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Study ID: ITI-007-503

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

Protocol Amendment 1 Date: 23 Aug 2021

TITLE PAGE

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

Protocol Number:	**ITI-007-503**
Protocol Amendment 1 Date	23 Aug 2021
Original Protocol Date:	05 May 2021
Compound:	Lumateperone
Study Phase:	3
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 #1: MAJOR CHANGES

Protocol Amendment 1 for Study ITI-007-503, dated 23 Aug 2021, provides revisions and clarifications to the Original Protocol (dated 05 May 2021). Major changes to the protocol are summarized in the table below.

Editorial corrections and minor revisions for consistent terminology usage are not summarized in this table.

Protocol Section	Revision	Rationale
Section 6.3.1 Inclusion Criteria	Added statement noting that VCT will continue to monitor for patient participation in other clinical trials.	Clarification
Section 6.4 Stopping Criteria	Updated the section title; modified discontinuation and patient-level stopping criteria (Section 6.4.1); and added a subsection for study stopping criteria (Section 6.4.2);	Based on feedback from FDA on ITI-007-501 protocol.
Section 7.1 Study Treatment, Supply (Section 7.1.1) and Storage (Section 7.1.2) Study Drug	Updated study treatment supply and storage information	Clarifications
Section 8.2.4 Clinical Laboratory Determination; Section 8.3 Pharmacokinetic Assessments; Section 10.3.2 Data Recording and Documentation	Changed Laboratory Procedure Manual to Laboratory Manual	Revised to be consistent with nomenclature for study site materials.
Section 9.4.5.1 Adverse Events Statistical Methods	Clarified the definition of treatment-emergent adverse events during the open-label treatment period.	Clarification
Section 9.4.5.5.1 Columbia Suicide Severity Rating Scale	Revised the planned analyses of C-SSRS data.	Revision

PROTOCOL APPROVAL—SPONSOR SIGNATORIES

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

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[redacted]

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LIST OF ABBREVIATIONS

ADT	Antidepressant treatment
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	human chorionic gonadotropin
BARS	Barnes Akathisia Scale
BMI	body mass index
BP	blood pressure
C–SSRS	Columbia–Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CRO	Contract research organization
CSR	Clinical study report
DSM-5	Diagnostic and Statistical Manual, 5th edition
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
ECT	electroconvulsive therapy
EDC	electronic data capture
ET	early termination
FDA	Food and Drug Administration
FOCBP	Female 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
ITI	Intra-Cellular Therapies, Inc.
IWRS	Interactive Web Response System
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
PK	pharmacokinetic
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 ($QTcF = QT/<RR>^{1/3}$)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson Angus Scale

SOC	system organ class
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-007-503	
Title of Study	An Open-label, Multicenter Trial to Assess the Safety and Tolerability of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder
Study Centers (Country)	Approximately 120 study centers (US and Non-US)
Development Phase	Phase 3
Objectives	**Primary Objective** To evaluate the safety and tolerability of lumateperone 42 mg administered orally once daily for approximately 26 weeks as adjunctive treatment to antidepressant therapy (ADT) in patients with major depressive disorder (MDD). **Secondary Objectives** To evaluate whether lumateperone 42 mg administered orally once daily for approximately 26 weeks as adjunctive treatment to ADT improves or maintains improvement of depressive symptoms in patients with MDD as measured by change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score and in the Clinical Global Impression Scale-Severity (CGI-S) score.
Study Design	This is an international, multicenter, open-label, fixed dose, 26-week study of patients with MDD. Eligible patients from the lead-in studies will enter the Open-label Safety Study at the Screening/Baseline Visit (Visit 1/Day 1), at which point patient eligibility will be assessed and informed consent obtained. At the Screening/Baseline Visit (Visit 1/Day 1), which is the same visit as Visit 8/Day 43 of the lead-in study, eligible patients will receive open-label lumateperone 42 mg once daily for approximately 26 weeks. Patients will continue their background ADT from the lead-in study. Patients will be seen for weekly visits through Visit 5/Week 4. Thereafter, visits will occur every two weeks. A Safety Follow-up visit will occur on Visit 17/Day 197, approximately 2 weeks after the last dose of open-label lumateperone 42 mg.
Number of Patients	Approximately 760 patients are planned to be enrolled in the Open-label Safety Study. No *de novo* patients will be enrolled.

Diagnosis and Main Criteria for Inclusion and Exclusion	***Main Inclusion Criteria*** Each patient entering the Open-label Safety Study must meet all of the following criteria: 1. In the opinion of the Investigator, the patient must have safely completed the lead-in study. 2. The patient must understand the written informed consent for the Open-label Safety Study, provide signed and witnessed written informed consent. 3. The patient is taking his/her ADT as prescribed from the lead-in study. 4. The patient must agree to continue using highly effective methods of birth control as specified in the lead-in study through the Safety-Follow-up Period of the Open-label Safety Study, or female patients or female partners of male patients must be of non-childbearing potential. All Inclusion Criteria are presented in Section 6.3.1. ***Main Exclusion Criteria*** Because all patients enrolled in the lead-in study were required to satisfy exclusion criteria for participation in the lead-in study, the Investigator should assess if there has been any change in patient health status. Any newly-emergent medical condition reported during the lead-in study must be evaluated by the Investigator and should be discussed with the Sponsor or designee before enrolling the patient in the study. Patients enrolling directly from the lead-in study to the Open-label Safety Study at Visit 1/Day 1 will be excluded if they meet the following criteria: 1. In the opinion of the Investigator, the patient is unable to comply with study procedures or judged to be inappropriate for the study; 2. In the opinion of the Investigator, the patient has a significant risk for suicidal behavior during the course of her/his participation in the study or is considered to be an imminent danger to her/himself or others, and/or: a. At the Screening/Baseline Visit (Visit 1/Day 1) the patient scores "yes" on Suicidal Ideation Items 4 and 5 of the C-SSRS since the last visit version (Visit 7/Week 5 of the lead-in studies); b. At the Screening/Baseline Visit (Visit 1/Day 1), the patient scores $\geq$ 5 on MADRS Item 10 (Suicidal Thoughts); 3. Based on the Investigator's clinical judgement, any abnormal clinical laboratory tests results obtained throughout the lead-in study that are considered clinically significant and preclude safe participation in the study. All Exclusion Criteria are presented in Section 6.3.2.
Duration of Study	Study duration will be approximately 26 weeks of open-label treatment, followed by a 2-week Safety Follow-up.
Investigational Product, Dosage, and Mode of Administration	Lumateperone 42 mg capsules, 42 mg/day adjunctive to ongoing background ADT, oral administration.

Criteria for Evaluation	
Safety Measures	AE recording, clinical laboratory measures, vital signs, electrocardiograms (ECGs), and physical examination; measures of extrapyramidal symptoms: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS); Columbia-Suicide Severity Rating Scale (C-SSRS); and pregnancy test (if applicable).
Efficacy Endpoints	Change from baseline in MADRS total score and CGI-S score.
Pharmacokinetic Measures	Optional blood samples for pharmacokinetic (PK) analysis of lumateperone and metabolites (IC200131, IC200161, IC200565, IC201308, and IC201309) will be collected. Three blood samples will be collected at Visit 2 at predose, between 0.5-to-1-hour postdose, and between 1.5 to 3 hours postdose. One sample will be collected at Visit 7.
Statistical Methods and Sample Size	Approximately 760 patients will be enrolled. The sample size is not based on statistical considerations, but is based on the number of patients who may be eligible based on participation in the lead-in study. It is expected that the majority of patients who safely complete the lead-in study will continue treatment for the full 26 weeks. All safety parameters will be summarized descriptively. Safety analyses will be based on the Safety Population defined as all patients who received at least one dose of open-label lumateperone 42 mg. Analyses of efficacy endpoints will be performed based on the patients in the Safety Population who have an available baseline efficacy value and at least one postbaseline efficacy assessment during the Open-label Treatment Period. Analyses will primarily consist of change from baseline descriptive summaries of MADRS total score and CGI-S scores. Individual plasma concentrations of lumateperone and metabolites will be listed and summarized by visit/timepoint. Plasma concentrations of lumateperone and potentially of selected metabolites will be analyzed using a population PK approach. The results from the population PK analyses will be presented in a separate report.

Table 1-1: Schedule of Evaluations

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

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

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

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

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

3 Height and BMI will only be collected at Visit 1 and waist circumference will only collected at Screening/Baseline Visit (Visit 1/Day 1) (which is the same as Visit 8/Day 43 of the lead-in study) and Visit 16/ET.

4 ECGs will be collected at Screening/Baseline Visit (Visit 1/Day 1; which is the same as Visit 8/Day 43 of the lead-in study), Visit 2, Visit 7, Visit 11, and Visit 16/ET. Unscheduled visits for repeat ECG assessments may be performed at any time for safety reasons or at the discretion of the Investigator.

5 Clinical laboratory assessments are to be taken after an overnight fast of at least 10 hours and will be collected at Screening/Baseline Visit (Visit 1/Day 1; (which is the same as Visit 8/Day 43 of the lead-in study), Visit 2, Visit 7, Visit 11, and Visit 16/ET. HbA1c and TSH (reflex free T3 and T4) collected at Screening/Baseline Visit (Visit 1/Day 1) and Visit 16/ET. Unscheduled visits for repeat laboratory assessments may be performed at any time for safety reasons or at the discretion of the Investigator. Hepatitis serology, performed in the lead-in study, will not be repeated at the Screening/Baseline Visit of the Open-label Study.

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

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

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

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

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

2. ETHICAL CONSIDERATIONS

2.1 Institutional Review Board and Independent Ethics Committee

Approval by the Institutional Review Board and Independent 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 and locally applicable regulations shall be obtained from each patient before entering the study or performing any study-specific procedure that involves risk to the patient. 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, each prospective patient will be given a full explanation of the study and be allowed to read the approved ICF. After receiving an explanation of study procedures, patients will have the opportunity to have any questions answered before signing the ICF. The Investigator must address all questions raised by the patient. Each patient will read, assent to an understanding of, and sign the ICF or other locally applicable authorization form. Each patient will be made aware that he/she may withdraw from the study at any time.

The Investigator 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. The Investigator shall retain the signed original ICF and HIPAA or other locally applicable form.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A list of Sponsor personnel responsible for study oversight is provided in the Study Reference Manual.

4. INTRODUCTION

Major depressive disorder (MDD) is a serious psychiatric disorder characterized by the presence of one or more major depressive episodes (MDE). Major depressive episodes may begin at any age; however, the average age of onset is in the mid-20s. The lifetime risk for MDD is estimated at 5% to 12% for men and 10% to 25% for women. Depression can have damaging effects on health and wellbeing, and leave one at risk for social withdrawal, alcohol abuse, and disrupted work, family, and social life (Kupferberg et al, 2016). MDD has a high mortality rate and up to 15% of patients with severe major depressive episodes die by suicide. In addition, individuals with MDD have high medical morbidity and are often plagued with more pain and physical illness than the general population.

Lumateperone (trade name CAPLYTA®) was approved by the Food and Drug Administration (FDA) on December 20, 2019 under NDA 209500 for the treatment of schizophrenia in adults. ITI, the Sponsor, is exploring the utility of lumateperone as adjunctive therapy in the treatment of MDD.

Although the mechanism of action is unknown, the efficacy of lumateperone could be mediated through a combination of antagonist activity at central serotonin 5-HT_{2A} receptors, serotonin reuptake inhibition, and postsynaptic antagonist activity at central dopamine D_2 receptors. Lumateperone's indirect glutamatergic modulation via activation of dopamine D_1 receptors in combination with serotonin reuptake inhibition may also play a role in antidepressant response. Importantly, lumateperone lacks potent off-target interactions that have been associated with side effects of other antipsychotic drugs.

Clinical data from 3 well-controlled studies in patients with schizophrenia (Studies ITI-007-005, ITI-007-301, and ITI-007-302) are consistent with respect to the pharmacological profile and prediction for antidepressant effects with favorable safety and tolerability. In addition to improving psychotic symptoms, lumateperone also improved symptoms of depression in patients with schizophrenia and comorbid depression at baseline. Similar improvements in depression symptoms were also seen in a one-year open label study of lumateperone in patients with schizophrenia (ITI-007-303). In this study, the favorable safety and tolerability profile was sustained.

Clinical data from 3 well-controlled bipolar depression studies (Studies ITI-007-401, ITI-007-404, and ITI-007-402) demonstrated efficacy in bipolar depression and confirmed lumateperone's tolerability and favorable safety profile. In Study ITI-007-404, once-daily lumateperone 42 mg met the primary and key secondary endpoints with statistically significant improvement over placebo at Week 6 (study endpoint), as measured by change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score and the Clinical Global Impression Scale, Bipolar version, Severity (CGI-BP-S) total score, respectively, and demonstrated statistically significant improvement on the CGI-BP-S depression.

In Study ITI-007-402, once-daily lumateperone 42 mg adjunctive to lithium or valproate met the primary and key secondary endpoints with statistically significant improvement over placebo at Week 6 (study endpoint), as measured by change from baseline in MADRS total score and the CGI-BP-S depression subscale.

In Study ITI-007-401, lumateperone did not meet its primary efficacy endpoint. Patients who continued in the optional open-label extension of lumateperone 42 mg maintained improvement and their depressive symptoms did not worsen.

Safety data from these studies and other trials with lumateperone, which has been administered to more than 3300 individuals for up to one year, show lumateperone to be well tolerated across a dose range from 0.7 to 126 mg, with a safety profile similar to placebo.

The purpose of the current study is to evaluate the safety and tolerability of lumateperone 42 mg as adjunctive treatment to antidepressant therapy (ADT) in patients with MDD. More detailed information about the known and expected benefits and risks and reasonably expected AEs is provided in the current lumateperone Investigator's Brochure.

5. STUDY OBJECTIVES

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

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

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

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

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

The study will be conducted as follows:

- A **Screening Period** of one day in duration. Potential patients rolling over from the lead-in studies will be evaluated for eligibility during the Screening/Baseline Visit (Visit 1/Day 1) which is the same visit as Visit 8/Day 43 of the lead-in study. Patients who meet all eligibility criteria at the Screening/Baseline Visit (Visit 1/Day 1) will be dispensed lumateperone 42 mg to be self-administered each evening without respect to food.
- A **26-week Open-label Treatment Period** during which patients will self-administer lumateperone, to be taken each evening, without respect to food. Background ADT should also continue as previously prescribed, with no change of dose from the lead-in studies. Patients will attend visits on Weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26. The Open-label Treatment Period will last a total of 26 weeks. A patient will be defined as a treatment completer if the patient completes the Open-label Treatment Period (all scheduled visits up to and including Visit 16/Week 26).
- A **2-week Safety Follow-up Period.** A Safety Follow-up visit will occur approximately 2 weeks after completion of the Open-label Treatment Period or after the Early Termination (ET) Visit. Any ongoing AEs at the Safety Follow-up Visit must be followed until resolution, until the AE stabilizes, until it is determined to be not clinically significant, or until the patient is lost to follow-up.

Patients who prematurely discontinue should be seen for an ET visit as soon as possible and will also be asked to return to for a Safety Follow-up visit approximately 2 weeks after Visit 16/ET visit.

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

The Schedule of Evaluations is presented in Table 1-1. Detailed descriptions of the procedures conducted at each study visit are provided in Section 8.4.

6.2 Scientific Rationale for Study Design

6.2.1 Study Design

Long term maintenance treatment of depression beyond the acute exacerbation of illness is standard of care, as MDD is for many patients a chronic, relapsing illness. Therefore, a longer-term, open label study to undertake safety monitoring and efficacy evaluations for periods greater than the time required to treat the symptoms of a depressive episode is warranted. This study allows patients who have participated in the double blind lead-in studies to start or continue treatment with lumateperone for up to 6 months, which is considered an adequate amount of time to collect safety, tolerability, and efficacy data to further the information gained in the acute treatment exposures.

6.2.2 Dose Selection

Lumateperone 42 mg was selected for this study was based on preclinical and clinical data, as well as the efficacy seen with this dose in bipolar depression studies ITI-007-404 and ITI-007-402. This dose delivers full occupancy of the cortical 5-HT_{2A} receptors (>85% occupancy) with modest striatal D_2 receptor occupancy and SERT occupancy. Data from human PET brain receptor occupancy studies with lumateperone indicate that a dose as low as 7 mg is associated with >85% occupancy of cortical 5-HT_{2A} receptors, while the 42-mg dose demonstrates approximately 40% striatal D_2 receptor occupancy. SERT occupancy has been demonstrated to be comparable to D_2 receptor occupancy. Moreover, in patients with schizophrenia and bipolar depression, once-daily oral administration of lumateperone 42 mg has been well tolerated with no dose titration needed and with a safety profile similar to placebo with up to 6 weeks' treatment duration.

6.3 Study Population

6.3.1 Inclusion Criteria

In addition to the Inclusion Criteria below, patients will be checked for previous participation in an ITI-007 clinical study and for duplicate enrollment by study site staff through Verified Clinical Trials (VCT).

Each patient entering the Open-label Safety Study must meet all of the following criteria:

1. In the opinion of the Investigator, the patient must have safely completed the lead-in study.

2. The patient must understand the written informed consent for the Open-label Safety Study, provide signed and witnessed written informed consent.

3. The patient is taking his/her ADT as prescribed from the lead-in study.

4. The patient must agree to continue using highly effective methods of birth control as specified in the lead-in study through the Safety-Follow-up Period of the Open-label Safety Study, or female patients or female partners of male patients must be of non-childbearing potential.

6.3.2 Exclusion Criteria

Because all patients enrolled in the lead-in study were required to satisfy exclusion criteria for participation in the lead-in study, the Investigator should assess if there has been any change in patient health status. Any newly-emergent medical condition reported during the lead-in study must be evaluated by the Investigator and should be discussed with the Sponsor or designee before enrolling the patient in the study.

Patients enrolling directly from the lead-in study to the Open-label Safety Study at the Screening/Baseline Visit (Visit 1/Day 1) will be excluded if they meet the following criteria:

1. In the opinion of the Investigator, the patient is unable to comply with study procedures or judged to be inappropriate for the study.

2. In the opinion of the Investigator, the patient has a significant risk for suicidal behavior during the course of her/his participation in the study or is considered to be an imminent danger to her/himself or others, and/or:

    a. At Visit 1/Day 1, the patient scores "yes" on Suicidal Ideation Items 4 or 5 of the C-SSRS "Since Last Visit" version;

    b. At Visit 1/Day 1, the patient scores ≥ 5 on the MADRS Item 10 (Suicidal Thoughts).

3. Based on the Investigator's clinical judgement, any abnormal clinical laboratory test or ECG results obtained throughout the lead-in study that are considered clinically significant and preclude safe participation in the study.

4. The patient is breast-feeding or pregnant; female patients of childbearing potential must have a negative urine pregnancy test at Visit 1/Day 1.

5. Has a positive urine drug test at Visit 1/Day 1. Positive tests attributable to prescription treatments (eg, opioids, benzodiazepines) may not be exclusionary if the use is not chronic and is able to be safely discontinued based on Investigator judgment and with the concurrence of the Sponsor or designee.

6. The patient has any other condition that may be detrimental to the patient if she/he participates in the study.

6.4 Stopping Criteria

6.4.1 Discontinuation of Patients from Therapy or Assessment: Patient-level Stopping Criteria

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

- Death
- AE
- Lack of efficacy (patients whose MDD symptoms worsen or are determined by the Investigator to not be adequately controlled prior to completing the open-label treatment period may be withdrawn from the study to start appropriate treatment at the Investigator's discretion)
- Protocol violation
- Study terminated by Sponsor
- Site terminated by Sponsor
- Withdrawal by subject or withdrawal of consent
- Lost to follow-up
- Pregnancy
- Other

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, including patients who discontinue due to lost to follow-up, 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 an ET Visit. All patients who prematurely discontinue from the study should return for the Safety Follow-up Visit.

6.4.2 Study Stopping Criteria

This study will be regularly monitored for safety and tolerability based on routine review of safety data. On a quarterly basis during study conduct, all open-label safety data (adverse events, clinical

laboratory measures, vital signs, ECGs, and C-SSRS) will be reviewed. If the Study Physician determines at any point during the open-label treatment period that the risk of study continuation outweighs the benefits, a determination to stop the study can occur in conjunction with discussions with the Head of Clinical Development or designee, the Head of Drug Safety and Pharmacovigilance, and the Chief Medical Officer.

6.5 Patient Replacement Procedures

Patients who prematurely discontinue from the study during the Open-label Treatment Period will not 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/IEC and competent local authorities (if applicable) 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 Lumateperone

Lumateperone will be dispensed only to eligible patients for self-administration under the supervision of the Investigator or sub-investigators or other designated personnel authorized to administer treatment.

Lumateperone will be self-administered orally as 42 mg capsules, once daily at approximately the same time in the evening with or without food.

For the subset of patients who consent to PK sampling, lumateperone will be self-administered on the evening before Visit 2. At Visit 2, lumateperone will be administered with approximately 240 ml of water at the study site after the patient has fasted for at least 10 hours. Patients will continue to fast for at least 2 hours after dosing. Patients will be instructed not to take an evening dose of lumateperone on this visit day. The next dose of lumateperone should be taken the following evening as prescribed.

Lumateperone will be supplied as capsules provided in treatment cards. Table 7-1 provides formulation information for lumateperone.

Lumateperone will be labeled according to local laws and regulations.

Table 7-1: Lumateperone Dosage and Composition

Lumateperone	
Dose	42 mg
Dose Frequency	Once daily in the evening
Route	Oral
Formulation	
[redacted]	[redacted]

7.1.1 Supply of Lumateperone

Lumateperone will be provided in treatment cards and shipped under ambient conditions. The treatment card for lumateperone will contain one 2 × 5 strip of capsules. Each blister card will contain a sufficient quantity of capsules for 1 patient for:

- 1 week (7 doses, plus 3 extra doses), to be dispensed at every visit through Visit 4/ Week 3;
- 2 weeks (14 doses, plus 6 extra doses), to be dispensed at every visit beginning with Visit 5/ Week 4 through for the duration of the 26-week treatment period.

7.1.2 Storage of Lumateperone

Lumateperone must be stored in a secure area, eg, a locked cabinet, protected from moisture, and kept at room temperature. Sites must report any temperature excursions as described in the Study Reference Manual or contact the Sponsor or its designee for further instructions.

7.2 Adjunctive Background Antidepressant Therapy

Antidepressant prescriptions will be provided to patients as needed through the duration of the study. Background ADT should continue as previously prescribed during the lead-in studies.

Any modifications to background ADT must be discussed with the Sponsor or designee prior to initiation of any changes.

7.3 Lumateperone Accountability

The Investigator will maintain accurate records of receipt of lumateperone, including dates of receipt. In addition, accurate records will be kept regarding when and how much lumateperone is dispensed and used by each patient in the study. Reasons for deviation from the expected dispensing regimen must also be recorded.

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

7.4 Method of Assigning Patients to Treatment Groups

After a patient signs the ICF at Visit 1 of the Open-label Treatment Period, site personnel will register the patient in the interactive web response system (IWRS). All rollover patients will be identified using the same Patient ID that was assigned by IWRS in the lead-in study.

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

7.5 Blinding

Not applicable. This is an open-label study.

7.6 Unblinding

Not applicable. This is an open-label study.

7.7 Monitoring Treatment Compliance

Medication adherence will be emphasized at every visit. Lumateperone compliance during any period will be closely monitored. Compliance is based on the number of capsules prescribed and number of capsules taken. At every visit, study staff will count the number of capsules remaining in the blister pack. Any irregularities in medication adherence should be discussed with the patient. All errors in medication dispensing or administration must be carefully documented. These errors may include providing the wrong dose, not taking the dose as prescribed, or losing medication.

In addition, at every visit, study staff will ask the patient about compliance with prescribed background ADT dosing regimen.

Any exceptions to non-compliance due to unusual circumstances should be discussed with the Sponsor or designee.

7.8 Prior and Concomitant Medications

7.8.1 Prior Medications

Patients should continue taking her/his ADT from the lead-in study as prescribed. Medication history, including the use of psychotropic medication or of any other medication, should be recorded at the Screening/Baseline Visit (Visit 1/Day 1).

7.8.2 Prohibited Medications

Use of the following products during the study is prohibited: alcohol, cannabis, illicit drugs, any known 5-HT_{2A} receptor antagonist or inverse agonist, any strong cytochrome P450 3A4 inhibitor or cytochrome P450 3A4 inducer, or any drugs with known psychotropic properties or any non-psychotropic drugs with potential central nervous system effects.

Any positive result on urine drug screen should be discussed with the Sponsor or designee.

7.8.3 Rescue Medications

Medications for the acute treatment of extrapyramidal symptoms and akathisia are allowed.

Zolpidem may be taken for insomnia, in the evening at bedtime and prior to midnight for the treatment of insomnia. If zolpidem is not available in specific regions, another sedative hypnotic may be approved by the Sponsor or designee.

The date of each dose of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded on the eCRF.

7.9 Treatment after Discontinuation

Patients whose depressive symptoms worsen or are determined by the Investigator not to be adequately controlled prior to completing the Open-label Treatment Period may, at the Investigator's discretion, be discontinued from the Open-label Treatment Period in order to start appropriate treatment. This new treatment will not be provided by the Sponsor. Patients who initiate a new treatment for depression during the study must be discontinued from the study and should also return for the Safety Follow-up visit.

All patients who prematurely discontinue from the Open-label Treatment Period regardless of cause should be seen for a final assessment at the ET Visit. All patients who prematurely discontinue from the Open-label Treatment Period should return for the Safety Follow-up visit.

8. EFFECTIVENESS, SAFETY, AND OTHER ASSESSMENTS

8.1 Effectiveness Assessments

8.1.1 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item scale designed to measure the overall severity of depressive symptoms (Montgomery and Åsberg, 1979). Individual items are rated by the Investigator or Sponsor-approved rater on a scale of 0 to 6 in which a score of 6 represents the most severe symptoms for each item assessed. Patients are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest. The MADRS total score ranges from 0 to 60. The MADRS will be completed by a Sponsor-approved rater.

8.1.2 Clinical Global Impression-Severity

The Clinical Global Impression Scale-Severity 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 Safety

All patients who receive study drug (ie, lumateperone 42 mg) will be evaluated for safety. Safety assessments will include incidence of AEs, C-SSRS assessment for suicidality, EPS assessment as measured by AIMS, BARS, and SAS scales, clinical laboratory evaluations, ECG evaluations, vital sign measurements, and physical examination and neurological findings. Additional details pertaining to safety assessments are provided in the Schedule of Evaluations (Table 1-1).

8.2.1 Adverse Events

8.2.1.1 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.

8.2.1.2 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.

8.2.1.3 Classification of Adverse Events and Serious Adverse Events

8.2.1.3.1 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 8.2.1.2).

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.

8.2.1.3.2 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 study drug caused the event?

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

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

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

8.2.1.4 Time Period and Frequency of AE and SAE Reporting

The Investigator will report all AEs from the time informed consent was obtained until the final protocol-defined study visit or last known dose date of study drug + 1 day, whichever is later.

The Investigator will report all SAEs from the time informed consent was obtained until 30 days after the last known dose date 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?"

8.2.1.5 Adverse Event Reporting Procedures

8.2.1.5.1 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 8.2.1.2 for the definition of SAEs and Section 8.2.1.5.2 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.

8.2.1.5.2 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 the Sponsor 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]

8.2.2 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 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:

ALT or AST $\geq 3 \times$ ULN and

Total bilirubin $\geq 2 \times$ ULN and

Alkaline phosphatase $< 2 \times$ 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 8.2.1.5.2) 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).

8.2.3 Pregnancy

Female patients will not be eligible for inclusion in the study if they have a positive pregnancy test at the Screening/Baseline Visit (Visit 1/Day 1). Any patient who becomes pregnant during the Open-label Treatment Period 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 consent was obtained until the final protocol-defined study visit or last known dose of study drug (if a final visit does not occur).

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.

While pregnancy itself is not considered to be an AE or SAE, any *pregnancy complication* or *elective termination* of a pregnancy for medical reasons will be reported as an AE or SAE. 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 8.2.1.5.2 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Pregnancy Notification/Outcome Form.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

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.

[redacted]

8.2.4 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected as specified in the Schedule of Evaluations (Table 1-1). Because the Screening/Baseline Visit (Visit 1) is the same visit as Visit 8/Day 43 of the lead-in study, laboratory assessments performed at Visit 8/Day 43 of the lead-in study are considered to be the Screening/Baseline laboratory assessments for this open-label study. Patients are required to fast for at least 10 hours before the collection of clinical laboratory blood tests at designated visits.

Laboratory results should be reviewed by the Investigator/sub-investigator throughout the study. Any abnormal laboratory results judged to be clinically significant should be discussed with the Sponsor or its designee. 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; red blood cell count with indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration); reticulocytes; white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) reported as percent (%) and absolute values; and platelet count.
- **Chemistry:** albumin; alkaline phosphatase; ALT; AST; bilirubin (total, direct); blood urea nitrogen; calcium; chloride; cholesterol (high-density lipoprotein [HDL] and low-density lipoprotein [LDL] will be calculated and reported); creatinine; creatine phosphokinase; gamma-glutamyl transferase; glucose; insulin; lactate dehydrogenase; phosphate; potassium; prolactin; sodium; triglycerides; total protein; uric acid. HbA1c and TSH (reflex

free T3 and T4) will be measured at the Screening/Baseline Visit (Visit 1/Day 1) and Visit 16/ET only.

- **Urinalysis**: macroscopic (pH, specific gravity, glucose, protein, ketones, bilirubin, nitrates, blood) and microscopic (red blood cells/high-power field, white blood cells/high-power field, casts, epithelial cells, crystals, granulation).
- **Urine Drug Screen (UDS)**: Urine testing for drugs (eg, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, methadone, opiates, phencyclidine) will be performed.
- **Urine and serum pregnancy tests**: Female patients who are of childbearing potential (FOCBP) will undergo a serum and a urine pregnancy test at Screening/Baseline Visit (Visit 1/Day 1). For all other visits, a urine pregnancy test will be performed. Unscheduled pregnancy tests may be administered at any time during the study at the Investigator's discretion.

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. Additional information regarding sample shipment is provided in the Laboratory Manual.

8.2.5 Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure [BP], body temperature, and body weight) will be assessed at every visit during the study as specified in the Schedule of Evaluations (Table 1-1). Height and BMI are assessed at the Screening/Baseline Visit (Visit 1/Day 1) only; waist circumference will be assessed at Screening/Baseline (Visit 1/Day 1) and Visit 16/ET.

Blood pressure and pulse 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.

8.2.6 Electrocardiograms

A 12-lead ECG will be performed as specified in the Schedule of Evaluations (Table 1-1). Each ECG assessment will be conducted after the patient has been resting quietly in the supine position and will comprise ten-second epochs from 12-lead ECGs. ECG parameters to be measured include HR, QRS, PR, QT, QTcB, QTcF and RR intervals.

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.

8.2.7 Other Safety Assessments

8.2.7.1 Columbia–Suicide Severity Rating Scale

The C-SSRS is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior (Posner et al, 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/Baseline (Visit 1/Day 1) and 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.

8.2.7.2 Extrapyramidal Scales

8.2.7.2.1 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" 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. There are an additional 2 items on dental status that are answered yes or no. The AIMS is to be completed at Screening/Baseline (Visit 1/Day 1) and Visits 2, 5, 7, 9, 11, 13, 15, and 16/ET as specified in the Schedule of Evaluations (Table 1-1).

8.2.7.2.2 Barnes Akathisia Rating Scale

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 6-point scale from 0 to 5. The BARS is to be completed at Screening/Baseline (Visit 1/Day 1) and Visits 2, 5, 7, 9, 11, 13, 15, and 16/ET as specified in the Schedule of Evaluations (Table 1-1).

8.2.7.2.3 Simpson-Angus Scale

The SAS is a measure of extrapyramidal side effects (Simpson &Angus, 1970). The SAS is used for assessment of antipsychotic-induced parkinsonism in both clinical practice and research settings. 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 Screening/Baseline (Visit 1/Day 1) and Visits 2, 5, 7, 9, 11, 13, 15, and 16/ET as specified in the Schedule of Evaluations (Table 1-1).

8.2.7.3 Physical Examination

A modified physical examination, including neurological and excluding genital/rectal 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 licensed to perform physical examinations.

8.3 Pharmacokinetic Assessments

For patients who consent to PK sampling, blood samples for determination of plasma concentrations of lumateperone (IC200056) and metabolites (IC200131, IC200161, IC200565, IC201308, and IC201309) will be collected at Visit 2 (Week 1) and Visit 7 (Week 8).

- On the evening prior to Visit 2, patients will self-administer lumateperone and record the date and time of lumateperone dosing.
- At Visit 2:
  - Patients will arrive at the site after a minimum of 10 hours fasting.
  - The site will record the patient-reported date and time of the prior dose of lumateperone.
  - Patients will receive a dose of lumateperone 42 mg and will continue to fast for at least 2 hours postdose. The date and time of the Visit 2 lumateperone dose must also be recorded.
  - Blood for PK samples will be collected predose (within 30 minutes prior to dosing), between 0.5 hour and 1-hour post-dose and between 1.5 hour and 3 hours post-dose. The date and time of PK sample collection at each timepoint must be recorded.
  - Patients will be instructed not to take an evening dose of lumateperone at Visit 2.
  - Patients will be instructed to resume lumateperone dosing as prescribed on the following day.
- At Visit 7:
  - The site will record the patient-reported date and time that lumateperone was taken on the evening before Visit 7.
  - A PK blood sample will be collected. The date and time of PK sample collection must be recorded.

Blood samples for PK analysis will be collected, processed, stored, and shipped as per instructions provided in the Laboratory Manual.

8.4 Schedule of Assessments

The schedule of study procedures and assessments is presented by visit in the Schedules of Evaluations (Table 1-1). 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/Baseline Visit (Visit 1/Day 1)

Informed consent and HIPAA (or other local authorization where applicable) must be obtained from the patient before any study procedures are conducted. The format and content of the ICF must have been agreed upon by the Investigator, the appropriate IRB/IEC, and the Sponsor.

After obtaining written informed consent, the following assessments and procedures are to be performed on Day 1 according to the Schedule of Evaluations in Table 1-1. All Screening assessments must be performed in person.

- Review of Inclusion/Exclusion criteria, including a review medical, psychiatric, and medication histories.
- ADT compliance check
- Physical examination
- ECG
- Vital signs (body temperature, blood pressure, and pulse), weight, height, waist circumference, and BMI
- MADRS
- CGI-S
- AIMS/BARS/SAS
- C-SSRS
- Blood draw and urinalysis (standard clinical labs, drug screening, and pregnancy testing for FOCBPs) after an overnight fast of at least 10 hours
- Review of AEs
- Dispense open-label lumateperone
- Dispense ADT prescription as needed.

8.4.2 Open-label Treatment Period

8.4.2.1 Visit 2/Week 1

- Lumateperone return and compliance check
- ADT compliance check
- Review of AEs
- Review of concomitant medications
- ECG
- Vital signs (body temperature, blood pressure, and pulse) and weight
- MADRS
- CGI-S
- AIMS/BARS/SAS
- C-SSRS
- Blood draw and urinalysis (standard clinical labs, drug screening, and pregnancy testing for FOCBPs) after an overnight fast of at least 10 hours
- **Patients who consent to PK sampling** should be in a fasted state for at least 10 hours prior to PK sampling and lumateperone dosing.
    - The site will record the patient-reported date and time of the prior evening's dose of lumateperone.
    - A PK blood sample will be collected predose (within 30 minutes prior to dosing). The date and time of PK sampling must be recorded.
    - Lumateperone 42 mg will be administered with approximately 240 mL water under fasted condition. The date and time of dosing must be recorded.
    - Additional PK blood samples will be collected between 30 mins and 1 hour postdose and between 1.5 and 3 hours postdose. The date and times of PK sampling must be recorded.
    - Patients will continue to fast for at least 2 hours postdose.
    - The next dose of lumateperone should be taken the following evening as prescribed.
- Dispense open-label lumateperone
- Dispense ADT prescription as needed.

8.4.2.2 Visit 3/Week 2 and Visit 4/Week 3

- Lumateperone return and compliance check
- ADT compliance check
- Review of AEs

- Review of concomitant medications
- Vital signs (body temperature, blood pressure, and pulse) and weight
- MADRS
- CGI-S
- C-SSRS
- Dispense open-label lumateperone
- Dispense ADT prescription as needed.

8.4.2.3 Visit 5/Week 4, Visit 9/Week 12, Visit 13/Week 20, and Visit 15/Week 24

- Lumateperone return and compliance check
- ADT compliance check
- Review of AEs
- Review of concomitant medications
- Vital signs (body temperature, blood pressure, and pulse) and weight
- MADRS
- CGI-S
- AIMS/BARS/SAS
- C-SSRS
- Urine pregnancy testing, for FOCBPs
- Dispense open-label lumateperone
- Dispense ADT prescription as needed.

8.4.2.4 Visit 6/Week 6, Visit 8/Week 10, Visit 10/Week 14, Visit 12/Week 18, and Visit 14/Week 22

- Lumateperone return and compliance check
- ADT compliance check
- Review of AEs
- Review of concomitant medications
- Vital signs (body temperature, blood pressure, and pulse) and weight
- C-SSRS
- Dispense open-label lumateperone
- Dispense ADT prescription as needed

8.4.2.5 Visit 7/Week 8 and Visit 11/Week 16

- Lumateperone return and compliance check
- ADT compliance check
- Review of AEs
- Review of concomitant medications
- ECG
- Vital signs (body temperature, blood pressure, and pulse) and weight
- MADRS
- CGI-S
- AIMS/BARS/SAS
- C-SSRS
- Blood draw and urinalysis (standard clinical labs, drug screening, and pregnancy testing for FOCBPs) after an overnight fast of at least 10 hours
- **Visit 7 only**: **For patients who consent to PK sampling**, one blood sample will be collected. The date and time of PK sampling must be recorded.
- Dispense open-label lumateperone
- Dispense ADT prescription as needed.

8.4.2.6 Visit 16/ET/Week 26

- Lumateperone return and compliance check
- ADT compliance check
- Review of AEs
- Review of concomitant medications
- Physical examination
- ECG
- Vital signs (body temperature, blood pressure, and pulse), weight, and waist circumference
- MADRS
- CGI-S
- AIMS/BARS/SAS
- C-SSRS
- Blood draw and urinalysis (standard clinical labs, drug screening, and pregnancy testing for FOCBPs)

8.4.3 Safety Follow-up Visit (Visit 17/Week 28)

At the Safety Follow-up Visit, the following procedures will be performed:

- Review of AEs
- Review of concomitant medications
- Vital signs (body temperature, blood pressure, and pulse), and weight
- MADRS
- C-SSRS.

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 important endpoints including primary and key secondary endpoints.

Continuous variables will be summarized using descriptive statistics (number of patients [n], mean, standard deviation [SD], median, minimum, and maximum, unless otherwise stated). Categorical variables will be summarized using frequency counts and percentages.

The baseline for each specific efficacy/safety change-from-baseline analysis endpoint is defined as the last measurement prior to the first dose of study treatment from the lead-in study.

9.2 Determination of Sample Size

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

9.3 Analysis Populations

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

- The Enrolled Population includes all patients who sign the informed consent for this Open-label Safety Study
- Safety Population includes all patients in the Enrolled Population who receive at least one dose of open-label lumateperone
- PK Population includes all patients in the Safety Population who have at least one evaluable PK sample.

9.4 Statistical Analyses

9.4.1 Patient Disposition

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

- The number of patients who were screened will be summarized overall by study center.
- The number of patients in the Safety Population will be summarized overall.

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

9.4.2 Demographics and Other Baseline Characteristics

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

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

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

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

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

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

9.4.3 Extent of Exposure and Treatment Compliance

9.4.3.1 Extent of Exposure

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

9.4.3.2 Measurement of Treatment Compliance

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

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

9.4.4 Efficacy Analyses

The efficacy analyses will be based on patients in the Safety Population with an available baseline efficacy value and at least one postbaseline efficacy assessment during the Open-label Treatment Period.

The efficacy endpoints are change from baseline in MADRS total score and change from baseline in CGI-S score.

9.4.4.1 MADRS Total Score

A descriptive summary for the change from baseline to each assessment visit in MADRS total score will be provided. Also, the number of patients who achieved remission (MADRS total score ≤ 12) will be provided. In addition, the responder rate (response is defined as at least 50% reduction in MADRS total score compared to baseline score) will be summarized.

9.4.4.2 CGI-S Score

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

9.4.5 Safety Analyses

Safety analyses will be performed using the Safety Population. The safety parameters will include AEs, clinical laboratory, vital sign, ECGs, BARS, AIMS, SAS, and C-SSRS.

9.4.5.1 Adverse Events

Adverse events will be recorded for each patient from the time informed consent was obtained until the final protocol-defined study visit or the last known dose date of lumateperone + 1 day.

SAEs will be reported from the time informed consent was obtained until 30 days after the last known dose date of lumateperone.

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

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

The number and percentage of patients reporting TEAEs will be tabulated by system organ class (SOC) and 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.

9.4.5.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI and conventional units) and changes from baseline values at each assessment timepoint and at the end of the Open-label Treatment Period will be summarized for each clinical laboratory parameter.

The number and percentage of patients with potentially clinically significant (PCS) postbaseline clinical laboratory values during the Open-label Treatment Period will be tabulated for the Safety Population. The criteria for PCS laboratory values and details on additional laboratory analyses will be provided in the SAP.

In addition, the number and percentage of patients meeting Hy's law criteria during the open-label treatment period will be provided for the Safety Population.

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 for the Safety Population.

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

9.4.5.4 Electrocardiograms

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 for the Safety Population.

The number and percentage of patients with PCS postbaseline ECG values will be summarized for the Open-label Treatment Period. 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 change from baseline to assessment visit and to the end of the Open-label Treatment Period in AIMS total score, BARS total score, and SAS total score will be summarized based on the Safety Population.

9.4.5.5.1 Columbia Suicide Severity Rating Scale (C-SSRS)

The number and percentage of patients with suicidality as measured by the C-SSRS will be summarized for the Open-label Treatment Period, where suicidality was defined as having at least one occurrence of suicidal ideation or at least one occurrence of suicidal behavior.

The distribution of responses for the most severe suicidal ideation and the most severe suicidal behavior will be summarized for lifetime history.

The distribution of responses for the most severe suicidal ideation and the most severe suicidal behavior at baseline and during the Open-label Treatment Period will be summarized.

Emergence of suicidal ideation, serious suicidal ideation, suicidal behavior, and worsening of suicidal ideation (ie, compared with the first dose of study treatment from the lead-in study) during the Open-label Treatment Period will be summarized.

The details of analyses of C-SSRS will be provided in the SAP.

9.4.6 Plasma Concentration Parameters

Individual plasma concentrations of lumateperone and metabolites (IC200131, IC200161, IC200565, IC201308, and IC201309) will be listed and summarized by visit/timepoint.

Plasma concentrations of lumateperone and potentially of selected metabolites will be pooled with data from other studies of lumateperone and analyzed using a population PK approach. The results from these analyses will be presented in a separate report.

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, before the start of the study:

- A completed and signed Form FDA 1572 or equivalent form, if applicable. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572 or equivalent form, if applicable, a new form must be completed and returned to the Sponsor.
- A fully executed contract
- The curricula vitae for the Investigator and all sub-investigators listed on Form FDA 1572 or equivalent form, 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 or equivalent form, if applicable
- 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/IEC
- 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
- A copy of the laboratory certifications and reference ranges
- 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 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 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 Laboratory 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. REFERENCES

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12. 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

13. INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study in accordance with this Protocol Amendment 1, ITI-007-503, dated 23 Aug 2021, 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