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

Protocol Version 2 Date: 23 May 2022

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

Protocol Number:	**ITI-007-304**
Original Protocol Date:	18 Dec 2020
Amendment #1 Date	10 Mar 2021
Amendment #2 Date	23 May 2022
Compound	Lumateperone
Sponsor	Intra-Cellular Therapies, Inc. [redacted]

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Acceptance of this document constitutes agreement that the information contained herein will not be disclosed to others without written authorization from the Sponsor. All financial and nonfinancial support for this study will be provided by Intra-Cellular Therapies, Inc. (ITI or ITCI). 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 ITCI.

This study will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), US Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and all applicable local regulations.

PROTOCOL AMENDMENT #2: MAJOR CHANGES

Protocol Amendment 2 for Study ITI-007-304, dated 23 May 2022, provides revisions and clarifications to Protocol Amendment 1 (dated 10 Mar 2021; see Appendix II for the Summary of Changes in Protocol Amendment 1). Major changes to the protocol are summarized in the table below.

New text is ***bold and italicized***; deleted text is displayed as ~~strikethroughs~~. Editorial and formatting corrections or minor revisions for consistent terminology usage are not summarized in this table.

Protocol Section	Revision	Rationale
Section 1, Table 1-1 (Schedule of Evaluations–Screening and Open-label Phases), Table 1-2 (Schedule of Evaluations-Double-blind Treatment Phase),and Section 6.1–Overall Study Design and Plan	***For both Table 1-1 and Table 1-2:*** ***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.*** ***At the end of Table 1-1 only:*** ***"… All Screening (V1), Baseline (V2), and Randomization (V14) assessments must be performed in person."***	**Added** Table Note permitting remote visits with approval from the Sponsor or Sponsor's representative for patients who may be unable to travel to the site for an in-person visit or if the site is unable to schedule an in-person visit.
Section 3–Study Administrative Structure	"***Contact information for the clinical vendors responsible for study conduct and a list of Sponsor study contacts are*** provided in the Study Reference Manual."	**Clarification:** In addition to the vendor contact information, Sponsor personnel contact information is also provided in the Study Reference Manual.

Protocol Section	Revision	Rationale
Section 6.1, Overall Study Design and Plan–Stabilization Phase	***NOTE: With approval from the Sponsor or Sponsor's representative, sites will be permitted to conduct remote visits if the patient is unable to travel to the site for an in-person visit or if the site is unable to schedule an in-person visit. However, all Screening (Visit 1), Baseline (Visit 2), and Randomization (Visit 14) assessments must be performed in person. For any remote visit that requires specific stability criteria to be met, at a minimum, Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Scale–Severity (CGI-S), Columbia–Suicide Severity Rating Scale (C-SSRS), and adverse event (AE) evaluation must be performed and documented.***	**Clarification** regarding in-person study visit assessments.
	• "… 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: o Completion of the 12-week SP through Visit 14 (end of Week 18) o PANSS total score ≤ 60 at Visit 14 (end of Week 18) o ***The 20% or greater decrease in PANSS total score from Baseline, which is required to enter the Stabilization Phase at Visit 8, must be maintained from Visit 8 through 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)~~…"	**Clarification** regarding eligibility for the Double-blind Treatment Phase
Section 6.4.2, Exclusion Criterion 24c	Corrected hemoglobin units: The patient has abnormal laboratory values or clinical findings at the Screening Visit that are judged to be clinically significant including, but not limited to: c. Hemoglobin < 8 ~~mg~~**/dL** (80 g/L) for females and ≤ 9 ~~mg~~**/dL** (90 g/L) for males	**Typographical correction.**
Section 7.1, Treatments Administered–3rd paragraph	Study drug will be supplied as capsules provided in blister cards. ***Each study drug kit, dispensed at weekly visits, contains a supply of 10 doses; 7 doses for daily administration as outlined per protocol, and 3 extra doses which allow for a ± 3-day window at any visit other than baseline.***	**Added** text pertaining to content of study drug kit.
Section 8.3.4, Clinical Laboratory Determinations–Chemistry	"…fasting insulin (assessed at Baseline (Visit 2), Visit 14 [end of Week 18], ~~Visit 24 [end of Week 34],~~ and Visit 29/ET Visit only);"	**Correction**: fasting insulin is not collected at Visit 24.
Section 8.3.4, Clinical Laboratory Determinations–Urinalysis	"**Urinalysis:** macroscopic (pH, specific gravity, glucose, protein, ketones, nitr***i***~~a~~tes, blood)	**Typographical correction:** assessment of nitrites in urine will be conducted.

Protocol Section	Revision	Rationale
Section 8.3.4, Clinical Laboratory Determinations–Urine Drug Screen	"…Urine drug (amphetamines, barbiturates, benzodiazepines, cannabinoids [THC], cocaine metabolites, methadone, opiates, phencyclidine~~, propoxyphene~~) and alcohol tests will be performed…"	**Deleted** "propoxyphene" from list of substances tested in urine drug screen.
Section 9.4.4.1, Primary Efficacy Parameter	"…Estimates of the hazard ratio and 95% confidence interval will be based on the Cox proportional hazards model with treatment group ~~and baseline PANSS total score~~ as the explanatory variable~~s~~. ***The proportional hazard assumption will be explored by the following graphical methods (Hess 1995):*** • ***Plotting the log of cumulative hazard functions vs. time*** • ***Arjas plot of estimated cumulative hazard rates vs. number of failures*** • ***Plot of scaled Schoenfeld residuals residual vs. time*** The cumulative distribution function of time to relapse will be characterized by the Kaplan-Meier curves. ***The proportion of relapse-free patients at Week 26 will be provided for the lumateperone group and for placebo group separately using the product limit estimator. The associated pointwise confidence intervals for the proportional of relapse-free patients at Week 26 will be constructed using the Greenwood's formula and the linear transformation. The treatment difference in proportion of relapse-free patients at Week 26 and associated confidence interval will also be provided (Klein et al. 2007). Interpretation of the treatment effects based on hazard ratio or cumulative difference in proportions of patients with relapse-free at Week 26 will be discussed based on the assumptions of each method…"***	**Modification** of the primary efficacy analysis based on FDA comments.

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LIST OF ABBREVIATIONS

AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	human chorionic gonadotropin
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
BP	blood pressure
C–SSRS	Columbia–Suicide Severity Rating Scale
CDSS	Calgary Depression Scale for Schizophrenia
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression Scale–Severity
DBTP	Double-blind Treatment Phase
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EDC	electronic data capture
EPS	Extrapyramidal symptoms
ET	early termination
FDA	Food and Drug Administration
FOCBP	Females of childbearing potential
FR	Federal Register
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	International Ethics Committee
IND	Investigational New Drug (application)

IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LOCF	last-observation-carried-forward
MMRM	mixed-effect model for repeat measurement
OC	observed case
PANSS	Positive and Negative Syndrome Scale
PSP	Personal and Social Performance Scale
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/<RR>^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/<RR>^{1/3}$)
RIP	Run-in Phase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson Angus Scale
SFU	Safety Follow-up
SCI-PANSS	Structured Clinical Interview for the Positive and Negative Syndrome Scale
SCID-5-CT	Structured Clinical Interview for DSM-5 Clinical Trials Version
SP	Stabilization Phase
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal

1. PROTOCOL SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study ITI-007-304	
Title of Study	A Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Lumateperone for the Prevention of Relapse in Patients with Schizophrenia
Study Centers (Country)	Approximately 60 study centers (United States and outside the United States)
Development Phase	Phase 3
Objectives	Primary objective: • To evaluate the efficacy and safety of lumateperone relative to placebo in the prevention of relapse of symptoms in patients with schizophrenia.
Study Design	This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in adult patients with a primary diagnosis of schizophrenia according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5). The study will be conducted in the following 5 phases: • A no-drug Screening Phase up to 7 days in duration during which patient eligibility will be assessed; • A 6-week, open-label Run-in Phase (RIP) during which all patients will receive oral lumateperone 42 mg/day starting at Visit 2; • A 12-week, open-label Stabilization Phase (SP) during which all patients will receive oral lumateperone 42 mg/day; • A Double-blind Treatment Phase (DBTP) 26 weeks in duration during which patients receive either lumateperone 42 mg or placebo (1:1 ratio); • A 2-week Safety Follow-up (SFU) Phase. All patients will be in an inpatient facility during the Screening Phase and for up to 3 weeks during the RIP. Patients may be discharged earlier during the RIP. While inpatient, patients may be issued day passes and allowed to leave the inpatient facility temporarily at the discretion of the Investigator. Patients who are issued day passes must be escorted by staff, caregiver, or approved designee. Safety and tolerability will be assessed throughout the study.
Number of Patients	Approximately 800 patients will be enrolled to allow for 200 randomized patients. However, the number of enrolled patients may be adjusted so that the goal of 200 randomized patients is met.
Diagnosis and Main Criteria for Inclusion and Exclusion	***Main Inclusion Criteria*** A patient will be considered eligible for participation in the trial if he/she meets the following inclusion criteria: 1. Provide written informed consent (signed or thumb-printed, in accordance with local regulations to ensure protection of patient's rights) obtained before the initiation of any study procedures; 2. Patient must identify a caregiver who provides consent to participate in the study; 3. Male or female, 18 to 60 years of age, inclusive; 4. Current diagnosis of schizophrenia according to DSM-5 criteria as determined by the modified Structured Clinical Interview for DSM-5 (modified SCID-5-CT); 5. Diagnosis of schizophrenia for a minimum of 1 year before Visit 1;

	6. Current psychotic episode < 4 weeks duration at Visit 1; 7. Positive and Negative Syndrome Scale (PANSS) total score ≥ 70 and ≤ 120 at Visit 1 and Visit 2. 8. Rating of ≥ 4 (moderate) on at least 2 of the following PANSS positive symptoms at Screening (Visit 1) and Baseline (Visit 2): delusions (P1); hallucinatory behavior (P3); conceptual disorganization (P2); and suspiciousness/persecution (P6). All Inclusion Criteria are presented in Section 6.4.1. ***Main Exclusion Criteria*** Patients who meet any of the following exclusion criteria will not be eligible to participate in the study: 1. Currently meets DSM-5 criteria for any of the following: a. Schizoaffective disorder, schizophreniform disorder, and other psychotic disorders, except for schizophrenia; b. Bipolar I or Bipolar II disorder; c. Intellectual developmental disorder, delirium, dementia, amnestic and other cognitive disorders; d. Known or suspected borderline or antisocial personality disorder or other DSM-5 personality disorder of sufficient severity to interfere with participation in this study; e. Substance use disorder (other than nicotine) within the 3 months prior to Visit 1 of this study; 2. Patients in their first episode of psychosis; 3. Treatment-resistant schizophrenia over the last 2 years, defined as little or no symptomatic response to at least 2 courses of antipsychotic treatment of an adequate duration (at least 6 weeks) and at a therapeutic dose (according to the package insert for the antipsychotic treatment); 4. History of intolerance or hypersensitivity to a typical or atypical antipsychotic or to designated rescue medications or any history of severe drug allergy or hypersensitivity; All Exclusion Criteria are presented in Section 6.4.2.
Duration of Treatment	Study duration will be approximately up to 47 weeks based on the following study phases: Screening Phase of up to 7 days followed by a 6-week open-label RIP; a 12-week open-label Stabilization Phase; a DBTP of 26 weeks; and a 2-week SFU Phase.
Test Product, Dosage, and Mode of Administration	Lumateperone 42 mg capsules, oral administration; 42 mg once daily
Reference Therapy, Dosage, and Mode of Administration	Placebo capsules, oral administration, once daily (DBTP only)

Criteria for Evaluation	
Primary Efficacy Endpoint	The primary efficacy endpoint is time to first symptom relapse during the DBTP, defined as the number of days from the randomization date to the first relapse date. Relapse during the DBTP is defined as meeting 1 or more of the following relapse criteria: • Psychiatric hospitalization or need for increased level of psychiatric care due to worsening of the patient's underlying condition; • Demonstrate an increase in PANSS total score by ≥ 30% for patients with PANSS total score ≥ 50 at randomization or demonstrate a ≥ 10-point or more increase in PANSS total score for patients who scored < 50 at randomization. NOTE: Patients should also meet this criterion at a second assessment that is 4 to 7 days apart unless, based on Investigator discretion, a second assessment cannot be performed due to severity of symptoms; • Demonstrate an increase ≥ 2 points in the Visit 14 Clinical Global Impression Scale-Severity (CGI-S) score. NOTE: The patient should also meet this criterion at a second assessment that is 4 to 7 days apart unless, based on Investigator discretion, a second assessment cannot be performed due to severity of symptoms; • Deliberate self-injury or aggressive/violent behavior; • 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: The patient should also meet this criterion at a second assessment that is 4 to 7 days apart unless, based on Investigator discretion, a second assessment cannot be performed due to severity of symptoms.
Additional Efficacy Endpoints	PANSS total score, CGI-S, Calgary Depression Scale for Schizophrenia (CDSS), and Personal and Social Performance Scale (PSP).
Safety Measures	Adverse event (AE) recording; clinical laboratory parameters (hematology, chemistry, urinalysis, prolactin); vital sign parameters (including orthostatic blood pressure); electrocardiograms (ECGs); physical examinations; C-SSRS; measures of extrapyramidal symptoms (EPS): Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), and pregnancy test (if applicable).

Statistical Methods and Sample Size	Detailed statistical methods will be described in a separate statistical analysis plan. ***Analysis Populations*** Run-in Phase Safety Population will consist of all patients who took at least 1 dose of open-label RIP study drug. Stabilization Phase Safety Population will consist of all patients who took at least 1 dose of SP study drug. Double-blind Safety Population will consist of all randomized patients who took at least 1 dose of double-blind study drug. Double-blind Intent-to-Treat (ITT) Population will consist of all patients in the Double-blind Safety Population. ***Efficacy Analyses*** The primary efficacy analysis will compare the time to relapse between placebo and lumateperone groups using the log-rank test based on the Double-blind ITT Population. Estimates of the hazard ratio and 95% confidence intervals will be based on the Cox proportional hazards model with treatment group and the baseline PANSS total score as the explanatory variables. The cumulative distribution function of time to relapse will be characterized by the Kaplan-Meier curves. All additional efficacy parameters will be analyzed by visit for the Double-blind ITT Population using the last-observation-carried-forward (LOCF) and observed cases (OC) approaches. ***Safety Analyses*** All safety parameters will be analyzed using descriptive statistics separately for the RIP, for the SP, and for the DBTP using the corresponding Safety Populations.

Table 1-1: 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 1-2: 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.

2. ETHICAL CONSIDERATIONS

2.1 Institutional Review Board and Independent Ethics Committee

Approval by the Institutional Review Board and International Ethics Committee (IRB/IEC) is required before the start of the study. A copy of the approval letter will be supplied to Intra-Cellular Therapies, Inc. (the Sponsor) or its designee along with a roster of IRB/IEC members. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the IRB/IEC of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs/IECs at the study centers in conformance with US CFR, Title 21, Part 56 and applicable local regulations.

2.2 Ethical Conduct of the Study

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. This clinical study will comply with the ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and GCP (ICH-E6; 62 FR 25692, March 2018), as well as CFR Part 312 and applicable local regulations.

2.3 Patient Information and Informed Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the study or performing any study-specific procedure that involves risk to the patient. If any institution-specific modifications to study-related procedures are proposed or made by the study site, the consent should be reviewed by the Sponsor, its designee, or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the study, all active participating patients must sign the revised form. The informed consent statement shall contain all the elements of informed consent listed in Appendix I.

Before any screening procedures, a consent form describing in detail the study procedures and risks will be given to the patient. The patient is required to read and review the document or have the document read to him/her. The Investigator or designee will explain the research study to the patient and answer any questions that may arise. Once the Investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing or thumbprinting the ICF prior to any study-related assessments or procedures. Patients will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed or thumb-printed informed consent document will be given to patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The Investigator will also sign the ICF and provide copies of the ICF and the HIPAA (Health Insurance Portability and Accountability Act) authorization or other locally applicable form to the patient. The Investigator shall retain the signed original ICF and HIPAA authorization or other locally applicable form.

2.4 Caregiver Information, Consent and Responsibility

Caregivers, after being given an explanation of the study, will give voluntary and written informed consent before participating in the study. Caregivers must sign or thumbprint the consent form before the patient is discharged from the inpatient facility.

Caregivers will read or be read (if he or she cannot read or write), assent understanding of, and sign or thumb-print an informed consent after having had an opportunity to discuss it with the study staff before signing; each caregiver will be made aware that he/she may withdraw oversight of the patient's caregiver role as it pertains to the study any time. A patient may have up to 2 persons designated as a caregiver at any given time. Each caregiver will provide a separate ICF, and a new ICF will be obtained from replacement caregivers. In addition, individual country regulations regarding procedures for obtaining informed consent will be followed.

When a patient is discharged, it is the responsibility of the Investigator to ensure, to the best of his/her ability, that the patient has a designated caregiver who has sufficient knowledge of and contact with the patient to assist the patient with: medication and visit schedule compliance; with providing the site information regarding the patient's current health status and underlying psychiatric condition, including any decompensation and worsening of symptoms; and to ensure that the medication is stored safely in the patient's place of residence. If the patient resides in an assisted-living facility, the Investigator must determine that the caregiver meets the above criteria. Any patient whose caregiver becomes unavailable will be discontinued from the study unless a suitable replacement can be found.

3. STUDY ADMINISTRATIVE STRUCTURE

Contact information for the clinical vendors responsible for study conduct and a list of Sponsor study contacts are provided in the Study Reference Manual.

4. INTRODUCTION

Schizophrenia is a chronic, disabling neuropsychiatric disease. The prevalence of schizophrenia in the United States is estimated to be 2.4 million adults and approximately 100,000 new cases are diagnosed each year (Chong et al, 2016). Its onset is generally in late adolescence or early adulthood. The course of schizophrenia is characterized by acute exacerbations of psychosis (delusions and hallucinations) and chronic negative symptoms (blunted affect, disorganization and paucity of spontaneous speech and thought, difficulty in abstract thinking, and impairment of social functioning) that persist throughout life, often with gradual deterioration of cognitive and social skills.

Relapses in schizophrenia are common and over time each relapse event is characterized by worsening symptoms, increased cognitive impairment, deteriorating social functioning, and poorer quality of life. Poor adherence with antipsychotic medication is associated with higher risk of relapse and hospitalization (Olivares et al, 2013). Non-adherent patients are more likely to be hospitalized for a mental health reason, more likely to visit the emergency room for a mental health reason, and more likely to relapse vs adherent patients. Products with improved benefit-risk profiles have the potential to reduce rates of relapse.

Lumateperone is a small-molecule with an innovative mechanism of action that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, three key neurotransmitters implicated in schizophrenia. Lumateperone has additional pharmacologic properties that are not shared by other atypical antipsychotics. It indirectly enhances glutamate neurotransmission via dopamine D_1 receptor activation, leading to increased activity at N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-isoxazoleproprionic acid (AMPA) receptors. In addition, lumateperone inhibits serotonin uptake at the serotonin transporter, a property it shares with selective serotonin receptor inhibitor antidepressants. Lumateperone also lacks activity at muscarinic, histaminergic, and $5\text{-}HT_{2C}$ receptors which are associated with metabolic and cardiovascular adverse effects of existing antipsychotic drugs.

On December 20, 2019, lumateperone 42 mg (CAPLYTA®) was approved by the US Food and Drug Administration for the treatment of schizophrenia in adults (CAPLYTA USPI, 2019). Lumateperone has been demonstrated to be safe and well tolerated in patients with schizophrenia at doses up to 84 mg. A 42-mg dose of lumateperone demonstrated statistically significant improvement in psychosis as demonstrated by a reduction in Positive and Negative Syndrome Scale (PANSS) total score compared with placebo after 28 days of oral administration in adult patients with schizophrenia. In addition, treatment with lumateperone was not associated with the increases in cardiometabolic, motor, and prolactin effects commonly seen with other antipsychotic medications.

The current relapse prevention study was designed to assess the efficacy, safety, and tolerability of long-term treatment with lumateperone for prevention of symptomatic relapse in adult patients with schizophrenia.

5. STUDY OBJECTIVES

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.

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

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 RIP of this study, and at least 200 patients are expected to be randomized in a 1:1 ratio (lumateperone: placebo) to the DBTP. The maximum per-patient study duration will be up to approximately 47 weeks.

NOTE: With approval from the Sponsor or Sponsor's representative, sites will be permitted to conduct remote visits if the patient is unable to travel to the site for an in-person visit or if the site is unable to schedule an in-person visit. However, all Screening (Visit 1), Baseline (Visit 2), and Randomization (Visit 14) assessments must be performed in person. For any remote visit that requires specific stability criteria to be met, at a minimum, Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Scale–Severity (CGI-S), Columbia–Suicide Severity Rating Scale (C-SSRS), and adverse event (AE) evaluation must be performed and documented.

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** (RIP) 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)
    - 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 Double-Blind Treatment Phase, 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 Double-blind Treatment Phase. All patients will have an Early Termination (ET) Visit and enter the Safety Follow-up Phase.

- An up to 26-week **Double-blind Treatment Phase** (DBTP) 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)
  - The 20% or greater decrease in PANSS total score from Baseline, which is required to enter the Stabilization Phase at Visit 8, must be maintained from Visit 8 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.

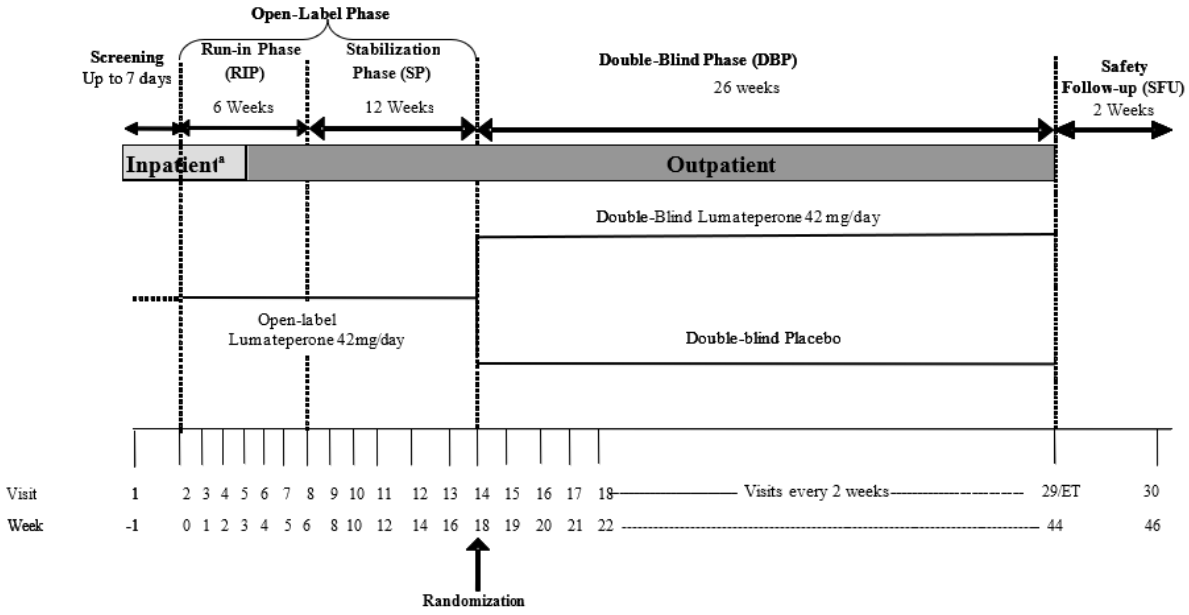
These criteria must be met at every visit in SP, with one excursion from these criteria allowed after the patient enters the SP. This excursion cannot occur at the randomization visit (Visit 14).

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** (SFU) Period: 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 period. 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 study design schematic is provided in Figure 6-1. The Schedule of Evaluations for the Screening, RIP, and SP is presented in Table 1-1; for the DBTP and SFU, in Table 1-2. Detailed descriptions of the procedures conducted at each study visit are provided in Section 8.4.

Figure 6-1: Study Design



a All patients will be admitted to an inpatient facility during the Screening Phase and for up to 3 weeks during the RIP. Patients may be discharged earlier during the RIP.
ET = early termination; RIP = Run-in Phase.

6.2 Relapse Criteria

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 in PANSS total score for patients who scored less than 50 at randomization (Note: Patients 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 Visit 14 CGI-S score by 2 or more points (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]);
- Deliberate self-injury or aggressive/violent behavior;
- Any suicidal ideation or homicidal ideation;
- Score of greater than 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 meet 1 or more of the above relapse criteria will be discontinued from the study, will proceed to the final ET assessment, and will return for the SFU visit.

6.3 Scientific Rationale for Study Design

6.3.1 Study Design

The placebo-controlled, fixed-dose, randomized-withdrawal design is considered standard to demonstrate effectiveness of long-term maintenance treatment.

The 6 weeks of open-label treatment in the RIP is designed to establish patients responding to lumateperone at 42 mg/day dose level; the 12 weeks of open-label treatment in the SP is designed to ensure sustained response following continuation treatment with lumateperone 42 mg/day dose at the end of the RIP.

The double-blind design is included to minimize systematic bias resulting from the scale raters, the patient, or Investigator knowing which treatment is being administered to patients. Randomization at the beginning of the DBTP is expected to minimize patient selection bias and increase baseline comparability of the 2 treatment groups.

The use of placebo control is critical to the study design both to understand the safety findings of the drug and to ensure that efficacy results can be interpreted. In this study, the placebo control is used during the DBTP to demonstrate the reemergence of schizophrenia symptoms upon withdrawal of lumateperone compared with patients who continue lumateperone treatment. Patients who continue on lumateperone treatment should maintain improvement in their schizophrenia symptoms, whereas those who switch to placebo should have a return of schizophrenia symptoms.

The fixed-dose design during the DBTP was selected to maintain patients at the lumateperone 42 mg/day dose level at which their schizophrenia symptoms had responded and to minimize the potential for relapse.

The variable duration of the DBTP with a maximum of 26 weeks was selected to provide sufficient time to demonstrate schizophrenia relapse upon withdrawal of lumateperone.

The 2-week SFU period allows continued patient monitoring after study drug has been discontinued.

6.3.2 Dose Selection

Lumateperone dose of 42 mg/day was selected for this study based on FDA approval of CAPLYTA for the treatment of adult patients with schizophrenia.

6.4 Study Population

6.4.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet the following inclusion criteria:

1. Provide written informed consent (signed or thumb-printed in accordance with local regulations to ensure protection of patient's rights) before initiation of any study procedures;
2. Patient must identify a caregiver who provides consents to participate in the study (See Section 2.4 for Caregiver Consent information);
3. Male or female, 18 to 60 years of age, inclusive;
4. Current diagnosis of schizophrenia according to DSM-5 criteria as determined by the modified Structured Clinical Interview for DSM-5 (modified SCID-5-CT);
5. Diagnosis of schizophrenia for a minimum of 1 year before Visit 1;
6. Current psychotic episode < 4 weeks duration at Visit 1;
7. PANSS total score ≥ 70 and ≤ 120 at Visit 1 and Visit 2;
8. Rating of at least 4 (moderate) on at least two of the following four PANSS positive symptoms: delusions (P1), hallucinatory behavior (P3), conceptual disorganization (P2), suspiciousness/persecution (P6) at Visit 1 and Visit 2;
9. Patient is capable of being compliant with self-administration of medication or has caregiver that can ensure compliance with study drug administration;
10. Negative pregnancy test at screening (applies to female patients of childbearing potential only [FOCBP]) and must have a negative pregnancy test at Baseline (Visit 2);
11. Normal physical examination findings, vital signs, clinical laboratory test results, and electrocardiogram (ECG) results or abnormal results that are judged not clinically significant by the Investigator;
12. Body mass index (BMI) between 18 and 40 kg/m^2, inclusive;
13. Patient and caregiver must be able to speak and understand the local language sufficiently to understand the nature of the study.

6.4.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study**.**

Psychiatric Criteria:

1. Currently meeting DSM-5 criteria for any of the following:
    a. Schizoaffective disorder, schizophreniform disorder, and other psychotic disorders, except schizophrenia;
    b. Bipolar I or Bipolar II Disorder;
    c. Intellectual developmental disorder, delirium, dementia, amnestic and other cognitive disorders;
    d. Known or suspected borderline or antisocial personality disorder or other DSM-5 personality disorder of sufficient severity to interfere with participation in this study;
    e. Substance use disorder (other than nicotine) within the 3 months prior to Visit 1 of this study;
2. Patients in their first episode of psychosis;
3. Treatment-resistant schizophrenia over the last 2 years, defined as little or no symptomatic response to at least 2 courses of antipsychotic treatment of an adequate duration (at least 6 weeks) and at a therapeutic dose (according to the package insert for the antipsychotic treatment);
4. History of intolerance or hypersensitivity to a typical or atypical antipsychotic or to designated rescue medications or any history of severe drug allergy or hypersensitivity;
5. In the opinion of the Investigator, the patient has significant risk for suicidal behavior during the course of his/her participation in the study or:
    a. At Screening (Visit 1), the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the Columbia–Suicide Severity Rating Scale (C-SSRS) within 6 months prior to screening; or
    b. At Screening (Visit 1), the patient has had 1 or more suicide attempts within 2 years prior to screening; or
    c. At Baseline (Visit 2), the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS since Screening (Visit 1); or
    d. The patient is considered to be an imminent danger to him/herself or to others.

Treatment-related Criteria:

6. Electroconvulsive therapy (ECT) in the 3 months before Visit 1;
7. Previous lack of response to ECT;
8. Treatment with a depot neuroleptic within 1 cycle before Visit 1;

9. Treatment with clozapine in the past 10 years (EXCEPTIONS FOR NON-US COUNTRIES: With prior approval from the Study Physician or designee, a history of episodic use of clozapine at doses ≤ 100 mg/day for the treatment of insomnia or past use of clozapine at doses ≤ 350 mg/day as treatment for schizophrenia symptoms in patients who had not demonstrated treatment resistance or intolerance to other antipsychotics and who did not require it for the treatment of suicidality);
10. Requiring concomitant treatment with any of the prohibited medications, supplements, or herbal products, including any psychotropic drug or any drug with psychotropic activity or with a potentially psychotropic component, except for the following (see Section 7.7.3 for details):
    a. Lorazepam (or other benzodiazepines in countries where lorazepam is not readily available which must be approved by the Study Physician or designee) for agitation, irritability, hostility, and restlessness;
    b. Zolpidem or other hypnotics for insomnia which must be approved by the Study Physician or designee;
    c. Diphenhydramine, benztropine or equivalent (eg, trihexyphenidyl), or propranolol for EPS or akathisia.
11. At Visit 2, requiring pharmacologic treatment for the control of EPS;
12. Prior participation in any investigational study of lumateperone (ITI-007) with a last dose within 1 year prior to Visit 1 of this study.

Other Medical Criteria:

13. Positive result from the blood alcohol test or from the urine drug screen (UDS) for prohibited medications or substances (EXCEPTIONS: Patients with a positive UDS for cannabinoids, opiates, barbiturates, or benzodiazepines may be allowed in the study provided that communication with the Study Physician or designee has occurred and the use of such products can be discontinued before participation in the study. Medically appropriate episodic use [up to 3 days] of narcotic analgesics for acute medical indications is allowed during the study; discussion with Study Physician or designee is recommended);

14. Female patients who meet the following criteria:
    a. Pregnant, breastfeeding, and/or planning to become pregnant and/or breastfeed during the study;
    b. Is not at least 1 year postmenopausal, surgically sterile (tubal ligation, tubal occlusion, bilateral oophorectomy, or hysterectomy), or practicing a highly effective method of contraception that will continue for the duration of the study. Highly effective contraception is defined as products, used alone or in combination, that result in a failure rate less than 1 percent per year when used consistently and correctly. Women using a hormonal contraceptive must have been doing so for at least 1 month before Visit 1 and must follow the package insert instructions concerning additional protection at times when doses might be missed. Rhythm, withdrawal, single-barrier contraceptive methods, and abstinence are not acceptable methods of contraception;
15. Any concurrent medical condition that, in the judgment of the Investigator, might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the patient's well-being;
16. Any cardiovascular disease that is clinically significant, unstable, or decompensated. Additionally, patients with any of the following conditions are excluded from participation in the study:
    a. History of congenital QTc prolongation or presence of QTc prolongation (QTcF > 450 msec for men and QTcF > 470 msec for women on screening ECG);
    b. Second-degree (if Mobitz II) or third-degree atrioventricular block;
    c. History (≤ 1 year before Visit 1) of clinically manifest ischemic heart disease including myocardial infarction, stable or unstable angina, coronary arteriography, or cardiac stress testing/imaging with findings consistent with coronary occlusion or infarction;
    d. Heart rate on supine vital sign measurement of < 50 bpm or > 120 bpm or any heart rate that is clinically symptomatic;
    e. Premature ventricular contractions associated with clinical symptoms and/or any complex premature ventricular contractions;
    f. Atrial fibrillation or flutter that is symptomatic or associated with uncontrolled heart rate or hemodynamic instability, requires anticoagulation, or is of recent (< 12 months) or unknown onset;
    g. Any blood pressure (BP) that is symptomatic or clinically significant, in the opinion of the Investigator;
17. Hypo- or hyperthyroidism, unless stabilized on appropriate pharmacotherapy with no change in dosage for at least 3 months before Visit 1;
18. Psychiatric symptoms possibly secondary to any other general medical condition (eg, Vitamin B-12/folate deficiency, Cushing syndrome, etc);

19. Gastric bypass or any condition that would be expected to affect drug absorption (gastric banding procedures are acceptable if not associated with absorption problems);
20. History of seizure disorder, stroke, significant head injury, tumor of the central nervous system, or any other condition that predisposes the patient toward a risk for seizure;
21. Known human immunodeficiency virus infection;
22. Positive test for hepatitis B surface antigen and/or hepatitis B core antibody immunoglobulin M at Screening;
23. Positive hepatitis C antibody at Screening (Visit 1), with the exception of patients for whom the reflex HCV RNA test is negative;
24. The patient has abnormal laboratory values or clinical findings at the Screening Visit that are judged to be clinically significant including, but not limited to:
    a. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN);
    b. Total bilirubin > 1.5 ULN;
    c. Hemoglobin < 8 g/dL (80 g/L) for females and ≤ 9 g/dL (90 g/L) for males;
    d. Absolute neutrophil count (ANC) < 1200 cells/µL (1.2×10^9/L);
    e. Thyroid-stimulating hormone (TSH) outside of the normal limits and clinically significant, as determined by the Investigator. Free T3 and free T4 will be measured if TSH level is out of the normal range. The patient will be excluded if the free T3 or free T4 level is out of range;
    f. Any other clinically significant abnormal laboratory result obtained at the Screening Visit.

    NOTE: Medical conditions that are stable with medication (eg, diabetes mellitus, hypercholesterolemia, and thyroid abnormalities) are allowed as long as the condition has been stable for at least 3 months prior to Screening, the associated medications are documented and kept stable during the study, and the condition is thought not to affect safe participation in the study, in the opinion of the Investigator and confirmed by the Study Physician or designee;
25. History of tardive dyskinesia (except for mild cases attributed to use of conventional agents), serotonin syndrome, or neuroleptic malignant syndrome;
26. History of syndrome of inappropriate antidiuretic hormone secretion.

Other Exclusion Criteria

27. Patient is homeless;
28. Treatment with any investigational product within the 6 months (or at least 5 half-lives, whichever is longer) before Visit 1;
29. Employee or immediate relative of an employee of Intra-Cellular Therapies, Inc., any of its affiliates or partners, or the study center;

30. Unable or unlikely to comply with the study protocol or is unsuitable for any other reason, as judged by the Investigator.

6.5 Discontinuation of Patients from Therapy or Assessment

A discontinuation will occur when a patient who ceases participation in the study, regardless of circumstances, before the completion of all study visits and procedures. Patients can be discontinued from the study for one of the following reasons:

- AE
- Lack of efficacy or insufficient therapeutic response
- Death
- Lost to follow-up
- Pregnancy
- Protocol violation, including lack of compliance
- Site terminated by Sponsor
- Study terminated by Sponsor
- Withdrawal of consent by the subject
- Other reasons such as physician decision, caregiver becomes unavailable, or administrative reasons
- Ineligible to continue to SP
- Ineligible to continue to DBTP
- Meeting criteria for a relapse event (applicable only to the DBTP).

NOTE*:* If a patient discontinues due to withdrawal of consent and either a concurrent AE was reported or concurrent lack of efficacy was documented, the study site should query and confirm the primary reason for discontinuation and record the primary reason for discontinuation on the electronic case report form (eCRF).

Patients who discontinue from the study and do not return to the study center for final assessments must be requested in writing to return to the study center for a final assessment. A copy of the letter, together with the source documentation, will be kept in the Investigator's files. The reason for premature discontinuation from the study will be recorded on the Study Termination Page of the eCRF. Study center staff may be contacted by the Sponsor after each premature discontinuation to ensure that proper characterization of the reason for discontinuation is captured.

All patients who prematurely discontinue from the study regardless of cause should be seen for final assessments at the ET Visit. All patients who prematurely discontinue from the study should return for the SFU visit.

Patients who do not meet inclusion criteria or who meet any exclusion criteria will be considered screen failures.

6.6 Patient Replacement Procedures

Patients who prematurely discontinue from the study during the RIP, SP, or DBTP periods will not be replaced.

6.7 Changes in the Conduct of the Study

Any amendment to this protocol will be provided by the Sponsor in writing to the Investigator. No protocol amendment may be implemented before it has been approved by the IRB/IEC and the signature page, signed by the Investigator, has been received by the Sponsor. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

Administrative changes, such as changes in study personnel, will be specified in the Study Reference Manual. Administrative changes will not require a protocol amendment.

7. STUDY TREATMENTS

7.1 Treatments Administered

Study drug will be administered only to eligible patients under the supervision of the Investigator or sub-investigators or other designated personnel authorized to administer treatment.

Study drug will be administered orally, once daily, in the evening, without respect to food. While the patient is inpatient, study drug will be administered by site staff. Once discharged, the patient will self-administer study drug orally, once daily, in the evening, without respect to food.

Study drug will be supplied as capsules provided in blister cards. Each study drug kit, dispensed at weekly visits, contains a supply of 10 doses; 7 doses for daily administration as outlined per protocol, and 3 extra doses which allow for a ± 3-day window at any visit other than baseline.

Table 7-1 provides formulation information for open-label lumateperone to be administered during the RIP and SP. Table 7-2 provides formulation information for blinded study drug to be administered during the DBTP.

Study drug will be labeled according to local laws and regulations.

Table 7-1: Study Drug: Open-Label Run-in and Open-label Stabilization Phases

	Lumateperone
Dose	42 mg/day
Route	Oral
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 7-2: Study Drug: Double-blind Treatment Phase

	Lumateperone	**Placebo**
Dose	42 mg/day	0
Route	Oral	Oral
Formulation	Capsule	Capsule
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

7.2 Handling, Storage, and Accountability of Study drug

7.2.1 Storage of Study drug

Study drug must be stored in a secure area at a room temperature between 15°C and 30°C (59°F-86°F). Sites must report any temperature excursions as described in the Pharmacy Manual or contact the Sponsor or its designee for further instructions.

Patients will be instructed to store study drug at room temperature at home, out of the reach of children.

7.2.2 Study Drug Accountability

At the end of the study, all study drug must be accounted for. In addition, at the end of the study, all unused study drug and empty study drug packages should be returned to the Sponsor or designee or destroyed, as per instructions provided by the Sponsor.

7.3 Method of Assigning Patients to Treatment Groups

After a patient provides informed consent at Screening (Visit 1), site personnel will register the patient in the interactive web response system (IWRS).

Study drug will be labeled with medication kit numbers. The IWRS will provide the study center with the specific medication kit number(s) for each randomized patient at the time of randomization. Study center personnel will dispense study drug according to the IWRS instructions. Study center personnel will also log onto the IWRS at subsequent visits to obtain a study drug kit number for dispensing study drug. Study centers will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

7.4 Blinding

During the RIP and SP, open-label lumateperone 42 mg will be provided.

During the DBTP, all study drug will be supplied in identical packaging, and will be similar in color, smell, taste, and appearance to maintain the double-blinding.

A list of randomization codes in permuted blocks will be generated by independent unblinded biostatistics personnel not participating in the conduct of the study using SAS Software, Version 9.4 or later (SAS Institute Inc, Cary, North Carolina). The list will be implemented by IWRS to identify the double-blind treatment assignment for each patient through the randomization codes. Personnel participating in the conduct of the study will not have access to the list of randomization codes.

7.5 Unblinding

During the DBTP, any unblinding at the study center should be done only in an emergency that requires the study drug to be identified for the medical management of the patient. The Investigator must notify the Sponsor immediately and a full written explanation must be provided if the blind is broken. Before study drug is unblinded, every attempt should be made to discuss the case with the Study Physician. Breaking the code at the study center will immediately disqualify the patient from further participation in the study.

Treatment codes may be broken by Drug Safety to comply with regulatory reporting requirements. In such cases, the study center staff will be kept blinded and the patient will not need to be disqualified from the study.

In an emergency, the Investigator can obtain the treatment assignment of any patient at his/her study center through the IWRS. In an emergency, the Investigator will access the IWRS to break the blind.

7.6 Monitoring Treatment Compliance

Study drug will be administered by qualified study personnel at the scheduled time and under the direction of the Investigator during the inpatient portion of the study. During the outpatient portion of the study, patients will self-administer study drug with the assistance of a caregiver, if applicable.

Study drug compliance during any study phase will be closely monitored by capturing the date of each dose. At each outpatient visit, every effort will be made to collect unused study drug before a new study drug kit is dispensed. If a patient does not return unused study drug at any outpatient visit, patient-reported compliance will be documented.

During the RIP, the SP, and the DBTP, compliance is based on number of capsules prescribed and number of capsules taken. At every visit during the RIP, SP, and DBTP, study staff will count the number of capsules remaining in the blister pack.

7.7 Prior and Concomitant Medications

7.7.1 Prior Medications

Tapering and discontinuation of psychotropic medications, with the exception of the allowed rescue medications, will take place during the Screening Phase lasting up to 7 days, to allow as much washout of these medications as clinically plausible. Patients will be staying in inpatient facilities during this washout period. A washout is not required for non-psychotropic medications; however, certain medications do have stability requirements as presented in the eligibility criteria.

Medication history, including the use of psychotropic medication during the previous 2 years and of any other medication during the previous 6 months, should be recorded at Visit 1. Thereafter, any changes in concomitant medications or new medications should be recorded in the eCRF.

7.7.2 Prohibited Medications

For the duration of this study, electroconvulsive therapy and additional psychotropic medications, including psychostimulants, are not allowed. Psychotropic medications include the following:

- Antipsychotics/neuroleptics, antidepressants (including monoamine oxidase-B inhibitors), stimulants, anticonvulsants/mood stabilizers, sedative/ hypnotics/ anxiolytics, dopamine-releasing drugs or dopamine agonists, and psychotropic drugs not otherwise specified (including herbal products);

Inducers and strong inhibitors of CYP3A4 are prohibited due to significant effects on lumateperone pharmacokinetics. Contact the Study Physician or designee for further guidance.

7.7.3 Rescue Medication

The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded on the eCRF. Contact the Study Physician for further guidance.

Medications for the conditions below are permitted with the following restrictions:

- ***Medications for <u>Insomnia</u>,*** such as zolpidem must be administered in the evening before midnight and as recommended by the respective prescribing information. Other insomnia medications must be approved by the Study Physician or designee. The medication must be documented on the concomitant medication page of the eCRF.

- ***Medications for EPS or akathisia*** that emerge or worsen during the study will be allowed. The need for continued use of these medications should be regularly assessed by the Investigator and documented appropriately. The EPS or akathisia must be documented on the AE page of the eCRF, and the medication must be documented on the concomitant medication page of the eCRF medications.

    - Diphenhydramine (50 mg/day)

    - Benztropine (up to 4 mg/day) or equivalent (eg, trihexyphenidyl up to 6 mg/day in divided doses)

    - Propranolol for the treatment of akathisia. Daily dose of propranolol depends on heart rate and blood pressure.

- ***Medications for anxiety, agitation, restlessness, irritability, and hostility*** that emerge or worsen during the study will be allowed. The anxiety, agitation, restlessness, irritability, or hostility must be documented on the AE and/or the medical history page of the eCRF, and each dose of the medication must be documented on the concomitant medication page of the eCRF.

    - Lorazepam may be used for the control of anxiety, agitation, restlessness, irritability, and hostility. Doses are not to exceed 4 mg/day between Visit 1 and Visit 4; doses are not to exceed 2 mg/day after Visit 4 and until Visit 6. The week after Visit 6 and until Visit 7 can be used to continue the down-taper, as slow taper of benzodiazepines is advised. Avoid abrupt discontinuation of these agents. After Visit 7, episodic use of up to 2 mg/day of lorazepam may be permitted with clearance from the Study Physician or designee. Substitution of lorazepam with other benzodiazepines is permissible in countries where lorazepam is not available. See Table 7-3 for details pertaining to benzodiazepine use;

      Other situations requiring treatment with these agents will be allowed at the Investigator's discretion after discussion with the Study Physician or designee;

    - Injectable agents are not allowed;

    - Switching of agents may be allowed after communication with the Study Physician or designee.

Table 7-3: Allowable Benzodiazepine Use

Drug	***From Visit 1 to Visit 4***	***After Visit 4 to Visit 6***	***After Visit 6 to Visit 7***	***After Visit 7[a]***
Lorazepam[b]	Up to 4 mg/day	Up to 2 mg/day	Continue down-taper to < 2 mg/day	Up to 2 mg/day

a Episodic use only with Study Physician or designee approval.
b Other benzodiazepines may only be used in regions where lorazepam is not available, with approval from the Study Physician or designee. Other situations requiring treatment with these agents required approval from the Study Physician or designee.

7.8 SPECIAL DIET, ACTIVITIES, AND OTHER RESTRICTIONS

7.8.1 Study Participation History

Patients will be checked for previous participation in any lumateperone clinical study and for duplicate enrollment by study site staff through Verified Clinical Trials (VCT).

7.8.2 Inpatient Stay

All patients will be admitted to an inpatient facility during the Screening Phase and for up to a maximum of 3 weeks at the beginning of the RIP. Patients may be discharged earlier during the RIP. While inpatient, patients may be issued day passes and allowed to leave the facility temporarily at the discretion of the Investigator. Patients who are issued day passes must be escorted by staff, caregiver, or other approved designee.

7.8.3 Alcohol and Other Substance Use

Patients with positive result from the blood alcohol test or from the UDS for prohibited medications or substances will be excluded (EXCEPTIONS: Patients with a positive UDS for cannabinoids, opiates, barbiturates, or benzodiazepines may be allowed in the study provided that communication with the Study Physician or designee has occurred and the use of such products can be discontinued before participation in the study. Medically appropriate episodic use [up to 3 days] of narcotic analgesics for acute medical indications is allowed during the study. Communication with Study Physician or designee is recommended).

7.9 Treatment After Discontinuation

Patients whose schizophrenia symptoms worsen or whose symptoms are determined by the Investigator not to be adequately controlled, or who are no longer considered appropriate for study continuation prior to completing the RIP, SP, or DBTP may, at the Investigator's discretion, be discontinued in order to start appropriate treatment. This new treatment will not be provided by the Sponsor. Patients who initiate a new treatment during the study must be discontinued from the study.

All patients who prematurely discontinue from the study regardless of cause should be seen for a final assessment at the ET Visit (Visit 29) and for SFU Visit (Visit 30).

8. EFFICACY, SAFETY, AND OTHER ASSESSMENTS

8.1 Diagnostic Assessment

8.1.1 Modified Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT)

The SCID-5-CT is a clinician-rated, semi-structured interview for making DSM-5 diagnoses (First et al, 2015). A modified SCID will be used in this study which contains the major depressive episode, manic episode, psychotic episode and associated symptoms, negative symptoms, schizophrenia subtypes, and substance abuse modules will be used in this study.

The modified SCID will be provided in the Study Reference Manual.

8.2 Efficacy Assessments

8.2.1 Structured Clinical Interview for the Positive and Negative Syndrome Scale Symptoms of Schizophrenia (SCI-PANSS)

The SCI-PANSS is a clinician-rated semi-structured interview used to administer the PANSS. The PANSS includes 3 scales and 30 items that measure symptom severity of patients with schizophrenia (Kay et al, 1987). The scale has seven items that comprise the Positive scale, seven items that comprise the Negative scale, and 16 items that make up the General Psychopathology scale. Each item is scored on a seven-point scale by a trained and Sponsor-approved rater.

8.2.2 Clinical Global Impression-Severity

The CGI-S provides the clinician's assessment of the overall severity of the patients psychopathology (Guy, 1976). The CGI-S asks the clinician: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" which is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

The CGI-S will be completed by a trained and Sponsor-approved rater.

8.2.3 Personal and Social Performance Scale

The Personal and Social Performance scale (PSP) is a clinician-rated measure of the severity of personal and social dysfunction (Morosini et al, 2000). The scale is a 100-point rating scale that is calculated based on ratings in four areas: 1) socially useful activities, 2) personal and social relationships, 3) self-care, and 4) disturbing and aggressive behavior. Each domain is rated on a six-point scale from absent (no problems), mild, manifest, marked, severe and very severe difficulties in a given area.

The PSP will be completed by a trained and Sponsor-approved rater.

8.2.4 Calgary Depression in Schizophrenia Scale

The CDSS was developed to assess the level of depression in schizophrenia, separate from positive, negative, and extrapyramidal symptoms associated with schizophrenia (Addington et al, 1990). Nine items are rated (0 = absent, 1 = mild, 2 = moderate, 3 = severe) based on a semi-structured clinical interview that assesses a patient's depression, hopelessness, self-deprecation, guilty ideas of reference, pathological guilt, morning depression, early wakening, suicidality, and observed depression (based on interviewer's observations during the entire interview). The CDSS depression score is obtained by adding each of the item scores.

The CDSS will be administered by a trained and Sponsor-approved rater.

8.3 Safety Assessments

8.3.1 Adverse Events

8.3.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A; 21 CFR 312.32[a]).

NOTE: Medical procedures scheduled prior to obtaining informed consent but occurring during the study and for a pre-existing condition which did not worsen should not be captured as AEs but the medical reason for the procedure should be listed in the medical history if related to a pre-existing condition.

8.3.1.2 Definition of Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

NOTE: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of study drug dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

8.3.1.3 Classification of Adverse Events and Serious Adverse Events

8.3.1.3.1 Severity

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 8.3.1.2).

Severity will be assessed according to the following scale:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research patient.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.3.1.3.2 Causality Assessment

For each reported AE and SAE, the Investigator must provide an assessment of causal relationship to study drug. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility the study drug caused the event?

Yes: There is evidence to suggest a causal relationship between the study drug and adverse event, ie:

- There is a reasonable temporal relationship between the study drug and the event, and/or

- The event is unlikely to be attributed to underlying/concurrent disease, other investigational products, or other factors, and/or
- Positive dechallenge and/or rechallenge exist

OR

No: There is no evidence to suggest a causal relationship between the study drug and adverse event, ie:

- There is no reasonable temporal relationship between the study drug and the event, or
- The patient did not take the study drug, or
- The event is likely to be attributed to underlying/concurrent disease, other investigational products, or other factors.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF.

8.3.1.4 Time Period and Frequency of AE and SAE Reporting

The Investigator will report all AEs/SAEs from the time informed consent was obtained until 30 days the last known dose of study drug (if the final visit does not occur). At each visit, patients are to be queried regarding any AEs that have occurred since the previous visit. Patients will be asked to volunteer information with a nonleading question such as, "How do you feel since your last visit?"

8.3.1.5 Adverse Event Reporting Procedures

8.3.1.5.1 Reporting Adverse Events

All AEs, including overdose with sequelae or intentional overdose of study drug or other medication, must be recorded on the appropriate AE reporting page of the patient's eCRF whether or not they are considered causally related to study drug. For every AE, the Investigator must:

- Provide an assessment of the seriousness of the event (ie, is it an SAE?), as well as the severity and casual relationship. See Section 8.3.1.2 for the definition of SAEs and Section 8.3.1.5.2 for SAE reporting procedures.

- Document all actions taken with regard to study drug;
- Detail any other treatment measures taken for the AE.

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to pre-study status, has resolved or stabilized, or can be explained as being unrelated to study drug. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

8.3.1.5.2 Reporting Serious Adverse Events

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained. Within 24 hours of learning of any AE that meets one of the criteria for an SAE, study center personnel must report the event to ProPharma Group on the SAE Form. In addition to completing the SAE form, the Study Physician may also be notified by telephone.

If, during follow-up, any nonserious AE worsens and eventually meets any SAE criterion, that AE should be recorded as a new SAE.

Preplanned hospitalizations (eg, elective procedures for pre-existing conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

The study center must email or fax the SAE form to the SAE email address below. Even if an initial report is made by telephone, the SAE form containing all available details must still be emailed or faxed within 24 hours of knowledge of the event at the study center.

Supplemental information should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF. All SAEs will be followed until resolution or stabilization. ***The Sponsor may contact the study center to solicit additional information or follow up on the event.***

[redacted]

8.3.2 Potential Hy's Law Cases

Study center personnel must report every patient who meets potential Hy's Law criteria from the time the ICF is signed until 30 days after the last known dose of study drug.

The criteria for potential Hy's law cases are as follows:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × upper limits of normal (ULN) and
- Total bilirubin ≥ 2 × ULN and
- Alkaline phosphatase < 2 × ULN

Study center personnel must report every subject who meets these potential criteria. Typically, these analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the ICF is signed for the study until 30 days after the last known dose of study drug.

A laboratory alert for potential Hy's Laws cases will be in place, and the laboratory must notify Investigators and the Sponsor immediately when the above criteria have been met. The Sponsor must be notified of any potential Hy's Law case as soon as possible (within 24 hours of learning of a potential Hy's Law case). Refer to the SAE reporting procedures (Section 8.3.1.5.2) even if no AE has occurred.

Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the Study Physician and in accordance with the FDA Guidance for Industry: Drug Induced Liver Injury—Pre-Marketing Clinical Evaluation, July 2009.

8.3.3 Pregnancy

Female patients will not be eligible for inclusion in the study if they have a positive pregnancy test at the Screening or Baseline Visit. Any patient who becomes pregnant must be discontinued from the study.

Study center personnel must report every pregnancy, including pregnancies in female partners of male study patients, from the time the ICF was signed until 30 days after the last dose of study drug.

Within 24 hours of learning of the pregnancy, study center personnel must report the event to the Sponsor on the Pregnancy Notification Form and email or fax it to the email address or fax number below even if no AE has occurred. Pregnancies in female partners of male patients occurring during the time frame described above must also be reported.

Any pregnancy in a study patient or in a female partner of a male study patient must be followed to term/termination. The outcome, including status of the mother and the child, must be reported to the Sponsor by completing a follow-up Pregnancy Outcome Form.

If the pregnancy is associated with an SAE (eg, spontaneous miscarriage or if the mother is hospitalized for hemorrhage), a separate SAE form must be filed as described in Section 8.3.1.5.2 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Pregnancy Notification/Outcome Form.

[redacted]

8.3.4 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected as specified in the Schedules of Evaluations (Table 1-1 and Table 1-2). Patients are required to fast for at least 8 hours before the collection of clinical laboratory blood tests.

During Screening, the Investigator/sub-Investigator should assess the clinical significance of any values that are outside the reference ranges provided by the central laboratory. Patients with abnormal screening laboratory results judged to be clinically significant will be excluded from the study.

Laboratory results should be reviewed by the Investigator/sub-investigator throughout the study. For safety reasons or at the discretion of the Investigator, repeat laboratory assessments may be performed at an unscheduled visit.

The following clinical laboratory levels will be measured:

- **Hematology:** hematocrit; hemoglobin; hemoglobin A1c (HbA1c; assessed at Screening, Visit 14 [end of Week 18], and Visit 29/ET Visit only); 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 platelets (platelet count).

- **Chemistry:** albumin; alkaline phosphatase; ALT; AST; bilirubin (total, direct); blood urea nitrogen; gamma-glutamyl transferase; calcium; creatinine; glucose; fasting insulin (assessed at Baseline [Visit 2], Visit 14 [end of Week 18], and Visit 29/ET Visit only); total cholesterol; high-density lipoprotein (HDL) cholesterol; low-density lipoprotein (LDL) cholesterol; triglycerides; phosphate; potassium; prolactin; lactate dehydrogenase; sodium; chloride; total protein; uric acid; creatine phosphokinase; and thyroid panel (at screening only, thyroid-stimulating hormone will be assayed and if the result is abnormal, the free thyroxine and free triiodothyronine will be assayed);

- **Urinalysis:** macroscopic (pH, specific gravity, glucose, protein, ketones, nitrites, blood) and microscopic–report only if present (red blood cells/high-power field, white blood cells/high-power field, casts, epithelial cells, crystals, granulation);

- **Hepatitis Screening:** Blood samples will be collected at Screening (Visit 1) from all patients in order to perform hepatitis B surface antigen, hepatitis B core antibody IgM, and hepatitis C antibody (immunoglobulin G) testing. Test results will be sent to the study site and must be reviewed before Baseline (Visit 2). Any patient who tests positive for hepatitis B surface antigen and/or hepatitis B core antibody IgM or positive hepatitis C antibody with a positive confirmatory hepatitis C RNA result will be excluded from participating in the study. Details regarding sample collection, processing, and shipping are provided in the Laboratory Manual.

- **Urine Drug Screen:** Urine drug (amphetamines, barbiturates, benzodiazepines, cannabinoids [THC], cocaine metabolites, methadone, opiates, phencyclidine) and alcohol tests will be performed. Medically appropriate episodic use [up to 3 days] of narcotic analgesics for acute medical indications is allowed during the study; communication with the Study Physician or designee is recommended Repeat testing is allowed only with approval of the Study Physician or designee;

- **Pregnancy Testing:** Female patients who are of childbearing potential will undergo serum and urine pregnancy tests at the study clinic at Screening (Visit 1), at all visits as specified in the Schedules of Evaluations (Table 1-1and Table 1-2) and, at the discretion of the Investigator, at an Unscheduled Visit. Urine pregnancy tests will be administered as urine dipsticks. If the pregnancy test at screening is positive, the patient will not be eligible to participate in the study. At all other visits, if the pregnancy test is positive, the patient will be discontinued from the study.

A central laboratory will be used to evaluate all urine and blood samples, which will be collected, processed, and stored according to the instructions provided in the Laboratory Manual.

8.3.5 Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure [BP], respiratory rate, body temperature, and body weight) will be assessed at every visit during the study. Height and BMI will be assessed at Screening (Visit 1) only. Waist circumference will be assessed at Screening (Visit 1), Visit 14 (end of Week 18), Visit 18 (end of Week 22), Visit 24 (end of Week 34), and at Visit 29/ET.

Blood pressure and heart rate will be measured twice: once after the patient is resting quietly in the supine position followed by once after at least 2 minutes in the standing positions.

BP may be measured either manually or by machine but using the same method consistently for each patient throughout the study.

Patients should be kept as calm and undisturbed as possible while BP and pulse rate measurements are taken (eg, there should be no talking while the BP is being measured). The same arm and BP cuff (appropriate to the arm circumference) should be used for all BP measurements.

Whenever possible, the patient's weight should be measured at the same time of day; the patient should wear his/her usual indoor clothing without jacket and shoes. For each patient, body weight and height should be determined using the same equipment during the study after ensuring its proper calibration.

8.3.6 Electrocardiograms

A 12-lead ECG will be performed during at the visits specified in the Schedules of Evaluations (Table 1-1 and Table 1-2).

Each ECG assessment will be conducted after the patient has been resting quietly in the supine position. Measurements (in msec) will be recorded for the following parameters: PR interval, QRS duration, and uncorrected QT interval; QTcB (Bazett corrected QT interval) and QTcF (Fridericia corrected QT interval) will be calculated.

The overall interpretation and determination of the clinical significance of ECG findings using the interpretation from the central ECG laboratory will be the responsibility of the Investigator and will be recorded in the patient's eCRF. For eligibility criteria, the values reported on the central ECG interpretation report, not the values that are printed on the tracing itself, will be used.

8.3.7 Other Safety Assessments

8.3.7.1 Extrapyramidal Scales

All EPS scales will be completed by a trained and Sponsor-approved rater.

8.3.7.1.1 Abnormal Involuntary Movement Scale (AIMS)

The AIMS (Guy 1976) measures facial and oral movements, extremity movements, and trunk movements. Seven items are rated on a scale from none (0) to severe (4). A score of "mild" in 2 or more categories or a score of "moderate" or "severe" in any 1 category results in a positive AIMS score (ie, the scores are not averaged). Additionally, overall severity is scored on the basis of severity of abnormal movements and incapacitation due to abnormal movements. The patient's awareness of and distress caused by the abnormal movements are also noted. The AIMS is to be completed at baseline and periodically in the study according to the Schedules of Evaluations (Table 1-1 and Table 1-2).

8.3.7.1.2 Barnes Akathisia Rating Scale (BARS)

The BARS is a rating scale for drug-induced akathisia developed by Barnes (1989). It includes the rating of observable restless movements, the subjective awareness of restlessness, and the distress associated with the akathisia. There is also a global rating for severity. The scale is completed by the investigator or an expert site-based rater after a standard examination. Objective akathisia, subjective awareness and subjective distress are rated on a 4-point scale from 0 to 3, yielding a total score from 0 to 9. The Global Clinical Assessment of Akathisia is rated separately, on a 5-point scale from 0 to 4. The BARS is to be completed at baseline and

periodically in the study according to the Schedules of Evaluations (Table 1-1 and Table 1-2).

8.3.7.1.3 Simpson-Angus Scale (SAS)

The SAS is a measure of extrapyramidal side effects (Simpson & Angus, 1970). Ten items including rating gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation are rated on a scale from 0 (normal) to 4 (extreme in severity). The SAS should be conducted by the investigator or an expert site-based rater in a room where the patient can walk a sufficient distance to allow a natural pace (eg, 15 paces). Each side of the body should be examined. The SAS is to be completed at baseline and periodically in the study according to the Schedules of Evaluations (Table 1-1 and Table 1-2).

8.3.7.2 Physical Examination

A modified physical examination, including neurological and excluding genital/rectal examinations, will be performed at the visits specified in the Schedules of Evaluations (Table 1-1 and Table 1-2). The examinations will be performed by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations.

8.3.7.3 Columbia–Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior (Posner, 2011). The C-SSRS will be completed by a trained and Sponsor-approved rater.

Suicidal ideation is classified on a 5-item scale:

1. Wish to be dead
2. Nonspecific active suicidal thoughts
3. Active suicidal ideation with any methods [not plan] without intent to act
4. Active suicidal ideation with some intent to act, without specific plan; and
5. Active suicidal ideation with specific plan and intent.

The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation.

Suicidal behavior categories are:

- Completed suicide
- Actual attempt
- Interrupted attempt
- Aborted attempt, and

- Preparatory acts or behavior

More than 1 classification can be selected provided it represents separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

The C-SSRS will be completed at all study visits. At Screening (Visit 1), the C-SSRS will be completed for the patient's lifetime history of suicidal ideation and behavior ("Baseline/Screening" version). At all other visits, the C-SSRS will be completed for suicidal ideation and behavior since the previous visit ("Since Last Visit" version). Before the patient leaves the study site, the Investigator or appropriately qualified designee will assess the patient's C-SSRS results.

The patient should not be released from the study center until the results of the C-SSRS are reviewed and the patient is not considered to be at risk. If there is doubt about whether a patient is at risk, the Investigator must obtain appropriate psychiatric consultation. The results of the C-SSRS will be recorded in the eCRF. The C-SSRS will be completed by a trained and Sponsor-approved rater.

8.4 Schedule of Assessments

The schedule of study procedures and assessments is presented by visit in the Schedules of Evaluations (Table 1-1 and Table 1-2). The descriptions of the procedures to be performed at each visit are provided below. Unscheduled visits for repeat study assessments may be performed at for safety reasons or at the discretion of the Investigator.

8.4.1 Screening Phase

During this no-drug Screening Phase (Visit 1 and Visit 2), patient eligibility will be determined. In addition, patients will be admitted for to an inpatient facility.

8.4.1.1 Screening (Visit 1)

After review of study procedures with the patient and obtaining written informed consent from the patient (see Section 2.4 for caregiver consent procedures), the following assessments and procedures are to be performed within 1 week prior to Baseline (Visit 2) according to the Schedule of Events in Table 1-1. All Screening assessments must be performed in person. In exceptional circumstances, the Screening Phase may be briefly extended to allow for receipt and review of screening laboratory results prior to the Baseline Visit (Visit 2).

- Review Inclusion/Exclusion criteria
- Review of medical and psychiatric history
- Review of prior and concomitant medications
- Physical examination
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight, height,

waist circumference, and BMI

- Modified SCID-5-CT, SCI-PANSS, CGI-S, C-SSRS
- BARS/AIMS/SAS
- Clinical laboratory assessments, hepatitis testing, UDS, and pregnancy testing (FOCBP only)
- Admission to inpatient unit.

8.4.1.2 Baseline (Visit 2)

Patients who meet eligibility criteria will be enrolled to receive lumateperone 42 mg/ day orally for 6 weeks. All Baseline assessments must be performed in person

- Review Inclusion/Exclusion criteria
- Review of AEs
- Review of concomitant medications
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, CDSS, PSP, C-SSRS
- BARS, AIMS, SAS
- Clinical laboratory assessments, UDS, and pregnancy testing (FOCBP only)
- Dispense open-label lumateperone

8.4.2 Run-in Phase

Patients will be in an inpatient facility for up to 3 weeks during the RIP. Patients may be discharged earlier, at the discretion of the Investigator.

8.4.2.1 Visit 3 (End of Week 1) and Visit 4 (End of Week 2)

- Review of AEs
- Review of concomitant medications
- Drug return (if applicable) and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Dispense open-label lumateperone

8.4.2.2 Visit 5 (End of Week 3)

- Review of AEs
- Review of concomitant medications
- Drug return (if applicable) and compliance check
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Clinical laboratory assessments and pregnancy testing (FOCBP only)
- Dispense open-label lumateperone

8.4.2.3 Visit 6 (End of Week 4) and Visit 7 (End of Week 5)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Dispense open-label lumateperone

8.4.2.4 Visit 8 (End of Week 6)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, CDSS, PSP, C-SSRS
- BARS, AIMS, SAS
- Clinical laboratory assessments, UDS, and pregnancy testing (FOCBP only)
- Assess patient eligibility to continue into the SP (see Section 6.1 for SP eligibility criteria)
- Dispense open-label lumateperone for patients continuing into the SP

8.4.3 Stabilization Phase

Patients may continue into the SP only if SB eligibility criteria are met (see Section 6.1 for SP eligibility criteria). During the SP, the assessments below will be performed (see Table 1-1 for additional details).

8.4.3.1 Visit 9 (End of Week 8)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Dispense open-label lumateperone

8.4.3.2 Visit 10 (End of Week 10)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Clinical laboratory assessments and pregnancy testing (FOCBP only)
- Dispense open-label lumateperone

8.4.3.3 Visit 11 (End of Week 12)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Dispense open-label lumateperone

8.4.3.4 Visit 12 (End of Week 14)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Clinical laboratory assessments and pregnancy testing (FOCBP only)
- Dispense open-label lumateperone

8.4.3.5 Visit 13 (End of Week 16)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Dispense open-label lumateperone

8.4.3.6 Visit 14 (End of Week 18)

Visit 14 (end of Week 18) will serve as the randomization visit for patients eligible to continue into the DBTP (see Section 6.1 for DBTP eligibility criteria). The following procedures will be performed:

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Physical Examination
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight, waist circumference
- SCI-PANSS, CGI-S, CDSS, PSP, C-SSRS
- BARS, AIMS, SAS

- Clinical laboratory assessments, UDS, and pregnancy testing (FOCBP only)
- Assess patient eligibility for randomization into the DBTP
- Randomization
- Dispense double-bind study drug

8.4.4 Double-blind Treatment Phase

The following assessments and procedures are to be performed during the DBTP according to the Schedule of Events in Table 1-2.

8.4.4.1 Visits 15-17 (End of Weeks 19-21)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Dispense double-blind study drug

8.4.4.2 Visit 18 (End of Week 22)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight, waist circumference
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Clinical laboratory assessments, UDS, and pregnancy testing (FOCBP only)
- Dispense double-bind study drug

8.4.4.3 Visit 19 (End of Week 24)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check

- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Dispense double-blind study drug

8.4.4.4 Visit 20 (End of Week 26)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), and weight
- SCI-PANSS, CGI-S, CDSS, PSP, C-SSRS
- BARS, AIMS, SAS
- Clinical laboratory assessments, UDS, and pregnancy testing (FOCBP only)
- Dispense double-bind study drug

8.4.4.5 Visits 21-23 (End of Weeks 28-32)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Visit 22 only: Pregnancy testing (FOCBP only)
- Dispense double-blind study drug

8.4.4.6 Visit 24 (End of Week 34)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight, waist circumference

- SCI-PANSS, CGI-S, CDSS, PSP, C-SSRS
- Clinical laboratory assessments, UDS, and pregnancy testing (FOCBP only)
- Dispense double-bind study drug

8.4.4.7 Visit 25 (End of Week 36)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Dispense double-blind study drug

8.4.4.8 Visit 26 (End of Week 38)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- PANSS, CGI-S, C-SSRS
- Pregnancy testing (FOCBP only)
- Dispense double-blind study drug

8.4.4.9 Visit 27 (End of Week 40)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- SCI-PANSS, CGI-S, C-SSRS
- BARS, AIMS, SAS
- Dispense double-blind study drug

8.4.4.10 Visit 28 (End of Week 42)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight
- PANSS, CGI-S, C-SSRS
- Dispense double-blind study drug

8.4.4.11 Visit 29/ET (End of Week 44)

- Review of AEs
- Review of concomitant medications
- Drug return and compliance check
- Physical Examination
- ECG
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight, waist circumference
- SCI-PANSS, CGI-S, CDSS, PSP, C-SSRS
- BARS, AIMS, SAS
- Clinical laboratory assessments, UDS, and pregnancy testing (FOCBP only)

8.4.5 Safety Follow-up Visit (Visit 30; End of Week 46)

At the Safety Follow-up Visit, the following procedures will be performed according to the Schedule of Events in Table 1-2.

- Review of AEs
- Review of concomitant medications
- Vital signs (blood pressure, pulse, body temperature, respiratory rate), weight.

9. STATISTICAL METHODS

9.1 General Considerations

The statistical analysis plan (SAP) will be finalized prior to database lock of the study and will include a more technical and detailed description of the statistical analyses described in this section.

9.2 Determination of Sample Size

The sample size and power calculations are based on the analysis of time to relapse in the Double-Blind Treatment Phase. 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 Double-Blind Treatment Phase 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 Run-In Phase and the Stabilization Phase are 60% and 50%, respectively.

9.3 Analysis Populations

The following analysis populations will be presented in the statistical analysis of the study:

- Enrolled Population includes all patients who underwent the Screening Visit, received a patient number, and signed the informed consent form;
- 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;
- 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;
- Open-label Intent-to-Treat (ITT) Population will consist of all patients in the RIP Safety Population who had at least 1 postbaseline (Visit 2) assessment of PANSS total score during the RIP or SP;
- Double-blind (DB) Safety Population will include all patients who completed the SP, were randomized into the DBTP, and who took at least 1 dose of randomized study drug during the DBTP;
- DB ITT Population will include all patients in the DBTP Safety Population.

9.4 Statistical Analyses

9.4.1 Patient Disposition

The number of patients in each study population will be summarized by treatment phase, by treatment group in the DBTP, and study center as follows:

- The number of patients who were screened will be summarized overall by study center.
- The number of patients in each Analysis Population will be summarized overall, by treatment group for the DBTP, and study center.

In addition,

- The number and percentage of patients who completed the RIP and SP and who prematurely discontinued from the RIP and SP will be summarized overall, and by reasons for premature discontinuation for the respective Safety Population.
- The number and percentage of patients who completed the DBTP and who prematurely discontinued from DBTP will be summarized overall, by treatment group, and by reasons for premature discontinuation for the Double-blind Safety Population.

9.4.2 Demographics and Other Baseline Characteristics

Demographic parameters (eg, age, sex, race, ethnicity, weight, body mass index, etc) and other baseline characteristics will be summarized overall for the RIP Safety and 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 by treatment group for the DB ITT Population.

Prior medical and surgical history will be summarized overall for the RIP Safety and SP Safety Populations. Prior medical and surgical history will be summarized 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 RIP and for SP, and by preferred term and treatment group for DBTP using corresponding Safety Populations. Patients with multiple occurrences of a medication in the same preferred term and study period will only be counted once within the preferred term and study phase.

9.4.3 Extent of Exposure and Treatment Compliance

9.4.3.1 Extent of Exposure

Exposure to study treatment for each treatment phase will be summarized by using the treatment duration, calculated as the number of days from the date of the first dose of study drug taken to the date of the last dose taken, inclusive, for each treatment phase. Descriptive statistics will be provided overall for the RIP and SP Safety Populations and by treatment group for the Double-blind Safety Population.

9.4.3.2 Measurement of Treatment Compliance

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

The total number of capsules actually taken during the treatment phase will be calculated from the study drug record. Descriptive statistics for study drug dosing compliance together with compliance category (eg, <80%, >120%) will be summarized for the RIP and SP Safety Populations and by treatment group for the DB Safety Population for each interval between 2 consecutive visits, as well as for the entire treatment phase.

9.4.4 Efficacy Analyses

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 recorded up to Visit 2 (Baseline). All efficacy analyses for the DBTP will be performed using the Double-blind ITT Population. Baselines for efficacy parameters in the DBTP will be defined as the last non-missing efficacy assessment at or before randomization.

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.

9.4.4.1 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.

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

- Psychiatric hospitalization due to worsening of the patient's underlying condition or need for increased level of psychiatric care;
- 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;
- Suicidal or homicidal ideation that was clinically significant as judged by the Investigator.

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 42 mg 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 proportional hazard assumption will be explored by the following graphical methods (Hess 1995):

- Plotting the log of cumulative hazard functions vs. time
- Arjas plot of estimated cumulative hazard rates vs. number of failures
- Plot of scaled Schoenfeld residuals residual vs. time

The cumulative distribution function of time to relapse will be characterized by the Kaplan-Meier curves. The proportion of relapse-free patients at Week 26 will be provided for the lumateperone group and for placebo group separately using the product limit estimator. The associated pointwise confidence intervals for the proportional of relapse-free patients at Week 26 will be constructed using the Greenwood's formula and the linear transformation. The treatment difference in proportion of relapse-free patients at Week 26 and associated confidence interval will also be provided (Klein et al, 2007). Interpretation of the treatment effects based on hazard ratio or cumulative difference in proportions of patients with relapse-free at Week 26 will be discussed based on the assumptions of each method.

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. The second sensitivity analysis is an extension of the placebo-based pattern mixture model (see Lu [2014] for the description of the model for longitudinal data analysis). The placebo-based pattern mixture model assumes that patients who discontinued from the lumateperone treatment group would have disease progression after discontinuation similar to that of placebo. The extended placebo-based pattern mixture model uses a sensitivity parameter to characterize the gradual deviation from the noninformative censoring underlying the primary analysis toward the informative censoring underlying the placebo-based pattern mixture model. The extended placebo-based pattern mixture model sensitivity analysis for time-to-event data is described as follows.

Let $h0(t)$ denote the baseline hazard function associated with the placebo group. Let $\beta 1$ denote the treatment effect in terms of log hazard ratio under noninformative censoring for lumateperone versus placebo. The hazard function associated with the lumateperone under noninformative censoring is thus given by $h1(t) = h0(t) \exp(\beta 1)$. Consider the extended placebo-based pattern mixture model sensitivity analysis. For the placebo group, we assume that patients with premature discontinuation would have comparable experience after discontinuation to their counterparts without premature discontinuation. For the lumateperone treatment 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 $h1(t) = h0(t) \exp((1-\phi)\beta 1)$ for $t > C$, where C denotes the time of premature discontinuation. The sensitivity parameter $\phi \in [0,1]$ characterizes the gradual deviation from the noninformative censoring with $\phi = 0$ toward the informative censoring underlying the placebo-based pattern mixture model with $\phi = 1$. A multiple imputation approach will be used to implement the extended placebo-based pattern mixture model.

The technical details are provided in the Appendix of the SAP.

9.4.4.2 Additional Efficacy Parameters

Additional efficacy parameters will include the following at each applicable postbaseline visit:

- Change from baseline in the PANSS total score
- Change from baseline in the PANSS positive subscale score
- Change from baseline in the PANSS negative subscale score
- PANSS response percentage (improvement ≥ 30%)
- Change from baseline in the Positive subscale
- Change from baseline in the Negative subscale
- Change from baseline in the general psychopathology subscale
- Percentage response (Improvements ≥30%)
- Change from baseline in the CGI-S score
- Change from baseline in the CDSS score
- Change from baseline in the PSP score

Descriptive statistics will be provided by visit for additional efficacy parameters for the Open-label ITT Population and by treatment group for the Double-blind ITT Population using both LOCF and observed cases approaches. The LOCF approach will be used to impute missing postbaseline values. Imputation of missing values will be performed for the open-label phase and the DBTP separately.

9.4.5 Safety Analyses

Safety analyses will be performed by RIP, SP, and DBTP treatment phases using the RIP, SP, and DBTP Safety Populations, respectively. The safety parameters will include AEs, clinical laboratory measures, vital signs, and ECG parameters.

9.4.5.1 Adverse Events

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

An AE that occurs during the any treatment phase will be considered a treatment-emergent AE

(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. If more than one AE is reported before the date of the first dose of open-label study drug during the RIP and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the treatment phase that were also coded to that preferred term. An AE that occurs more than 1 day after the date of the last dose of study drug will not be counted as a TEAE.

The number and percentage of patients reporting TEAEs during the RIP or SP, and in each treatment group during the DBTP will be tabulated by system organ class (SOC) and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship to study drug, based on the corresponding Safety Populations. 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.

Additional details pertaining to analyses of AE data will be provided in the SAP.

9.4.5.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI and conventional units) and changes from baseline values at each assessment timepoint will be summarized overall for the RIP and SP Safety Populations and by treatment group for the DBTP based on the corresponding Safety Population for each clinical laboratory parameter.

The number and percentage of patients with potentially clinically significant (PCS) postbaseline clinical laboratory values will be tabulated overall for the RIP and SP and by treatment group for the DBTP, based on the corresponding Safety Populations. The criteria for PCS laboratory values and details on additional laboratory analyses will be provided in the SAP.

9.4.5.3 Vital Signs

Descriptive statistics for vital signs (eg, pulse rate, systolic and diastolic blood pressure, body weight) and changes from baseline values at each visit, at the end of the treatment period, and at the end of the study will be presented overall for the RIP and SP, and by treatment group for the DBTP, based on the corresponding Safety Populations.

Vital sign values will be PCS if they meet the observed-value and the change-from-baseline-value criteria as detailed in the SAP. Details on additional vital sign analyses will be provided in the SAP.

9.4.5.4 Electrocardiogram

Descriptive statistics for ECG parameters (eg, ventricular heart rate, QTc interval, QRS interval) and changes from baseline values at each assessment timepoint will be summarized overall for the RIP and SP and by treatment group for the DBTP, based on the corresponding Safety Populations.

The number and percentage of patients with PCS postbaseline ECG values will be summarized by treatment group. The criteria for PCS ECG values and details on additional analyses of ECG parameters will be provided in the SAP.

9.4.5.5 Other Safety Parameters

Descriptive statistics for EPS scales (AIMS, BARS, SAS) will be summarized overall for the RIP and SP and by treatment group for the DBTP, based on the corresponding Safety Populations.

9.5 INTERIM ANALYSIS

No interim analysis is planned for this study.

9.6 Data And Safety Monitoring Board

Not applicable.

9.7 Protocol Deviations

A deviation from the protocol is an unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/IEC and agreed to by the Investigator. A major protocol deviation occurs when there is nonadherence to the protocol by the patient or Investigator that results in a significant, additional risk to the patient, or to the primary efficacy assessment. Major protocol deviations can include, for example, nonadherence to inclusion or exclusion criteria or nonadherence to ICH GCP guidelines and may lead to the patient being withdrawn from the study.

The Investigator or designee must document and explain any deviation from the approved protocol. The IRB/IEC should be notified of all major protocol deviations in a timely manner.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL MONITORING

10.1 Study Termination

The Sponsor reserves the right to terminate the study in its entirety or at a specific study center before study completion.

10.2 Investigator Obligations

10.2.1 Documentation

The Investigator must provide the following to the Sponsor or designee, before the start of the study:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the Sponsor for submission to the FDA
- A fully executed contract
- The curricula vitae for the Investigator and all sub-investigators listed on Form FDA 1572, including a copy of each physician's license
- Financial disclosure agreement completed and signed by the Investigator and all Sub-investigators listed on Form FDA 1572.
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB.
- A copy of the IRB-/IEC-approved ICF
- A copy of the HIPAA authorization form, or other applicable local privacy forms
- A list of the IRB/IEC members or the US Department of Health and Human Services general assurance number
-
- The Investigator's Statement page in this protocol signed and dated by the Investigator

10.2.2 Performance

The Investigator must demonstrate reasonable efforts to recruit qualified patients for the study.

10.2.3 Use of Investigational Materials

Study drug must be stored in a secured place and must be locked. At study initiation, a representative from the Sponsor will inventory the study drug at the study center. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The Sponsor may supply forms on which to record the date the study drug was received and a dispensing record in which to record each patient's use. All unused study drug must be returned to the Sponsor-designated central depot.

10.2.4 Case Report Forms

All patient data relating to the study, except for data electronically transmitted (eg, central laboratory results), will be recorded on eCRFs to be provided by the Sponsor through the EDC system. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct by electronically signing the completed eCRFs submitted to the Sponsor. The Investigator must maintain and retain accurate documentation that supports the information entered into the EDC system for source document verification and possible regulatory inspection.

10.2.5 Retention and Review of Records

Records and documents pertaining to the conduct of this study, including eCRFs, source documents (eg, medical records, laboratory reports), consent forms, regulatory documents, and medication inventory records must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the Sponsor.

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of records after the required retention period.

The Investigator must permit access to any documentation relating to the study upon request of the Sponsor or applicable regulatory authorities. If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

10.2.6 Patient Confidentiality

All patient records will be identified by patient identification number only. Patients' names are not to be transmitted to the Sponsor. The Investigator will keep a master patient list on which the patient identification number and the full name, address, and telephone number of each patient are listed.

10.3 Data Quality Assurance

10.3.1 Data Monitoring

Before any patient enters the study, a representative of the Sponsor will meet with the Investigator and the study center personnel to review the procedures to be followed during the study. Electronic data capture (EDC) functionality training is provided via computer-based training to train Investigators and authorized designees on recording the data in the eCRFs using the EDC system.

The Investigator will maintain complete source documents (eg, signed ICFs, written or electronic medical records, pharmacy records). Source documents provide evidence for the existence of study patients and substantiate the integrity of the data collected in the eCRF. The Investigator will make available to the study monitor source documents (written notes and electronic medical records, if used), signed ICFs, and all other study-related documents.

Study monitors, appointed by the Sponsor, will perform ongoing source document verification to confirm that data entered into the eCRF are accurate, complete, and verifiable from source documents; that the safety and rights of patients are protected; and that the study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. After the first patient is enrolled, the study monitors will periodically monitor the progress of the study by conducting on-site visits. In addition to on-site source document verification, study monitors will review study progress remotely, possibly warranting more frequent communication and/or study center visits. Details of monitoring activities are provided in the Monitoring Plan.

10.3.2 Data Recording and Documentation

Data collection will involve the use of the EDC system, to which only authorized personnel will have access. Patient data are to be entered into the EDC system by the Investigator or designee using their assigned EDC user account. The Investigator or designee will record all patients' study data in the eCRF, unless the data are transmitted to the Sponsor electronically (eg, laboratory data). Data entered in the eCRF must be consistent with the source documents or the discrepancies must be explained. The Investigator is responsible for verifying that all data entries are accurate and correct. The Investigator may need to request previous or external medical records to support study data.

The Sponsor is responsible for the data management of this study, including quality checking of the data. The Sponsor or designee will review study data for completeness, logic, and protocol adherence, using a combination of manual review and programmatic edit checks. After data entry into the EDC system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edit checks, data monitoring, and reviews, queries may be electronically issued to the study center and should be answered electronically via the EDC system. Each query will carry identifying information (assigned username, date, and time) to assist the Sponsor and the Investigator on the origin of the data clarification request and the response provided by the Investigator. All data changes made to the patient's data via a data query will be approved by the Investigator prior to final database lock.

The Investigator or designee will be responsible for approving all changes performed on the data and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past. After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, and regulatory documents) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, the FDA, or other health authorities.

Source documents will be used at the study centers and may include a patient's medical record, hospital charts, clinic charts, the Investigator's patient study files, as well as the results of diagnostic tests such as laboratory tests, ECGs, etc. A centralized clinical laboratory will be used for the analysis of all blood samples. Additional information on the collection and handling of samples is detailed in the Study Reference Manual.

10.4 Reporting and Publication

All data generated in this study are the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

11. APPENDICES

Appendix I. Elements of Informed Consent

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained for each patient participating in a clinical research study. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence).
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA or other local health authority, the Sponsor, the IRB/IEC, or an authorized contract research organization may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB/IEC may be required.)
- For EU countries, the ICF will include a statement of whom to contact, including relevant phone and email address, for questions about patient data confidentiality or data breach' per GDPR.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled
- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable

- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent
- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study
- A statement of permission, providing consent for the patient to participate (eg, "I agree to participate . . .")
- A place for the patient's signature and date of signing of the ICF
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.
- A copy of the signed consent form must be given to the patient.

Appendix II. Amendment #1 Summary of Changes

Amendment 1 to the Original Protocol for Study ITI-007-304, dated 18 Dec 2020, specifies revisions to the Original Protocol. All changes to the protocol are summarized in the following sections.

- New text is identified as ***bold, italicized***, ***underlined*** font
- Deleted text is identified with ~~strikethroughs~~
- Protocol version and the associated protocol version date have been globally updated on the Sponsor and Investigator signature pages and in the document headers and are not summarized.

Minor editorial and grammatical revisions are not summarized.

PROTOCOL LOCATION	*Protocol Approval-Sponsor Signatories* Sponsor Personnel ***Updated*** list of Sponsor signatories.
PROTOCOL LOCATION	*Section 1. Synopsis* Inclusion Criterion 8 ***Correction*** to the required PANSS positive symptom ratings. 8. Rating of ~~≤~~ ≥ 4 (moderate) on at least 2 of the following PANSS positive symptoms at Screening (Visit 1) and Baseline (Visit 2)…
PROTOCOL LOCATION	*Section 1. Table 1-2 Schedule of Evaluations: Double-blind Treatment and Safety Follow-up Periods* Footnote b ***Clarification*** that HbA1c and fasting insulin are to be measured only at Visit 29/Early Termination Visit. b. "…HbA1c and fasting insulin are to be measured at ~~Visits 24 and~~ ***Visit*** 29/ET Visit only."
PROTOCOL LOCATION	*Section 3. Investigators and Study Administrative Structure* Sponsor Personnel ***Updated*** list of Sponsor personnel responsible for study oversight.
PROTOCOL LOCATION	*Section 6.4.2. Exclusion Criteria* Exclusion Criterion 24 ***Corrected*** hemoglobin and absolute neutrophil count criteria. 24c. Hemoglobin ~~>~~ ≤ 8 mg/dL (80 g/L) for females and ≤ 9 mg/dL (90 g/L) for males; 24d. Absolute neutrophil count (ANC) ≤ 1200 cells/µL (1.2×10^9/L);
PROTOCOL LOCATION	*Section 7.7.2. Prohibited Medications* ***Clarified*** list of prohibited medications. For the duration of this study, electroconvulsive therapy and additional psychotropic medications, including psychostimulants, are not allowed~~, with the exceptions listed below~~. Psychotropic medications include the following…
PROTOCOL LOCATION	*Section 8.3.1.5.2. Reporting Serious Adverse Events* ***Updated*** the Medical Emergency Contact Phone Numbers. [redacted]

PROTOCOL LOCATION	*Section 8.4.1.1. Screening (Visit 1) and Section 8.4.1.2 Baseline (Visit 2)* ***Clarified*** that admission to the inpatient will occur at the end of the Screening Visit. 8.4.1.1 Screening (Visit 1): ***Admission to inpatient unit*** Section 8.4.1.2 Baseline (Visit 2): ~~Admission to inpatient unit~~
PROTOCOL LOCATION	*Section 9.4.4.1. Primary Efficacy Parameter-Relapse Criteria* ***Clarified*** the 1st and 3rd relapse criteria during the DBTP • Psychiatric hospitalization due to worsening of the patient's underlying condition ***or need for increased level of psychiatric care***;… • Increase in the ~~Visit 13~~ CGI-S score by 2 or more points ***from Visit 14***…

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INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study in accordance with Protocol Amendment #2 (ITI-007-304, dated 23 May 2022) and with all applicable government regulations and GCP guidance, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal and/or local regulations and ICH guidelines.

I will not disclose information regarding this clinical investigation or publish results of the investigation without prior authorization from Intra-Cellular Therapies, Inc.

_____	_____
Investigator Signature	Date
_____	_____
Investigator Name (printed)	Site Number

Signature Page for VV-CLIN-001199 v1.0

