NCT05732194

Study ID: ITI-333-002

Title: A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of ITI-333 in Healthy Subjects

Protocol Amendment Version 1.0 Date: November 06, 2023

A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of ITI-333 in Healthy Subjects

Protocol Number:	**ITI-333-002**
[redacted]	[redacted]
Protocol Amendment 1 Date	06 Nov 2023
Compound:	ITI-333
Study Phase:	1
Sponsor:	Intra-Cellular Therapies, Inc. [redacted]

Confidentiality Statement

PROTOCOL AMENDMENT 1: SUMMARY OF CHANGES

Protocol Amendment 1 for Study ITI-333-002, dated 06 Nov 2023, provides revisions to the Original Protocol [redacted].

A tabular summary list of changes to the protocol is provided below. New text is ***bold and italicized***; editorial corrections, minor revisions for consistency, and formatting changes are not summarized.

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

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LIST OF ABBREVIATIONS

AE	adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
AUC_{0-tau}	area under the plasma concentration-time curve from time zero to the end of dosing interval
[redacted]	[redacted]
[redacted]	[redacted]
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFR	Code of Federal Regulations
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	maximum observed plasma drug concentration
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	[redacted]
ET	early termination
[redacted]	[redacted]

FDA	Food and Drug Administration
FR	Federal Register
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency
[redacted]	[redacted]
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
IUD	intrauterine device
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond(s)
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT interval corrected for heart rate using the Fridericia formula
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SpO_2	Oxygen saturation
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
T_{max}	time to reach maximum observed plasma drug concentration
UDS	urine drug screen
ULN	upper limit of normal
[redacted]	[redacted]
[redacted]	[redacted]

1. PROTOCOL SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study ITI-333-002	
Title of Study	A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of ITI-333 in Healthy Subjects
Study Center (Country)	1 (United States of America)
Development Phase	1
Objectives	[redacted]: • To determine the safety and tolerability of ITI-333 after multiple oral administration of ascending ITI-333 doses in healthy subjects • To determine the pharmacokinetics of ITI-333 [redacted] after multiple oral administration of ascending ITI-333 doses in healthy subjects. [redacted]
Study Design	This study will be conducted as a single-center, randomized, double-blind, placebo-controlled, dose escalation study of ITI-333 in up to 4 sequential cohorts. Subjects will be screened up to 21 days prior to dosing with study drug. Subjects will be admitted to the study center on Day -1 and assessed for continued eligibility. On Day 1, subjects will be randomized to receive either ITI-333 or placebo. Dosing of study drug will occur after an overnight fast of at least 10 hours. Each subject will receive an oral dose of study drug once daily for 14 days. Sentinel dosing will be used in each cohort. The first 2 subjects randomized in each cohort will receive either ITI-333 or placebo. Dosing of the remaining subjects within each cohort (5 subjects randomized to ITI-333; 1 subject randomized to placebo) will occur after a minimum of 24 hours from the Day 7 dosing of the sentinel group, to ensure adequate evaluation of safety and tolerability by the Investigator and Sponsor Study Physician. Subjects in each cohort will be randomized to receive an oral dose of either ITI-333 or placebo once daily for 14 days. The planned doses are as follows: • Cohort 1: 0.75 mg ITI-333 (n=6) or placebo (n=2) • Cohort 2: 1.5 mg ITI-333 (n=6) or placebo (n=2) • Cohort 3: 3 mg ITI-333 (n=6) or placebo (n=2) • Cohort 4: 6 mg ITI-333 (n=6) or placebo (n=2) [redacted] After completion of Cohorts 1 through 4, analyses of PK and safety data will be performed. Following the review of PK and safety data, stopping criteria may be modified. Serial PK blood samples to determine plasma concentrations of ITI-333 [redacted] will be collected [redacted] on Day 14

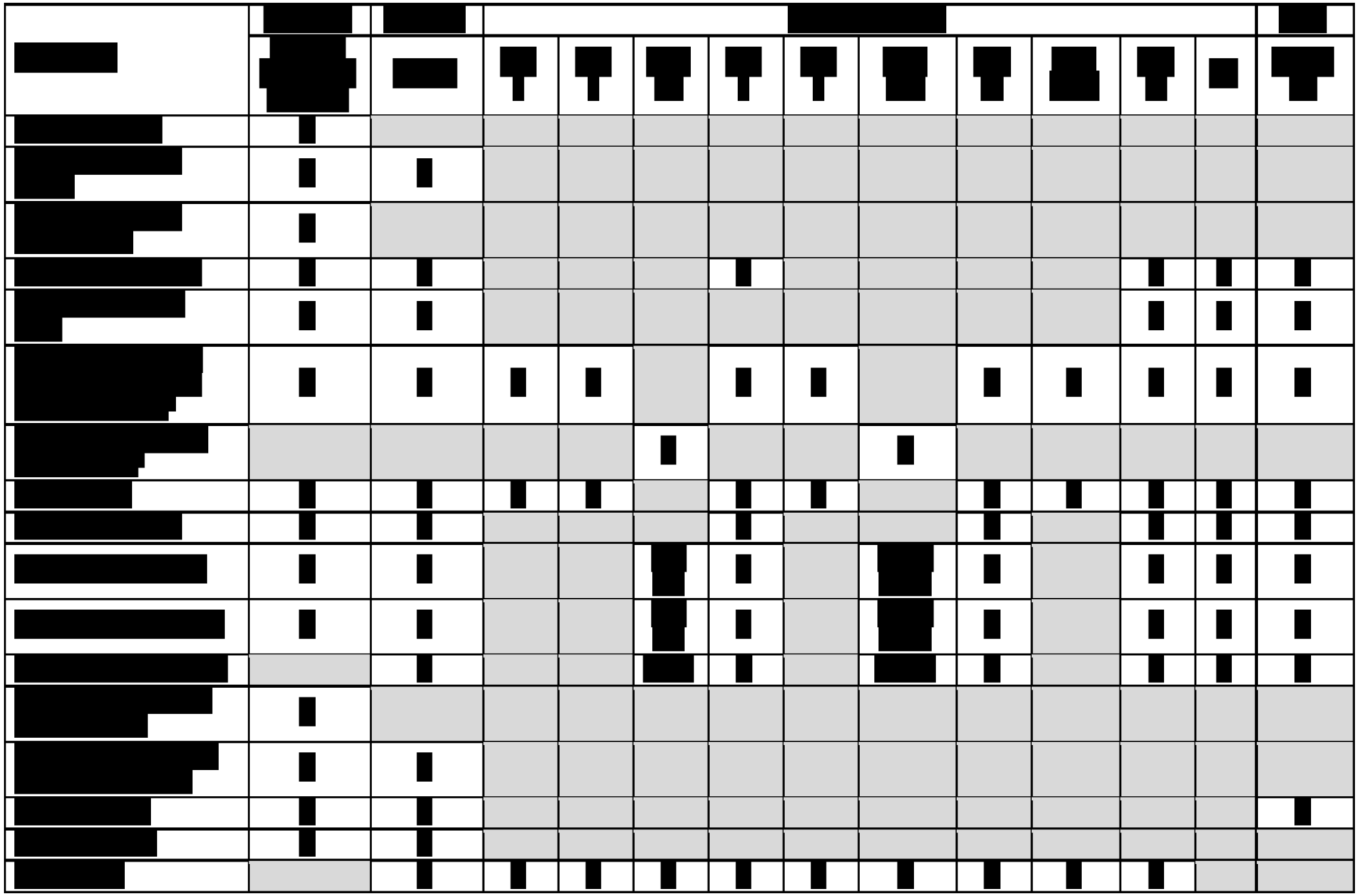
	(predose) and up to 72 hours after the last dose administration on Day 14. [redacted] Following completion of all specified procedures, subjects will be discharged on Day 17. Subjects will return for a safety follow-up visit on Day 24 (± 1). Upon completion of each cohort, a Data Monitoring Committee (DMC) will review safety and PK data to determine the progression of dose escalation. Dosing for the next higher dose cohort will not begin until the dose in the preceding cohort is deemed safe and tolerable and PK has been evaluated.
Number of Subjects	A total of 32 healthy subjects (8 subjects per dose cohort) are planned for randomization. Within each cohort, 8 subjects will be randomized to receive multiple doses of ITI-333 (6 subjects) or placebo (2 subjects).
Main Criteria for Inclusion and Exclusion	***Inclusion Criteria:*** • Able to provide written, informed consent; • Healthy male or female subjects between 18 and 45 years of age, inclusive at time of consent; • Body mass index (BMI) between 18.0 and 32.0 kg/m^2, inclusive at Screening, and a minimum body weight of 50 kg at Screening. All Inclusion Criteria are presented in Section 6.3.1. ***Exclusion Criteria***: • Clinically significant abnormality within 2 years of Screening that in the Investigator's opinion may place the subject at risk or interfere with study outcome variables; this includes, but is not limited to, history of or current cardiac, hepatic, renal, neurologic, gastrointestinal, pulmonary, endocrinologic, hematologic, or immunologic disease or history of malignancy; • Any clinical condition or procedure (eg, gastric bypass or cholecystectomy) that may affect the absorption, distribution, biotransformation, or excretion of ITI-333. Subjects with a history of appendectomy are eligible for study participation; • Current or recent (within 3 months prior to Screening) unstable angina; a history of myocardial infarction within 3 months prior to Screening; or a history of a clinically significant cardiac arrhythmia; • History of psychiatric condition that in the Investigator's opinion may be detrimental to participation in the study; • Likely allergy or sensitivity to ITI-333 or its excipients based on known allergies or hypersensitivities to drugs with shared pharmacology which may be suggestive of an increased potential for an adverse reaction to ITI-333; • Received any medication including herbal medication, excluding non-hormonal IUD, within 5 half-lives or 14 days (whichever is longer) prior to dosing with study drug on Day 1; occasional use of acetaminophen (≤ 1 g/day) or ibuprofen (≤ 400 mg/day) during this period may be allowed on a case-by-case basis upon approval by the Sponsor; • [redacted] • Consumption of any food or beverage containing grapefruit, pomelo, poppy seeds, or Seville oranges within 48 hours prior to dosing with study drug on Day 1; • Females who are currently breastfeeding. All Exclusion Criteria are presented in Section 6.3.2.

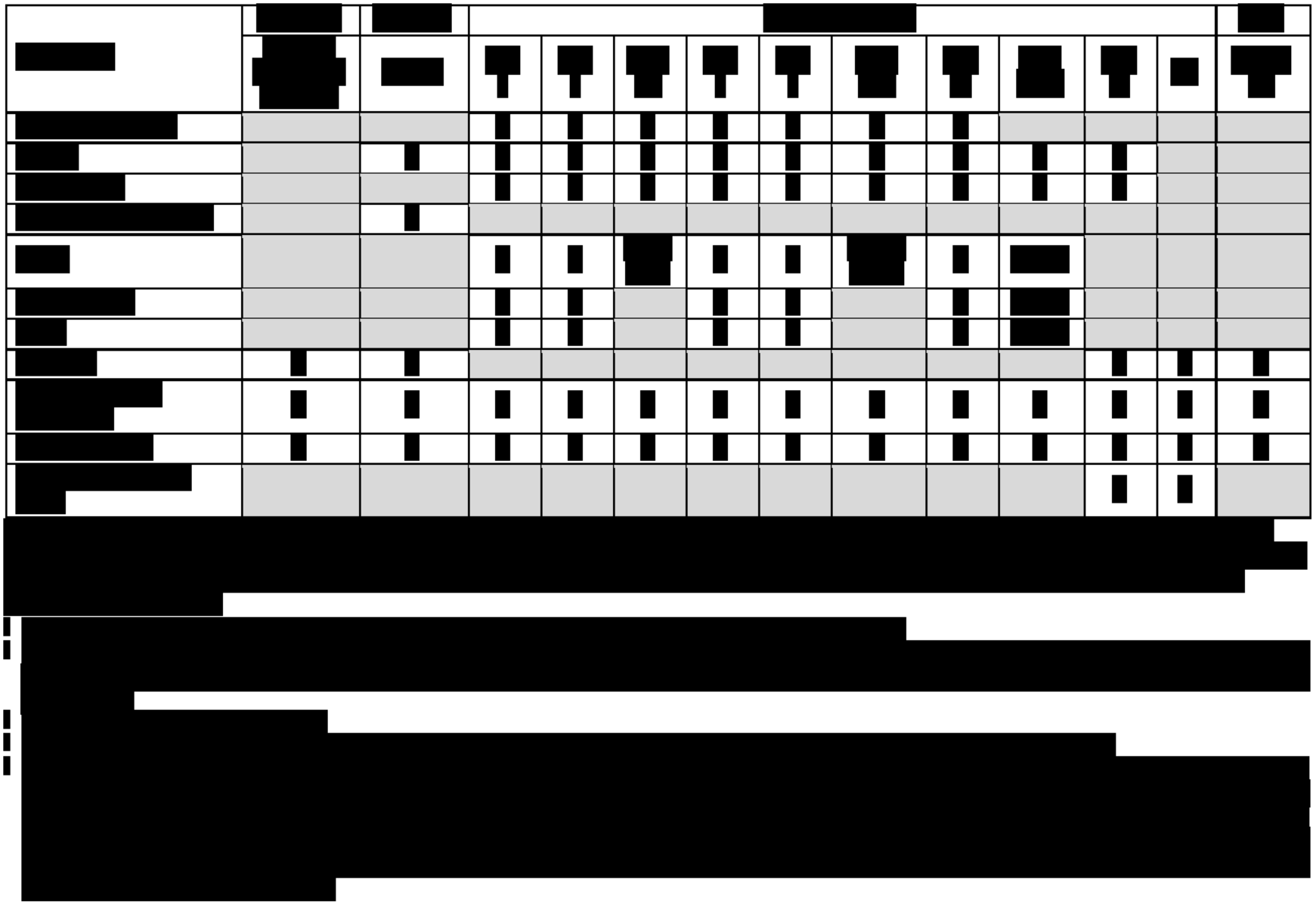
Duration of Treatment	Study duration includes a Screening Period up to 21 days prior to dosing on Day 1, an inpatient Treatment Period of up to 17 days, and a Safety Follow-up Visit 10 days (± 1) day after the last dose of study drug. Therefore, the total study duration for each subject will be up to 46 days, including the Screening Period.
Test Product, Dosage, and Mode of Administration	ITI-333 [redacted] will be supplied to the study center by the Sponsor [redacted]. The planned ITI-333 doses in each cohort are: • Cohort 1: 0.75 mg ITI-333 once daily for 14 days • Cohort 2: 1.5 mg ITI-333 once daily for 14 days • Cohort 3: 3 mg ITI-333 once daily for 14 days • Cohort 4: 6 mg ITI-333 once daily for 14 days. Dose escalations other than the planned dosed specified above may be evaluated based on safety and PK assessments but they will not exceed 2-fold. [redacted]
Reference Product, Dosage, and Mode of Administration	Placebo [redacted], once daily for 14 days.
Pharmacokinetic Measures	Blood samples to determine plasma concentrations of ITI-333 [redacted] will be collected at the following timepoints: • [redacted] • Day 14: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose. [redacted]
Safety Measures	The safety and tolerability of ITI-333 will be assessed throughout the study via: • Adverse events (AEs) • Vital signs (blood pressure, [redacted] SpO_2, [redacted] weight, and body mass index [BMI]) • 12-lead electrocardiogram (ECG) • Clinical laboratory tests [redacted] • Prior and concomitant medications • Physical examination • [redacted] • Pregnancy test (where applicable)
[redacted]	[redacted]

	[redacted]
[redacted]	[redacted]
Statistical Methods	Detailed statistical methods will be described in separate statistical analysis plan(s). **Analysis Populations:** ***Enrolled Population:*** The Enrolled Population will include all subjects who sign the informed consent form. ***Randomized Population:*** The Randomized Population will include all enrolled subjects who are randomized. ***Safety Population:*** The Safety Population will include all randomized subjects who receive at least one dose of study drug. ***Pharmacokinetic Populations:*** The PK Population for ITI-333 [redacted] will include all subjects in the Safety Population who have no major protocol deviation which may impact PK and have measurable plasma concentrations to provide a reliable estimate of at least one [redacted] PK parameter (ie, C_{max}, AUC). Subjects with emesis at or before 2 × median T_{max} of ITI-333 may be excluded from the PK Populations. [redacted] **Pharmacokinetic Analysis**: Individual subject plasma concentration vs actual sampling time data for ITI-333 [redacted] will be used to derive the PK parameters using non-compartmental PK analysis. The following PK parameters will be evaluated following dosing on [redacted] Day 14: [redacted] **Day 14:** • Area under the plasma concentration-time curve (AUC) from time zero to the end of dosing interval ($AUC_{0\text{-}tau}$) • Maximum observed plasma drug concentration over a dosing interval (C_{max}) • Time to reach maximum observed plasma drug concentration over a dosing interval (T_{max}). [redacted]

	• [redacted] Plasma concentration data of ITI-333 [redacted] will be listed by subject using the Safety Population. For each analyte, plasma concentrations will be summarized using descriptive statistics by cohort, treatment day, and nominal sampling time using the PK Population. Descriptive statistics will be used to summarize PK parameters of ITI-333 [redacted] by cohort, using the PK population. [redacted] **Safety Analysis:** Safety data will be summarized using the Safety Population. AEs, including serious AEs (SAEs), treatment-emergent adverse events (TEAEs), treatment discontinuation due to AEs, TEAEs by severity, and TEAEs by relationship to study drug will be summarized by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts. Descriptive statistics will be provided for vital signs measurements; clinical laboratory test results; and 12-lead ECG at each timepoint and for changes from baseline at each timepoint by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts. [redacted]

[redacted]





2. ETHICAL CONSIDERATIONS

2.1 Institutional Review Board

Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Investigator. A copy of the approval letter will be supplied to Intra-Cellular Therapies, Inc. (the Sponsor) or its designee along with a roster of IRB members. During the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet, advertisements, and amendments (if any) will be approved by the IRB at the study center in conformance with applicable 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 Subject Information and Informed Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each subject before entering the study or performing any study-specific procedure that involves risk to the subject. If the ICF is revised during the study, all active participating subjects must sign the revised form. The informed consent statement shall contain all the elements of informed consent listed in Appendix I of this protocol.

Before any screening procedures, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. After receiving an explanation of study procedures, subjects will have the opportunity to have any questions answered before signing the ICF. The Investigator must address all questions raised by the subject. Each subject will read, assent to an understanding of, and sign the ICF. Each subject will be made aware that he/she may withdraw from the study at any time.

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

3. STUDY ADMINISTRATIVE STRUCTURE

Contact information for vendors responsible for study conduct and a list of Sponsor contacts will be provided to the study center.

4. INTRODUCTION

ITI-333 uniquely combines high affinity binding to μ-opioid and serotonin 5-HT_{2A} receptors. In addition to the potential benefits conferred by ITI-333 affinity for μ-opioid receptors, the affinity of ITI-333 for 5-HT_{2A}, in concert with μ-opioid receptors, suggests a potentially unique functional pharmacological interaction that may have utility in the treatment of opioid use disorder (OUD) and the associated psychiatric comorbidities (eg, depression and anxiety).

Nonclinical data demonstrate that ITI-333 functions as a biased μ-opioid receptor ligand with partial agonist activity, acting as an antagonist to block effects of high doses of morphine in both pain and motor activity models while acting alone to provide potent analgesia in models of acute and chronic pain. However, when given to rodents at doses comparable to those that block the effect of morphine and well in excess of those required for analgesia, ITI-333 elicits no signs of physical dependence or tolerance after chronic dosing or after abrupt withdrawal of the compound.

In models designed to evaluate the safety pharmacology, ITI-333 did not induce biologically relevant effects on cardiovascular function in conscious cynomolgus monkeys and did not produce significant changes in respiratory rate, tidal volume, or minute volume in conscious rats. Evaluation of ITI-333 effects on gastrointestinal (GI) function showed that ITI-333 alone had no effect on GI propulsion in rats and yet ITI-333 blocked morphine-induced slowing of GI motility in rats. These data suggest that ITI-333 effectively mitigates some of the adverse symptoms associated with opioid use. ITI-333 lacks opioid-like abuse liability as it was not self-administered by rodents or non-human primates. Importantly, ITI-333 attenuates physical signs of naloxone-induced precipitated withdrawal in opioid dependent animals, indicating ITI-333 may alleviate symptoms of opioid withdrawal in humans.

[redacted]

[redacted]

Details on the profile of ITI-333 are provided in the current ITI-333 Investigator's Brochure.

5. STUDY OBJECTIVES

[redacted]

- To determine the safety and tolerability of ITI-333 after multiple oral administration of ascending ITI-333 doses in healthy subjects
- To determine the pharmacokinetics of ITI-333 [redacted] after multiple oral administration of ascending ITI-333 doses in healthy subjects.

[redacted]

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

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

This study will be conducted as a single-center, randomized, double-blind, placebo-controlled, dose escalation study of ITI-333 in up to 4 sequential cohorts with 8 healthy male and female subjects to be randomized in each cohort, for a total of approximately 32 subjects. The study will be performed at 1 study center in the United States.

The study will be conducted as follows:

- A Screening Period of up to 21 days prior to dosing on Day 1
- A Treatment Period from Days 1-17
- A Safety Follow-up (SFU) Visit on Day 24 ± 1.

Following Screening, eligible subjects will be admitted to the study center on Day -1. On Day 1, subjects will be randomized to receive an oral dose of either ITI-333 (n=6) or placebo (n=2) once daily for 14 days. The planned doses in each cohort are as follows:

- Cohort 1: 0.75 mg ITI-333 (n=6) or placebo (n=2)
- Cohort 2: 1.5 mg ITI-333 (n=6) or placebo (n=2)
- Cohort 3: 3 mg ITI-333 (n=6) or placebo (n=2)
- Cohort 4: 6 mg ITI-333 (n=6) or placebo (n=2).

[redacted]

Sentinel dosing will be used in each cohort: the first 2 subjects in each cohort will receive either ITI-333 or placebo. Dosing of the remaining subjects within each cohort (5 subjects will receive ITI-333, 1 subject will receive placebo) will occur after a minimum of 24 hours from the Day 7 dosing of the sentinel group, to ensure adequate evaluation of safety and tolerability by the Investigator and Sponsor Study Physician.

A DMC will review safety and PK data to determine the progression of dose escalation before proceeding to the next cohort. Details related to the DMC and the review of the data will be provided in the DMC charter. Dosing for the next higher dose cohort will not begin until the dose in the preceding cohort is deemed safe and tolerable. Dose escalations other than the planned doses specified above may be evaluated based on safety and PK assessments but they will not exceed 2-fold. [redacted]

[redacted]

[redacted]

6.2 Scientific Rationale for Study Design

6.2.1 Study Design

The design of this study is commonly used for the first-in-human multiple ascending dose evaluation of new investigational products. This study is designed as a randomized, double-blind and placebo-controlled study to avoid bias in the assessment of safety and tolerability of ITI-333. Subjects will receive an oral dose of study drug (either ITI-333 or placebo) once daily for 14 days.

Subjects will be dosed in sequential cohorts starting with the lowest dose. In addition, sentinel dosing will be used for each cohort. The first 2 subjects (1 active, 1 placebo) in each cohort will receive either ITI-333 or placebo. Dosing of the remaining subjects will occur after at least 24 hours post Day 7 dose of the sentinel group and after review of safety and tolerability data by the Investigator and Sponsor Study Physician. Subjects in the subsequent cohorts will be dosed after safety, tolerability, and PK have been evaluated in the previous cohort. Each cohort will include 6 subjects who will receive active study drug (ITI-333) and 2 subjects who will receive placebo.

[redacted]

6.3 Study Population

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

6.3.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for enrollment:

1. Able to provide written, informed consent;
2. Healthy male or female subjects between 18 and 45 years of age, inclusive at time of consent;
3. Body mass index (BMI) between 18.0 and 32.0 kg/m^2, inclusive at Screening, and a minimum body weight of 50 kg at Screening;
4. Female subject:
    a. Of nonchildbearing potential defined as either permanently sterilized (at least 4 months post-surgical sterilization which may include bilateral salpingectomy, tubal ligation or tubal occlusion, hysterectomy, or oophorectomy with or without hysterectomy) or postmenopausal (defined as amenorrhea for at least 12 consecutive months and documented follicle-stimulating hormone [FSH] level > 40 IU/mL; in the event a subject's menopausal status has been clearly established and yet FSH levels are not consistent with a postmenopausal status, determination of the subject's eligibility to be included in the study will be at the Investigator's discretion following consultation with the Sponsor); OR
    b. Of childbearing potential and willing to practice one of the following highly effective methods of birth control: vasectomized partner or non-hormonal intrauterine device; OR willing to use 2 of the following methods: vaginal diaphragm with spermicide, condom with spermicide, or sponge with spermicide; OR remain abstinent from Screening through 90 days after the last dose of study drug; AND
    c. Of childbearing potential or nonchildbearing potential with a negative serum pregnancy test at screening and a negative urine pregnancy test on Day -1;
5. Male subject who is permanently sterile (defined as bilateral orchidectomy or vasectomy, provided the absence of sperm has been medically confirmed) or if fertile (defined as post-puberty and not permanently sterile) must be willing to use a condom or remain abstinent AND abstain from sperm donation from Day -1 through 90 days after the last dose of study drug;
6. Willingness to follow protocol-defined restrictions;

7. Willing to be confined to the clinical research unit for the duration of the inpatient period of the study, and, in the opinion of the Investigator, willing and able to comply with all Investigator and staff instructions.

6.3.2 Exclusion Criteria

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

1. Clinically significant abnormality within 2 years of Screening that in the Investigator's opinion may place the subject at risk or interfere with study outcome variables; this includes, but is not limited to, history of or current cardiac, hepatic, renal, neurologic, gastrointestinal, pulmonary, endocrinologic, hematologic, or immunologic disease or history of malignancy;
2. Any clinical condition or procedure (eg, gastric bypass or cholecystectomy) that may affect the absorption, distribution, biotransformation, or excretion of ITI-333. Subjects with a history of appendectomy are eligible for study participation;
3. Current or recent (within 3 months prior to Screening) unstable angina; a history of myocardial infarction within 3 months prior to Screening; or a history of a clinically significant cardiac arrhythmia;
4. History of psychiatric condition that in the Investigator's opinion may be detrimental to participation in the study;
5. Any history of Substance Use Disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (American Psychiatric Association, 2022);
6. Any suicidal ideation including but not limited to wishes to be dead or any thought of killing self within 6 months of Screening, any suicide attempt within 2 years prior to Screening based on the Columbia-Suicide Severity Rating Scale (C-SSRS), and/or any current concerns for subject's safety as assessed by the Investigator;
7. Previously participated in an investigational study of ITI-333;
8. Likely allergy or sensitivity to ITI-333 or its excipients based on known allergies or hypersensitivities to drugs with shared pharmacology which may be suggestive of an increased potential for an adverse reaction to ITI-333;

[redacted]

11. Clinically significant abnormal findings in vital sign assessments, including oxygen saturation (SpO_2) < 96% and respiratory rate < 12 breaths per minute, supine systolic blood pressure > 140 mm Hg or < 90 mm Hg, or supine diastolic blood pressure > 90 mm Hg or < 50 mm Hg, or supine pulse rate > 100 bpm or < 45 bpm at Screening or Day -1. One repeat of vital signs assessment may be performed to confirm out of range values;

12. Has a QT interval corrected for heart rate using Fridericia formula > 450 msec in males or > 470 msec in females, or evidence of clinically significant bundle branch blocks on ECG at Screening or Day -1 (Note: right bundle branch block is acceptable). No repeat ECG assessments are allowed to confirm out of range values;
13. Clinically significant abnormal findings in the results for clinical laboratory tests obtained at Screening or Day -1;
14. ALT, AST, and gamma-glutamyl transferase (GGT) that are > 1.5 × the upper limit of normal at Screening or Day -1 or bilirubin (total or direct) that is above normal reference ranges at Screening or Day -1. No repeat testing is allowed to confirm out of range values;

[redacted]

16. History of hepatitis B or hepatitis C or demonstration of hepatitis B surface antigen or hepatitis C antibody at Screening;
17. History of human immunodeficiency virus (HIV) infection, or demonstration of HIV Type 1 or Type 2 antibodies at Screening;
18. Has a positive drug of abuse, alcohol, or cotinine test at Screening or Day -1;
19. Demonstration of an active COVID-19 infection on Day -1 or received a COVID-19 vaccination within 21 days prior to dosing with study drug on Day 1 or plans to receive a COVID-19 vaccination during the study;
20. Received any medication including herbal medication, excluding non-hormonal IUD, within 5 half-lives or 14 days (whichever is longer) prior to dosing with study drug on Day 1; occasional use of acetaminophen (≤ 1 g/day) or ibuprofen (≤ 400 mg/day) during this period may be allowed on a case-by-case basis upon approval by the Sponsor;

[redacted]

22. Ingestion or use of any investigational medication or device within 60 days prior to dosing with study drug on Day 1;
23. Donated > 500 mL blood or plasma within 30 days prior to dosing with study drug on Day 1 or has lost > 1200 mL of blood within 4 months prior to dosing with study drug on Day 1;
24. Consumption of any food or beverage containing grapefruit, pomelo, poppy seeds, or Seville oranges within 48 hours prior to dosing with study drug on Day 1;
25. Consumption of alcohol within 48 hours prior to dosing with study drug on Day 1;
26. Consumption of any product containing caffeine or xanthine-containing products within 24 hours prior to dosing with study drug on Day 1;
27. Is a smoker or has used nicotine or nicotine-containing products within 6 months of Screening; this includes, but is not limited to cigarettes, e-cigarettes, and nicotine replacement;

28. Has participated in strenuous activity within 48 hours prior to dosing with study drug on Day 1;
29. Directly or indirectly involved in the conduct and administration of this study as an investigator, sub-investigator, study coordinator or other study staff member, or an employee of the Sponsor or a first-degree family member, significant other or relative residing with one of the above persons involved directly or indirectly in the study;
30. Planning or scheduled for any surgical procedure or dental care during the duration of the study;
31. Females who are currently breastfeeding;
32. Any subject judged by the Investigator to be inappropriate for the study.

6.4 Discontinuation of Subjects from Therapy or Assessment

A premature discontinuation will occur when a subject who receives at least one dose of study drug ceases participation in the study, regardless of circumstances, before the completion of all study visits and procedures. Subjects can be prematurely discontinued from the study for the following reasons:

- Death
- AE
- Lost to follow-up
- Pregnancy
- Physician decision
- Protocol violation
- Study terminated by Sponsor
- Withdrawal by subject
- Other

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

All subjects who received study drug and prematurely discontinue from the study regardless of cause should undergo final assessments at the Early Termination (ET) Visit at the time of discontinuation. In addition, subjects should return to the study center for the SFU Visit 10 days (± 1 day) after the last dose of study drug.

Subjects who are 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.

6.4.1 Subject Replacement Procedures

Subjects who prematurely discontinue from the study for any reason may be replaced at the discretion of the Sponsor. Replacement subjects will be assigned a new study identification number not previously assigned.

6.5 Changes in the Conduct of the Study

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

7. STUDY DRUGS

7.1 Study Drugs Administered

Subjects will receive ITI-333 or placebo on Days 1 through 14 orally, after a fast of at least 10 hours. On Days 1 and 14, subjects will continue to fast for at least 4 hours after dosing. On Days 2 through 13, subjects will continue to fast for at least 2 hours postdose. No water is to be ingested for 1 hour before and 1 hour after dose administration.

[redacted]

Sentinel dosing will be used for each cohort. The first 2 subjects (1 active, 1 placebo) in each cohort will receive either ITI-333 or placebo. Dosing of the remaining subjects within the cohort (5 active, 1 placebo) will occur after a minimum of 24 hours from the Day 7 dosing of the sentinel group, to ensure adequate evaluation of safety and tolerability by the Investigator and Sponsor Study Physician.

Subjects in each cohort will receive ITI-333 (n=6) or placebo (n=2) [redacted] once daily for 14 days according to a randomization scheme. The planned doses in each cohort are as follows:

- Cohort 1: 0.75 mg ITI-333 (n=6) or placebo (n=2) once daily for 14 days
- Cohort 2: 1.5 mg ITI-333 (n=6) or placebo (n=2) once daily for 14 days
- Cohort 3: 3 mg ITI-333 (n=6) or placebo (n=2) once daily for 14 days
- Cohort 4: 6 mg ITI-333 (n=6) or placebo (n=2) once daily for 14 days.

The DMC will review safety and PK data to determine the progression of dose escalation. The dose escalation with each subsequent cohort will not exceed 2-fold. Dosing for the next higher dose cohort will not begin until the dose in the preceding dose group is deemed safe and tolerable. Up to 4 dose cohorts are planned in this study, although additional cohorts may be added. The duration of the treatment period may also be adjusted after evaluation of available safety, tolerability, and PK data from preceding cohorts.

[redacted]

7.1.1 ITI-333

ITI-333 [redacted]

Study drug will be labeled in accordance with all applicable regulatory requirements. The lot number(s) for the study drug will be provided to the study center on the packing list with the study

drug shipment. A certificate of analysis and Good Manufacturing Practice compliance statement will be provided to the study center pharmacy.

7.1.2 Placebo

The oral placebo [redacted]

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

[redacted]

7.2.2 Handling and Storage

Storage conditions for the ITI-333 [redacted] and placebo are provided in the Study Reference Manual.

7.2.3 Study Drug Accountability

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

At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled. All drug accountability documents will be retained by the Investigator, and copies will be provided to the Sponsor or designee.

7.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned a 6-digit identification number after providing written informed consent. Details on the subject numbering will be provided in the Study Reference Manual.

Subjects in each cohort will receive ITI-333 or placebo according to the randomization scheme. Within each cohort, 6 subjects will be randomized to ITI-333 and 2 subjects will be randomized to placebo.

Randomization will be based on a randomization schedule prepared by the Sponsor statistician or designee prior the start of the study. The randomization schedule will be provided to the unblinded pharmacist and bioanalytical staff. Subjects will be considered randomized once the subject's randomization number has been assigned.

Subjects who are withdrawn from the study after study drug has been administered may be replaced following a discussion between the Sponsor and Investigator. Replacement subjects will be assigned a new number.

7.4 Blinding and Unblinding Procedures

A number of measures, described below, will be undertaken in order to maintain the blind on this trial. Measures include:

- Administration of an identical-appearing placebo;
- [redacted]
- Unblinded pharmacy staff or other appropriate unblinded staff will be identified at the study center. The unblinded staff will agree to not provide any information or documentation to the Investigator and clinical site staff that may reveal the treatment assignment;
- Unblinded bioanalytical staff or other appropriate unblinded staff will be identified at the bioanalytical lab. The unblinded staff will agree to not provide any information or documentation to the Investigator, study center staff, or sponsor that may reveal the treatment assignment;
- Should any blinded study personnel need to become unblinded (ie, for safety reasons) dissemination of this information will be restricted to only those personnel who need to know to perform medical or other study duties. The unblinding of personnel will be documented;
- Should any blinded study personnel inadvertently become unblinded for any reason, the Investigator or designee will promptly disclose this unblinding to the Sponsor so that corrective action to preserve the blind can be initiated in consultation with applicable members of the study team (ie, sponsor, vendors, study center). The unblinding will be documented.

Unblinding of treatment assignment during the study is discouraged and should occur only if it is absolutely necessary to know what treatment the subject received. If the Sponsor or Investigator deems identification of the study drug is necessary for the purpose of providing urgent subject care, and knowledge of the subject's treatment assignment (ITI-333 or placebo) will alter subsequent care, the randomization code for that single subject can be obtained from the unblinded pharmacist. The date and reason for the unblinding must be recorded on the subject's eCRF. When possible, the Sponsor should be notified prior to unblinding; otherwise, the Sponsor must be notified within 24 hours after unblinding.

DMC members will receive unblinded data for review.

If stopping criteria (Section 8.1.4) are met, unblinding of subject(s) may occur based on the recommendation of the DMC.

Treatment codes may be broken by Drug Safety for regulatory reporting purposes.

7.5 Monitoring Treatment Compliance

All doses will be administered by qualified study center staff to ensure that the correct doses are given at the scheduled time. The treatments will be administered by qualified study personnel under the direction of the Investigator. A study personnel witness will verify that the study drug has been given correctly.

Details of the exact date and time of administration (day/month/year, h:min) [redacted] will be recorded in the eCRF.

7.6 Prior and Concomitant Medications

The use of prior and concomitant medications and therapies will be recorded in the subject's eCRF. Any treatment given after dosing, other than the study drug, and including all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications, is to be considered a concomitant medication.

7.6.1 Prior medications

Subjects are not allowed to have received an investigational drug or device within 60 days prior to dosing with study drug on Day 1 or have taken medication including herbal medication (except non-hormonal IUD) within 5 half-lives or 14 days prior to dosing with study drug on Day 1 (whichever is longer).

[redacted]

Occasional use of acetaminophen (≤ 1 g/day) or ibuprofen (≤ 400 mg/day) during the screening period may be allowed on a case-by-case basis upon approval by the Sponsor.

Subjects must not have received a COVID-19 vaccination within 21 days prior to dosing with study drug on Day 1 or plan to receive a COVID-19 vaccine during the study.

7.6.2 Concomitant Medications

The following concomitant medications are allowed during the study:

- Non-hormonal IUD
- Aloe for topical treatment at ECG pad sites.

The use of concomitant medications (except medications listed above) during this study is prohibited, unless deemed necessary by the Investigator to treat AEs. [redacted]

The Investigator will make every effort to contact the Sponsor prior to administration of any concomitant medication for the treatment of AEs. It is the responsibility of the Investigator to ensure that details regarding the medication are recorded in the eCRF.

7.7 General Considerations and Restrictions

7.7.1 Meals and Dietary Restrictions

Consumption of any food or beverage containing grapefruit, pomelo, poppy seeds, or Seville oranges is not allowed from within 48 hours prior to dosing with study drug on Day 1 through completion of the last PK sample collection.

No water is to be ingested for 1 hour before and 1 hour after each dose administration; during the rest of the study, water will be available *ad libitum*.

Subjects will be fasted for at least 10 hours prior to each administration of study drug and prior to tests for chemistry. Subjects will continue to fast for at least 4 hours after dosing on Days 1 and 14; and for at least 2 hours postdose on Days 2-13.

All meals provided while in the study center will be standardized, low-fat meals (< 20 g) and should not contain any foods or beverages that are restricted. All study procedures and meals should be scheduled at approximately the same time throughout the study, as appropriate. A copy of the menu with nutritional content of each component of each meal and snack will be made available to the Sponsor before the start of the study.

7.7.2 Caffeine, Alcohol, Nicotine, and Activity Restrictions

To be eligible in the study, subjects must have a negative alcohol test at Screening and Day -1. Subjects must abstain from consuming alcohol within 48 hours prior to dosing with study drug on Day 1 and through completion of the last PK sample collection.

Consumption of caffeine- and xanthine-containing products is not allowed within 24 hours prior to dosing with study drug on Day 1 and through completion of the last PK sample collection.

Subjects must not have used nicotine or nicotine containing products within the 6 months prior to Screening. Subjects must agree to abstain from nicotine and nicotine containing products from Screening through completion of all study procedures at the SFU Visit.

Subjects must refrain from strenuous activity from 48 hours prior to dosing with study drug on Day 1 through to completion of all study procedures at the SFU Visit.

8. ASSESSMENTS

8.1 Safety

8.1.1 Adverse Events

8.1.1.1 Definition of Adverse Event

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

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

[redacted]

8.1.1.2 Definition of Serious Adverse Event

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

- Results in death
- Is life threatening

NOTE: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject 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 subject 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 inpatient 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.

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

8.1.1.3 Classification of Adverse Events and Serious Adverse Events

8.1.1.3.1 Severity

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the subject's eCRF. Severity, which is a description of the intensity of manifestation of the AE, is distinct from seriousness, which implies a subject outcome or AE-required treatment measure associated with a threat to life or functionality (Section 8.1.1.2). Severity will be assessed according to the following scale:

Mild: A type of 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 subject.

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

8.1.1.3.2 Causality Assessment

For each occurrence of an AE or SAE, the Investigator must provide an assessment of causal relationship to study drug [redacted]. The causality assessment must be recorded on the appropriate AE reporting page of the subject's eCRF. Causal relationship must be assessed by answering the following question:

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

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

- There is a reasonable temporal relationship between the study drug and the event, and
- The event is unlikely to be attributed to underlying/concurrent disease, other drugs or other factors, and/or
- Positive de-challenge and/or re-challenge exist

OR

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

- There is no reasonable temporal relationship between the study drug and the event, or
- The event is likely to be attributed to underlying/concurrent disease, other drugs, [redacted] or other factors, and/or
- The subject did not take the study drug.

[redacted]

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 assess 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 subject's eCRF.

8.1.1.4 Time Period and Frequency of AE and SAE Reporting

The Investigator will report all AEs/SAEs from the time informed consent was obtained until 30 days after the last dose of study drug.

At each visit, subjects are to be queried regarding any AEs that have occurred since the previous visit. Subjects will be asked to volunteer information with a nonleading question such as, "How do you feel since your last visit?"

All AEs must be followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be clinically stable.

8.1.1.5 Adverse Event Reporting Procedures

8.1.1.5.1 Reporting Adverse Events

All AEs, including overdose with sequelae or intentional overdose of study drug or other medication, must be recorded on the appropriate AE reporting page of the subject'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?), [redacted] for the definition of SAEs and Section 8.1.1.5.2 for SAE reporting procedures.
- Document all actions taken with regard to study drug [redacted]
- 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 last dose of the study drug.

8.1.1.5.2 Reporting Serious Adverse Events

The Sponsor is required to inform 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, the study center staff must report the event to the Sponsor on the SAE Report Form. In addition to completing the SAE Report Form, the Study Physician may also be notified by telephone.

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

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

The study center must email or fax the SAE Report Form to the SAE email address or fax number below. Even if an initial report is made by telephone, the SAE Report Form completed with 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 subject's eCRF. All SAEs will be followed until resolution or stabilization. ***The Sponsor or designee may contact the study center to solicit additional information or follow up on the event. A response is required within 24 hours of the request.***

[redacted]

[redacted]

8.1.2 Pregnancy

Female subjects will not be eligible for inclusion in the study if they have a positive pregnancy test at Screening or Day -1. Any subject who becomes pregnant must be discontinued from the study.

Study center staff must report every pregnancy, including pregnancies in female partners of male study subjects, from the time the ICF was signed until 90 days after the last dose of study drug.

Within 24 hours of learning of the pregnancy, study center staff must report the event to the Sponsor on the Pregnancy Notification and Outcome Form and email/fax it to the pregnancy email/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 Report Form must be filed as described in Section 8.1.1.5.2 with the appropriate serious criterion (eg, hospitalization) indicated on the SAE Report Form in addition to the Pregnancy Notification and 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 subject that has received at least one dose of study drug or in a female partner of a male study subject that has received at least one dose of study drug 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 Notification and Outcome Form.

[redacted]

[redacted]

8.1.3 Potential Hy's Law Cases

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

- ALT or AST ≥ 3 × ULN and
- Total bilirubin ≥ 2 × ULN and
- Alkaline phosphatase (ALP) < 2 × ULN.

Analytes may come from multiple samples taken within a 24-hour period.

The laboratory must notify the Investigator when the above criteria are met.

Within 24 hours of learning of a potential Hy's Law case:

- Study center staff must immediately report every case to the Sponsor from the time the ICF is signed for the study until 30 days after the final protocol-defined study visit or the last known dose of the study drug (if the final visit does not occur);
- Study center staff must report the case to the Sponsor on a Potential Hy's Law form and email or fax it to the email address or fax number below, even if no AE has occurred;
- If the potential Hy's Law case is associated with an SAE (eg, hepatic failure), a separate SAE Report Form must be filed as described in Section 8.1.1.5.2 with the appropriate serious criterion (eg, hospitalization) indicated on the SAE Report Form.

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).

[redacted]

[redacted]

[redacted]

[redacted]

8.1.5 Opioid-specific Safety Considerations

Respiratory depression is the most serious potential side effect of opioids. While nonclinical data support the expectation that ITI-333 lacks respiratory liability, particular care will be given to monitor subjects for this side effect.

Prior to study drug administration, SpO_2 and respiratory rate must be within acceptable ranges, $\geq$ 96% and $\geq$ 12 breaths per minute, respectively, for study drug administration to occur. If values are lower than these thresholds and are sustained for $\geq$ 5 minutes, study drug should not be administered. Subject may be withdrawn from the study at the Investigator's discretion following consultation with the Sponsor.

After study drug administration, if respiratory difficulty is observed, then, with the exception of vital signs monitoring, no further study procedures (eg, PK sample collection) will be conducted until the respiratory difficulty has resolved. Careful attention will be paid to oxygen saturation and, for safety, oxygen will be available for emergency use during all experimental sessions. Subjects will be instructed to take a deep breath if their oxygen saturation falls below 92%. Such requests are generally effective in restoring normal oxygen saturation in preoperative patients given opioids. In the unlikely event that prompted breaths do not bring the oxygen saturation above 92% within 1 min, supplemental oxygen will be administered through a nasal cannula and the flow rate adjusted as necessary.

In addition, resuscitation equipment and naloxone injection will be available in the testing area for intravenous administration if respiration is or becomes seriously depressed (ie, if a subject is not able to respond to verbal commands to take deep breaths). In such an event, naloxone (0.4 mg to 0.8 mg intravenously) would be administered, followed by subsequent doses every 1 min until the subject responds to verbal commands to breathe deeply (with the total naloxone dose not to exceed 10 mg). During the time of apnea, participants will be ventilated with an Ambu Bag. If significant respiratory depression were to occur, the affected individual would be monitored for three hours for signs of recurrent respiratory depression. Careful subject selection and selection of doses should preclude the occurrence of such an event. Should the Investigator deem these treatments insufficient, then he/she must provide or arrange for medical care as per recognized clinical standards for opioid overdose.

8.1.6 Clinical Laboratory Determinations

[redacted] During Screening, the Investigator/Sub-Investigator should assess the clinical significance of any values that are outside the reference ranges provided by the laboratory; subjects with abnormalities judged to be clinically significant will be excluded from the study.

Tests for chemistry should be done after a minimum of 10 hours fasting. Laboratory results should be reviewed by the Investigator/sub-Investigator throughout the study.

[redacted]

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

[redacted]

Laboratory results will be forwarded to the Investigator for review. Any abnormalities deemed clinically significant by the Investigator will be recorded as AEs in the subject's eCRF. Any clinically significant abnormal laboratory values that persist should be followed by the Investigator in consultation with the Sponsor (or designee). Such events should be followed as described in Section 8.1.1.4.

The Investigator should file all copies of the laboratory reports in the subject's source documents.

8.1.7 Electrocardiograms

[redacted]

ECG timepoints may be adjusted and/or additional ECG measurements may be included after review of available safety, and PK data from preceding cohorts.

[redacted]

Each ECG assessment will be conducted after the subject has been resting quietly in the supine position for at least 5 minutes and will comprise ten-second epochs from 12-lead ECGs. [redacted] ECG assessments will be reviewed by the Investigator or designee and evaluated for clinical significance.

8.1.8 Vital Signs

[redacted] Details on vital sign measurements taken during the CPT are provided in Section 8.5.2.

Vital signs will include blood pressure (BP), [redacted] SpO_2, [redacted]. Blood pressure and pulse will be measured in both the supine and standing positions with measurements performed after at least 5 minutes lying down and then at 1 and 3 minutes after rising from the supine position to standing.

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

Vital signs timepoints may be adjusted and/or additional vital signs may be included after review of available safety and PK data from preceding cohorts.

[redacted]

[redacted]

Prior to study drug administration [redacted], SpO_2 must be within acceptable ranges; ≥ 12 breaths per minute and ≥ 96%, respectively, for drug administration to occur. If values are lower than these thresholds and are sustained for ≥ 5 minutes, study drug should not be administered.

8.1.9 Other Safety Assessments

8.1.9.1 Physical Examination

[redacted]

The examinations will be performed by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations.

The examination should include evaluation of appearance; skin; head and neck; eyes, ears, nose, and throat; chest and lungs; heart; abdomen; extremities and neurological exam. All physical examination findings must be documented in the source documents and recorded in the eCRF.

[redacted]

[redacted]

8.2 Pharmacokinetic Assessments

Blood samples (~ 4 mL each) for determination of plasma concentrations of ITI-333 [redacted] will be collected at the following time points:

- [redacted]
- **Day 14**: predose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours post Day 14 dose.

PK timepoints may be adjusted after review of available safety and PK data from preceding cohorts. The PK sample collection period after the last dose on Day 14 may also be extended if longer than expected elimination half-lives are observed for the parent drug and/or metabolites.

[redacted]

Detailed instructions for collection, processing, storage, and shipping of blood PK samples for bioanalysis will be provided in the Study Reference Manual.

[redacted]

[redacted]

[redacted]

8.6 Schedule of Evaluations

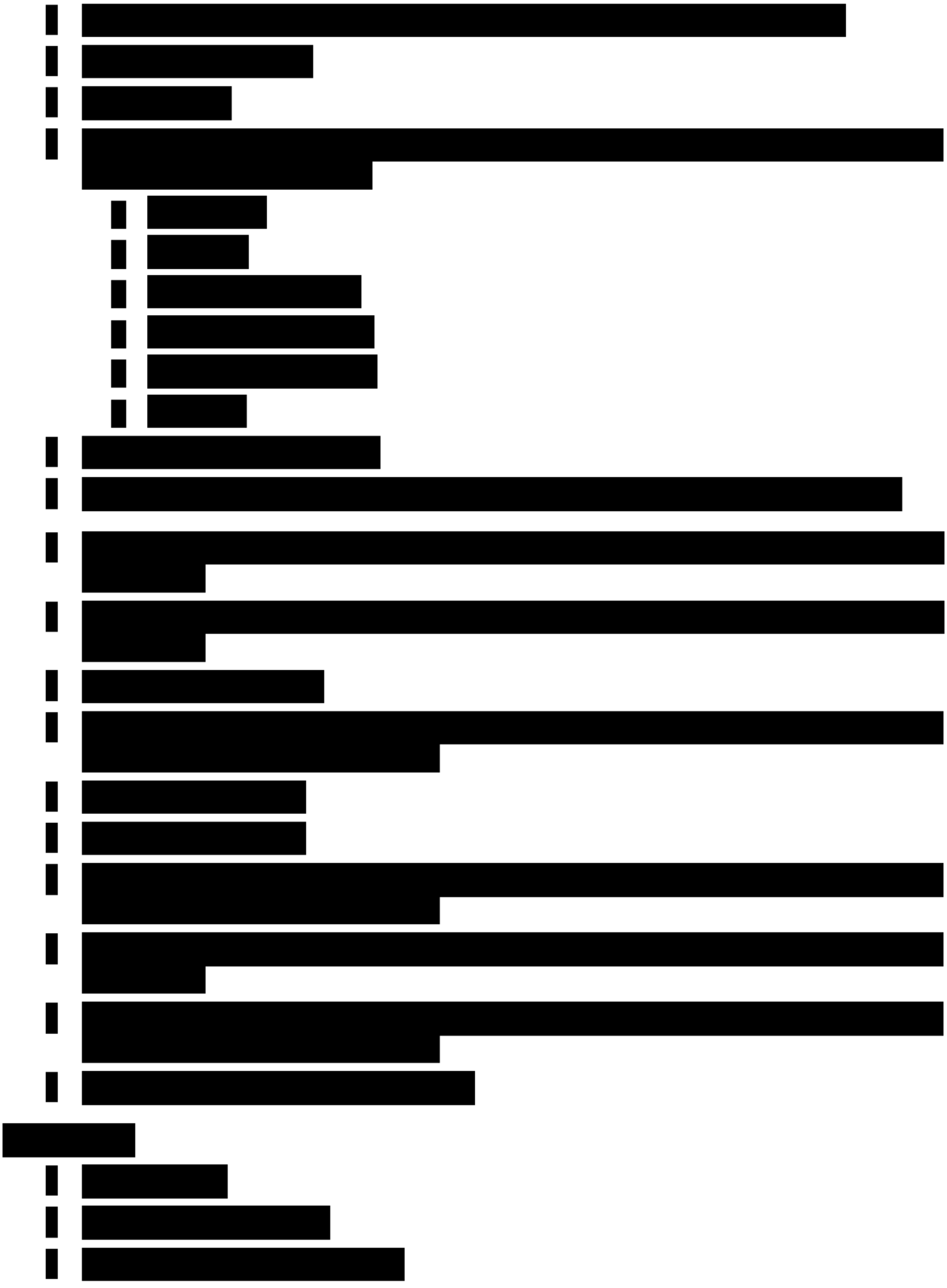
Study procedures and assessments are tabulated by day in the Schedule of Evaluations in Table 1-1.

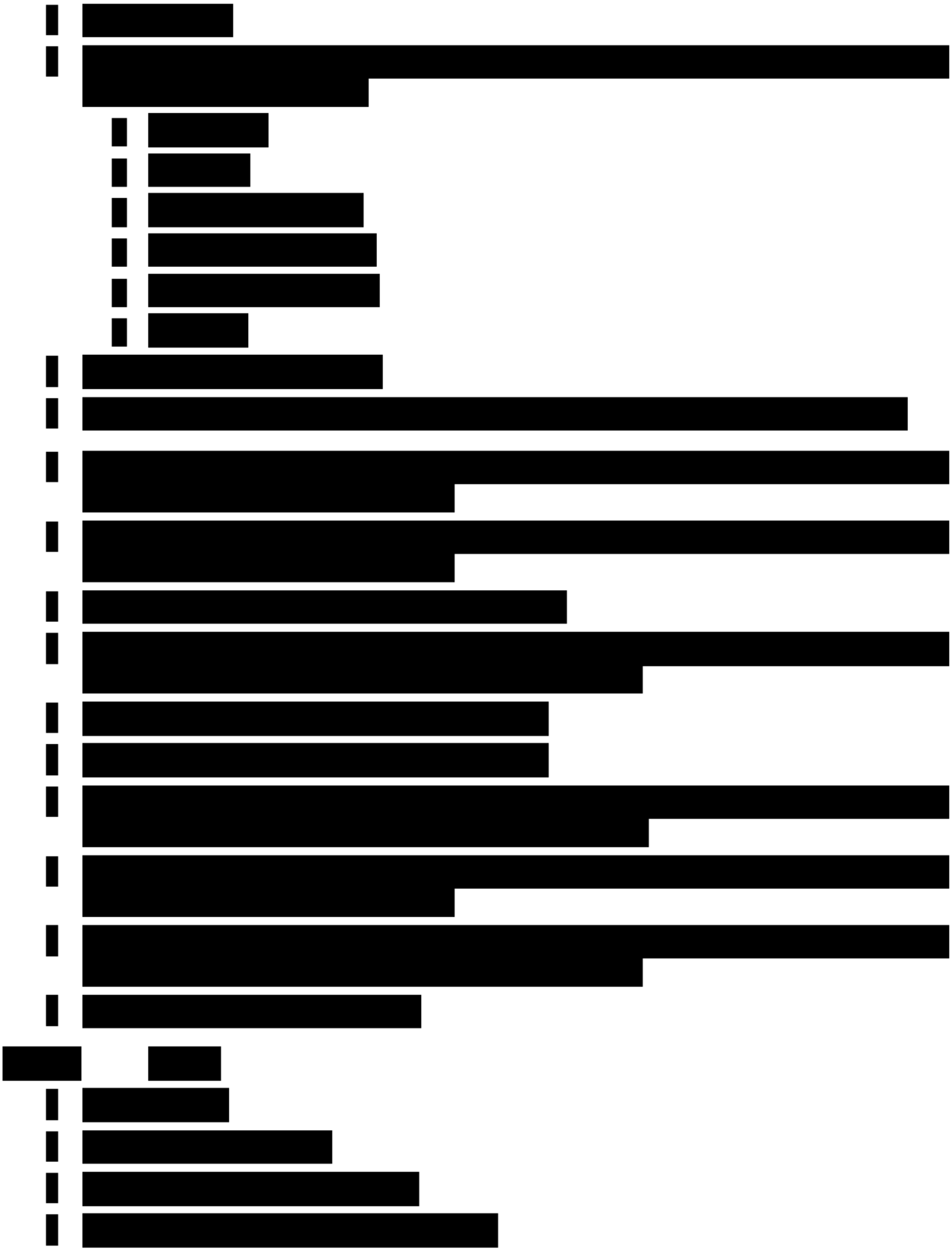
There are times where the protocol requires more than one procedure to be completed at the same time point. In these cases, the following will apply to postdose assessment time points:

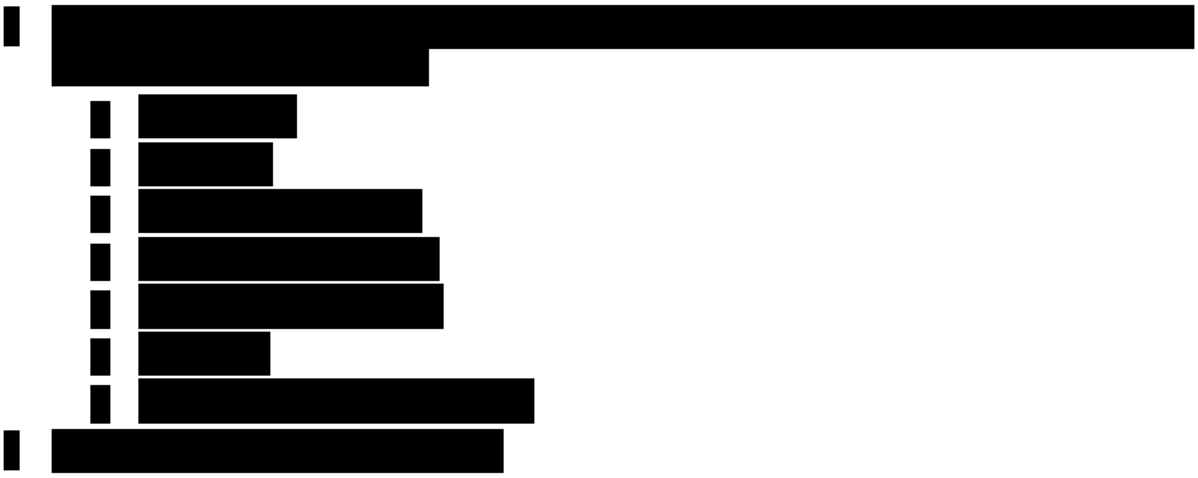
- Collection of PK samples should take priority over the timing of other procedures scheduled at the same time point so that the timing of the PK sample collection is at, or as close as possible to, the scheduled time. Wider windows will be allowed around the collection time point for other assessments so that if multiple assessments (eg, ECG, vitals, and PK) are scheduled for the same time point then all assessments can be made within the applicable windows. For example, ECG assessments can start earlier than the scheduled time point, yet within the collection window, to allow for more accurate timing of PK sample collection.
- [redacted]
- Additional information regarding the order of assessments when multiple assessments are scheduled at the same time is provided in the Study Reference Manual.

[redacted]

[redacted]







9. STATISTICAL METHODS

9.1 General Considerations

The statistical analysis plans (SAPs) will be finalized prior to locking the database 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.

9.2 Determination of Sample Size

Approximately 32 subjects are planned for randomization in 4 cohorts. Within each cohort, 6 subjects will be randomized to receive multiple oral doses of ITI-333 and 2 subjects will be randomized to receive placebo. The sample size for each cohort was determined based on historical experience with multiple-dose safety and tolerability studies.

9.3 Analysis Populations

The following analysis populations will be defined for this study:

Enrolled Population: The Enrolled Population will include all subjects who sign the informed consent form.

Randomized Population: The Randomized Population will include all enrolled subjects who are randomized.

Safety Population: The Safety Population will include all randomized subjects who receive at least one dose of study drug.

Pharmacokinetic Populations: The PK Population of ITI-333 [redacted] will include all subjects in the Safety Population who have no major protocol deviation which may impact PK and have measurable plasma concentrations to provide a reliable estimate of at least one [redacted] PK parameter (ie, C_{max}, AUC). Subjects with emesis at or before 2 × median T_{max} of ITI-333 may be excluded from the PK Population.

[redacted]

9.4 Statistical Analyses

9.4.1 Subject Disposition

The number and percentage of subjects who complete the study and who prematurely discontinue from the study will be summarized by cohort and treatment, ITI-333 combined across all cohorts, placebo combined across all cohorts, and total across all cohorts, and by reasons for premature discontinuation for the Safety Population.

9.4.2 Demographic and Other Baseline Characteristics

Demographic parameters (eg, age, race, ethnicity, sex, weight, height, BMI) and other baseline characteristics will be summarized by cohort and treatment, ITI-333 combined across all cohorts, placebo combined across all cohorts, and total across all cohorts for the Safety Population.

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 by system organ class and preferred term and by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts for the Safety Population.

9.4.3 Prior and Concomitant Medication

A prior medication will be defined as any other medication which started and stopped before the first dose of study drug. A prior concomitant medication will be defined as any other medications which started before and stopped after the first dose of study drug. A concomitant medication will be defined as any other medication which started after the first dose of study drug but before the end of the treatment period.

Prior, prior concomitant, and concomitant medication use will be coded using the latest version of the World Health Organization Drug Dictionary and listed by therapeutic class for the Safety Population.

9.4.4 Extent of Exposure and Treatment Compliance

9.4.4.1 Extent of Exposure

Each subject will receive an oral dose of ITI-333 once daily for 14 days. Exposure to study drug 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) for exposure to study drug will be presented by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts for the Safety Population.

9.4.4.2 Treatment Compliance

Treatment compliance is defined as the total number of study doses actually taken by a subject during the study divided by the number of study doses that were expected to be taken during the study multiplied by 100. The total number of study doses actually taken during the study will be calculated from the study treatment record in which only entire doses administered will be counted. Descriptive statistics for treatment compliance will be presented by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts for the Safety Population.

9.4.5 Safety Analyses

The safety analysis will be performed based on the Safety Population. Safety variables will include AEs, clinical laboratory parameters, vital signs, ECG parameters [redacted]. For each safety parameter, the last assessment made before administration of the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

9.4.5.1 Adverse Events

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

An AE (classified by preferred term) is considered a treatment-emergent adverse event (TEAE) if it starts as a new event or if an AE severity increases from the time of the first dose of study drug until 10 days after the last dose of study drug. A new event is an event that either did not occur before, or started 2 days or more after, the end date of the previous event for the same preferred term. Severity increase is referring to an increase in severity during the treatment period for a continuous event.

The number and percentage of subjects reporting TEAEs by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts will be tabulated by SOC and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship to study drug. If there is more than one AE that is coded to the same preferred term for the same subject, that subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and relationship to study drug, respectively.

The incidence of serious adverse events (SAEs) and of AEs leading to premature treatment discontinuation of the study by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts will also be summarized by SOC and preferred term. Listings will be presented for SAEs, for AE leading to treatment discontinuation, and for subjects who died.

AEs will be reviewed for any signal suggestive of abuse potential using standardized MedDRA queries for drug abuse, dependence, and withdrawal.

9.4.5.2 Clinical Laboratory Parameters

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) for clinical laboratory values (in SI and conventional units) and changes from baseline [redacted] will be presented by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts.

[redacted]

9.4.5.3 Vital Signs

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) for vital sign values and changes from baseline [redacted] will be presented by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts.

[redacted]

9.4.5.4 Electrocardiograms

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) for 12-lead ECG parameter values and changes from baseline [redacted] will be presented by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts.

[redacted]

[redacted]

[redacted]

9.4.6 Analyses of Pharmacokinetic Endpoints

PK analyses will be performed using plasma concentrations of ITI-333 [redacted]. Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful analysis.

Individual plasma concentration data of ITI-333 [redacted] will be presented in data listings by subject using the Safety Population. Plasma concentration data [redacted] will be summarized by cohort, [redacted] and nominal sampling time using descriptive statistics using the PK population. Mean and individual

plasma concentration vs time profiles will be presented in figures on both linear and semilogarithmic scales.

The following plasma PK parameters will be calculated for ITI-333 [redacted], as applicable, using non-compartmental methods. Actual PK sampling times will be used in the estimation of PK parameters.

[redacted] **Day 14**:

- Area under the plasma drug concentration-time curve (AUC) from time zero to the end of dosing interval ($AUC_{0\text{-}tau}$)
- Maximum observed plasma drug concentration over a dosing interval (C_{max})
- Time to reach maximum observed plasma drug concentration over a dosing interval (T_{max})

[redacted]

The individual PK parameters of ITI-333 [redacted] will be presented in data listings. PK parameters of each analyte will be summarized by cohort using descriptive statistics using the PK Population.

[redacted].

[redacted]

Details of pharmacokinetic analysis will be specified in the SAP.

[redacted]

9.5 Interim Analysis

An interim review of safety and PK data will be conducted by the DMC (see Section 9.6).

The outcome of the interim reviews will inform the decision to enroll the next cohort in the study and which dose of ITI-333 is to be administered.

After the completion of Cohorts 1 through 4, analyses of study data will be performed following database lock and unblinding of study treatment. If stopping criteria are modified and additional cohort(s) are added, these analyses will be considered interim analyses. If there are no changes to stopping criteria, these analyses will be considered final analyses.

9.6 Data Monitoring Committee (DMC)

An independent DMC will be formed. Details on the composition of the DMC will be provided in the DMC charter which will be finalized prior to randomization of any subject.

The DMC will be provided with unblinded clinical safety data and PK data in order to fully evaluate the safety, tolerability, and PK of ITI-333 at each cohort. The DMC will provide recommendations on the conduct of the trial, specifically dose escalation. DMC will also review available data when any stopping criteria are met within a cohort. Details related to the DMC and the review of the data will be provided in the DMC charter.

9.7 Protocol Deviations

A deviation from the protocol is an unanticipated departure from the procedures or processes. A major protocol deviation occurs when there is nonadherence to the protocol by the subject or Investigator that results in a significant, additional risk to the subject, or may have an effect on the integrity of the study data. Major protocol deviations can include, for example, nonadherence to inclusion or exclusion criteria or nonadherence to ICH GCP guidelines and may lead to the subject being withdrawn from the study.

The Investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Investigators will be notified in writing by the clinical monitor of protocol deviations. The IRB should be notified of all major protocol deviations in a timely manner in accordance with IRB reporting guidelines.

A listing of major protocol deviations will be provided for the Safety Population.

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. If, during the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the Sponsor for submission to the FDA
- A fully executed contract
- The curricula vitae for the Investigator and all sub-Investigators listed on Form FDA 1572, including a copy of each physician's license
- Financial disclosure agreement completed and signed by the Investigator and all sub-Investigators listed on Form FDA 1572
- A copy of the original IRB approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB
- A copy of the IRB-approved ICF
- A copy of the applicable local privacy forms
- A list of the IRB members
- 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 subjects for the study.

10.2.3 Use of Investigational Materials

Study drug must be stored in a secured place and must be locked. 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 subject's use. All unused study drug will either be destroyed at the study center upon approval by the Sponsor or returned to the Sponsor-designated central depot, as instructed by the Sponsor.

10.2.4 Case Report Forms

All subject 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 Subject Confidentiality

All subject records will be identified by subject identification number only. Subjects' names are not to be transmitted to the Sponsor.

10.3 Data Quality Assurance

10.3.1 Data Monitoring

Before any subject enters the study, a representative of the Sponsor will meet with the Investigator and the study center staff 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 subjects 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 monitor or designee, 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 subjects 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 subject is enrolled, the study monitor or designee, will periodically monitor the progress of the study by conducting on-site or remote 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. Subject 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 subjects' 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. 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 subject'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 subject 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 subject 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 subject's medical record, clinic charts, the Investigator's subject study files, as well as the results of diagnostic tests such as laboratory tests, ECGs, etc.

[redacted]

11. REFERENCES

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. 5th Ed., Text Revision*. American Psychiatric Association; 2022.

Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 Published: November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed on December 7, 2022.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266-77.

12. APPENDICES

12.1 Appendix I. Elements Of Informed Consent

Procedures will comply with 21 CFR, Parts 50 (Subpart D) and 312. Signed informed consent will be obtained from each subject participating in a clinical research study. The consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the subject's participation
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research. If the subject 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 subject
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA, the Sponsor, the IRB, or an authorized contract research organization may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research subject's rights and whom to contact in the event of a research-related injury to the subject. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB may be required.)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled
- A statement that the particular treatment or procedures may involve risks to the subject (or to the embryo or fetus if the subject may become pregnant) that are at present unforeseeable
- The expected circumstances for which the subject's participation may be terminated by the Investigator without regard to subject consent
- Any additional costs to the subject that may result from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for an orderly termination of the subject's participation

- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject.
- The approximate number of subjects involved in the study
- A statement of permission providing subject's consent to participate (eg, "I agree to participate. . .")
- A place for the subject's signature and date of signing of the ICF
- A statement indicating that information about this study may be entered, if required, into a databank that is publicly accessible at www.ClinicalTrials.gov.
- A copy of the signed consent form must be given to the subject.

13. INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study in accordance with Protocol Amendment 1 for Study ITI-333-002 (dated 06 Nov 2023) 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)