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Study ID: ITI-007-020

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

Statistical Analysis Plan Version Final Date: March 09, 2022

Statistical Analysis Plan

ITI-007-020

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

Version:	Final
Date:	09 Mar 2022
Compound:	Lumateperone
Study Phase:	1b
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.

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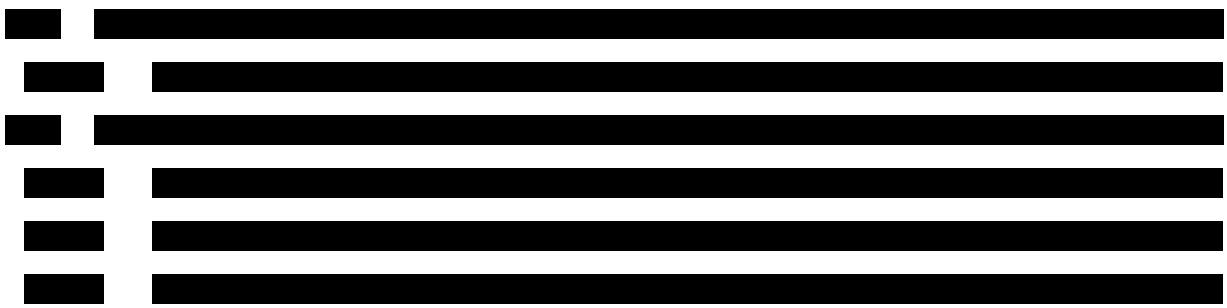

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1. LIST OF ABBREVIATIONS

AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
bpm	beats per minute
C-SSRS	Columbia-Suicide Severity Rating Scale
CGI-S	Clinical Global Impression Scale-Severity
ECG	electrocardiogram, electrocardiographic
ET	early termination
eCRF	electronic case report form
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond(s)
PCS	potentially clinically significant
PK	pharmacokinetic
PT	preferred term
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Fridericia formula
SAE	serious adverse event

SAP	statistical analysis plan
SAS	Simpson Angus Scale
SD	standard deviation
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
WHO	World health organization

2. INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the safety data as outlined and/or specified in the protocol Version 5.0 of Study ITI-007-020 dated 28 Feb 2022. Specifications of tables, figures, and data listings are contained in a separate document. The statistical analysis for pharmacokinetic parameters will be specified in a separate document.

2.1 Overall Study Design and Plan

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

The study will be conducted as follows:

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

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

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

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

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

Safety and tolerability will be assessed throughout the study. The Schedule of Evaluations for this study is presented in Table 2.1-1.

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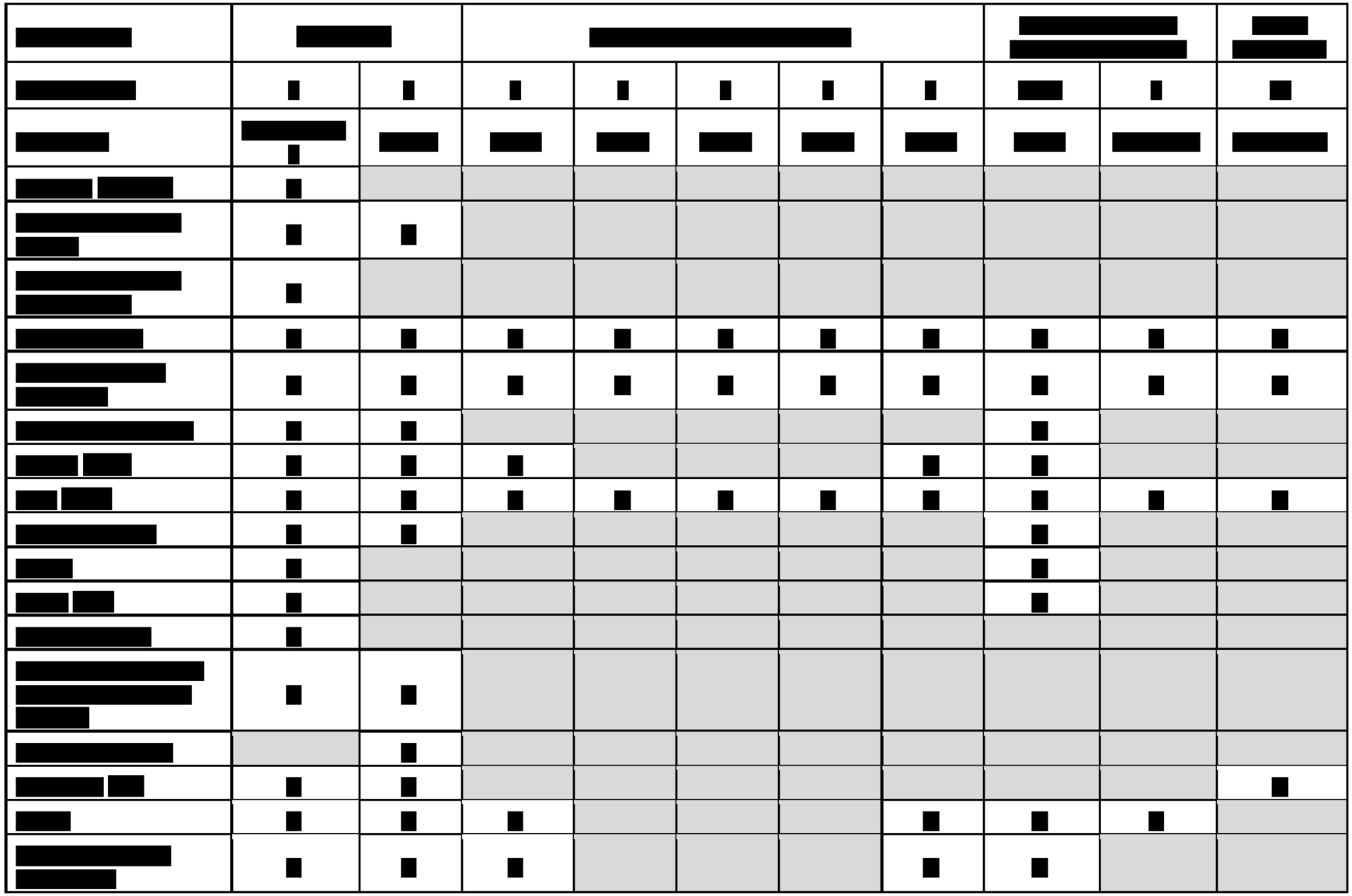

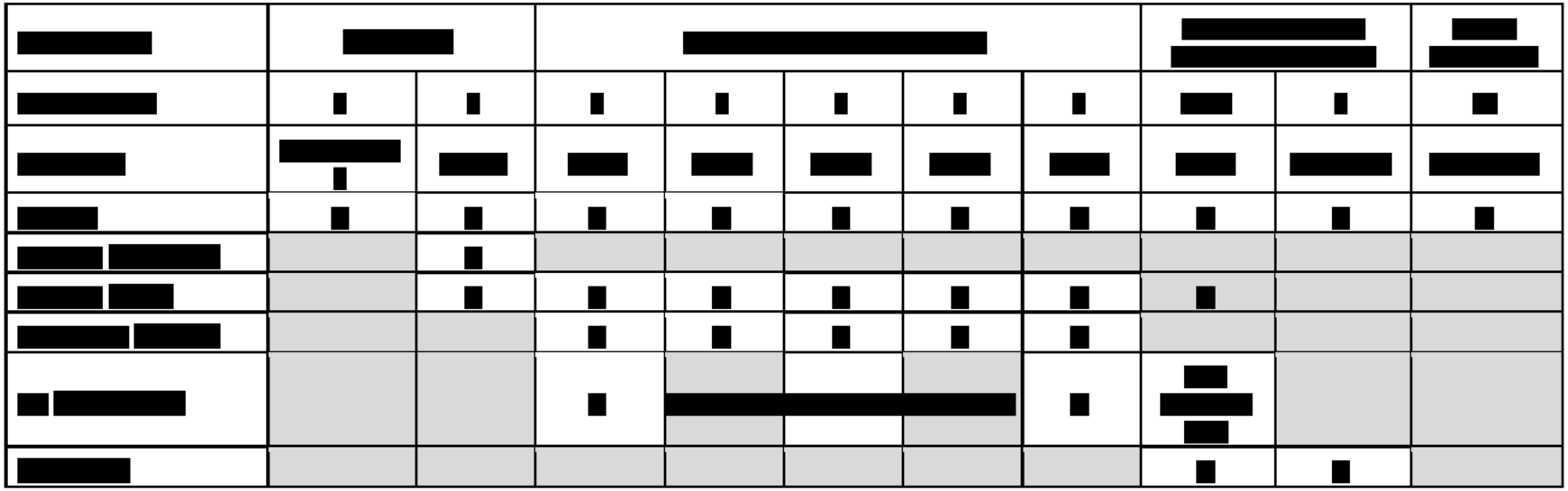

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3. STUDY OBJECTIVES

The objectives of this study are:

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

4. ANALYSIS SETS

The Enrolled Set includes all patients whose legally authorized representative provided informed consent and all patients who provided written assent.

The Safety Set includes all patients who took at least 1 dose of study drug.

The analysis in the study will be based on Safety Set unless otherwise stated.

5. SUBJECTS DISPOSITION

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

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

6. PROTOCOL DEVIATION

Major protocol deviations will be presented in a data listing.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

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

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

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Extent of Exposure and Compliance

Exposure to study drug during Open-label Treatment Period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of study drug taken to the date of the last dose taken, inclusive. Descriptive statistics (n, mean, median, SD, minimum, and maximum) will be presented overall (and by dose if more than one dose is administered).

8.2 Prior and Concomitant Medication

Prior and concomitant medication use will be listed with the therapeutic class included. Medications will be classified as follows:

- A 'prior medication' is any medication that started and stopped prior to the first dose of study drug during Open-label Treatment Period.
- A 'prior concomitant medication' is any medication that started before the first dose of study drug and stopped or was ongoing after the first dose of study drug during the Open-label Treatment Period.
- A 'concomitant medication' is any medication taken on or after the first dose of study drug during the Open-label Treatment Period.

9. SAFETY ANALYSES

The safety analysis will be performed based on the Safety Set as specified in the Statistical Analysis Plan (SAP). Safety variables will include adverse events (AE), clinical laboratory, vital signs, ECG, CGI-S, C-SSRS, SAS, BARS, and AIMS. For each safety parameter, the last assessment made before the first dose of study drug will be used as the baseline for all analyses of that safety parameter unless other stated.

In general, the summary of safety parameters will be presented overall (and by dose if more than one dose is administered).

9.1 Adverse Events

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

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

The number and percentage of patients reporting TEAEs will be tabulated overall (and by dose if more than one dose is administered), by SOC and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship to study drug. If more than one AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summary by severity and by relationship to study drug.

In addition, a listing of patients who discontinued because of an AE and a listing of subjects with serious AEs and patients who died (if any) will be presented.

9.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI and conventional units) at baseline, postbaseline, and changes from baseline values at each assessment timepoint during the Open-label Treatment Period will be summarized overall (and by dose if more than one dose is administered) for the Safety Set 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 overall (and by dose, if applicable) for the Safety Set. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least one postbaseline assessment. The numerator is the total number of patients with available non-PCS baseline values and at least one PCS postbaseline value.

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Criteria for potential Hy's Law cases is defined by a post baseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × ULN, along with total bilirubin (TBL) ≥ 2 × ULN and a non-elevated alkaline phosphatase (ALP) < 2 × ULN, all based on blood draws collected within a 24-hour period. Potential Hy's Law criteria without time window is defined by maximum of post baseline elevation of ALT or AST ≥ 3 × ULN, along with maximum of post baseline elevation of TBL ≥ 2 × ULN.

One listing for patients who meet the potential Hy's Law criteria will be provided.

9.3 Vital Signs

Descriptive statistics for vital signs (eg, pulse rate, systolic and diastolic BP, temperature, and respiratory rate) at baseline, postbaseline, and changes from baseline values at each assessment timepoint during the Open-label Treatment Period of the study will be presented overall (and by dose if more than one dose is administered) for the Safety Set.

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9.4 Electrocardiograms

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

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9.5 Other Safety Parameters

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9.5.2 Abnormal Involuntary Movement Scale (AIMS)

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

The (non-global) AIMS total score is the sum of items 1 through 7. The possible range for the AIMS total score is 0 to 28. Higher values of the total AIMS score indicate increased severity in abnormal movement. If one or more of the AIMS total score items are missing at a visit, the score will be set to missing.

Descriptive statistics for AIMS total scores at baseline, postbaseline, and changes from baseline values at each assessment timepoint during the Open-label Treatment Period will be summarized overall (and by dose if more than one dose is administered) for the Safety Set.

[redacted]

[redacted]

[redacted]

10. SAMPLE SIZE CONSIDERATION

A sample size of [redacted] patients is expected to provide a 95% confidence interval within 60% and 140% of the geometric mean estimates of CL/F and V_z/F with at least 80% power assuming an inter-subject variability of 66%. If preliminary analyses of PK data show increased inter-subject variability in CL/F and V_z/F, additional patients may be enrolled, for up to [redacted] patients dosed. Subjects who prematurely discontinue from the study may be replaced.

11. STATISTICAL SOFTWARE

Statistical analyses of safety parameters will be performed using version 9.4 or newer of Statistical Analysis Software.

12. DATA HANDLING CONVENTIONS

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13. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

Not Applicable.

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