NCT05061719

Study ID: ITI-007-503

Title: An Open-label, Multicenter Trial to Assess the Safety and Tolerability of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder

SAP Version 1 Date: 24 Jun 2024

Statistical Analysis Plan

ITI-007-503

An Open-label, Multicenter Trial to Assess the Safety and Tolerability of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder

Version:	0.1
Date:	24 Jun 2024
Compound:	Lumateperone
Study Phase:	3
Sponsor:	Intra-Cellular Therapies, Inc. [redacted]

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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
AST	aspartate aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
bpm	beats per minute
CGI-S	Clinical Global Impression Scale-Severity
CPK	creatine phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
ET	Early Termination
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
LLN	lower limit of normal
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MINI	MINI International Neuropsychiatric Interview
msec	millisecond(s)
OH	orthostatic hypotension
PCS	potentially clinically significant
PK	pharmacokinetic
PT	preferred term
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/RR^{½}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/RR^{⅓}$)
SAE	serious adverse event

SAP	statistical analysis plan
SAS	Simpson Angus Scale
SD	standard deviation
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 Protocol Amendment 1 (dated 23 Aug 2021) of Study ITI-007-503.

Study ITI-007-503 ("Study 503") is an international, open-label, multicenter, 6-month study to assess the safety and tolerability of lumateperone as adjunctive therapy in patients with MDD. The Study will be performed at approximately 120 study centers. No *de novo* patients will be enrolled.

Patients who have safely completed the lead-in studies may be eligible to participate in this Open-label Safety Study. Lead-in study completion is defined as a patient who completes the double-blind treatment period (ie, all scheduled visits up to and including Visit 8) of the lead-in study.

The study will be conducted as follows:

- A **Screening Period** of one day in duration. Potential patients rolling over from the lead-in studies will be evaluated for eligibility during the Screening/Baseline Visit (Visit 1/Day 1) which is the same visit as Visit 8/Day 43 of the lead-in study. Patients who meet all eligibility criteria at the Screening/Baseline Visit (Visit 1/Day 1) will be dispensed lumateperone 42 mg to be self-administered each evening without respect to food.
- A **26-week Open-label Treatment Period** during which patients will self-administer lumateperone, to be taken each evening, without respect to food. Background ADT should also continue as previously prescribed, with no change of dose from the lead-in studies. Patients will attend visits on Weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26. The Open-label Treatment Period will last a total of 26 weeks. A patient will be defined as a treatment completer if the patient completes the Open-label Treatment Period (all scheduled visits up to and including Visit 16/Week 26).
- A **2-week Safety Follow-up Period.** A Safety Follow-up visit will occur approximately 2 weeks after completion of the Open-label Treatment Period or after the Early Termination (ET) Visit. Any ongoing AEs at the Safety Follow-up 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 prematurely discontinue should be seen for an ET visit as soon as possible and will also be asked to return to for a Safety Follow-up visit approximately 2 weeks after Visit 16/ET visit.

The maximum per-patient study duration for the Open-label Safety Study will be approximately 28 weeks.

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 Protocol.

Table 2-1: Schedule of Evaluations

Study Period	*Screening /Baseline Visit*[1]	*Open-label Treatment Period*[2]															*Safety Follow Up*
Visit Number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16/ ET*	*17*
Study Day	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**
Study Week	*0*	**1 (+/-3 days)**	**2 (+/-3 days)**	**3 (+/-3 days)**	**4 (+/-3 days)**	**6 (+/3 days)**	**8 (+/-3 days)**	**10 (+/-3 days)**	**12 (+/-3 days)**	**14 (+/-3 days)**	**16 (+/-3 days)**	**18 (+/-3 days)**	**20 (+/-3 days)**	**22 (+/-3 days)**	**24 (+/-3 days)**	**26 (+/-3 days)**	**28 (+/-3 days)**
Informed consent	X																
Inclusion/Exclusion criteria	X																
Physical examination	X															X	
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[4]	X	X					X				X					X	
Clinical laboratory assessments (hematology, serum chemistry, urinalysis)[5]	X	X					X				X					X	
Urine drug testing[6]	X	X					X				X					X	
Serum/urine pregnancy test[7]	X	X			X		X		X		X		X		X	X	
MADRS	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	
AIMS/BARS/SAS	X	X			X		X		X		X		X		X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling		X[8]					X[9]										
AEs/SAEs	X	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	X
ADT prescription dispensation[10]	X																
ADT compliance check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	*Screening /Baseline Visit*[1]	*Open-label Treatment Period*[2]															*Safety Follow Up*
Visit Number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16/ ET*	*17*
Study Day	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**
Study Week	*0*	**1 (+/-3 days)**	**2 (+/-3 days)**	**3 (+/-3 days)**	**4 (+/-3 days)**	**6 (+/3 days)**	**8 (+/-3 days)**	**10 (+/-3 days)**	**12 (+/-3 days)**	**14 (+/-3 days)**	**16 (+/-3 days)**	**18 (+/-3 days)**	**20 (+/-3 days)**	**22 (+/-3 days)**	**24 (+/-3 days)**	**26 (+/-3 days)**	**28 (+/-3 days)**
Lumateperone dispensation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Lumateperone return and compliance check		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Scale; CGI-S = Clinical Global Impression Scale Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ET = Early Termination; HbA1c = hemoglobin A1c; MADRS = Montgomery-Åsberg Depression Rating Scale; MINI = Mini-International Neuropsychiatric Interview; PK = pharmacokinetic; SAE=Serious Adverse Event; SAS=Simpson Angus Scale.

1 The Screening/Baseline Visit (Visit 1/Day 1) is the same visit as Visit 8/Day 43 of the lead-in study. In addition to the specified Inclusion and Exclusion criteria for this Open-label Safety Study, medical, psychiatric, and medication histories from the lead-in study will be considered for eligibility at the Screening/Baseline Visit of the Open-label Safety Study. A MINI would not be repeated at the Screening/Baseline Visit (Visit 1/Day 1).

2 During the Open-label Treatment Period, if the patient is unable to travel to the site for an in-person visit or if sites are unable to schedule in-person visits (eg, a natural disaster, pandemic), sites will be permitted to conduct remote visits with approval from the Sponsor or designee. If on-site laboratory and ECG assessments are not feasible, local laboratory and ECG testing are permitted if determined clinically necessary by the Investigator. Remote assessments of MADRS, CGI-S, C-SSRS, and AIMS, BARS, SAS may also be performed, if feasible. Screening/Baseline Visit (Visit 1/Day 1) must be performed in person.

3 Height and BMI will only be collected at Visit 1 and waist circumference will only collected at Screening/Baseline Visit (Visit 1/Day 1) and Visit 16/ET.

4 ECGs will be collected at Screening/Baseline Visit (Visit 1/Day 1), Visit 2, Visit 7, Visit 11, and Visit 16/ET. Unscheduled visits for repeat ECG assessments may be performed at any time for safety reasons or at the discretion of the Investigator.

5 Clinical laboratory assessments are to be taken after an overnight fast of at least 10 hours and will be collected at Screening/Baseline Visit (Visit 1/Day 1), Visit 2, Visit 7, Visit 11, and Visit 16/ET. HbA1c is collected at Screening/Baseline Visit (Visit 1/Day 1) and Visit 16/ET. Unscheduled visits for repeat laboratory assessments may be performed at any time for safety reasons or at the discretion of the Investigator. Hepatitis serology, performed in the lead-in study, will not be repeated at the Screening/Baseline Visit of the Open-label Study.

6 An unscheduled urine drug test may be conducted at any time during the study at the Investigator's discretion.

7 Female patients of childbearing potential must have a negative urine pregnancy test. Because the Screening/Baseline Visit (Visit 1/Day 1) serum pregnancy test results will not be available at the Screening/Baseline Visit (Visit 1/Day 1), patients will be discontinued immediately upon receipt of a positive serum pregnancy test result. For all other visits, a urine pregnancy test will be performed. Unscheduled pregnancy tests may be administered at any time during the study at the Investigator's discretion.

[8] Patients who consent to PK sampling will take the evening dose the day before Visit 2; the date and time of this dose should be recorded as reported by the patient. At Visit 2, patients will be administered the Visit 2 dose of lumateperone at the study site after an overnight fast of at least 10 hours and will continue to fast for at least 2 hours after dosing. The date and time of lumateperone administration at Visit 2 must be recorded. PK sampling will be collected at Visit 2 at predose (within 30 minutes prior to dosing), between 0.5 hour and 1-hour post-dose and between 1.5 hour and 3 hours post-dose. The date and time of PK sample collection at each timepoint must be recorded. Patients will be instructed not to take an evening dose of lumateperone at Visit 2. The next dose of lumateperone should be taken the next evening as prescribed. ADT should be taken as prescribed throughout the PK sampling period.

[9] Patients who consent to PK sampling will have one blood sample collected at Visit 7. The patient-reported date and time of lumateperone administration prior to PK sampling on the evening before Visit 7 should be recorded. The date and time of PK sample collection must be recorded.

[10] Antidepressant prescriptions will be provided to patients as needed through the duration of the study.

3. STUDY OBJECTIVES

The primary objective of the Open-label Safety Study is to evaluate the safety and tolerability of lumateperone 42 mg administered orally once daily for approximately 26 weeks as adjunctive treatment to ADT in patients with MDD.

The secondary objective of the Open-label Safety Study is to evaluate whether lumateperone 42 mg administered orally once daily for approximately 26 weeks as adjunctive treatment to ADT improves or maintains improvement of depressive symptoms in patients with MDD as measured by change from baseline in the MADRS total score and change from baseline in the CGI-S score.

4. ANALYSIS POPULATIONS

4.1 Enrolled Population

The Enrolled Population includes all patients who sign the informed consent for this open label safety study.

4.2 Safety Population

Safety Population includes all patients in the Enrolled Population who receive at least one dose of open-label lumateperone.

5. SUBJECT DISPOSITION

The number of patients in each study population will be summarized by 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 Population will be summarized overall.

In addition, the number and percentage of patients who complete the Open-label Treatment Period and who prematurely discontinued from the Open-label Treatment Period will be summarized overall and by reasons for premature discontinuation for the Safety Population.

6. PROTOCOL DEVIATIONS

Major protocol deviations for the study will be defined as in the Protocol Deviation Management Plan for the Study. The number and percentage of patients with major protocol deviations during the Open-label Treatment Period will be provided overall for the Safety Population.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Prior medical and surgical history at the enrollment of lead-in studies will be summarized for the Safety Population.

Baseline efficacy parameters MADRS total score and CGI-S score will be summarized by for the Safety Population.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Extent of Treatment Exposure

Exposure to open-label lumateperone for the Safety Population will be summarized for treatment duration, calculated as the number of days from the date of the first dose of open-label lumateperone taken to the date of the last dose taken, inclusive. The number and percentage of patients with each treatment duration category will be summarized, respectively.

8.2 Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the total number of capsules of lumateperone actually taken by a patient during the treatment period divided by the number of capsules of lumateperone that is expected to be taken during the Open-label Treatment Period multiplied by 100.

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

8.3 Prior and Concomitant Medication

Prior medication is defined as any medication taken before the date of the first dose of open-label lumateperone. *Prior concomitant medication* is any medication that started before the date of the first dose of open-label lumateperone and stopped or is ongoing after the date of the first dose of open-label lumateperone. *Concomitant* medication is defined as any medication taken on or after the date of the first dose of open-label study drug.

Prior, prior concomitant, and concomitant medication use will be summarized as the number and proportion of patients who received each prior, prior concomitant, and/or concomitant medication within each therapeutic class and preferred term. Multiple medications used by a patient will only be counted once.

Any medication that started after the date of the last dose of open-label lumateperone will not be included in the summary but will be included in the patient data listings.

9. EFFICACY ANALYSES

The efficacy analyses will be based on patients in the Safety Population with an available baseline efficacy value and at least one postbaseline efficacy assessment during the Open-label Treatment Period. Baseline is defined as the last measurement prior to the first dose of double-blind treatment during the lead-in studies (Studies ITI-007-501 and ITI-007-502).

9.1 MADRS Total Score

Descriptive statistics for the change from baseline to each assessment visit in MADRS total score will be provided for each scheduled visit. Also, the number of patients who achieved remission (MADRS total score ≤ 10) will be provided for each scheduled visit. In addition, the responder rate (response is defined as at least 50% reduction in MADRS total score compared to baseline score) will be provided for each scheduled visit.

9.2 CGI-S Score

A descriptive summary for the change from baseline to each assessment visit in CGI-S score will be provided for each scheduled visit.

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. Baseline is defined as the last measurement prior to the first dose of double-blind treatment during the lead-in studies (Studies ITI-007-501 and ITI-007-502).

10.1 Adverse Events

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

An AE that occurs during the Open-label Treatment Period will be considered a treatment-emergent AE (TEAE) if it starts as a new event or if its severity increases during the Open-label Treatment Period. An AE that occurs more than 1 day after the date of the last dose of open-label lumateperone will not be counted as a TEAE.

The number and percentage of patients reporting TEAEs will be tabulated by system organ class (SOC) and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to study drug. 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 drug.

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

The number and percentage of patients reporting serious AEs (SAEs) during the Open-label Treatment Period will be tabulated by SOC and PT. Also, the number and percentage of patients reporting AEs leading to drug withdrawal 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.

The incidence of extrapyramidal symptom (EPS) TEAEs will be summarized by PT and treatment group and will be sorted by decreasing frequency. 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 SI and conventional units) and changes from baseline values at each assessment timepoint and at the end of the Open-label Treatment Period will be summarized for each clinical laboratory parameter:

- **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; ALT; AST; bilirubin (total, direct); blood urea nitrogen; 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 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 Open-label Treatment Period will be tabulated. 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 during the Open-label Treatment Period. 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/µL	< 1.0	—
Platelet count	10^3/µL	≤ 75	≥ 700
White blood cell (WBC) count	10^3/µL	≤ 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
Blood urea nitrogen (BUN)	mg/dL	—	≥ 30
Calcium	mg/dL	< 7	> 12
Chloride	mEq/L	< 90	> 115
Total Cholesterol	mg/dL	—	≥ 300
CPK	mg/dL	—	≥ 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 +

ALT = alanine aminotransferase; AST = aspartate aminotransferase; 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.

[a] Criteria refer to conventional units.

The number and percentage of patients with shifts from baseline at the end of Open-label Treatment Period according to normal range and PCS criteria (PCS Low, Low, Normal, High, PCS High) for each parameter 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 Open-label 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.

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 Open-label Treatment Period will be presented.

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 Open-label Treatment Period will be tabulated 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, mmHg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Supine Diastolic blood pressure, mmHg	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%

bpm = beats per minute.

[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.

The number and percentage of patients with orthostatic hypotension during the Open-label Treatment Period will be provided for the Safety Population. Orthostatic hypotension 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 orthostatic hypotension during the Open-label Treatment Period and Safety Follow-up Period will be provided. A listing of all AEs occurring in patients who experienced orthostatic hypotension 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 Open-label Treatment Period will be summarized.

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 Open-label Treatment Period will be tabulated 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 open-label 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 Open-label 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	—	> 30 and ≤ 60
QTcB, msec	—	Increase of > 60
QTcF, msec	—	> 30 and ≤ 60
QTcF, msec	—	Increase of > 60

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

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

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 Open-label Treatment Period) will be presented 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 Open-label Treatment Period) will be presented 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 Open-label Treatment Period) will be presented 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 for lifetime history (assessed at the enrollment of lead-in studies), baseline, Open-label Treatment Period, and Safety Follow-up for the Safety Population. Baseline of C–SSRS for each patient is defined as the last non-missing 'since last visit' assessment before the first dose of study treatment during the lead-in studies. The distribution of responses for the most severe suicidal ideation and most severe suicidal behavior will be presented.

The severity of suicidal ideation will be presented in the following order:

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

The severity of suicidal behavior will be presented in the following order:

- Preparatory acts or behavior
- Aborted attempt
- Interrupted attempt

- Actual attempt
- Completed Suicide (for Open-label Treatment Period and for Safety Follow-up only)

For each analysis period (lifetime, baseline, Open-label Treatment Period, and safety follow-up), 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 Open-label Treatment Period will be tabulated for the Safety Population:

- Emergence of suicidal ideation (no suicidal ideation at Baseline, and any type of suicidal ideation during Open-label Treatment Period)
- 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] during Open-label Treatment Period)
- Worsening of suicidal ideation (most severe suicidal ideation during Open-label Treatment Period was more severe than it was at Baseline)
- Emergence of suicidal behavior (no suicidal behavior at Baseline, and any type of suicidal behavior during Open-label Treatment Period).

11. HEALTH OUTCOMES ANALYSES

Not applicable.

12. INTERIM ANALYSIS

An interim analysis is planned and will be based on patients who complete or early term the study on or before 30 Apr 2024.

13. SAMPLE SIZE CONSIDERATION

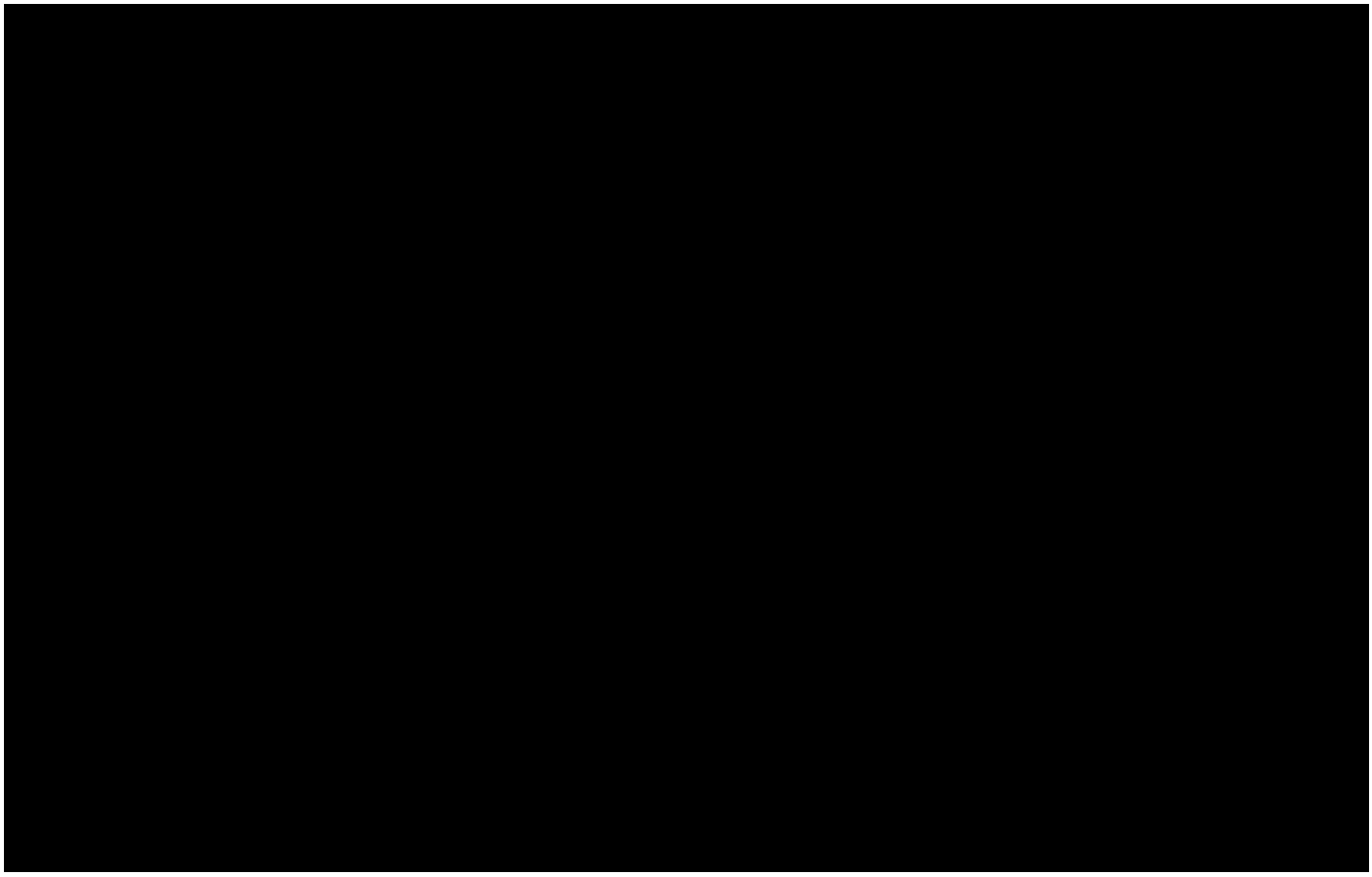
The sample size is not based on statistical power considerations, but is based on the number of patients who may be eligible based on participation in the lead-in studies. It is expected the majority of patients who safely complete the lead-in studies will participate in this 26-week open-label safety study.

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



If more than one assessment is available in the same analysis window for MADRS or for CGI-S, the later/latest record will be selected and assigned to the derived visit.

Table 15-2 presents the visits assigned for AIMS, BARS, and SAS corresponding to the range of treatment days (window) during which an actual visit may have occurred.

Table 15-3 presents the visits assigned for clinical laboratory and ECG assessments corresponding to the range of treatment days (window) during which an actual visit may have occurred.

Table 15-4 presents the visits assigned for vital sign assessments corresponding to the range of treatment days (window) during which an actual visit may have occurred.

[redacted]

15.2 Repeated or Unscheduled Assessments of Safety Parameters

For visits with 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 for the visit. If repeated or unscheduled AIMS, BARS, SAS, vital signs or ECGs occur, apply the time-window rule and select the last non-missing values for each visit or endpoint.

All assessments during the Open-label Treatment Period will be included in PCS value determination and will be presented in the data listings.

15.3 Missing Date of Open-Label Study Treatment

When the date of the last dose of open-label study treatment taken during the Open-label 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 open-label 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 open-label 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 open-label 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 open-label study treatment is missing for an AE that started on or after the first dose date of open-label study treatment, a causality of *yes* will be assigned. The imputed values for relationship to open-label 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 open-label study treatment, then the day and month of the date of the first dose of open-label 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 open-label 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 open-label 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 open-label study treatment, then the day of the date of the first dose of open-label 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 open-label study treatment or 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 open-label 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 open-label study treatment or 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 open-label 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 open-label study treatment, the date of the first dose of open-label study treatment will be assigned to the missing start date;
- If the stop date is before the date of the first dose of open-label 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 open-label study treatment, then the month and day of the date of the first dose of open-label 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 open-label 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 open-label 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 open-label study treatment, then the day of the date of the first dose of open-label 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 open-label study treatment or 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 open-label 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 open-label study treatment or 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 open-label 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 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 open-label study treatment, then the month and day of the date of the last dose of open-label 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 open-label 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 open-label 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 open-label 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 open-label 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 open-label 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 open-label study treatment or 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 open-label 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 as shown in Table 15-5, 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 15-5: 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).

16. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

No major changes made to the analyses specified in the latest protocol amendment for Study ITI-007-503 Amendment 1 (dated 23 Aug 2021).

17. REFERENCES

None.

18. APPENDICES

None.