduled visits for repeat ECG assessments may be performed at any time for safety reasons or at the discretion of the Investigator.

i Site staff will administer open-label study drug while patients are in the inpatient facility. Study drug dispensing and study drug return will be performed by site staff after patients have been discharged from the inpatient facility.

Table 2-2: Schedule of Evaluations: Study ITI-007-304—Double-blind Treatment and Safety Follow-up Phases

	Double-blind Treatment Phase															*SFU*
Visit No.	*15[a]*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29/ET*	*30*
End of Study Week	**19**	**20**	**21**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**
Physical exam															X	
Clinical laboratory tests[b]				X		X				X					X	
Urine drug screen[c]				X		X				X					X	
Pregnancy test[d]				X		X		X		X		X			X	
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[f]				X		X				X					X	
SCI-PANSS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CDSS						X				X					X	
PSP						X				X					X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BARS/AIMS/SAS	X	X	X	X	X	X	X	X	X		X		X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensing	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study drug return	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

NOTE: During study conduct, 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, sites will be permitted to conduct remote visits with approval from the Sponsor or Sponsor's representative. If on-site laboratory and ECG assessments are not feasible, local laboratory and ECG testing is permitted if clinically indicated as per Investigator judgement. Remote assessments of PANSS, CGI-S, CDSS, PSP and C-SSRS should be performed if possible with caregiver input if available. However, for any visit that requires specific stability criteria to be met, PANSS, CGI, C-SSRS and AE evaluation must be performed and documented at a minimum.

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CDSS = Calgary Depression in Schizophrenia Scale CGI-S = Clinical Global Impressions–Severity; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; FOCBP = females of childbearing potential; HbA1c = hemoglobin A1c; ICF = informed consent form; PSP = Personal and Social Performance scale; SAS = Simpson-Angus Scale; SCI-PANSS = Structured Clinical Interview for the Positive and Negative Syndrome Scale; SP = Stabilization Phase.

a For eligible patients, randomization to the DBTP will occur on the last day of the SP (Visit 14/End of Week 18) which will serve as the Baseline Visit for the DBTP.

b Patients are required to have fasted for at least 8 hours. Unscheduled visits for repeat laboratory assessments may be performed at any time for safety reasons or at the discretion of the Investigator. HbA1c and fasting insulin are to be measured at Visit 29/ET Visit only.

c An unscheduled visit for urine drug and alcohol screening test can be conducted at any time during the study at the Investigator's discretion.

d At all specified visits, urine and serum pregnancy tests will be administered to FOCBP. Urine pregnancy testing will use a urine dipstick

e At all visits, vital signs include respiratory rate, body temperature, pulse rate, blood pressure, and body weight. Waist circumference should be measured at Visits 18, 24, and 29/ET Visit. Blood pressure and pulse rate are to be assessed while the patient is supine and standing.

f Unscheduled visits for repeat ECG assessments may be performed at any time for safety reasons or at the discretion of the Investigator.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the efficacy and safety of lumateperone relative to placebo in the prevention of relapse of symptoms in patients with schizophrenia.

4. ANALYSIS POPULATIONS

4.1 Enrolled Population

Enrolled Population includes all patients who underwent the Screening Visit, received a patient number, and signed the informed consent form (ICF).

4.2 RIP Safety Population

RIP Safety Population will consist of all patients in the Enrolled Population who took at least 1 dose of open-label study drug during the RIP. OL Safety population is the same as the RIP Safety population.

4.3 SP Safety Population

SP Safety Population will consist of all patients in the RIP Safety Population who took at least 1 dose of open-label study drug during the SP.

4.4 Open-label Intent-to-Treat Population

Open-label (OL) Intent-to-Treat (ITT) Population will include all patients in the RIP Safety Population who had at least 1 postbaseline assessment of PANSS during the RIP or SP.

4.5 Randomized Population

Randomized Population will include all patients who completed the SP and were randomized to double-blind study drug.

4.6 Double-blind Safety Population

Double-blind (DB) Safety Population will include all patients who completed the SP, were randomized into the DBTP, and took at least 1 dose of randomized study drug during the DBTP.

4.7 Double-blind Intent-to-Treat Population

DB ITT Population will include all patients in the DB Safety Population.

5. PATIENTS DISPOSITION

The number of patients in the Screened, RIP Safety, SP safety and OL ITT Populations will be summarized overall by study center. The number of patients in the DB Safety, and DB ITT Populations will be summarized by treatment group and study center.

Screen-failure patients (ie, patients screened but not included in the RIP Safety Population) and the associated reasons for failure will be summarized overall for the Enrolled Population.

The number and percentage of patients who prematurely discontinued from the RIP, who completed the RIP, who met or did not meet the criteria to enter the SP at the end of RIP, who entered the SP, and who entered the SFU phase will be summarized overall and by reasons for premature discontinuation for the RIP Safety Population.

The number and percentage of patients who prematurely discontinued from the SP, who completed the SP, who met or did not meet the criteria to enter the DBTP at the end of the SP, who entered the DBTP, and who entered the SFU phase will be summarized overall and by reasons for premature discontinuation for the SP Safety Population.

The number and percentage of patients who prematurely discontinued from the OLTP, who completed the OLTP, who met or did not meet the criteria to enter the DBTP at the end of the OLTP, who entered the DBTP, and who entered the SFU phase will be summarized overall and by reasons for premature discontinuation for the RIP Safety Population.

Similarly, the number and percentage of patients who completed the DBTP who prematurely discontinued from the DBTP, and who entered the SFU phase will be summarized overall, by treatment group, and by reasons for premature discontinuation for the DB Safety Population.

6. PROTOCOL DEVIATIONS

The number and percentage of patients with major protocol deviations will be summarized overall for the RIP for the RIP Safety Populations, for the SP for the SP Safety Populations, and for the entire OLTP for the RIP Safety Population and by treatment group for the DBTP for the DB Safety Population. Supportive listings will also be provided.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Baseline efficacy parameters will be summarized overall for the OL ITT Population and by treatment group for the DB ITT population.

Medical and surgical history/physical findings will be summarized overall for the RIP Safety and the SP Safety Populations and by treatment group for the DB Safety Population.

Prior, prior concomitant, and concomitant medications of each treatment phase, defined by start and stop dates relative to study medication administration of each treatment phase, will be summarized by preferred term for the RIP, for the SP and for the OLTP, and by preferred term and treatment group for the DBTP using corresponding Safety Populations. Patients with multiple occurrences of a medication in the same preferred term and treatment phase will only be counted once within the preferred term and treatment phase.

- *Prior medication* is defined as any other medication which started and stopped before the date of the first dose of open-label study drug.
- *Prior concomitant medication* during the RIP is defined as any other medication which started before the date of the first dose of open-label study drug and stopped or is ongoing after the date of the first dose of open-label study drug during the RIP.
- *Concomitant medication* during the RIP is defined as any medication which started on or after the date of the first dose of open-label RIP study drug, and before the date of last dose of open-label RIP study drug.
- *Prior concomitant medication* during the SP is defined as any other medication which started before the date of the first dose of open-label SP study drug and stopped or is ongoing after the date of the first dose of open-label SP study drug.
- *Concomitant medication* during the SP is defined as any medication which started on or after the date of the first dose of open-label SP study drug, and before the date of last dose of open-label SP study drug.
- *Prior concomitant medication* during the OLTP is defined as any other medication which started before the date of the first dose of open-label study drug and stopped or is ongoing after the date of the first dose of open-label study drug.
- *Concomitant medication* during the OLTP is defined as any medication which started on or after the date of the first dose of open-label study drug, and before the date of last dose of open-label study drug.
- *Prior concomitant medication* during the DBTP is defined as any other 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* during the DBTP is defined as any medication which started on or after the date of the first dose of double-blind study drug, and 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 and concomitant medications use will be coded by drug name and therapeutic class. Prior medications will be summarized by the number and percentage of patients for the RIP Safety Population, the SP Safety Population, and by treatment group for the DB Safety Population, separately. Prior concomitant medications, and concomitant medications during the RIP/OLTP will be summarized overall for the RIP Safety Population. Prior concomitant medications, and concomitant medications during the SP will be summarized overall for the SP Safety Population. Prior concomitant medications, and concomitant medications during the DBTP will be summarized overall and by treatment group for the DB Safety Population.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Extent of Exposure

Exposure to open-label lumateperone during the RIP for the RIP Safety Population, and during the SP for the SP Safety Population, will be summarized separately based on treatment duration. Treatment duration is defined as the number of days from the date of first dose date of open-label lumateperone taken to the date of last dose date of open-label lumateperone taken during the RIP or SP, inclusive. Exposure to open-label lumateperone during the entire OLTP will also be summarized for the RIP Safety Population. Descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) will be presented.

Exposure to double-blind study drug for the DB Safety Population during the DBTP will be summarized by treatment group based on treatment duration, calculated as the number of days from the first dose date of double-blind study drug taken to the last dose date of double-blind study drug taken, inclusive. Descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) will be presented.

Patient-years during the RIP and during the SP are defined as total exposure to open-label study drug in years during the RIP or SP, respectively. Patient years during the RIP for the RIP Safety Population and patient-years during the SP for the SP Safety Population will be summarized by overall. Patient years during the entire OLTP will also be summarized by overall for the RIP Safety Population.

Patient-years during the DBTP, defined as total exposure to double-blind study drug in years, will be summarized by treatment group for the DB Safety Population. Patient years of exposure to lumateperone during the entire study (OLTP and DBTP) will also be summarized for the OL Safety Population.

8.2 Treatment Compliance

Dosing compliance for a specified phase 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 for the same phase multiplied by 100. The total number of capsules actually taken during a specific time phase is calculated as the sum of capsules taken during that phase as obtained from the study medication record. The number of capsules prescribed to be taken for a specific treatment phase is calculated by multiplying the number of days in that phase by the number of capsules prescribed per day.

Descriptive statistics for open-label study drug compliance will be presented by overall for the RIP for the RIP Safety Population, by overall for the SP for the SP Safety Population, and by overall for the entire OLTP for the RIP Safety Population. Descriptive statistics for double-blind study drug compliance will be presented by treatment group for the DBTP for the DB Safety Population.

9. EFFICACY ANALYSES

All efficacy analyses for the DBTP will be performed using the Double-blind ITT Population. Baseline for efficacy parameters in the DBTP will be defined as the last non-missing efficacy assessment prior to the first dose of double-blind study drug. In addition, all efficacy analyses for the RIP and SP will be performed using the Open-label ITT Population. Baseline for efficacy parameters in the RIP and SP will be defined as the last non-missing efficacy assessment before the first dose of open-label study drug.

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance and all confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

9.1 Primary Efficacy Parameter

The primary endpoint is the time to first symptom relapse during the DBTP, defined as the number of days from the randomization date to the relapse date. The relapse date is defined as the date the patient first meets the relapse criteria if a second assessment confirms the relapse or a second assessment is not needed.

Relapse during the DBTP is defined as meeting any one of the following criteria:

- Psychiatric hospitalization or need for increased level of psychiatric care due to worsening of the patient's underlying condition;
- Increase in PANSS total score by ≥ 30% for patients who scored 50 or higher at randomization or a 10-point or more increase for patients who scored less than 50 at randomization at 2 consecutive visits (Note: Patient should also meet this criterion at a second assessment that is 4 to 7 days apart [exception: Based on severity for safety reasons the Investigator has discretion not to perform a second assessment]);
- Increase in the CGI-S score by 2 or more points from Visit 14 (NOTE: Patient should meet this criterion at a second assessment that is 4 to 7 days apart [exception: Based on severity for safety reasons the Investigator has discretion not to perform a second assessment]);
- Deliberate self-injury or aggressive/violent behavior;
- Any Suicidal or homicidal ideation; PANSS item scores > 4 on 1 or more of the following PANSS items: P1, P2, P3, P6, P7, G8 or G14. (NOTE: Patient should also meet this criterion at a second assessment that is 4 to 7 days apart [exception: based on severity for safety reasons, the Investigator has discretion not to perform a second assessment]).

Patients who do not meet any of the above relapse criteria will be considered censored at the time of completion or discontinuation of the DBTP.

The primary efficacy analysis will compare the time to relapse between lumateperone and placebo treatment groups using the log-rank test. Estimates of the hazard ratio and 95% confidence interval will be based on the Cox proportional hazards model with treatment group as the explanatory variable. The cumulative distribution function of time to relapse will be characterized by the Kaplan-Meier curves. In addition, the proportion of relapse free patients at Week 26 will be provided for both the lumateperone group and placebo group from the Kaplan-Meier estimator,

with variance estimated by the Greenwood formula. The confidence intervals for the survival function will be derived using the asymptotic distribution of the Kaplan-Meier estimator (Borgan, 1990). The SAS codes for primary efficacy analysis are provided in Appendix I**.**

The graphical method for assessing the assumption of the proportional hazard in Cox model will be applied. For a single treatment group (binary) covariate, the proportional hazard model can be rewritten as $\log[-\log S(t)] = \log[-\log S_0(t)] + \beta_1$ where $S(t)$ is the survival probability function for the lumateperone, $S_0(t)$ is the survival probability function for the placebo group and β_1 is the log of hazard ratio for lumateperone versus placebo. The plot of log of cumulative hazard functions (i.e, negative log transformation of the Kaplan-Meier estimate) against time will be provided to check for equidistance between two curves, which will explore whether the constant hazard ratio assumption holds (Hess, 1995).

Two sensitivity analyses will be performed to assess the robustness of the primary analysis results to the possible violation of the noninformative censoring assumption. The first sensitivity analysis assumes that patients who discontinued without meeting any of the relapse criteria during the DBTP relapsed instead of being censored at the date of discontinuation. The second sensitivity analysis is based on the placebo-based pattern mixture model (see Lu [2015] for the description of the model for time-to-event data analysis). The placebo-based pattern mixture model assumes that patients who discontinued from lumateperone group would have disease progression after discontinuation similar to that of placebo and uses a sensitivity parameter to characterize the gradual deviation from the noninformative censoring underlying the primary analysis toward the informative censoring, which assumes that the hazard of relapse for patients in the lumateperone group after discontinuation is the same as the hazard of relapse for patients in the placebo group. The placebo-based pattern mixture model for time-to-event data is described as follows.

Let $h_0(t)$ denote the baseline hazard function and β_1 denote the treatment effect in terms of log hazard ratio under noninformative censoring for lumateperone versus placebo. The hazard function associated with lumateperone under noninformative censoring is thus given by $h_1(t) = h_0(t)e^{\beta_1}$. For placebo group, we assume that patients with premature discontinuation would have comparable experience after discontinuation to their counterparts without premature discontinuation. For the lumateperone group, each dropout time point for lumateperone patients defines a missing data pattern, and for each missing data pattern, we assume that patients with premature discontinuation would have disease progression after discontinuation somewhere between their counterparts without premature discontinuation and patients in the placebo group. Specifically, we assume that $h_1(t) = h_0(t)e^{(1-\emptyset)\beta_1}$ for $t > C$, where C denotes the time of premature discontinuation. The sensitivity parameter $\emptyset \in [0,1]$ characterizes the gradual deviation from the noninformative censoring with $\emptyset = 0$ toward the informative censoring underlying the placebo-based pattern mixture model with $\emptyset = 1$. A multiple imputation approach will be used to implement the extended placebo-based pattern mixture model. More technical details including SAS codes are provided in Appendix II.

9.2 Secondary Efficacy Parameters

The secondary efficacy parameter is the time to relapse or all cause discontinuation during the DBTP, defined as the number of days from the randomization date to the relapse date in the primary efficacy analysis or discontinuation date. The secondary efficacy analysis will compare the time to relapse or all cause discontinuation between lumateperone and placebo treatment groups using the log-rank test. Estimates of the hazard ratio and 95% confidence interval will be based on the Cox proportional hazards model with treatment group as the explanatory variable. The cumulative distribution function of time to relapse or all cause discontinuation will be characterized by the Kaplan-Meier curves. Patients who did not relapse or discontinue during the DBTP will be considered censored at the time of completion of the DBTP.

9.3 Additional Efficacy Parameters

Additional efficacy parameters will include the following at end of DBTP and each applicable postbaseline visit:

- Change from baseline in the PANSS total score
- Change from baseline in the PANSS positive subscale
- Change from baseline in the PANSS negative subscale
- PANSS response percentage (improvement $\geq$ 30%)
- Change from baseline in the PANSS general psychopathology subscale
- Change from baseline in the CGI-S score
- Change from baseline in the Calgary Depression Scale for Schizophrenia (CDSS) score
- Change from baseline in the Personal and Social Performance (PSP) score

Descriptive statistics for baseline, observed value and change from baseline will be provided at each postbaseline visit for the continuous additional efficacy parameters by overall for the RIP/SP and by treatment group for the DBTP.

Patients with missing PANSS total score at each postbaseline visit will be considered as non-responders at that visit. The baseline of PANSS total score in the PANSS response analysis will be the last non-missing PANSS total score before the first dose of open-label study drug.

The additional efficacy analysis will be performed for the time to relapse during the DBTP, defined as the number of days from the randomization date to the relapse date. The relapse date is defined as the date the patient meets the relapse criteria at the first visit for the relapsed criteria of PANSS total score, CGI-S score and PANSS individual item scores in the primary efficacy analysis, or the date the patients meets the relapse criteria for psychiatric hospitalization or need for increased level of psychiatric care, or deliberate self-injury or aggressive/violent behavior, or any suicidal or homicidal ideation.

Patients who do not meet any of the relapse criteria will be considered censored at the time of completion or discontinuation of the DBTP.

The log-rank test will be used to compare the time to relapse between lumateperone and placebo treatment groups. Estimates of the hazard ratio and 95% confidence interval will be based on the Cox proportional hazards model with treatment group as the explanatory variable. The cumulative distribution function of time to relapse will be characterized by the Kaplan-Meier curves.

Exploratory subgroup analyses will be performed based on the time to relapse during the DBTP based on the DB ITT Population for the following:

- Region (US; Non-US)
- Sex (Male; Female)
- Age group (≤ 40 years; > 40 years)
- Race group (White; Non-White)

The log-rank test will be used to compare the time to first symptom relapse between lumateperone and placebo treatment in the subgroup analyses. Estimates of the hazard ratio and 95% confidence interval will be based on the Cox proportional hazards model with treatment group as the explanatory variable.

9.4 Multiple Comparisons

A fixed sequence testing procedure will be used to control the overall Type I error at level of 0.05 for testing the primary and the secondary efficacy parameters. If the primary comparison for lumateperone vs placebo achieves statistical significance at 0.05 level, then the secondary parameter will be tested at the 0.05 level.

10. SAFETY ANALYSES

The safety analyses will be performed for the RIP Safety, SP safety and DB Safety Populations. The summarization will be overall for the RIP, for the SP, and for the OLTP and by treatment group for the DBTP. The summarization for OLTP will be based on RIP safety population.

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); 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 study drug (Visit 2) will be used as the baseline for all analyses of that safety parameter, unless stated otherwise.

10.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0 or newer.

An AE (classified by preferred term) occurring during the RIP or thereafter will be considered a treatment-emergent adverse event (TEAE) if it starts as a new event or if its severity increases during the RIP or thereafter. A new event is 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 RIP or thereafter. An AE that occurs after the date of the last dose of study drug plus one day will not be considered a TEAE and not summarized but will be included in the listings.

The number and percentage of patients reporting TEAEs during the RIP/SP/OLTP will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. The number and percentage of patients reporting TEAEs during the DBTP will be tabulated for each treatment group by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 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 summarization by severity and by relationship to study drug, respectively.

The incidence of common (≥ 5% of patients in lumateperone and twice rate of placebo and ≥ 2% of patients in lumateperone and higher rate of placebo) TEAEs during the DBTP will be summarized by preferred term and treatment group and sorted by decreasing frequency for lumateperone group for the DB Safety Population.

The incidence of serious adverse events (SAEs) and AEs leading to premature discontinuation of the study during the RIP/SP/OLTP will be summarized by system organ class and preferred term. The incidence of serious adverse events (SAEs) and AEs leading to premature discontinuation of the study drug during the DBTP will be also summarized for each treatment group by system organ class and preferred term and will be sorted by decreasing frequency for lumateperone group. Listings will be presented for patients with SAEs, patients with AEs leading to premature discontinuation, patients who died (if any) and patients who died (if any) with AEs.

The incidence of extrapyramidal symptom (EPS) TEAEs will be summarized by PT during the RIP/SP/OLTP, and for each treatment group by PT during the DBTP and will be sorted by decreasing frequency for lumateperone 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 PTs 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

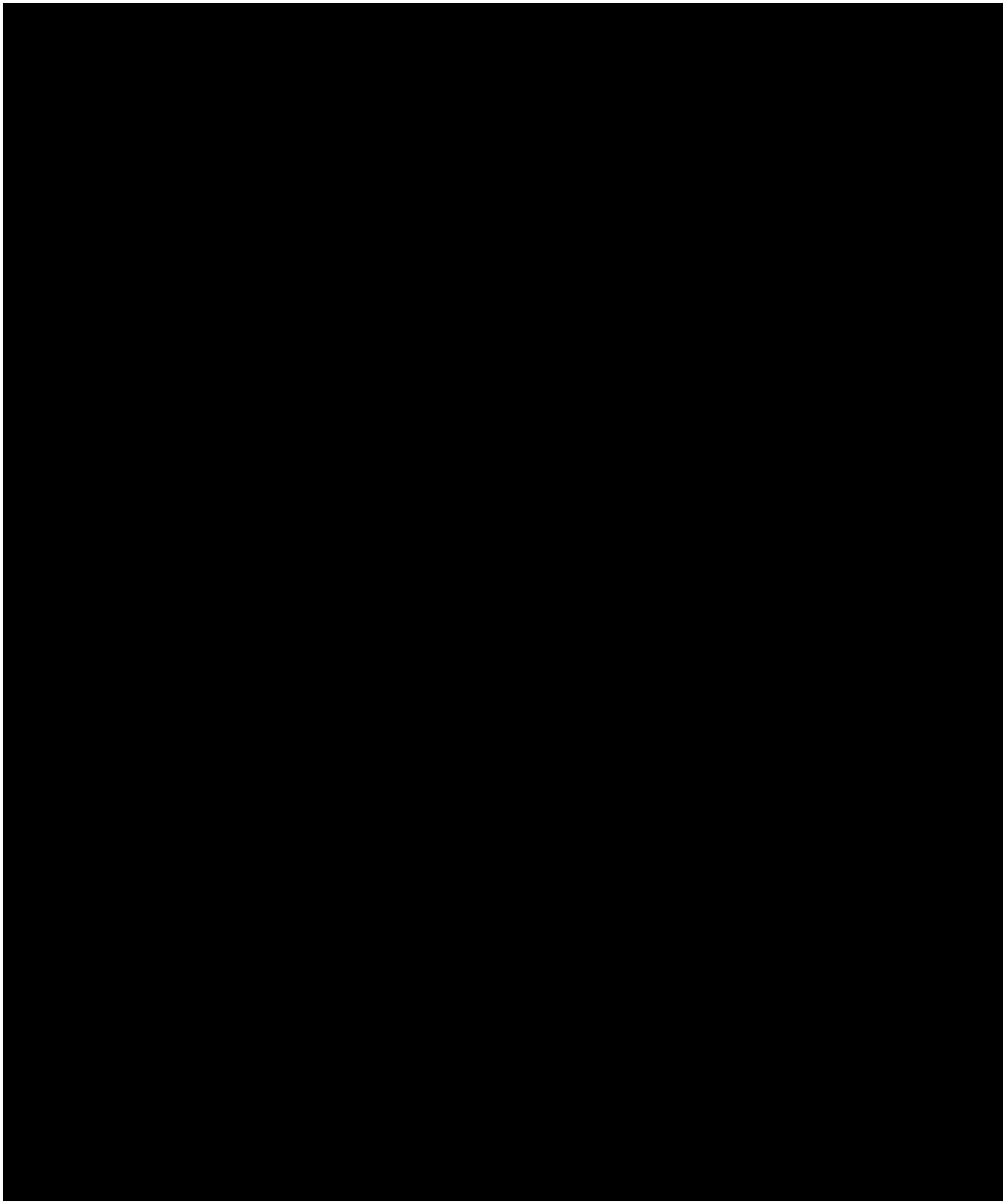
Descriptive statistics (n, mean, SD, minimum, median, and maximum) for clinical laboratory values (in SI and conventional units) and change from baseline values will be presented at each assessment timepoint (including the end of each treatment phase) by overall for the RIP/SP/OLTP, and by treatment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

Hematology: Hematocrit, hemoglobin, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hemoglobin A1c, reticulocytes, white blood cell count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophils, and platelets,

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

Urinalysis: Specific gravity, pH, protein, glucose, ketones, nitrates and blood.

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 with PCS postbaseline clinical laboratory values will be tabulated overall during the RIP/OLTP for the RIP Safety Population, overall during the SP for the SP Safety Population and by treatment group during the DBTP for the DB Safety Population. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least one postbaseline assessment during each treatment phase. The numerator is the total number of patients with available non-PCS baseline values and at least one PCS postbaseline value during each treatment phase. A supportive listing of patients with PCS postbaseline values will be provided using RIP Safety Population, including the patient ID, baseline, and postbaseline (including non-PCS) values. In addition, a listing of all AEs for patients with PCS clinical laboratory values will also be provided for the RIP Safety Population.



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

The number and percentage of patients who meet the following criteria of elevated liver function-related laboratory values will be tabulated overall for the RIP/SP/OLTP and by treatment group for the DBTP. For patients in the RIP Safety Population who meet at least one of the following criteria, a supportive listing of the hepatic laboratory parameter values for those patients will also be provided. The criteria for elevated liver function-related laboratory values are specified below:

- 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 (TBL): ≥ 2 × ULN
- ALP: ≥ 1.5 × ULN
- Combined Elevation in ALT or AST, and TBL: ALT or AST > 3 × ULN, TBL ≥ 1.5 × ULN and ALT or AST > 3 × ULN, TBL ≥ 2 × ULN
- Potential Hy's Law cases: ALT or AST ≥ 3 × ULN, TBL ≥ 2 × ULN and ALP < 2 × ULN, all based on blood draws collected within a 24 hour period.

10.3 Vital Signs

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

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 the Table 10-3. The number and percentage of patients who have PCS postbaseline vital sign values will be tabulated overall for the RIP/SP/OLTP and 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 postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value. A listing of all patients with PCS postbaseline values will be provided and will include the patient ID, baseline, and postbaseline (including non-PCS) values. In addition, a listing of all AEs for patients who had PCS post-baseline vital sign values will be provided.

Orthostatic hypotension (OH) 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 stand-up position. The number and percentage of patients with orthostatic hypotension will be

provided overall for the RIP/SP/OLTP and by treatment group for the DBTP. The percentages will be calculated relative to the number of patients who have available non-OH at baseline and have orthostatic change value at postbaseline. The numerator will be the total number of patients with available non-OH baseline value and OH postbaseline value. A supportive listing will be provided including the Patient ID, baseline and postbaseline systolic and diastolic BP values (supine and standing).

[redacted]

10.4 Electrocardiograms

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for 12-lead ECG assessments (eg, heart rate, QRS duration, PR interval, QT interval, and corrected QT [QTc] intervals) and changes from baseline at each assessment visit and at the end of each treatment phase will be presented overall for the RIP/SP/OLTP and by treatment group for the DBTP.

ECG parameter values will be considered PCS if they meet or exceed the criterion value or the change from baseline value listed in the Table 10-4. The number and percentage of patients who have PCS postbaseline ECG values will be tabulated overall for the RIP/SP/OLTP and by treatment group for the DBTP. The percentages will be calculated relative to the number of patients who have available non-PCS baseline values and at least 1 postbaseline 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 postbaseline assessment for PCS criteria based on changes. The numerator will be the total number of patients with non-PCS baseline values and at least 1 PCS postbaseline value for PCS criteria based on the actual values and the total number of patients with available baseline values and at least 1 PCS postbaseline value for PCS criteria based on the changes. A listing of all patients with PCS postbaseline values will be provided and will include the patients ID, baseline, and postbaseline (including non-PCS) value. In addition, a listing of all AEs for patients who had PCS ECG values will be provided.

Shift tables from baseline to the end of each treatment phase in the overall interpretation of the ECG will be presented overall for the RIP/SP/OLTP and by treatment group for the DBTP for the following categories: normal; abnormal. A listing of patients with post-baseline significant ECG abnormalities according to the overall interpretation will be provided.



10.5 Other Safety Parameters

Other safety parameters include the C-SSRS, 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 overall for lifetime history (assessed at the screening visit), for the RIP/SP/OLTP and by treatment group for the DBTP and for the post DBTP. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior will also be presented. 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 phase for suicidal ideation and for suicidal behavior separately. In addition, the number and percentage of patients with the following emergence of suicidal ideation or of suicidal behavior will be summarized overall for the RIP/SP/OLTP and by treatment group for the DBTP and for the post DBTP.

- 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).

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

10.5.2 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 each treatment phase will be presented overall for the RIP/SP/OLTP and by treatment group for the DBTP.

10.5.3 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 each treatment phase will be presented overall for the RIP/SP/OLTP and by treatment group for the DBTP.

10.5.4 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 each treatment phase will be presented overall for the RIP/SP/OLTP and by treatment group for the DBTP.

11. INTERIM ANALYSIS

No interim analysis is planned for this study.

12. SAMPLE SIZE CONSIDERATION

The sample size and power calculations are based on the analysis of time to relapse in the DBTP. A relapse rate at 26 weeks of 50% in the placebo group and 25% in the lumateperone group, and a common discontinuation rate at 26 weeks of 30% for both groups in the DBTP before relapse or completion of the study, were assumed based on historical relapse studies of similar compounds. At least 200 randomized patients (100 per treatment group) will provide at least 90% statistical power to detect a significant difference in the time to relapse between lumateperone and placebo using the log-rank test at the 0.05 significance level. To achieve the aforementioned number of randomized patients, approximately 800 patients need to be enrolled in this study if the response rates during the RIP and the SP are 60% and 50%, respectively.

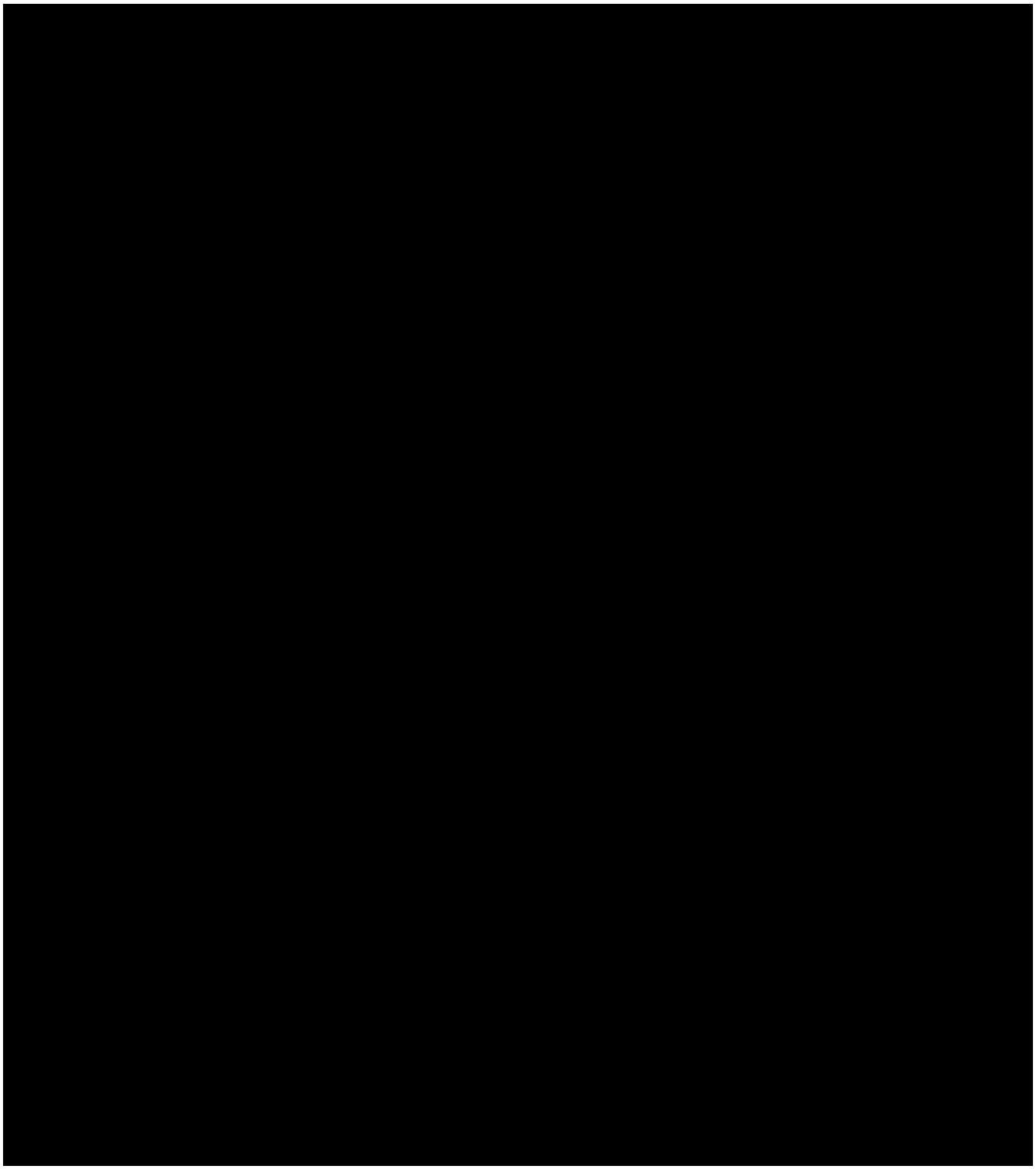
13. STATISTICAL SOFTWARE

Statistical analyses of 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.





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

14.2 Derived Efficacy Variables

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

PANSS responder is defined as patients with 30% or more improvement in PANSS total score relative to baseline of OLTP. Percent improvement is calculated as corrected PANSS total score minus baseline corrected PANSS total score divided by baseline corrected PANSS total score multiplied by 100. Corrected PANSS total score is the PANSS total score minus 30.

14.3 Repeated or Unscheduled Assessments

If a patient has repeated assessments before the first dose of open-label study drug, the results from the final assessment made before the first dose of open-label study drug will be used as baseline for safety parameters. If a patient has repeated assessments before the first dose of double-blind study drug, the results from the final assessment made before the first dose of double-blind study drug will be used as baseline for efficacy parameters. If postbaseline assessments are repeated or unscheduled assessments occur, the scheduled assessment will be used for generating summary statistics. However, all postbaseline 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 open-label or double-blind study drug in the study 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 available dosing record date in each treatment phase will be used as the last dose date.

14.5 Missing Data for Adverse Events

14.5.1 Missing Severity Assessment

If severity is missing for an AE that occurred before the date of the first dose of 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 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.

14.5.2 Missing Relationship to Study Drug

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

14.6 Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, 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 open-label study drug, the month and day of the first dose of open-label 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 open-label 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 open-label 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 open-label study drug, the day of the first dose of open-label 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 open-label 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 open-label 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 open-label 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 open-label 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 open-label study drug, the date of the first dose of open-label study drug will be assigned to the missing start date
- If the stop date is before the date of the first dose of open-label study drug, the stop date will be assigned to the missing start date

14.7 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.

14.7.1 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 open-label study drug, the month and day of the first dose of open-label 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 open-label 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 open-label 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 open-label study drug, the day of the first dose of open-label 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 open-label 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 open-label 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 open-label 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 open-label study drug, the first day of the month will be assigned to the missing day.

14.7.2 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

Major changes made to the analyses specified in the current protocol amendment for Study ITI-007-304, Amendment #2 (dated 23 May 2022) are as follows:

- Section 9.2: the secondary efficacy parameter time to relapse or all cause discontinuation, and secondary efficacy analysis to compare time to relapse or all cause discontinuation between lumateperone and placebo groups are added in the SAP
- Section 9.4: multiple comparison and sequential testing for the primary efficacy analysis and secondary efficacy analysis are added in the SAP
- In Section 10.1, TEAE definition has been changed:

In protocol amendment 2.0, TEAE is defined as an AE that will be considered a TEAE if it was not present before the date of the first dose of open-label study drug during the RIP or was present before the date of the first dose of study drug during the RIP but increased in severity during any treatment phase.

The definition of TEAE is revised as the following: An AE will be considered a TEAE during RIP or thereafter if it starts as a new event or if its severity increases during the RIP or thereafter. A new event is 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 RIP or thereafter.

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17. REFERENCES

Borgan Ø and Liestøl K. A note on confidence interval and bands for the survival curves based on transformations. Scandinavian Journal of Statistics, 1990; 18: 35–41.

Hess K. Graphical methods for assessing violations of the proportional hazards assumption in cox regression. Stat. Med, 1995; 14(15):1707-1723.

Lu K, Li D, and Koch GG. Comparison between two controlled multiple imputation methods for sensitivity analyses of time-to-event data with possibly informative censoring. Statistics in Biopharmaceutical Research, 2015.

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