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

Statistical Analysis Plan Version 1.0 Date: November 13, 2023

Statistical Analysis Plan

ITI-333-002

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

Original SAP Date:	13 Nov 2023
Compound:	ITI-333
Study Phase:	1
Sponsor:	Intra-Cellular Therapies, Inc. [redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

1. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
[redacted]	[redacted]
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
[redacted]	[redacted]
[redacted]	[redacted]
ECG	electrocardiogram, electrocardiographic
ET	early termination
LLN	lower limit of normal of laboratory reference range
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond(s)
[redacted]	[redacted]
PK	pharmacokinetic
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT interval corrected for heart rate using the Fridericia formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SFU	Safety Follow-up
SOC	system organ class
SpO_2	oxygen saturation
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
ULN	upper limit of normal of laboratory reference range

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 Protocol Amendment #1 of Study ITI-333-002 dated 06 Nov 2023. Specifications of tables, figures, and data listings are contained in a separate document. [redacted]

Study ITI-333-002 is 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, eligible subjects will be randomized to receive either ITI-333 or placebo. 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.

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. The planned doses are as follows:

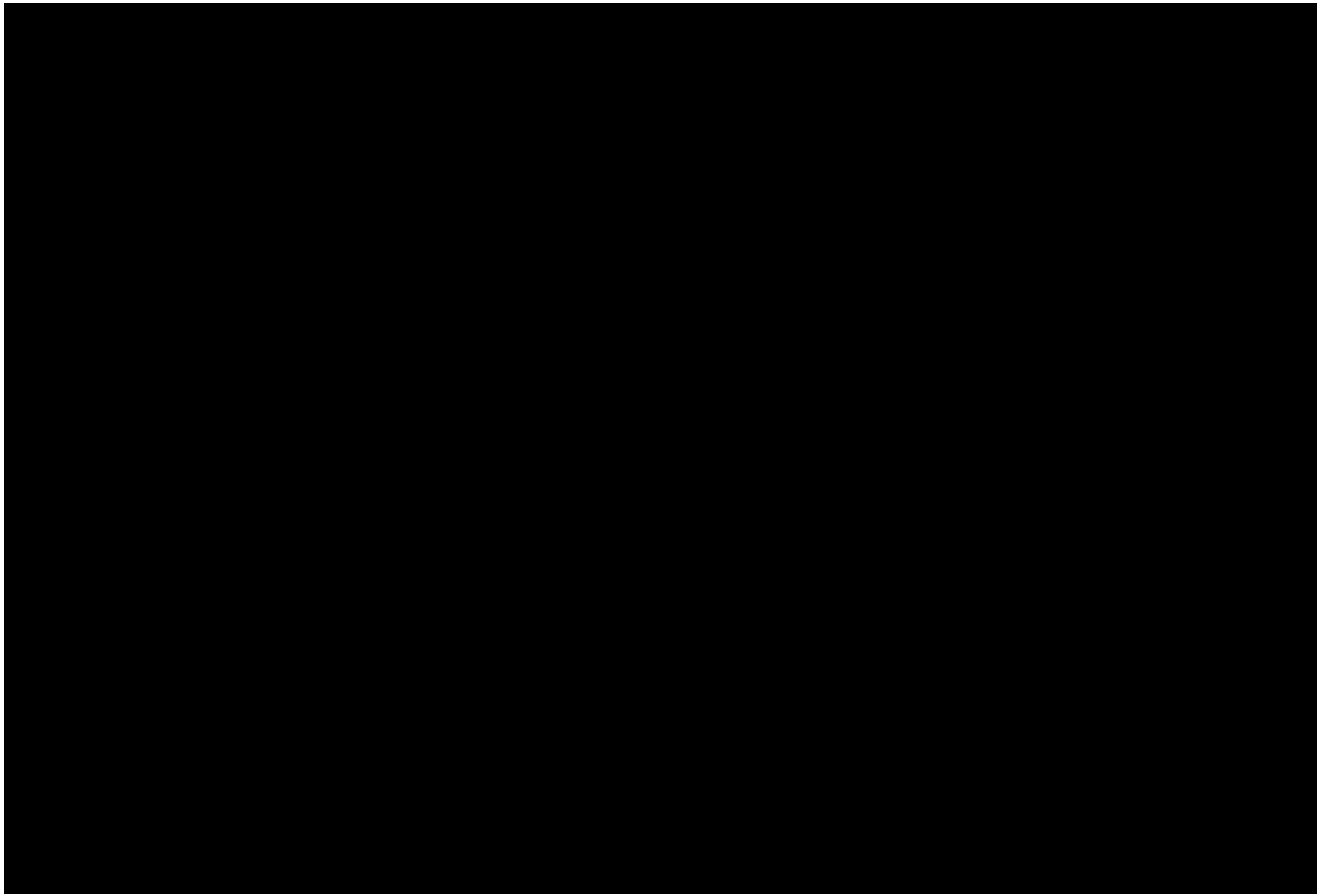
- Cohort 1: 0.75 mg ITI-333 (n=6) or placebo (n=2)
- Cohort 2: 1.5 mg ITI-333 (n=6) or placebo (n=2)
- Cohort 3: 3 mg ITI-333 (n=6) or placebo (n=2)
- Cohort 4: 6 mg ITI-333 (n=6) or placebo (n=2)

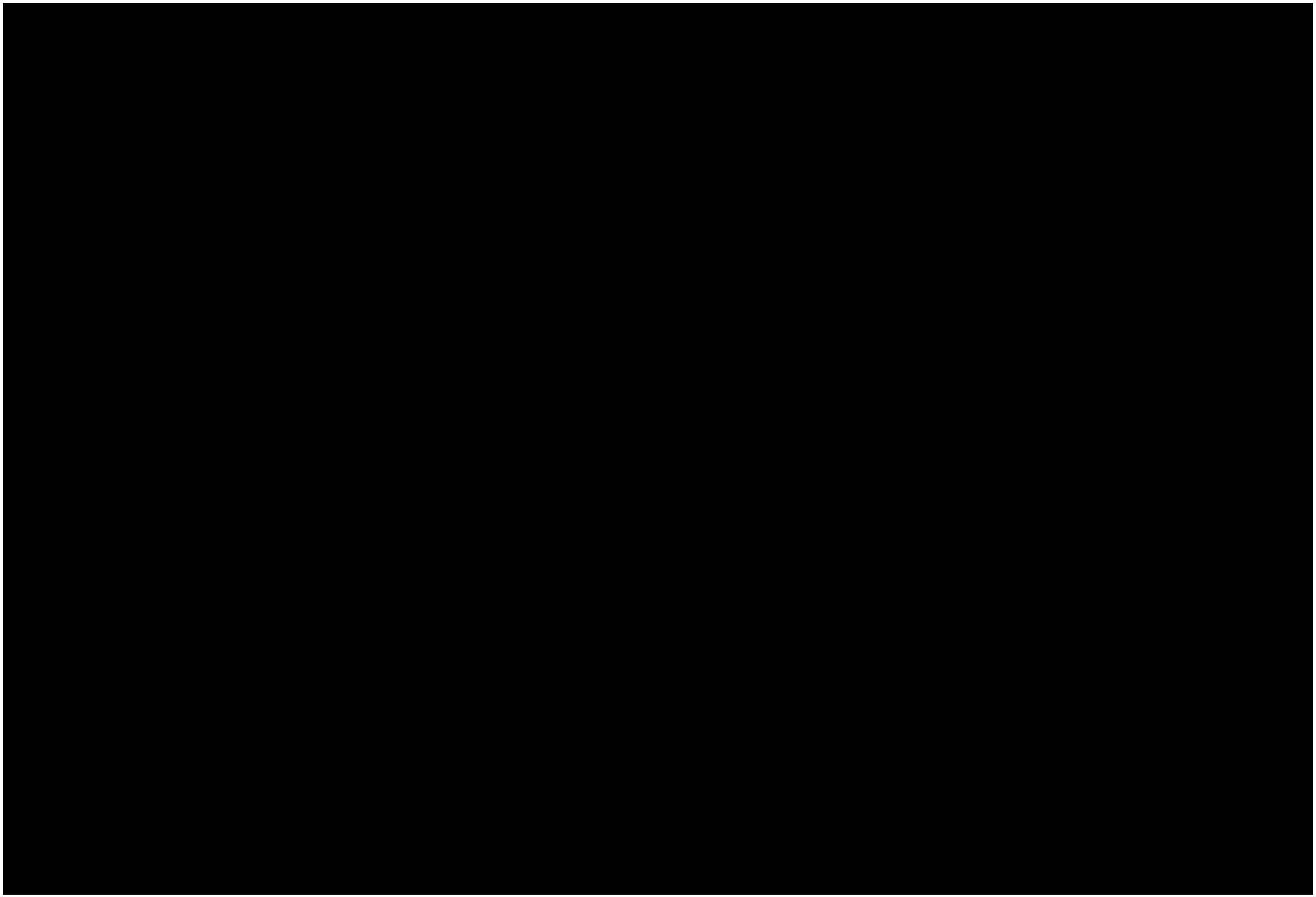
Dose escalations other than the planned doses specified above may be evaluated based on safety and pharmacokinetic (PK) assessments but they will not exceed 2-fold. [redacted]

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.

Safety and tolerability will be assessed throughout the study. [redacted]

[redacted]





3. STUDY OBJECTIVES

3.1 [redacted] Objectives

- 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]

4. ANALYSIS POPULATION

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.

[redacted]

5. SUBJECT DISPOSITION

Screen failures (ie, subjects in the Enrolled Population who are screened but not randomized) and the associated reasons for failure to randomize will be tabulated by cohort for the Enrolled Population.

The number of subjects who were randomized 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 Randomized Population. The number and percentage of subjects who complete the treatment period and who prematurely discontinue from the treatment period 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 discontinuation for the Safety Population. The number and percentage of subjects who complete the safety follow-up and who prematurely discontinue from the safety follow-up will be analyzed in a manner similar to the analyses for the treatment period. Subjects who discontinue prematurely from the treatment period and/or the safety follow-up will be listed for the Safety Population.

6. PROTOCOL DEVIATION

A listing of major protocol deviations will be provided for the Safety Population. The categorization of the major protocol deviations is detailed in the Protocol Deviation Management Plan.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic (eg, age, race, ethnicity, and sex) and other baseline characteristics (eg, weight, height, and body mass index [BMI]) 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 history, surgical procedures or physical findings will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class (SOC), preferred term and by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts for the Safety Population.

8. PRIOR AND CONCOMITANT MEDICATION

A prior medication will be defined as any medication other than study drug which started and stopped before the first dose of study drug. A prior concomitant medication will be defined as any medication other than study drug which started before and stopped after the first dose of study drug. A concomitant medication will be defined as any medication other than study drug which started after the first dose of study drug but before the end of the treatment period. Any medication started after the end of the treatment period will not be considered as a concomitant medication.

Medications other than study drug use will be coded using the latest version of the World Health Organization Drug Global (WHODG) and listed for the Safety Population.

9. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 Extent of Exposure

Each subject will receive an oral dose of study drug 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.

9.2 Treatment Compliance

Treatment compliance is defined as the total number of study doses actually taken by a subject divided by the number of study doses that were expected to be taken multiplied by 100. The total number of study doses actually taken will be calculated from the study drug dosing record. 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.

10. SAFETY ANALYSES

The safety analysis will be performed based on the Safety Population, unless otherwise specified. Safety parameters will include adverse events (AE), clinical laboratory parameters, vital signs, ECG, [redacted].

For each safety parameter other than AE, the last non-missing assessment made before the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

10.1 Adverse Events

Adverse events (AEs) will be coded using the latest version of MedDRA.

An AE (classified by preferred term) is considered a treatment-emergent adverse event (TEAE) if it started as a new event or if an AE severity increased 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 refers to an increase in AE severity 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 for the summarization by severity and most related occurrence for the summarization by relationship to study drug.

The incidence of serious adverse events (SAEs) and of AEs leading to premature discontinuation of the study drug 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, AEs leading to discontinuation of study drug, and subjects who died based on the Enrolled Population.

AEs will be reviewed for any evidence suggestive of abuse potential using standardized MedDRA queries (SMQs) for drug abuse, dependence, and withdrawal. Adverse events identified through SMQs by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts will be summarized by preferred term. A supportive listing will be presented for drug abuse and dependence AEs.

10.2 Clinical Laboratory Parameters

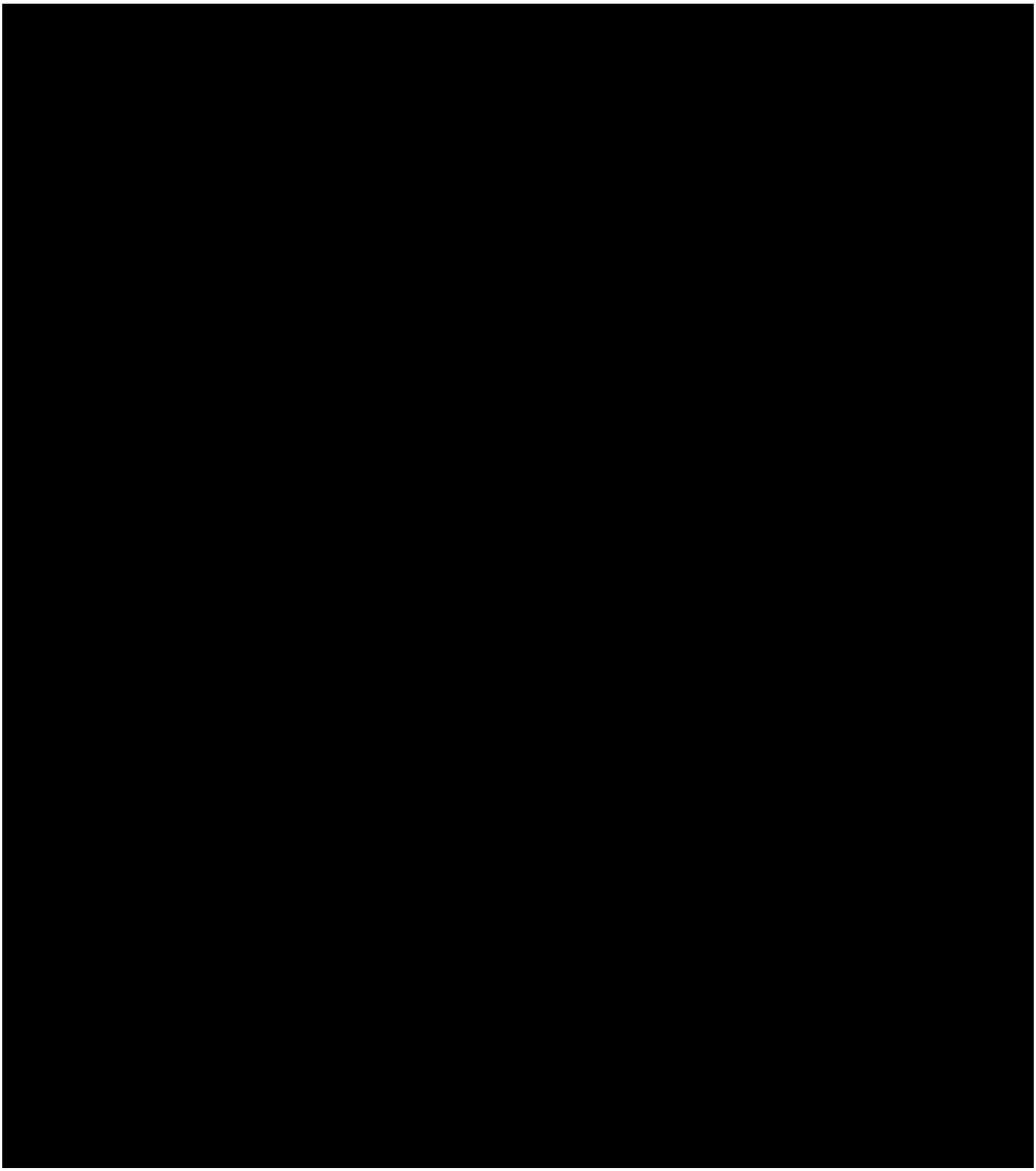
Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) for clinical laboratory values (in SI and conventional units) at baseline, postbaseline, and changes from baseline [redacted] will be presented by cohort and treatment, ITI-333 combined across all cohorts, and placebo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

[redacted]

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

The clinical laboratory parameters in tests of liver function [redacted] will be grouped and analyzed in the chemistry group.

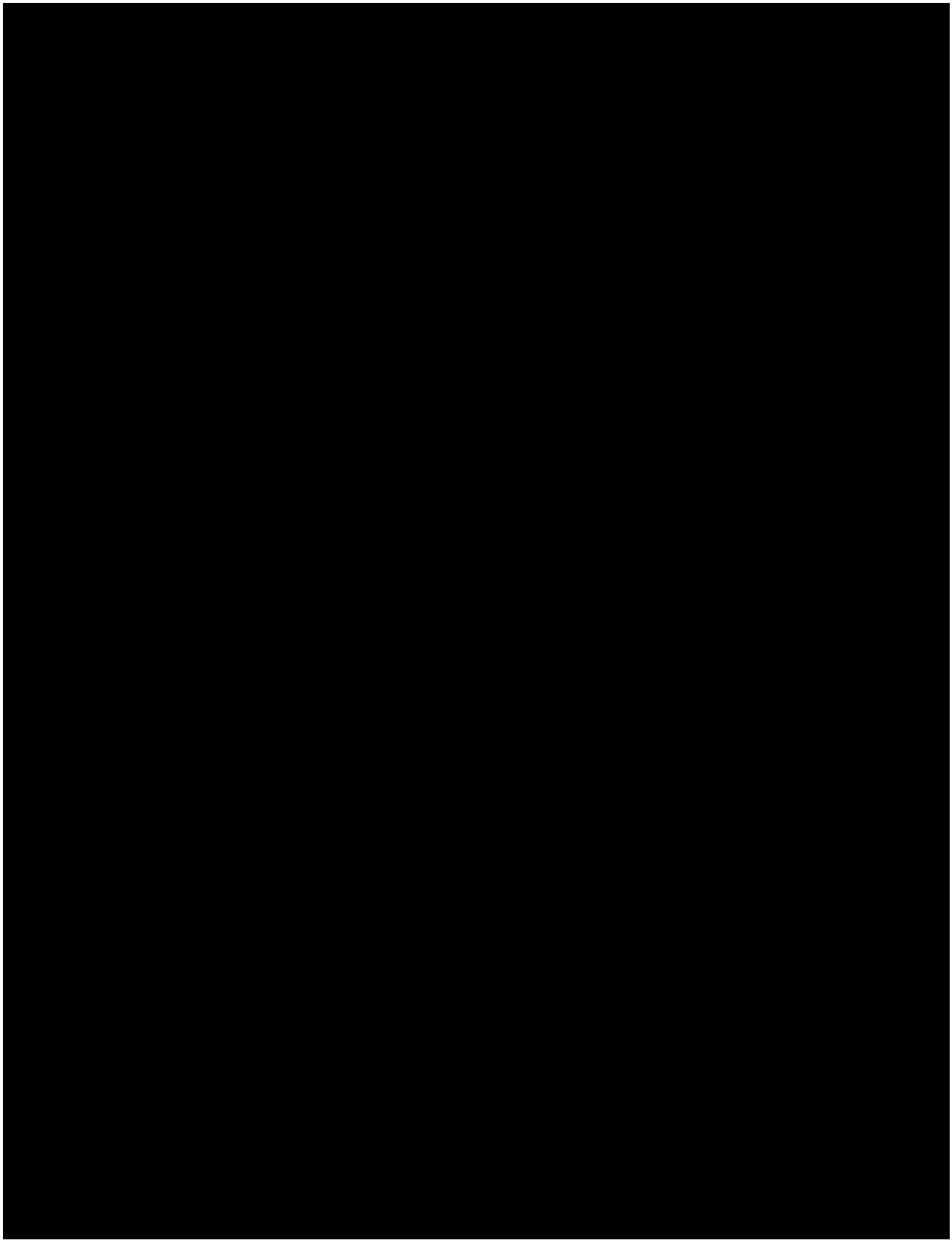
[redacted]



A potential Hy's Law case is defined as concurrent elevations in ALT or AST (≥ 3 × ULN) and total bilirubin (≥ 2 × ULN), with alkaline phosphatase < 2 × ULN, based on blood draws collected within a 24-hour period.

10.3 Vital Signs

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) for vital signs (supine BP), SpO_2, and weight values at baseline, postbaseline, and changes from baseline will be presented by cohort and treatment, ITI-333 combined across all cohorts, and placebo combined across all cohorts.



10.4 Electrocardiograms

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) for 12-lead ECG parameters ([redacted]QTcF [redacted]) at baseline, postbaseline, 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]

[redacted]

13. INTERIM ANALYSIS

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

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.

14. SAMPLE SIZE CONSIDERATION

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.

15. STATISTICAL SOFTWARE

Statistical analyses of safety parameters will be performed using SAS version 9.4 (or newer).

16. DATA HANDLING CONVENTIONS

16.1 Repeated or Unscheduled Assessments

16.1.1 Baseline and postbaseline Assessments

If a subject has repeated assessments before the first dose of study drug, then the results from the final assessment made before the first dose of study drug will be used as baseline. If postbaseline assessments are repeated or unscheduled assessments occur, the scheduled assessment will be used for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

16.2 Missing Data for Adverse Events

16.2.1 Missing Severity Assessment

If severity is missing for an AE that occurred before the first dose of study drug, then a severity of *mild* will be assigned. If the severity is missing for an AE that occurred on or after the first dose of study drug, then a severity of *severe* will be assigned. The imputed values for severity will be used for the incidence summary; the actual values will be presented in data listings.

16.2.2 Missing Relationship to Study Drug

If the relationship to study drug is missing for an AE that occurred after the first dose of study drug, then a causality of *Yes* will be assigned. The imputed values for relationship to study drug will be used for the incidence summary; the actual values will be presented in data listings.

16.2.3 Missing Start Date

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

Missing Month and Day

- If the year of the incomplete start date is the same as the year of the first dose of study drug, the month and day of the first dose of study drug will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the first dose of study drug, *December 31* will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the first dose of study drug, *January 1* will be assigned to the missing fields.

Missing Month Only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete start date are the *same* as the month and year of the first dose of study drug, the day of the first dose of study drug will be assigned to the missing day.
- If either the year of the incomplete start date is before the year of the date of the first dose of study drug or if both years are the same, but the month of the incomplete start date is *before* the month of the date of the first dose of study drug, the *last* day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of study drug or if both years are the same, but the month of the incomplete start date is *after* the month of the date of the first dose of study drug, the *first* day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is *after* the date of the first dose of study drug, the date of the first dose of study drug will be assigned to the missing start date.
- If the stop date is *before* the date of the first dose of study drug, the stop date will be assigned to the missing start date.

16.2.4 Missing Stop Date

Since subjects are confined to the site, all AEs that occurred during the treatment period will be recorded in the source documentation. Missing stop dates are not expected. In rare cases, missing stop dates may be discovered during EDC data review prior to database lock. These missing stop dates will be queried and resolved/updated by the site staff. For AEs that occurred after the end of the treatment period and until 10 days after the last dose of study drug, extra efforts should be made to retain the AE stop date as it is a relatively short recall period.

16.2.5 Unknown or Incomplete Start/Stop Time

Since subjects are confined to the site, all AEs that occurred during the treatment period will be recorded in the source documentation. Unknown or incomplete start and/or stop times are not expected. In rare cases, missing times may be discovered during EDC data review prior to database lock. These missing times will be queried and resolved/updated by the site staff. For AEs that occurred after the end of the treatment period, unknown or incomplete start times will be assigned as ‘00:01’ and unknown or incomplete stop times will be assigned as ‘23:59’.

16.3 Missing Date Information for Prior or Concomitant Medications

For prior, prior concomitant, or concomitant medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a subject, the start date will be inputted first.

16.3.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior, prior concomitant, or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing Month and Day

- If the year of the incomplete start date is the *same* as the year of the first dose of study drug, the month and day of the first dose of study drug will be assigned to the missing fields.
- If the year of the incomplete start date is *before* the year of the first dose of study drug, *December 31* will be assigned to the missing fields.
- If the year of the incomplete start date is *after* the year of the first dose of study drug, *January 1* will be assigned to the missing fields.

Missing Month Only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete start date are the *same* as the month and year of the first dose of study drug, the day of the first dose of study drug will be assigned to the missing day.
- If either the year of the incomplete start date is *before* the year of the date of the first dose of study drug or if both years are the *same,* but the month of the incomplete start date is *before* the month of the date of the first dose of study drug, the *last day* of the month will be assigned to the missing day.
- If either the year of the incomplete start date is *after* the year of the date of the first dose of study drug or if both years are the *same,* but the month of the incomplete start date is *after* the month of the date of the first dose of study drug, the *first* day of the month will be assigned to the missing day.

16.3.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior, prior concomitant, or concomitant medication stop date. If the imputed stop date is *before* the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing Month and Day

- If the year of the incomplete stop date is the *same* as the year of the last dose of study drug, the month and day of the last dose of study drug will be assigned to the missing fields.
- If the year of the incomplete stop date is *before* the year of the last dose of study drug, *December 31* will be assigned to the missing fields.
- If the year of the incomplete stop date is *after* the year of the last dose of study drug, *January 1* will be assigned to the missing fields.

Missing Month Only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete stop date are the *same* as the month and year of the last dose of study drug, the day of the last dose of study drug will be assigned to the missing day.
- If either the year of the incomplete stop date is *before* the year of the date of the last dose of study drug or if both years are the *same,* but the month of the incomplete stop date is *before* the month of the date of the last dose of study drug, the *last* day of the month will be assigned to the missing day.
- If either the year of the incomplete stop date is *after* the year of the date of the last dose of study drug or if both years are the *same,* but the month of the incomplete stop date is *after* the month of the date of the last dose of study drug, the *firs*t day of the month will be assigned to the missing day.

16.3.3 Unknown or Incomplete Start/Stop Time

All non-study-drug medications can be classified as prior, prior concomitant, or concomitant medications without their start and/or stop times, except those medications started and/or stopped on the same date as the first dose of study drug. However, since subjects are confined to the site, all medications taken during the treatment period will be administered by site staff, or designee, and recorded in the source documentation. Unknown or incomplete start and/or stop times are not expected. In rare cases, missing times may be discovered during EDC data review prior to database lock. These missing times will be queried and resolved/updated by the site staff.

16.4 Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, the coded value will need to be appropriately determined for use in the statistical analyses [redacted]. The actual values as reported in the database will be presented in the data listings.

[redacted]

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

[redacted]

17. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

There are no changes to the analyses specified in the protocol.

18. REFERENCE

No references are cited.

Signature Page for VV-CLIN-003169 v1.0