NCT04779177

Study ID: ITI-007-020

Title: An Open-label Multiple Dose Study to Determine the Pharmacokinetics, Safety, and Tolerability of Lumateperone in Patients, Ages 13 to 17 Years, Diagnosed with Schizophrenia or Schizoaffective Disorder

Protocol Amendment Version 5.0 Date: February 28, 2022

An Open-label Multiple Dose Study to Determine the Pharmacokinetics, Safety, and Tolerability of Lumateperone in Patients, Ages 13 to 17 Years, Diagnosed with Schizophrenia or Schizoaffective Disorder

Protocol Number:	ITI-007-020
[redacted]	[redacted]
Compound:	Lumateperone
Study Phase:	1b
Sponsor:	Intra-Cellular Therapies, Inc. [redacted]
IND	079690

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. 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, US Code of Federal Regulations applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312), and all applicable local regulations.

PROTOCOL VERSION 5: MAJOR CHANGES

Protocol Version 5 for Study ITI-007-020, dated 28 Feb 2022, provides revisions and clarifications to the Protocol Version 4.0 (dated 14 Dec 2021; see Appendix II for the Summary of Changes for Protocol Version 4.0). Major changes to the protocol are summarized in the table below.

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

[redacted]	[redacted]	[redacted]
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Protocol Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Protocol Section	Revision	Rationale
[redacted]	[redacted]	[redacted]

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LIST OF ABBREVIATIONS

AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
aPTT	partial thromboplastin time
AST	aspartate aminotransferase
AUC	Area under the plasma concentration time curve
AUC_{0-24}	Area under the plasma concentration time curve from time zero to 24 hours
AUC_{0-t}	Area under the plasma concentration time curve from time zero to the last measurable concentration
AUC_{0-inf}	Area under the plasma concentration time curve from time zero to infinity
[redacted]	[redacted]
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
[redacted]	[redacted]
CGI-S	Clinical Global Impression Scale-Severity
CL/F	Apparent oral clearance
C_{max}	Maximum plasma drug concentration
CRU	Clinical research unit
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EDC	electronic data capture
ET	early termination
FDA	Food and Drug Administration
FR	Federal Register
λz	Terminal elimination rate constant
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
IND	Investigational New Drug (application)
IRB	Institutional Review Board
LAR	Legally authorized representative
PT	prothrombin time
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Fridericia formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SOC	System organ class
$t_{1/2}$	Terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	Time of maximum concentration of drug in plasma
ULN	upper limit of normal
V_Z/F	Apparent volume of distribution

1. PROTOCOL SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study ITI-007-020	
Title of Study	An Open-label, Multiple Dose Study to Determine the Pharmacokinetics, Safety, and Tolerability, of Lumateperone in Patients, Ages 13 to 17 Years, Diagnosed with Schizophrenia
Study Centers (Country)	Approximately 3 study centers in the United States.
Development Phase	Phase 1b
Objectives	• To determine the pharmacokinetic (PK) profile of lumateperone at steady state following once daily oral administration for 5 days in adolescent patients, aged 13 to 17 years; • To assess the safety and tolerability of lumateperone following oral administration for 5 days in adolescent patients, ages 13 to 17 years.
Methodology	This is a multiple-dose, open-label study of oral lumateperone in patients, aged 13 to 17 years, diagnosed with schizophrenia. CAPLYTA® (lumateperone 42 mg) is approved in the United States for the treatment for schizophrenia in adults. The purpose of this study is to evaluate the PK safety, and tolerability of oral lumateperone in adolescent patients, aged 13 to 17 years. Adolescent patients with schizophrenia or schizoaffective disorder may be screened for eligibility (Day -14 to Day -1). Patients who are currently receiving antipsychotic treatment must wash off current medication with Investigator supervision. Eligible patients will be admitted to an inpatient clinical research unit (CRU) on Day -1. A thorough baseline assessment will be conducted prior to the first dose of lumateperone on Day 1. Oral lumateperone will be administered under fasted conditions, once daily in the morning for 5 days (Days 1 to 5). After the final post-dose assessments are conducted on Day 6, patients considered to be stabilized may be discharged from the inpatient CRU on Day 6. Patients requiring additional time for stabilization may remain in the CRU up to Day 10. Patients aged 13 to 17 years will receive lumateperone 42 mg. [redacted]

	Blood samples for PK analysis following oral lumateperone administration will be collected on Days 1 and 5 [redacted] Time of study drug administration and time of collection of each blood sample must be recorded. Safety and tolerability will be assessed throughout the study.
Number of Patients	Approximately 18 to 24 patients are planned.
Diagnosis and Main Inclusion and Exclusion Criteria	***Main Inclusion Criteria:*** A patient will be considered eligible for participation in the trial if the following inclusion criteria are satisfied at the Screening Visit and upon admission to the CRU (Day -1): 1. Able to provide consent as follows: • Legally authorized representative of the patient must provide written, informed consent; • Patient must assent to study enrollment 2. Male or female patients between 13 and 17 years of age, inclusive, at Screening; 3. Clinical diagnosis of schizophrenia or schizoaffective disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); 4. Free from acute exacerbation of psychosis for at least 3 months prior to Screening; 5. CGI-S score ≤ 4; 8. Ability to swallow capsules; and 9. Willing to be confined to an inpatient unit for the duration of the inpatient period of the study, and, in the opinion of the Investigator, willing to comply with all Investigator and staff instructions. All Inclusion Criteria are presented in Section 6.3.1.
	Main Exclusion Criteria: A patient presenting with any of the following characteristics will be excluded from the study: 1. Has a primary psychiatric diagnosis other than schizophrenia or schizoaffective disorder; 2. Reports having experienced suicidal ideation (Type 4 or 5 on the Baseline/Screening version of the Columbia-Suicide Severity Rating Scale [C-SSRS]) within 6 months prior to Screening, any suicidal behavior within 2 years prior to Screening (any "Yes" answers on Suicidal Behavior section of C-SSRS), and/or the investigator assesses the patient to be a safety risk to him/herself or others; 3. History of a clinically significant cardiac disorder and/or abnormal screening electrocardiogram (ECG) or a QT interval corrected for heart rate using Fridericia formula > 450 msec in males or > 470 msec in females;

	4. Clinically significant abnormality within 2 years of Screening that in the Investigator's opinion may place the patient at risk or interfere with study outcome variables; this includes, but is not limited to, history or clinical presentation of a neurodevelopmental disorder or history of other clinically significant neurologic, hepatic, renal, gastrointestinal, respiratory, hematologic, endocrine or immunologic disease or history of malignancy. All Exclusion Criteria are presented in Section 6.3.2.
Test Product, Dosage, and Mode of Administration	Lumateperone 42 mg; lumateperone 28 mg Once daily oral administration.
Duration of Treatment	5 days
Reference Therapy, Dosage, and Mode of Administration	Not applicable.
Criteria for Evaluation	
Pharmacokinetic Endpoints	The following PK Parameters will be calculated for Days 1 and 5 for lumateperone [redacted] • Time of maximum concentration of drug in plasma (T_{max}) • Maximum plasma drug concentration (C_{max}) • Whenever possible, relative ratios of metabolite to parent will be calculated • Area under the plasma concentration time curve (AUC) from time zero to the last measurable concentration (AUC_{0-t}) • AUC from time zero to the end of the dosing interval, tau (AUC_{0-tau}) • Area under the plasma concentration time curve (AUC) from time zero to infinity (AUC_{0-inf}) - only for Day 1, as data permit • Terminal elimination rate constant (λz) • Terminal elimination half-life ($t_{½}$) • Apparent oral clearance (CL/F) [redacted] • Apparent volume of distribution (V_Z/F) [redacted].
Safety Measures	Safety will be assessed by: • Adverse event (AE) recording, clinical laboratory parameters (hematology, serum chemistry and urinalysis), vital sign parameters (blood pressure and heart rate, respiration rate, body temperature, weight, height, and BMI), 12-lead ECGs, and physical examinations, including neurological findings, pregnancy test, concomitant medications • [redacted] • [redacted] Abnormal Involuntary Movement Scale (AIMS) • Measure of suicidality: C-SSRS
Statistical Methods	Detailed statistical methods will be described in a separate statistical analysis plan. ***Analysis Sets:*** Enrolled Set: Includes all patients who signed the informed consent form (ICF) and will be used to describe patient disposition. Safety Set: Includes all patients who receive at least one dose of study drug. PK Set: Includes all patients who received at least one dose of study drug,

had no major protocol deviation that may impact PK analyses, and had at least one evaluable PK parameter. Patients who experience emesis within 2 times the median T_{max} after receiving an oral dose may be excluded from the PK analysis.

Pharmacokinetic Analysis

Plasma concentrations of lumateperone [redacted]

Analyses will be performed for parent drug [redacted] using non-compartmental methods.

Individual plasma concentrations will be presented in data listings. Plasma concentration data will be summarized over time (and by dose, if applicable) using descriptive statistics. Mean and individual plasma concentration vs time profiles will be presented in figures on both linear and semi-logarithmic scales. The individual PK parameters will be presented in data listings and summarized using descriptive statistics. Geometric means will be included for C_{max}, AUC_{0-t}, AUC_{0-inf}, AUC_{0-tau}, CL/F, and V_Z/F.

[redacted]

The PK data may be included in a population PK analysis pooled with adult patient data. The results from the population PK analysis will be reported in a separate report.

Safety Analysis

All safety data (AEs, safety laboratory results, vital sign measurements, 12-lead ECG results, physical examinations, [redacted], AIMS, [redacted] will be presented in the data listings. Adverse events will be summarized overall (and by dose if more than one dose is administered) for patients in the Safety Set. Adverse events will also be summarized by severity, relationship to study drug, serious AEs, and AEs leading to discontinuation from the study.

Patient disposition, demographics, and baseline characteristics will be summarized overall (and by dose if more than one dose is administered) for patients in the Safety Set. Baseline values, postbaseline values, and changes from baseline of safety laboratory results, vital sign measurements, 12-lead ECG, [redacted] AIMS results will be summarized overall (and by dose if more than one dose is administered) at each time point using descriptive statistics. [redacted]

Sample Size

[redacted]

[redacted]

[redacted]	[redacted]		[redacted]					[redacted]		
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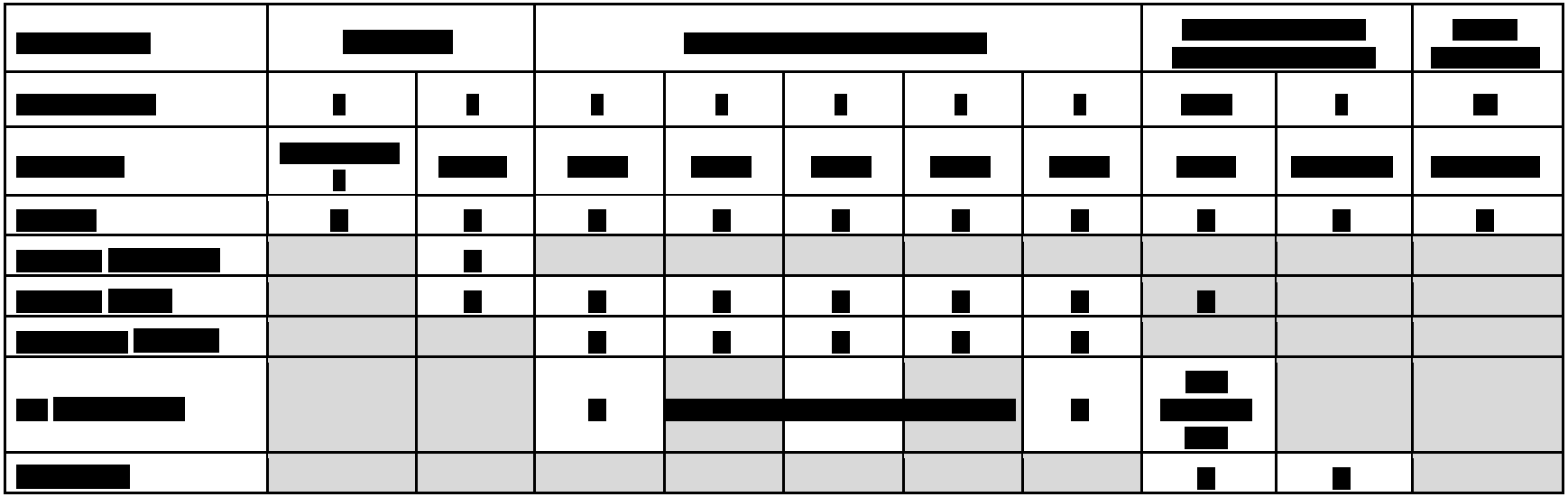

- [redacted]
- [redacted]

2. ETHICAL CONSIDERATIONS

2.1 Institutional Review Board

Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Investigator. 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 members. During the course of the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), age-appropriate assent form, information sheet advertisements, and amendments (if any) will be approved by the IRBs at the study centers in conformance with US CFR, Title 21, Part 56.

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.

2.3 Patient Information and Informed Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 and 21 CFR Part 50, Subpart D shall be obtained from the legally authorized representative (LAR) in accordance with local laws or regulations and before entering the study or performing any study-specific procedure that involves risk to the patient. Adolescent patients should be informed to the fullest extent possible about the study in language and terms they are able to understand. Patients should provide written assent by signing the assent form or the ICF. Patients who reach the age of consent or become an emancipated minor while participating in the study will be required to provide written consent. In all cases, patients and their LARs should be made aware of their rights to decline to participate or to withdraw from the study at any time.

If the ICF is revised during the study, all active participating patients must assent and their LARs 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, each prospective patient will be given a full explanation of the study. After receiving an explanation of study procedures, patients and their LARs will have the opportunity to have any questions answered before signing the ICF. The Investigator must address all questions raised by the patient. Attention should be paid to signs of undue distress in adolescent patients who are unable to clearly articulate their distress.

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

3. INVESTIGATORS AND 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 severe brain disorder that affects 1% to 2% of the world's population. This chronic and disabling disorder is characterized by "positive" symptoms such as hallucinations and delusions, "negative" symptoms such as flattened affect and social withdrawal, and cognitive deficits. According to the National Institute of Mental Health (NIMH), symptoms of schizophrenia usually emerge in people aged 16 to 30 years, but schizophrenia in teens can be difficult to diagnose because the first signs might include irritability, depressed mood, social difficulties, and a drop in grades. These clinical signs are common in teens and may not necessarily correspond to the emergence of schizophrenia. A combination of these factors together with symptoms such as increasing paranoia and suspiciousness, increased social withdrawal, and a family history of psychosis contribute to the "prodromal" period that occurs prior to the onset/diagnosis of schizophrenia.

Childhood-onset schizophrenia, before the age of 13, is very rare with an incidence of less than 0.04% (Driver et al, 2013), and accurate diagnosis is very challenging with a drug-free inpatient observation period proving more helpful than outpatient assessments for differential diagnosis (Gochman et al, 2011). Limited and transient psychotic symptoms are common in many childhood disorders and even among healthy children, which contributes to the difficulty with differential diagnosis. Onset of schizophrenia during the mid and late teens is more common, and an estimated 12% to 33% of adults with schizophrenia may have first symptoms and signs of schizophrenia before age 18 (Kumra et al, 2008). Adult diagnostic criteria and assessment measures can be used successfully in an unmodified manner for adolescent schizophrenia (Hollis, 2000). Hollis also summarized the clinical features of schizophrenia and treatment in adolescent schizophrenia. Clinical features of schizophrenia in adolescents include poor premorbid functioning, cognitive dysfunction indicated by below average IQ, and prominent negative symptoms. Adolescent patients with schizophrenia often have a family history of psychosis and/or schizophrenia. The disorder generally has a slow onset with gradual presentation of behavioral disturbances but follows a severe course that is difficult to treat in this young patient population. Sadly, adolescent schizophrenia has been associated with extremely poor social outcomes. Currently available antipsychotics approved for the treatment of schizophrenia in adolescents include risperidone, aripiprazole, quetiapine, and paliperidone, and lurasidone. Although antipsychotic treatment has been shown to reduce positive psychotic symptoms in adolescents, currently available treatments insufficiently improve negative symptoms or social functioning and are associated with adverse events such as motor and cognitive impairment, weight gain and dyslipidemia, and hyperprolactinemia. Olanzapine is approved for use in adolescents with schizophrenia, but its label recommends it only as a second-line treatment given its propensity to cause weight gain and hyperlipidemia. Notably, children and adolescents have been observed to be more sensitive to antipsychotic adverse effects than adults (Correll, 2008).

CAPLYTA® (lumateperone 42 mg oral capsule) was approved for the treatment of schizophrenia in adults in the United States in December 2019. The efficacy of CAPLYTA 42 mg was demonstrated in two placebo-controlled trials, showing a statistically significant separation from placebo on the primary endpoint, the Positive and Negative Syndrome Scale (PANSS) total score. The most common adverse reactions in adults (≥ 5% and twice the rate of placebo) for the recommended dose of CAPLYTA vs placebo were somnolence/sedation (24% vs. 10%) and dry mouth (6% vs. 2%). In pooled data from short-term studies, mean changes from baseline in weight

gain, fasting glucose, triglycerides and total cholesterol were similar between CAPLYTA and placebo. The incidence of extrapyramidal symptoms was 6.7% for CAPLYTA and 6.3% for placebo.

Pursuant to the FDA postmarketing requirement for CAPLYTA (PMR 3760-1), this study will be an open-label, multiple-dose study to demonstrate the safety, tolerability, and pharmacokinetics (PK) of lumateperone in patients aged 13 to 17 years diagnosed with schizophrenia or schizoaffective disorder.

5. STUDY OBJECTIVES

The objectives of this study are:

- To determine the PK profile of lumateperone at steady state following once daily oral administration for 5 days in adolescent patients aged 13 to 17 years

- To assess the safety and tolerability of lumateperone following oral administration for 5 days in adolescent patients aged 13 to 17 years.

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

Study ITI-007-020 is a Phase 1b, multicenter, open-label study to evaluate the safety, tolerability, and PK of lumateperone as treatment for adolescent patients with schizophrenia or schizoaffective disorder. This study will be performed at approximately 3 study centers in the United States.

The study will be conducted as follows:

- A **Screening Period** of up to 14 days: Adolescent patients with stable schizophrenia or schizoaffective disorder maintained on not more than one oral antipsychotic for the treatment of schizophrenia (ie, can be stable without antipsychotic medications or stable on a single antipsychotic) may be screened for eligibility (Day -14 to Day -1). The washout of current antipsychotic medication and anti-anxiety medications (except lorazepam) will be carried out for a period of 4 to 7 days prior to Day 1 and may be implemented on an inpatient basis during the Screening Period based on the Investigator's clinical judgment. An extension to the Screening Period and/or washout may be allowed with the approval of the Sponsor.

- A 5-day **Open-label Treatment Period**: Oral lumateperone will be administered under fasted conditions, once daily in the morning for 5 days (Days 1 to 5).

- An up to 5-day **Standard-of-Care Stabilization Period**: After the final post-dose assessments are conducted on Day 6, patients will be returned to standard-of-care antipsychotic treatment. If, in the opinion of the Investigator, a patient is considered to be stable he/she may be discharged after completion of all Day 6 assessments. If, in the opinion of the Investigator, patients require additional time for stabilization, they may remain in the CRU between Days 7 and 10. Additional days for stabilization may be approved by the Sponsor.

- A **Follow-up Visit** will be conducted approximately 14 days after the last dose of study drug.

The maximum per-patient study duration will be approximately 5 weeks.

The Schedule of Evaluations is presented in Table 1-1. Detailed descriptions of the procedures conducted at each study visit are provided in Section 8.3.

6.2 Scientific Rationale for Study Design

6.2.1 Study Design

The study is designed to determine the PK profile of lumateperone in adolescent patients with schizophrenia.

6.2.2 Dose Selection

Patients aged 13 to 17 years will receive lumateperone 42 mg/day. [redacted]

[redacted].

6.3 Study Population

Patients must meet all inclusion criteria and none of the exclusion criteria in order to be eligible to participate in the study. Patients who do not meet the criteria for participation in the study may be re-screened upon approval by the Sponsor.

6.3.1 Inclusion Criteria

A patient will be considered eligible for participation in the trial if the following inclusion criteria are satisfied at the Screening Visit (Visit 1) and upon admission (Day -1):

1. Able to provide consent as follows:
   - Legally authorized representative of the patient must provide written, informed consent;
   - Patient must assent to study enrollment;
2. Male or female patients between 13 and 17 years of age, inclusive, at the time of providing informed consent;
3. Clinical diagnosis of schizophrenia or schizoaffective disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5);
4. Free from acute exacerbation of their psychosis for at least 3 months prior to Screening;
5. Clinical Global Impression – Severity (CGI-S) score ≤ 4;
6. Female patients of childbearing potential must have a negative serum pregnancy test at the Screening Visit (Visit 1) and a negative urine pregnancy test on Day -1 (upon admission to the CRU) and
   - Agree to remain abstinent, or
   - Agree to practice double barrier forms of birth control in which 2 of the following precautions are used: vaginal diaphragm, intrauterine device, oral contraceptive pills or injectable, birth control implant, or condom or sponge with spermicide from Screening through to completion of the study or upon early termination;
   - Not be breastfeeding.
7. Body mass index (BMI) equal to or within the 5th and 95th percentiles according to age- and gender-specific CDC Clinical Growth Charts, 2000 at Screening;

8. Ability to swallow capsules, and
9. Willing to be confined to an inpatient unit for the duration of the inpatient period of the study, and, in the opinion of the Investigator, willing to comply with all Investigator and staff instructions.

6.3.2 Exclusion Criteria

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

1. Has a primary psychiatric diagnosis other than schizophrenia or schizoaffective disorder;
2. Reports having experienced suicidal ideation (Type 4 or 5 on the Baseline/Screening version of the Columbia-Suicide Severity Rating Scale [C-SSRS]) within 6 months prior to Screening, any suicidal behavior within 2 years prior to Screening (any "Yes" answers on Suicidal Behavior section of C-SSRS), and/or the investigator assesses the patient to be a safety risk to him/herself or others;
3. History of a clinically significant cardiac disorder and/or abnormal screening electrocardiogram (ECG) or a QT interval corrected for heart rate using Fridericia formula > 450 msec in males or > 470 msec in females;
4. Clinically significant abnormality within 2 years of Screening that in the Investigator's opinion may place the patient at risk or interfere with study outcome variables; this includes, but is not limited to, history or clinical presentation of a neurodevelopmental disorder or history of other clinically significant neurologic, hepatic, renal, gastrointestinal, respiratory, hematologic, endocrine or immunologic disease or history of malignancy;
5. Surgical or medical condition (active or chronic) that in the Investigator's opinion may interfere with drug absorption, distribution, metabolism, or excretion of the study drug or any other condition that may place the patient at risk;
6. Meets Diagnostic and Statistical Manual of Mental Disorders (5th Edition) criteria for substance use disorder within 6 months before Screening;
7. Positive result for drugs of abuse, alcohol, or cotinine at Screening or Day -1. The drug screen may be repeated once based on Investigator judgement as approved by the Sponsor;
8. Major surgery or blood loss within 4 months prior to Day -1;
9. History of clinically significant drug allergy or sensitivity, including a known sensitivity or idiosyncratic reaction to lumateperone or drugs of the same class, any metabolites, or any compound listed in the study formulation;
10. Clinically significant abnormal findings in serum chemistry, coagulation, hematology, or urinalysis results obtained at Screening;
11. History of human immunodeficiency virus (HIV) infection;
12. History of hepatitis B or hepatitis C infection or demonstration of hepatitis B surface antigens or hepatitis C antibodies;

13. Has had exposure to any investigational product within 90 days or 5 half-lives (whichever is longer) prior to Day -1;
14. Ingested any medication or herbal supplements (excluding hormonal birth control, documented current antipsychotic therapy, documented current anti-anxiety medications, lorazepam, or multivitamins) within 5 half-lives or 14 days (whichever is longer) prior to Day -1;
15. In the opinion of the Investigator, the patient is unable to safely undergo washout of antipsychotic treatment (excluding depot antipsychotic) for a period of 4 to 7 days prior to Day 1.
16. Use of depot antipsychotic within 3 treatment cycles prior to Day -1;
17. Patients cannot be treatment-naïve, must not be on > 1 antipsychotic at the Screening Visit, or have ever taken clozapine;
18. Consumed grapefruit-, alcohol-, or xanthine-containing products within 24 hours before receipt of study drug on Day 1;
19. Is a current tobacco or nicotine user;
20. Has participated in strenuous activity or contact sports within 24 hours before study drug dosing on Day 1;
21. In the opinion of the Investigator, the patient is not otherwise suitable for entry into the study.

6.4 Discontinuation of Patients from Therapy or Assessments

A premature discontinuation will occur when a patient who received a dose of study drug ceases participation in the study, regardless of circumstances, before the completion of study visits and procedures through Day 6. Patients can be prematurely discontinued from the study after careful consideration for one of the following reasons:

- Death
- AE
- Lost to follow-up
- Pregnancy
- Physician decision
- Protocol violation
- Study terminated by Sponsor
- Withdrawal by subject
- Withdrawal by parent/guardian/LAR
- Other.

***NOTE**:* If a patient discontinues from the study due to withdrawal of assent or due to withdrawal of parent/guardian/LAR consent and a concurrent AE was reported, 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 are lost to follow-up and do not return to the study center for the Follow-up Visit 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 a final assessment at the early termination (ET) Visit (Visit 8). All patients who prematurely discontinue from the study should return for the safety follow-up visit.

6.5 Patient Replacement Procedures

Patients who prematurely discontinue from the study during the Open-label Treatment Period may be replaced.

6.6 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 and the signature page, signed by the Investigator, has been received by the Sponsor. An amendment may be implemented by Investigator based only on patient safety concerns. However, the Sponsor must be informed of such change immediately. The IRB must be informed in writing of such an amendment; IRB approval must be obtained within reasonable time limits.

7. STUDY TREATMENT

7.1 Treatment Administered

Open-label lumateperone will be administered only to eligible patients under the supervision of the Investigator or sub-investigators or other designated personnel authorized to administer treatment. Open-label lumateperone will be administered orally once daily for 5 days, from Day 1 through Day 5. Study drug should be administered at the same time each day ± 15 minutes. Study drug will be administered with about 240 mL of water. On Days 1 and 5, lumateperone will be administered following an overnight fast of at least 10 hours; fasting will continue for at least 4 hours postdose. On Days 2-4, lumateperone will be administered after an overnight fast of at least 8 hours; this fast will continue for at least 2 hours post dose. Water can be provided as desired except for 1 hour before and 1 hour after dosing.

Open-label lumateperone will be supplied as capsules provided in 2×5 blister cards. Table 7-1 provides formulation information for lumateperone.

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

[redacted]

Table 7-1: Lumateperone Capsules

	Lumateperone 42 mg	**Lumateperone 28 mg**
Frequency	Once daily	Once daily
Route	Oral	Oral
Formulation	Capsule	Capsule
[redacted]	[redacted]	[redacted]

7.2 Preparation, Handling, Storage, and Accountability of Study Drug

7.2.1 Storage of Study Drug

Study drug must be stored in a secure area (eg, a locked cabinet) while in storage at the study site, protected from moisture, and kept at a room temperature between 15°C and 30°C (59°F-86°F).

7.2.2 Study Treatment Accountability

The Investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study. To satisfy regulatory requirements regarding drug accountability at study completion, all study drug will be reconciled and retained or destroyed according to applicable regulations.

7.3 Method of Assigning Patients to Treatment Groups

This is an open-label study. After LAR consent and patient assent is received at Screening (Visit 1), site personnel will assign a 6-digit patient identification number to the patient. The patient identification number will start with the 3-digit site number assigned by the Sponsor followed by 3 digits starting with 001, assigned by the site.

7.4 Blinding

Not applicable. This is an open-label study.

7.5 Unblinding

Not applicable. This is an open-label study.

7.6 Monitoring Treatment Compliance

Study drug compliance will be closely monitored by capturing the date and time of each dose. Dosing will occur while the patient is on the inpatient unit and under direct supervision of study center personnel. After oral administration of study drug, a mouth check will be performed to verify that the dose was swallowed.

Compliance is based on number of capsules prescribed and number of capsules taken.

7.7 Prior and Concomitant Medications

7.7.1 Prior Medications

The following prior medication restrictions apply to all patients:

- Patients are not allowed to have received an investigational drug within 90 days or 5 half-lives (whichever is longer) prior to Day -1;
- Patients are not allowed to have ever taken clozapine;
- Patients are not allowed to have used medication or herbal supplements within 14 days or 5 half-lives (whichever is longer) prior to Day -1, with the exception of hormonal birth control, current antipsychotic therapy, current anti-anxiety medications, lorazepam, or multivitamins;
- Current antipsychotic therapy and anti-anxiety medications (except lorazepam) must be washed off prior to Day -1 (see Section 7.8 for additional washout details);

- Use of depot antipsychotic within 3 treatment cycles prior to Day -1.
- Use of lorazepam must be discontinued on Day -1.

7.7.2 Concomitant Medications

The use of concomitant medications (except oral contraceptives) during this study is prohibited, unless necessary to treat AEs. Any other treatment, other than study drug, is to be considered a concomitant medication including all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications.

If the Investigator determines that a patient requires medication to treat an AE during the study, the Sponsor (or designee) must be contacted.

7.8 Washout of Antipsychotic and Anti-anxiety Medications

Patients must be washed off current antipsychotic and anti-anxiety medications (except lorazepam) for a period of 4 to 7 days prior to Day 1. Patients requiring washout may be admitted to the CRU prior to Day -1. An extension of the washout may be allowed with the approval of the Sponsor.

7.9 Special Diet or Activities

7.9.1 Dietary Restrictions

Patients are required to abstain from consumption of grapefruit-containing products and xanthine-containing products (eg, coffee, energy drinks, tea, chocolate) from 24 hours prior to Day 1 dosing until completion of Day 6 procedures.

Patients will be required to fast as follows:

- For at least 10 hours prior to Screening and study drug administration on Days 1 and 5 and continue to fast for at least 4 hours postdose.
- For at least 8 hours prior to study drug administration on Days 2-4 and continue to fast for at least 2 hours postdose.
- On Day 6, blood will be collected for clinical laboratory tests after an overnight fast.

Water is allowed as desired except for 1 hour before and 1 hour after study drug administration. Study drug will be administered with approximately 240 mL of water.

During patient confinement, meals will be provided as follows:

- ***On Days 1 through 5***, patients will receive low-fat meals and snacks provided by the clinical site at regimented times.
    - ***On Days 1 and 5***, lunch will be provided at approximately 4 hours postdose (ie, after the required 4-hour postdose fast) and dinner will be provided between 10-11 hours postdose; snack will be provided after dinner. A snack may also be provided between lunch and dinner.

- ***On Days 2-4***, snack will be provided at approximately 2 hours postdose (after the required 2-hour postdose fast on these days). Lunch, dinner, and other snacks will be provided at approximately the same times as Days 1 and 5.

- On other days of confinement, meals will be provided as deemed appropriate by the clinical site.

7.9.2 Alcohol and Tobacco

During the study, patients are required to abstain from alcohol and tobacco use.

7.9.3 Activity

During the study, patients are required to abstain from strenuous exercise from the time of admission to the inpatient unit through to discharge from the CRU.

7.10 Treatment After Discontinuation

Patients whose symptoms worsen or are determined by the Investigator not to be adequately controlled prior to completing the Open-label Treatment Period may be discontinued from the treatment period in order to start appropriate treatment. Patients must undergo all ET Visit assessments. Upon completion of ET assessments, the patient should immediately enter into the Standard-of-Care Stabilization Period.

All patients who prematurely discontinue from the study should return for the Follow-up Visit.

8. SAFETY, PHARMACOKINETIC, AND OTHER ASSESSMENTS

8.1 Safety

8.1.1 Adverse Events

8.1.1.1 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.

8.1.1.2 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 medication 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.

8.1.1.3 Classification of Adverse Events and Serious Adverse Events

8.1.1.3.1 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 8.1.1.2). Severity will be assessed according to the following scale:

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

8.1.1.3.2 Causality Assessment

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

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

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

- There is a reasonable temporal relationship between the study medication 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 medication and adverse event, ie:

- There is no reasonable temporal relationship between the study medication and the event, or
- The patient did not take the study medication, 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.

8.1.1.4 Time Period and Frequency of AE and SAE Reporting

The Investigator will report:

- All AEs from the time informed consent and assent are obtained through the Follow-up Visit (Visit 10)
- All SAEs, from the time informed consent and assent are obtained until 30 days after the last dose of study drug. 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?"

8.1.1.5 Adverse Event Reporting Procedures

8.1.1.5.1 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 8.1.1.2 for the definition of SAEs and Section 8.1.1.5.2 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.

8.1.1.5.2 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 and assent are obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study center personnel must report the event to the Sponsor on the SAE Form.

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

Preplanned hospitalizations (eg, elective procedures for pre-existing conditions that did not worsen) are excluded from SAE reporting.

The study center must email the SAE form to the SAE email address below. Even if an initial report is made by telephone, the SAE form completed with all available details must still be emailed 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]

[redacted]

8.1.2 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 and assent is obtained until 30 days after the final protocol-defined study visit or the last known dose of study drug (if the final visit does not occur).

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 (ALP) < 2 × ULN

Typically, all 4 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period.

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 8.1.1.5.2) 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.

8.1.3 Pregnancy

Study center personnel must report every pregnancy from the time the ICF was signed and assent was obtained until 30 days after the last dose of study drug. Within 24 hours of learning of the pregnancy, the study center personnel must report the event to the Sponsor on the Pregnancy Form and email the information even if no AE has occurred.

Any patient who becomes pregnant must be discontinued immediately and followed to term/termination and the outcome reported by completing a follow-up Pregnancy Form. If the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), a separate SAE form must be completed as described in Section 8.1.1.5.2 with the appropriate serious criterion (eg, hospitalization) indicated on the SAE form in addition to the Pregnancy Form.

[redacted]

8.1.4 Clinical Laboratory Determinations

[redacted] 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 abnormalities judged to be clinically significant will be excluded from the study. All laboratory results must be reviewed by the Investigator/sub-investigator throughout the open-label treatment and safety follow-up periods. Additional safety laboratory assessments may be scheduled at the Investigator's discretion.

Patients are required to fast for at least 10 hours before collection of clinical laboratory blood tests.

[redacted]

The patient will not be eligible for inclusion in the study if she has a positive pregnancy test during the Screening Period. Any pregnancies that occur in females who have received study drug must be reported promptly to the Sponsor and the patient must be discontinued. Pregnancies will be followed through to termination or completion and 30 days post-delivery to assess general health of the baby.

All clinical laboratory results will be forwarded to the Investigator for review. Any abnormalities deemed clinically significant by the Investigator will be recorded as AEs in the patient's eCRF. Any clinically significant abnormal laboratory values that persist should be followed by the Investigator in consultation with the Sponsor (or designee). Such events should be followed as described in Section 8.1.1.

The Investigator should file all copies of the reports in the patient's study chart.

Additional details regarding sample collections, processing, and specific testing can be found in the Laboratory Manual.

8.1.5 Vital Signs

Vital signs (systolic and diastolic blood pressure [BP], pulse, temperature, and respiratory rate) will be assessed at every visit during the open-label treatment and stabilization periods. Weight, height, and BMI will be assessed as specified in the Schedule of Evaluations (Table 1-1). Additional vital sign measurements may be performed at the Investigator's discretion.

BP and radial pulse rate will be measured twice:

- Blood pressure should be measured once after patient has been in the supine position for approximately 5 minutes followed by once in the standing position. The standing measurements should be assessed approximately 2 minutes after standing. BP may be measured manually or by machine.

- Radial pulse rate should be measured after BP measurements. Radial pulse rate should only be measured manually and for a sufficient time to acquire an accurate measurement.

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.

8.1.6 Electrocardiograms

A 12-lead ECG will be performed after the patient has rested quietly in the supine position at visits specified in the Schedule of Evaluations (Table 1-1).

ECGs will be performed and electronically transmitted to a central ECG laboratory for analysis according to the instructions provided by the central ECG laboratory. Measurements (in msec) will be recorded for the following parameters: [redacted]

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. Additional ECG assessments may be performed at the Investigator's discretion.

8.1.7 Other Safety Assessments

8.1.7.1 Physical Examination

Complete physical examinations, excluding genitourinary examinations, will be performed at the visits specified in the Schedule of Evaluations (Table 1-1). The examinations will be performed by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations.

[redacted]

[redacted]

[redacted]

[redacted]

8.1.7.4 Abnormal Involuntary Movement Scale

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" (2) 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 visits as specified in the Schedule of Evaluations (Table 1-1).

[redacted]

[redacted]

[redacted]

[redacted]

8.2 Pharmacokinetic Assessments

Blood samples for PK assessments following oral lumateperone administration will be collected on Days 1 and 5 [redacted].

PK parameters to be assessed are described in Section 9.7.

[redacted]

[redacted]

[redacted]

8.4 Schedule of Assessments

The schedule of study procedures and assessments is presented by visit in the Schedule of Evaluations (Table 1-1). The descriptions of the procedures to be performed at each visit are provided below.

If multiple assessments are scheduled at the same time (eg, 1 h post-dose), the order of assessments should ensure that ECG measurements and vitals are taken prior to PK samples within the applicable time window so that the stress of blood sampling does not impact vitals or ECG measurements. As guidance, the preferred order of assessments is:

ECG → **Vitals** → **PK** → **Other assessments eg, physical exams**

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
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  - [redacted]
  - [redacted]
- [redacted]

[redacted]

9. STATISTICAL METHODS

9.1 General Considerations

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

9.2 Determination of Sample Size

[redacted]

9.3 Analysis Populations

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

- The Enrolled Set includes all patients whose LAR provided informed consent and all patients who provided written assent.
- Safety Set includes all patients who take at least 1 dose of study drug.
- The Pharmacokinetic Set includes all patients who take at least 1 dose of study drug and had at least one evaluable PK parameter and had no major protocol deviation that may impact PK analyses. Patients who experience emesis within 2 times the median T_{max} after receiving one oral lumateperone dose may be excluded from the PK analysis.

9.4 Patient Disposition

The number of patients who were screened, failed screening and enrolled in the study will be summarized overall.

The number and percentage of patients who completed the Open-label Treatment Period and who prematurely discontinued from the Open-label Treatment Period will be summarized overall (and by dose if more than one dose is administered) and by reason for premature discontinuation.

9.4.1 Demographics and Other Baseline Characteristics

Demographic parameters (eg, age, race, ethnicity, sex, weight, height, BMI) and other baseline characteristics will be summarized overall (and by dose if more than one dose is administered).

Descriptive statistics (n, mean, median, SD, minimum, and maximum) will be presented for continuous variables. Frequency distributions (counts and percentages) will be presented for categorical variables.

Medical and surgical history and physical findings will be summarized overall (and by dose if more than one dose is administered), by System Organ Class (SOC) and preferred term.

9.4.2 Extent of Exposure and Treatment Compliance

9.4.3 Extent of Exposure

Exposure to study drug during Open-label Treatment Period will be summarized for 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. Descriptive statistics (n, mean, median, SD, minimum, and maximum) will be presented overall (and by dose if more than one dose is administered).

9.4.4 Prior and Concomitant Medication

Prior and concomitant medication use will be listed with the therapeutic class included.

9.5 Efficacy Analyses

Not applicable.

9.6 Safety Analyses

The safety analysis will be performed based on the Safety Set as specified in the SAP. Safety variables will include AEs, clinical laboratory parameters, vital signs, ECG parameters, [redacted] AIMS [redacted] results. For each safety parameter, the last assessment made before the first dose of open-label study drug will be used as the baseline for all analyses of that safety parameter.

The safety data from the first 4 patients will be reviewed prior to continuing with the 42 mg dose in the remaining patients. If lumateperone 42 mg is not tolerated, the remaining patients will be administered open-label lumateperone 28 mg.

9.6.1 Adverse Events

Adverse events will be coded by SOC and preferred term using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

An AE will be considered a treatment-emergent AE (TEAE) if it was not present before the first dose of open-label study drug or was present before the first dose of open-label study drug but increased in severity after the first dose. If more than one AE is reported before the first dose of open-label study drug 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 Open-label Treatment Period that were also coded to that preferred term. An AE that occurs more than 1 day after the last dose of open-label study drug will not be counted as a TEAE.

The number and percentage of patients reporting TEAEs will be tabulated overall (and by dose if more than one dose is administered), by SOC and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship to study drug. If more than one AE is coded

to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summary by severity and by relationship to study drug.

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

9.6.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI and conventional units) at baseline, postbaseline, and changes from baseline values at each assessment timepoint will be summarized overall (and by dose if more than one dose is administered) for the Safety Set for each clinical laboratory parameter.

[redacted]

9.6.3 Vital Signs

Descriptive statistics for vital signs (eg, pulse rate, systolic and diastolic BP, body weight and height) at baseline, postbaseline, and changes from baseline values at each assessment timepoint, and at the end of the study will be presented overall (and by dose if more than one dose is administered) for the Safety Set.

[redacted]

9.6.4 Electrocardiogram

Descriptive statistics for ECG parameters [redacted] at baseline, postbaseline, and changes from baseline values at each assessment timepoint will be summarized overall (and by dose if more than one dose is administered) for the Safety Set.

[redacted]

9.6.5 Other Safety Parameters

Descriptive statistics for [redacted], and AIMS at baseline, postbaseline, and changes from baseline values at each assessment timepoint for each of these assessments will be summarized overall (and by dose if more than one dose is administered) for the Safety Set.

For the C-SSRS, the number and percentage of patients who have suicidal ideation or suicidal behavior will be summarized overall (and by dose if more than one dose is administered) for the Safety Set. The details will be provided in the SAP.

9.7 Plasma Concentration Parameters

The following PK parameters will be calculated for Days 1 and 5 for lumateperone [redacted] using noncompartmental methods:

- Time of maximum concentration of drug in plasma (T_{max})
- Maximum plasma drug concentration (C_{max})
- Whenever possible, relative ratios of metabolite to parent will be calculated
- Area under the plasma concentration time curve (AUC) from time zero to the last measurable concentration (AUC_{0-t})
- AUC from time zero to the end of the dosing interval, tau (AUC_{0-tau})
- Area under the plasma concentration time curve (AUC) from time zero to infinity (AUC_{0-inf}) – only for Day 1, as data permit
- [redacted]
- Terminal elimination half-life ($t_{½}$)
- Apparent oral clearance (CL/F) [redacted]
- Apparent volume of distribution (V_Z/F) [redacted]

For Day 1 AUC calculations, the predose concentration on Day 2 will serve as the 24-hour measurement post Day 1 dose administration.

Individual plasma concentrations will be presented in data listings. Plasma concentration data will be summarized over time (and by dose, if applicable) using descriptive statistics. Mean and individual plasma concentration versus time profiles will be presented in figures on both linear and semi-logarithmic scales. The individual PK parameters will be presented in data listings and summarized using descriptive statistics. Geometric means will be included for C_{max}, AUC_{0-t}, AUC_{0-inf}, AUC_{0-tau}, CL/F, and Vz/F.

[redacted]

9.8 Interim Analysis

After the first 4 patients have received lumateperone 42 mg and completed the Open-label Treatment Period, safety data and, if available, PK data will be reviewed to confirm the dose recommendation for the remaining patients.

[redacted]

9.9 Protocol Deviations

A deviation from the protocol is an unanticipated departure from the procedures or processes approved by the Sponsor and the IRB 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 should be notified of all major protocol deviations in a timely manner in accordance with IRB reporting procedures.

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 its 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 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, as stated in Section 6.6.
- A copy of the IRB-approved ICF and age-appropriate assent form
- A copy of the HIPAA authorization form, or other applicable local privacy forms
- A list of the IRB 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 adolescent 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 numbers of each patient and patient's LAR 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 or designee source documents (written notes and electronic medical records, if used), signed ICFs, and all other study-related documents.

Study monitors or designees, 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 monitor or designee, 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 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 Laboratory Manual.

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12. APPENDICES

Appendix I. Elements of Informed Consent

Procedures will comply with 21 CFR, Parts 50 (Subpart D) and 312. Signed informed consent will be obtained from the LAR for each patient participating in a clinical research study and assent will be obtained from the patient. The 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, the Sponsor, the IRB, 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 may be required.)
- 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 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 LAR consent
- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's or LAR'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's LAR.
- The approximate number of patients involved in the study
- A statement of permission providing LAR consent for the patient to participate (eg, "I agree to participate . . .") and patient assent to participate
- A place for the LAR'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 and LAR.

Appendix II. Protocol Version 4.0–Summary of Changes

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Section 1-Synopsis: Statistical [redacted]	[redacted]	[redacted]

Protocol Section	Revision	Rationale
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Protocol Section	Revision	Rationale
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13. INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR SIGNATURE PAGE

I agree to conduct Study ITI-007-020 in accordance with this protocol, dated 28 Feb 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.

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

Signature Page for VV-CLIN-000938 v1.0

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