Statistical Analysis Plan for Interventional Studies (Early Phase)

Sponsor Name: HanAll Pharmaceutical International Inc.

Protocol Number: HL192-PD-CA-P101

Protocol Title: A Randomized, Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics of Single and Multiple Doses as Well as the Food Effect of Orally Administered ATH-399A in Healthy Adult Participants

Protocol Version and Date: Amendment III 30-Nov-2023

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Revision History

Version	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
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0.2	05-Oct-2023	[redacted]	Incorporation of Sponsor Comments
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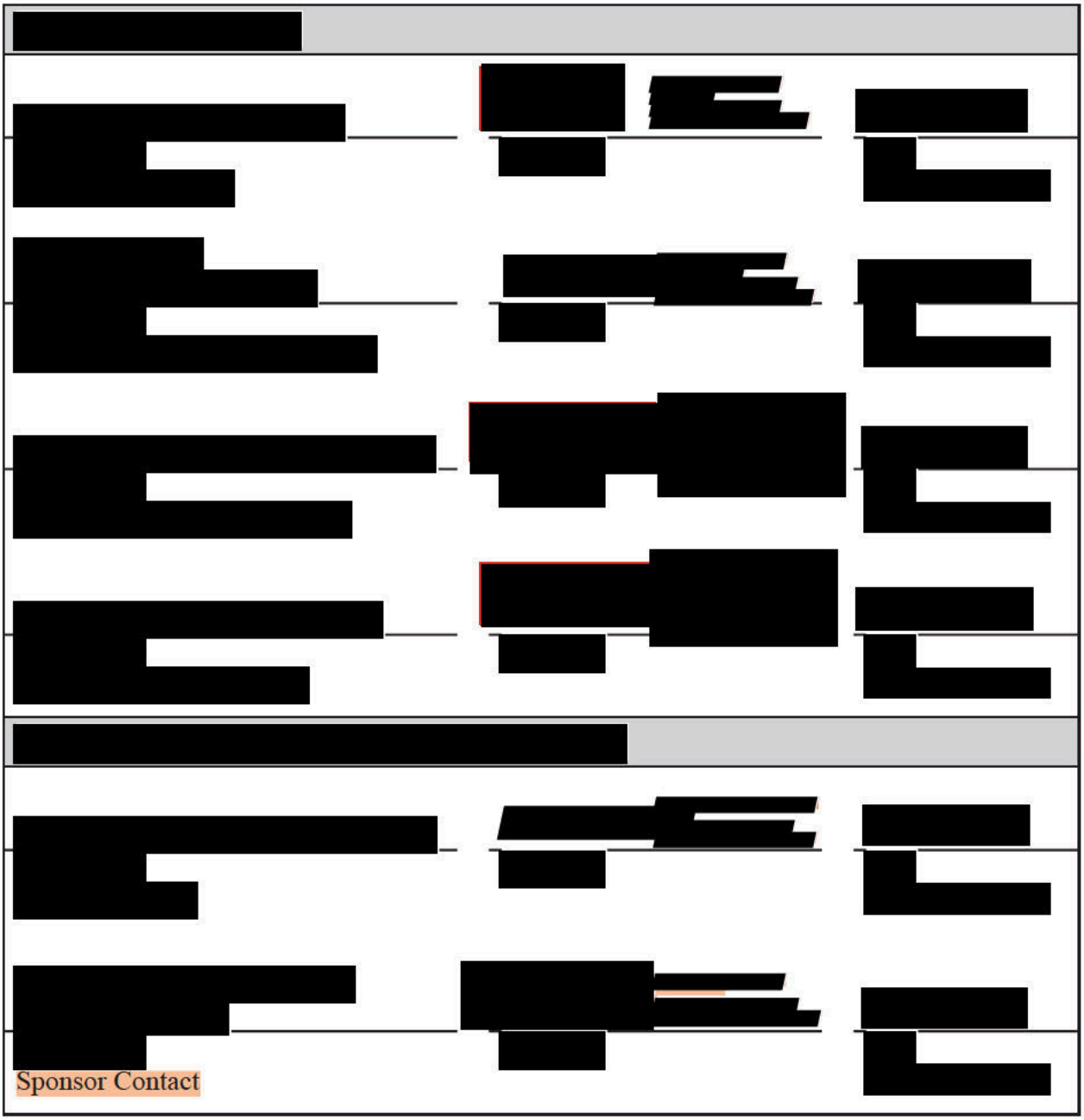
1.0	04-Mar-2024	[redacted]	Initial document

Approvals

I confirm that I have reviewed this document and agree with the content.



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Glossary of Abbreviations

Abbreviation	Description
AE	adverse event
Ae_{0-t}	cumulative urinary excretion from time zero to time t
ANOVA	analysis of variance
AR	accumulation ratio
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time zero to 24-hours post-dose
AUC_{0-inf}	area under the concentration-time curve from time zero to infinity (extrapolated)
AUC_{0-t}	area under the concentration-time curve from time zero to time of last observed concentration
$AUC_{0-\tau}$	area under the concentration-time curve, for one dosing interval (τ) at steady state
BLQ	below the lower limit of quantification
BMI	body mass index
CI	confidence interval
Cl/F	apparent body clearance
Cl_R	Renal clearance, calculated as Ae_{0-t} /AUC_{0-t}
Cl_{ss}/F	apparent body clearance at steady state
C_{max}	maximum observed concentration
$C_{max\ ss}$	maximum observed concentration at steady state
C_{min}	minimum observed concentration
$C_{min\ ss}$	minimum observed concentration at steady state
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
C_{avg}	average drug concentration at steady-state
CV	coefficient of variation
df	degrees of freedom
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FSH	follicle stimulating hormone

Abbreviation	Description
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
λ_z	individual estimate of the terminal elimination rate constant
ln	natural logarithm
LSM	least-squares means
MAD	multiple ascending dose
max	maximum
MedDRA®	Medical Dictionary for Regulatory Activities
min	minimum
N	number of participants
n	number of observations
N/A	not applicable
OLS	ordinary least squares
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
p-value	probability value
QD	once daily
QTcF	corrected QT interval using Fridericia's formula
REML	restricted maximum likelihood
R^2	R-squared
R_{max}	Maximal rate of urinary excretion
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
SOP	standard operating procedure
SRC	Safety Review Committee
$t_{1/2\ el}$	terminal elimination half-life
TBD	to be determined
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings

Abbreviation	Description
T_{lag}	time of observation prior to the first observation with a measurable (non-zero) concentration
T_{max}	time of maximum observed concentration
$T_{max\ ss}$	time of maximum observed concentration at steady state
T_{Rmax}	Time of maximal urinary excretion
V_z/F	apparent volume of distribution
$V_{z\ ss}/F$	apparent volume of distribution at steady state
vs	versus
WHO Drug	World Health Organization Global Drug Dictionary

1. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is based on the following documents:

- Protocol HL192-PD-CA-P101 Amendment III, dated 29-Nov-2023
- Electronic case report form (eCRF) version 0.14, dated 14-Aug-2023

The plan may change due to unforeseen circumstances; any changes made after the plan has been finalized will be documented. No revision to the SAP is required for changes which do not affect the statistical analysis methods, definitions, or rules defined in this document. If additional analyses are required to supplement the planned analyses described in the SAP, the changes and justification for the changes will be outlined in the associated clinical study report (CSR). No change will be made without prior approval of the Sponsor. Changes from the analysis planned in the protocol are detailed in Section 11.

When applicable, all methodologies and related processes will be conducted according to [redacted] standard operating procedures (SOPs), as appropriate. Shells for all statistical tables, listings, and figures referred to in this SAP will be presented in a separate document.

1.1 Responsibilities

[redacted] will perform the statistical analyses and are responsible for the production and quality control of all tables, figures, and listings (TFLs).

1.2 Timings of Analyses

Interim Analysis:

There are no planned interim analyses for this study. Nevertheless, blinded safety and PK data extracts will be available for Safety Review Committee (SRC) meetings.

Final Analysis:

The final safety, tolerability, and pharmacokinetic (PK) analysis will be completed after all participants complete the final study visit or terminate early from the study, and the database has been locked.

2. Study Objectives

2.1 Part 1a (SAD)

2.1.1 Primary Objectives

- To assess the single dose safety and tolerability of ATH-399A in healthy male and female participants in up to 5 different ascending dose level groups.

2.1.2 Secondary Objectives

- To evaluate the single dose plasma PK of ATH-399A in healthy male and female participants in up to 5 different ascending dose level groups.
- To determine concentration of ATH-399A and identify its metabolites in blood and urine in healthy male and female participants after a single dose in up to 5 different ascending dose level groups.

2.2 Part 1b (Food Effect)

2.2.1 Primary Objectives

- To assess the single dose safety and tolerability of ATH-399A in healthy male and female participants under fasted and fed conditions.

2.2.2 Secondary Objectives

- To evaluate the single dose plasma PK of ATH-399A in healthy male and female participants under fasted and fed conditions.

2.3 Part 2 (MAD)

2.3.1 Primary Objectives

- To assess the safety and tolerability of multiple doses of ATH-399A in up to 2 ascending dose groups in healthy male and female participants.

2.3.2 Secondary Objectives

- To assess the plasma PK of multiple doses of ATH-399A in up to 2 ascending dose groups in healthy male and female participants.

3. Study Description

This study will be a first-in-human evaluation of the safety and pharmacokinetics of single and multiple doses of ATH-399A in healthy adults in the 18-55 year age range, multiple doses in healthy participants in the >55-80 year age range, and will also evaluate the effect of food on ATH-399A safety, tolerability and PK. This is a randomized, Phase 1 three-part study. Part 1a is a placebo-controlled, double-blind, single ascending dose (SAD) safety, tolerability, and PK evaluation of ATH-399A. Part 1b is an open-label, single dose, food-effect, safety, tolerability, and PK evaluation of ATH-399A. Part 2 is a placebo-controlled, double-blind, multiple ascending dose (MAD) safety, tolerability, and PK evaluation of ATH-399A in 2 different age groups.

3.1 Participant Selection

Up to approximately 76 healthy, non-smoking, male and female volunteers, with body weight ≥50.0 kg for men and ≥45.0 kg for women and body mass index within the range of 18.0-30.0 kg/m^2, will be enrolled in this study. For Part 1a, approximately 40 healthy male and female participants, aged between 18-55 (inclusive) years will be enrolled. For Part 1b, approximately 12 healthy male and female participants, aged between 18-55 (inclusive) years with a minimum of 3 participants of each gender will be enrolled. For Part 2, approximately 16 healthy male and female participants, aged between 18-55 (inclusive) years with a minimum of 2 participants of each gender per cohort will be enrolled, along with an additional cohort of approximately 8 healthy male and female participants, aged between >55-80 (inclusive) years with a minimum of 2 participants of each gender.

3.2 Determination of Sample Size

The sample size for each stage was determined based on standard practice in Phase 1 food effect, SAD, and MAD studies empirically and was not powered for statistical significance. Cohort sizes were selected based on those commonly utilized in similar Phase 1 studies and thus generally considered sufficient to assess safety, tolerability, and estimate PK parameters.

3.3 Treatment Assignment

3.3.1 Part 1a (SAD)

Participants allocated to the SAD part will receive a single dose of ATH-399A, or matching placebo, under fasting conditions. The planned dose levels and regimens are listed in Table 3.3-1, below.

Table 3.3-1: SAD Treatments

Cohort Number	Number of Participants Receiving ATH-399A	Number of Participants Receiving Placebo	Planned Dose
1	6 (1 sentinel, 5 non-sentinel)	2 (1 sentinel, 1 non-sentinel)	5 mg
2	6 (1 sentinel, 5 non-sentinel)	2 (1 sentinel, 1 non-sentinel)	10 mg
3	6 (1 sentinel, 5 non-sentinel)	2 (1 sentinel, 1 non-sentinel)	20 mg
4	6 (1 sentinel, 5 non-sentinel)	2 (1 sentinel, 1 non-sentinel)	40 mg
5	6 (1 sentinel, 5 non-sentinel)	2 (1 sentinel, 1 non-sentinel)	80 mg

For each dose level, 6 participants will receive ATH-399A and 2 participants will receive placebo. Each cohort will utilize sentinel dosing, with one participant receiving ATH-399A and one participant receiving placebo. For Cohorts 1-3, provided no clinically significant safety issues are noted in the 48 hours after dosing the initial 2 participants in the cohort, the 6 remaining participants in the cohort will be dosed. For Cohorts 4 and 5, provided no clinically significant safety issues are noted in the 96 hours after dosing the initial 2 participants in the cohort, the 6 remaining participants in the cohort will be dosed.

The SRC will consider the data on a cohort basis, but also on the basis of cumulative information across cohorts as the study progresses. All dose levels will be considered completed following SRC approval.

3.3.2 Part 1b (Food Effect)

Participants allocated to the food effect part will be randomized to one of the 2 sequences, AB or BA, and will receive the following study treatments in each period:

- **Treatment A**: Single dose of ATH-399A after a high-calorie, high-fat breakfast.
- **Treatment B**: Single dose of ATH-399A after fasting.

For treatment A, participants will complete a supervised fast of at least 10 hours before their meal. Drug administration will occur approximately 30 minutes after the meal has been started. For treatment B, participants will fast for at least 10 hours before until at least 4 hours after dosing. Selection of the dose to be administered in Part 1b will depend on the results of Part 1a. [redacted]

3.3.3 Part 2 (MAD)

Participants allocated to the MAD part will receive daily doses of ATH-399A, or matching placebo, under fasting conditions, for 12 consecutive days. The planned dose levels and regimens are listed below in Table 3.3-2.

Table 3.3-2: MAD Treatments

Cohort Number	Number of Participants Receiving ATH-399A	Number of Participants Receiving Placebo	Planned Dose
1	6	2	TBD mg
2	6	2	TBD mg
3	6	2	TBD mg

Each cohort will include 8 participants, 6 participants will receive ATH-399A and 2 participants will receive placebo. [redacted]

Dose levels of ATH-399A will be based on data from Part 1 (Part 1a and 1b) and recommendation from the SRC. From Day 1 to Day 12, participants will receive either ATH-399A or placebo once daily (QD) for a total of twelve (12) consecutive days.

3.4 Randomization

Randomization schemes will be generated using SAS® for Windows software, prior to study execution. Block randomization will be used, and one randomization scheme will be produced for each cohort separately.

Participants will be randomized to treatments on Day 1. For Parts 1a and 2 (SAD and MAD, respectively), participants will be randomized 6:2 to active:placebo. In Parts 1a and 2, the first two participants in each cohort will be sentinel participants and will be randomized 1:1 to active:placebo. For Part 1b (food effect) participants will be randomized to 1 of 2 ATH-399A treatment condition sequences (AB or BA).

Each participant will be randomly assigned a 5-digit randomization number. For Part 1a, they will begin with "11" and "12" for Cohorts 1 and 2, respectively. For Part 1b, they will begin with "10". For Part 2, they will begin with "21" and "22" for Cohorts 1 and 2, respectively. For Parts 1a and 2, these numbering systems will be continued for each cohort until all cohorts are enrolled. Each randomization number corresponds to a treatment assignment on the randomization scheme. For Part 1a, sentinel participants will be assigned to the first 2 randomization numbers of their cohort (i.e., 11001, 11002 for Cohort 1, and 12001, 12002 for Cohort 2). For Part 2, sentinel participants will also be assigned to the first 2 randomization numbers of their cohort (i.e., 21001, 21002 for Cohort 1, 22001, 22002 for Cohort 2, and 23001, 23002 for Cohort 3).

3.5 Blinding

This is a randomized study using active drug (ATH-399A) and placebo control. Parts 1a and 2 are double-blind, while part 1b is randomized and open-label. Randomization to treatment group will be performed after participants have been deemed eligible for study participation. Blinding will be used in Parts 1a and 2 to reduce potential bias during data collection and evaluation of clinical endpoints. The participants and the clinical personnel involved in the collection, monitoring, revision, or evaluation of adverse events (AEs), or personnel who could have an impact on the outcome of the study will be blinded with respect to the participant's treatment assignment (active or placebo). Blinding will be maintained until at least the clinical phase of the study is completed, i.e., when reporting and evaluation of all AEs have been completed for all cohorts.

Blinded PK results will be available during the course of the study. These results will be reported without revealing the participant's identity.

3.6 Participant Withdrawal and Replacement

Participants may be automatically replaced if they withdraw/discontinue after randomization but prior to any dosing. Replacement of participants who withdraw/discontinue post dose will be at the discretion of the Sponsor. Procedures will be performed according to the site's SOP.

If a participant is replaced, the replacement participant will receive the same treatment assigned to the original participant and will be assigned a randomization number which reflects the original participant's randomization number plus 100 (e.g., a participant assigned to randomization number 11001 would be replaced by a participant assigned to randomization number 11101).

4. Endpoints

4.1 Part 1a (SAD)

4.1.1 Primary Endpoints

- Changes from baseline in vital signs, electrocardiograms (ECGs), clinical laboratory tests, telemetry, physical examination, neurological examination, Columbia Suicide Severity Rating Scale (C-SSRS), and the overall incidence of AEs and serious adverse events (SAEs).

4.1.2 Secondary Endpoints

- Area under the concentration time curve from time zero to time of last observed concentration (AUC_{0-t}), area under the concentration-time curve from time zero to infinity (extrapolated) (AUC_{0-inf}), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination rate constant (λ_z), and terminal elimination half-life ($t_{1/2\ el}$).
- Concentrations of ATH-399A and identification of its major metabolites in blood and urine.

4.2 Part 1b (Food Effect)

4.2.1 Primary Endpoints

- Changes from baseline in vital signs, ECGs, clinical laboratory tests, telemetry, physical examination, neurological examination, C-SSRS, and the overall incidence of AEs and SAEs.

4.2.2 Secondary Endpoints

- AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, λ_z, and $t_{1/2\ el}$.

4.3 Part 2 (MAD)

4.3.1 Primary Endpoints

- Changes from baseline in vital signs, ECGs, clinical laboratory tests, telemetry, physical examination, neurological examination, C-SSRS, and the overall incidence of AEs and SAEs.

4.3.2 Secondary Endpoints

- AUC_{0-t}, AUC_{0-inf}, C_{max}, C_{max} at steady-state ($C_{max\ ss}$), minimum plasma concentration (C_{min}), average plasma concentration (C_{avg}), T_{max}, T_{max} at steady-state ($T_{max\ ss}$), area under the curve for the defined dosing interval ($AUC_{0-\tau}$ [AUC_{0-24}, Day 12 dose]), AUC_{0-24} (Day 1 dose), λ_z, $t_{½\ el}$, and accumulation ratio (AR).

5. Analysis Populations

All participants' inclusion status into each analysis population will be determined after database lock but prior to unblinding. Participants will be analyzed according to the treatment received.

5.1 Safety Population

The safety population will include all participants who receive at least one dose of study drug (active or placebo). The safety population will be used for all safety and tolerability summaries and analyses.

5.2 Pharmacokinetic (PK) Population

The PK population will include all participants who receive at least one dose of ATH-399A and provide at least one plasma or urine concentration measure.

In addition, any participant with a protocol deviation or AE deemed to affect PK may be excluded from the PK population. Participants may also be excluded from the PK population based upon the following: inclusion and exclusion criteria, acceptable times for visit dates and measurements, compliance with treatment, the nature and quality of the data, and withdrawal. Before the final analysis, the pharmacokineticist, in agreement with the Sponsor, will make the final decision of which participants will be included in the PK population, based on the datasets received.

6. General Aspects for Statistical Analysis

6.1 General Methods

SAS for Windows software will be used to perform all statistical analyses. All relevant data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by study part, treatment, participant number, and assessment date/time. For the purposes of the summary tables, all participants randomized to placebo will be pooled into a single placebo group (i.e., All placebo). Unless otherwise stated, there will also be an overall section for all ATH-399A doses combined (i.e., All ATH-399A). All summaries will be presented separately for each study part. Unless otherwise stated, the descriptions of the analyses which follow apply to all study parts.

The following labels for treatment will be used on all tabulations where the results are displayed by treatment or sequence, in the following order:

Part 1a:

- All Placebo
- ATH-399A 5 mg
- ATH-399A 10 mg
- ATH-399A 20 mg
- ATH-399A 40 mg
- ATH-399A 80 mg
- All ATH-399A

Part 1b:

- Treatment A (Fed)
- Treatment B (Fasted)

or

- Sequence AB
- Sequence BA

Part 2:

- All Placebo
- ATH-399A TBD mg
- ATH-399A TBD mg
- ATH-399A TBD mg
- All ATH-399A

6.2 Summary Statistics:

Unless otherwise stated, continuous variables will be summarized using the number of observations (n), and the statistics mean, median, standard deviation (SD), minimum (min) and maximum (max). The min and max values will be presented to the same number of decimal places as recorded in the eCRF, mean and median will be presented to one more decimal place than the raw data, and the SD will be presented to two more decimal places than the raw data.

Summaries of change from baseline variables will include only participants who have both a baseline value and corresponding value at the timepoint of interest. Categorical and binary variables will be summarized with frequency counts and percentages. Percentages will be rounded to one decimal place, with the denominator being the number of participants (N) in the relevant population, unless otherwise stated.

All digits will be used for PK and statistical calculations. For PK tables and listings, the final reportable results or data will be presented by rounding off to two decimal digits, except for the following situations (this applies to individual data and descriptive statistics):

- Terminal elimination rate constant (λ_z) data shall be rounded off to four decimal places.
- PK parameters related to time, such as time of maximum observed concentration (T_{max}) must be reported with the same precision as the actual sampling time, rounded to three decimal places.
- Concentration versus time data, as well as maximum observed concentration (C_{max}) shall be reported as they appear in the corresponding dataset.
- Ratios and 90% CIs, intra- and inter-participant coefficients of variation (CV), and CV (%) will be presented to two decimal places.

Only data from protocol scheduled (“nominal”) visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables (unless they were used as baseline) but will be included in the listings.

6.3 Key Definitions

Baseline:

Unless stated otherwise, baseline is defined as the last value prior to the first dose. Post baseline will be considered as all measurements collected after study drug administration. "Unknown", "Not Done", "Not Applicable" and other classifications of missing data will not be considered when calculating baseline observations unless the finding is a valid categorical observation.

Study Day:

Study day will be calculated using first study drug administration date as the reference date. If the date of interest occurs on or after the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date) + 1. If the date of interest occurs prior to the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date). There will be no study Day 0.

Concomitant Medication:

Concomitant medication is defined as any medication taken by participants after dosing until the last study day.

6.4 Missing Data

There will be no imputation for missing data, unless otherwise specified. Missing data shall be presented in participant listings as either "-" (unknown or not evaluated) or "N/A" (not applicable), with the corresponding definition in the footnotes. Missing descriptive statistics, or probability values (p-values), which cannot be estimated shall be presented as "-".

For inclusion in concomitant medication and AE tables, incomplete start and stop dates on the eCRF will be imputed as follows:

- If the stop date is incomplete, the following rules will be applied:
    - Missing day: Assume the last day of the month
    - Missing day and month: Assume the last day of the year
    - Missing day, month, and year: Assume that the event/medication is continuing
    - In the case of the death of a participant, and if the imputed end date is after the date of death, the end date will be imputed as the date of death
- If the stop date is incomplete, imputed end date will be used instead of reported end date
- If the start date is incomplete, the following rules will be applied:
    - Missing day: Assume the first day of the month; however, if the partial date and the date of first study drug administration lie within the same month and year and the date of first study drug administration is not after the stop date of the event/medication, set to the date of study drug administration. Otherwise, set to the stop date of the event/medication.

- Missing day and month: Assume January 1st; however, if the partial date and the date of first study drug administration lie within the same year and the date of first study drug administration is not after the stop date of the event/medication, set to the date of first study drug administration. Otherwise, set them to stop date of the event/medication.
- Missing day, month, and year: Assume date of first study drug administration if it is not after the stop date for the event/medication. Otherwise, set them to stop date for the event/medication.

In the case of withdrawal of consent, all data from participants who withdraw from the study will be included in all summaries up to the time of withdrawal. For all other withdrawals, all data captured will be included in the safety summaries.

For PK analysis, only observed concentration data will be used in the data analysis except for concentration values below the lower limit of quantification (BLQ). No attempt will be made to extrapolate or interpolate estimates for missing data.

7. Study Population

7.1 Participant Disposition

The number of participants who were screened, who screen failed, who were enrolled, who were dosed, who completed the study, and who were discontinued from the study, along with reasons for discontinuation, will be summarized. The data will be presented by study part, cohort (sequence for Part 1b), and overall (frequency and the percentage of participants) and presented by participant in a data listing.

Participants who initially screen fail may be determined eligible for a rescreen. These participants will only be counted under a given cohort as screened once. If they fail the rescreen, they will also only be counted as a screen fail once.

Participants may also meet study criteria, but may not be needed for a given cohort. These will be considered screen failures. These participants may subsequently be assigned as standby to replace participants who drop out of the cohort before dosing or rescreened for another cohort. Standby participants will be considered enrolled in a cohort. Participants who rescreen into another cohort within the same study part will be counted as screened for both cohorts, but only once for the study part overall. Participants who rescreen into another cohort in another study part will be counted as screened for both cohorts and study parts.

7.2 Protocol Deviations

Participant data will be reviewed regularly throughout the study according to the protocol deviation/non-compliance plan (PDNCP). All protocol deviations will be categorized and presented by participant in a data listing.

7.3 Inclusion and Exclusion Criteria

All recorded inclusion and exclusion criteria status will be presented by participant in a data listing. Each participant's inclusion or exclusion from each analysis population will also be presented in a data listing.

7.4 Demographics and Other Baseline Characteristics

All demographics (age, sex, race, and ethnicity) and baseline body measurements (height, weight, and BMI) will be summarized by study part and treatment (sequence for Part 1b), and presented by participant in a data listing. For Parts 1a and 2, summary tables will be presented by dose (study drug and placebo) and by study drug overall. For Part 1b, summary tables will be presented by sequence and overall.

Descriptive statistics (n, mean, SD, min, median, and max) will be calculated for continuous variables using the last results obtained prior to study drug administration. Frequency counts and percentages will be tabulated for categorical and binary variables.

7.5 Medical History

Medical history will be presented by participant in a data listing. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify medical history terms by system organ class (SOC) and preferred term (PT). Output data will include the MedDRA version used in the study.

7.6 Medications

Medications taken by participants before dosing will be documented as prior medications and medications taken by participants after dosing until the last study day will be documented as concomitant medications. Prior and concomitant medications will be presented by participant in a data listing. The latest version of the World Health Organization Global Drug Dictionary (WHO Drug) will be used to classify medications by anatomical therapeutic chemical (ATC) classification code (2^{nd} level) and preferred name. When 2^{nd} level classification code is not available, 1^{st} level classification will be used instead. Output data will include the WHO Drug version used in the study.

7.7 Drug, Cotinine, and Alcohol Screens

The results of drug, cotinine, and alcohol screens will be presented by participant in data listings.

7.8 Pregnancy Screening

Pregnancy tests will be administered to women of child-bearing potential. The follicle stimulating hormone (FSH) level will be tested in postmenopausal women. All results will be presented by participant in data listings.

7.9 Additional Screening Tests

The results of serology tests and COVID-19 tests will be presented by participant in data listings.

8. Pharmacokinetic (PK) Analyses

Phoenix® WinNonlin® software will be used for all PK analyses. Statistical analyses will be performed using SAS for Windows software.

All PK concentration and PK parameter analyses will be conducted on the PK population.

Plasma and urine concentrations of ATH-399A will be listed by participant and treatment and summarized by treatment and timepoint, using descriptive statistics, for the PK population. Individual and mean plasma concentration-versus-time profiles will be presented graphically for both linear and semi-log scale by treatment for the PK population. Descriptive statistics (n, arithmetic mean, SD, minimum, median, maximum, coefficient of variation [CV%], geometric mean and geometric CV%) of the plasma PK parameters will be provided by study part and treatment.

[redacted]

8.1 Data Presentation

PK concentrations will be listed and summarized by nominal sampling time and treatment. For all PK analyses, concentration values below the quantification limit (BLQ) that occur before the first measurable concentration of the study drug will be set to "0.00"; BLQ values that occur after first measurable concentration will be set to "missing". No imputations will be made on BLQ concentrations.

Invalid concentration values (due to bioanalytical or clinical issue) that occur prior to dosing will be replaced by "0.00". Invalid concentration values that occur after dosing will be set to "missing" for tabulation, graphical representation, and calculation purposes.

The actual clock time for dosing and the actual clock time for each PK sample collection will be recorded. For all sampling times, the actual sampling duration will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times, expressed in hours and rounded off to three decimal places, will be used to calculate the PK parameters. Pre-dose sampling times will always be reported as zero (0.000), regardless of the time difference. Nominal sampling times will be used in concentration tables and mean graphs, while actual sampling times for post-dose samples will be used in the individual graphs. Actual sampling times for post-dose samples also will be used for PK parameter derivation, unless the actual sampling time is missing, in which case, the nominal time will be used.

8.2 Pharmacokinetic (PK) Parameters

8.2.1 Part 1a (SAD)

For Part 1a, the following PK parameters will be calculated, whenever possible, by non-compartmental methods for ATH-399A:

Table 8.21-1: SAD Plasma PK Parameters

Parameter	Definition
AUC_{0-t}	area under the concentration-time curve from time zero until the last observed concentration
AUC_{0-inf}	area under the concentration-time curve from time zero to infinity (extrapolated)
C_{max}	maximum observed concentration
T_{max}	time when the maximum concentration is observed
$t_{1/2\ el}$	terminal elimination half-life
λ_z	terminal elimination rate constant

Table 8.21-2: SAD Urine PK Parameters

Parameter	Definition
Ae_{0-t}	Cumulative urinary excretion from time zero to time t, calculated as the sum of the amounts excreted over each collection interval
R_{max}	Maximal rate of urinary excretion, calculated by dividing the amount of drug excreted in each collection interval by the time over which it was collected
T_{Rmax}	Time of maximal urinary excretion, calculated as the midpoint of the collection interval during which R_{max} occurred
Cl_R	Renal clearance, calculated as Ae_{0-t} /AUC_{0-t}

8.2.2 Part 1b (Food Effect)

For Part 1b, the PK parameters presented in Table 8.2.2-1 will be calculated, whenever possible, by non-compartmental methods for ATH-399A.

Table 8.2.2-1: Food Effect Plasma PK Parameters

Parameter	Definition
AUC_{0-t}	Area under the concentration-time curve from time zero until the last observed concentration
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity (extrapolated)
C_{max}	Maximum observed concentration
T_{max}	Time when the maximum concentration is observed
$t_{1/2\ el}$	Terminal elimination half-life
λ_z	Terminal elimination rate constant

8.2.3 Part 2 (MAD)

For Part 2, the PK parameters presented in Table 8.2.3-1 will be calculated, whenever possible, by non-compartmental methods for ATH-399A:

Table 8.2.3-1: MAD Plasma PK Parameters

Parameter	Definition
AUC_{0-24}	Area under the concentration-time curve from time zero to 24-hours post-dose
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
C_{avg}	Average observed concentration
T_{max}	Time when the maximum concentration is observed
$AUC_{0-\tau}$	Area under the concentration-time curve, for one dosing interval (τ) at steady state. In this study, τ = 24 hours (AUC_{0-24})
AUC_{0-t}	Area under the concentration-time curve from time zero until the last observed concentration
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity (extrapolated)
$T_{max\ ss}$	Time when the maximum concentration is observed at steady-state

Parameter	Definition
$C_{max\ ss}$	Maximum observed concentration at steady state
$t_{1/2\ el}$	Terminal elimination half-life
λ_z	Terminal elimination rate constant
AR	Accumulation ratio

Note: λ_z will be the negative of the estimated slope of the linear regression of the ln-transformed concentration versus time profile in the terminal elimination phase. The Best-fit method, in Phoenix WinNonlin, will be used to calculate the λ_z from at least 3 concentration data points excluding the C_{max}. Rsq adjusted, the goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z must be ≥ 0.8. If the λ_z cannot be measured (e.g.: fewer than 3 non-zero concentrations in the terminal elimination phase or Rsq adjusted < 0.8), the PK parameters derived from λ_z ($AUC_{0\text{-}inf}$, $t_{½\ el}$, Cl/F, V_z/F, and $V_{z\ ss}$/F) will be presented in the listing with a flag and excluded from descriptive statistics. The timepoint where ln-linear λ_z calculation begins (λ_z Lower) and the actual sampling time of the last measurable concentration used to estimate the λ_z (λ_z Upper), as well as the Rsq adjusted for the ln-linear regression for the calculation of the elimination rate constant will be reported.

Note: If the Residual area is more than 20%, the individual result should be flagged as well as all parameters depending on $AUC_{0\text{-}inf}$. All the derived parameters (i.e., $AUC_{0\text{-}inf}$, $t_{½\ el}$, Cl/F, and V_z/F) will be flagged accordingly.

For Part 2, plasma concentration observed before treatment administrations (C_{trough}) and during repeated dosing (Day 9, Day 10, Day 11, and Day 12) will also be presented.

Area under the concentration-time curve (AUC) parameters will be calculated using the linear up log down trapezoidal method, where the linear trapezoidal rule is used any time the concentration data are increasing and the logarithmic trapezoidal rule is used any time that the concentration data are decreasing.

8.3 Assessment of Dose Proportionality

For Part 1a, the power model approach will be performed on $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} data to assess the dose proportionality. For Part 2, the power model approach will be performed on C_{max}, $AUC_{0\text{-}\tau}$, $C_{max\ ss}$, $C_{min\ ss}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ data to assess the dose proportionality.

The power model will include the PK parameter as the response variable and dose (mg) as the explanatory variable. For this model, the variable dose will be treated as a continuous variable. All treatments will be considered for the analysis (a minimum of three different treatments are required in order to conduct the analysis).

The form of the model is as follows:

PK Parameter = $e^{\alpha} \times \text{Dose}^{\beta} \times e^{\epsilon}$, where Dose ≥ 0, and e^{ϵ} represents the associated error.

Thus, perfect dose proportionality is met when $\beta=1$ (ignoring error). This becomes a linear relationship following a natural-log transformation, to which a linear regression will be fit by ordinary least squares (OLS):

$\ln(\text{PK Parameter}) = \alpha + \beta \times \ln(\text{Dose}) + \epsilon$ where Dose > 0, and ϵ represents the associated error.

The estimate of β together with a 90% confidence interval (CI) will be provided (for each PK parameter model), and this will be used to quantify dose proportionality. The following criterion may be used for exploratory dose proportionality evaluations: If the (two-sided) 90% CI for β is wholly contained within the interval, [1+ln(0.5)/ln(ρ), 1+ln(2)/ln(ρ)], then dose proportionality is suggested across the investigated dose range.[a] Here, ρ is defined as the ratio of the highest to lowest dose. This interval criterion will be reported along with the corresponding 90% CI estimate for β (presented to three decimal places).

The SAS code for the analysis model will follow the format below (using the Mixed Procedure to fit the linear regression). The input variables, datasets, and labels are depicted in italicized red text and have been given generic names.

```
proc mixed data=dataset order=data;
  model ln_pk_parameter = ln_dose / solution;
  estimate 'Beta Estimate' ln_dose 1 / cl alpha=0.1;
  ods output estimates =estimates;
run;
```

The PK parameter values estimated from the power model will be plotted against dose. This plot will also include individual participant values and mean ± SD (separately by treatment or dose level).

For Part 1a, an analysis of variance (ANOVA) will be performed on the untransformed T_{max}, $t_{1/2\ el}$, and λ_z data. For Part 2, an ANOVA will also be performed on the untransformed T_{max}, $T_{max\ ss}$, $t_{1/2\ el}$, and λ_z data. The SAS output for each model will be provided in listings.

The SAS code for the analysis model will follow the format below (using the Mixed Procedure to fit the linear regression). The input variables, datasets, and labels are depicted in italicized red text and have been given generic names.

```
proc mixed data=dataset order=data;
  class dose;
  model pk_parameter = dose;
  lsmeans dose;
  ods output estimates =estimates;
run;
```

8.4 Attainment of Steady State

For Part 2, a repeated measures analysis will be carried out on natural log-transformed pre-dose concentrations (Days 9 to 12) to determine attainment of steady-state for ATH-399A. The approach is based on the comparison of natural log-transformed trough concentration values. The response variable will be the natural log-transformed pre-dose concentration and the model will include dose, visit, and dose-by-visit interaction as fixed effects and participant within dose as repeated effect. The model will be fit using restricted maximum likelihood and the Kenward-Roger degrees of freedom approximation.[b] An unstructured covariance matrix will be used; if the unstructured covariance matrix fails to converge, simpler covariance matrix structures such as compound symmetry will be considered.[c]

The SAS code will follow the format below. The input variables, datasets, and labels are depicted in italicized red text and have been given generic names.

```
proc mixed data=dataset;
      class dose visit participant;
      model ln_ctrough = dose visit dose*visit / ddfm=KR;
      repeated / type=un subject=participant(dose);
      lsmeans dose*visit;
run;
```

Contrasts will be tested between each dosing timepoint and the pooled mean over all outstanding dosing timepoints (i.e., Day 9 pre-dose value versus the average pre-dose value of Days 10 through 12, Day 10 pre-dose value versus the average pre-dose value of Days 11 through 12, Day 11 pre-dose value versus the pre-dose value of Day 12).

The first non-significant comparison will be concluded to be the dose number (Day x) at which steady state concentrations are attained. If the dose*time effect is found statistically significant, these contrasts will be done separately for each dose level. The p-value for difference of least-squares means (LSM) will be provided.

8.5 Analysis of Accumulation Ratio

For Part 2, an ANOVA model will be used to explore the degree of accumulation after repeated dosing by comparing natural log-transformed AUC on Day 12 ($AUC_{0-\tau}$) with Day 1 (AUC_{0-24}), natural log-transformed C_{max} on Day 12 ($C_{max\ ss}$) with Day 1 (C_{max}), and also to compare untransformed T_{max} on Day 12 ($T_{max\ ss}$) with Day 1 (T_{max}). For each PK parameter, statistical comparisons will be performed across the visits (Day 1 and 12). The estimated ratio (Day 12/Day 1) of model-adjusted geometric means will be used to perform this comparison for AUC and C_{max}.

To estimate the geometric mean ratio, a linear mixed effects model will be fit to the data. The response variable will be the natural log-transformed PK parameter, and the model will include dose, visit, and dose-by-visit interaction as fixed effects and participant within dose as random effect. The model will be fit using restricted maximum likelihood and the Kenward-Roger degrees of freedom approximation.[b]

From this model, the difference in means will be estimated for Day 12 versus Day 1 per dose, accompanied by a corresponding (two-sided) 90% CI. The point estimate and confidence endpoints will be exponentiated using base *e* in order to obtain a point and interval estimate for the ratio of geometric means. These transformed CIs will indicate the degree of accumulation across Day 12 versus Day 1 at each dose, and for each PK parameter. Furthermore, the p-values of overall F tests for dose, visit, and dose-by-visit interaction effects will be reported to four decimal places.

The SAS code to fit the model will follow the format below (using the Mixed Procedure). The input variables, datasets, and labels are depicted in italicized red text and have been given generic names.

```
proc mixed data= dataset order= data;
      class participant dose visit;
      model ln_PK_parameter = dose|visit / ddfm= kr solution;
      random participant(dose);
      estimate 'TBD mg Day 12 vs Day 1' visit -1 1
                  dose*visit  -1 1
                                          0 0
                                          0 0 / cl alpha= 0.1;
      /* etc… */
      ods output estimates= estimates tests3= tests;
```

run;

8.6 Assessment of Food Effect

To assess the food effect on ATH-399A exposure in Part 1b, the values of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} calculated for the two diet regimens (fed and fasted) will be evaluated by ANOVA, with terms for sequence, period, and treatment as fixed effects and participant within sequence as a random effect. The exposure measurements (AUCs and C_{max}) will be natural log-transformed prior to analysis. The model will be fitted using restricted maximum likelihood and the Kenward-Roger degrees of freedom approximation.**Error! Bookmark not defined.**

The 90% CI for the ratio of the geometric means for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} obtained between the fed and fasted conditions will be calculated. The absence of a food effect will be concluded when the 90% CI for the ratio of means (geometric means based on log transformed data) of fed and fasted conditions fall within 80% - 125% for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}.

The SAS code for the analysis model for ANOVA will follow the format given below (using the Mixed Procedure to fit the linear regression). The input variables, datasets, and labels are depicted in italicized red text and have been given generic names.

```
proc mixed data= dataset;
      class participant treatment sequence period;
      model var = treatment sequence period / solution ddfm=KR;
      random participant(sequence);
      lsmeans treatment / cl alpha=0.1;
      estimate 'fed vs fasting' treatment 1 -1 / cl alpha=0.1;
      ods output estimates = estimates covparms = covparms;
run;
```

Intra- and inter-participant CV% will also be estimated.

9. Pharmacodynamic (PD) Analyses

There will be no PD analyses for this study.

10. Safety

Safety and tolerability analysis will be performed for all participants in the safety population. No inferential statistical analysis of safety data is planned. For Parts 1a and 2, summary tables will be presented by dose (study drug and placebo) and by study drug overall. For Part 1b, summary tables will be presented by treatment and overall.

10.1 Administration

Study drug administration will be listed by participant. A listing will also be provided with first participant enrolled date, first participant first dose date, last participant first dose date, first participant exit date, last participant last dose date, and last participant exit date, for each study part and overall.

10.2 Adverse Events (AEs)

AEs will be coded using the latest version of the MedDRA. Output data will include the MedDRA version used in the study. AEs will be grouped by SOC and PT and summarized by actual treatment. The summary tables will present the number and percentage of total participants and number of events by SOC and by PT.

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), defined as AEs that commence on or after the time of first study drug administration. Any AE that first occurs pre-dose but worsens in intensity after the first study drug administration will also be considered a TEAE. AEs without an onset date or time, or AEs with an onset date of the date of first study drug administration but without an onset time, will be defined as treatment-emergent, unless an incomplete date (e.g., month and year) clearly indicates that the event started prior to administration of first study drug, or the AE stop date indicates that the event started and stopped prior to administration of first study drug.

TEAEs will be attributed to the last treatment administered. TEAEs continuing after dosing in the next treatment period will be evaluated on a case-by-case basis.

The number and percentage of participants experiencing TEAEs and the number of TEAEs will be tabulated. Participants who experience the same TEAE (in terms of MedDRA PT) more than once will only be counted once per treatment or period, however, the total number of events will be counted per category. This also applies to sub-categories displayed in the summaries.

The following summaries will be presented:

- Overall summary of TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and intensity
- TEAEs by SOC, PT, and relationship to study drug
- Serious TEAEs by SOC and PT

The Investigator will make an assessment of intensity for each AE and SAE reported during the study per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grading criteria:

- Grade 1: Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- Grade 2: Moderate, minimal, local, or non-invasive treatment indicated; limiting age-appropriate instrumental activities of daily life.
- Grade 3: Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily life.
- Grade 4: Life-threatening consequences; urgent treatment indicated.
- Grade 5: Death related to AE.

The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. All AEs will be assigned a causality attribution as follows:

- Related: There is a reasonable likelihood of a causal relation between study drug and the AE.
- Not related: There is reasonable certainty that the cause of the AE is another etiology such as concomitant medication, disease progressions or other medical conditions and not related to study treatment.

All AEs will be listed. The following listings will be included: Non-TEAEs, TEAEs, and serious AEs.

10.3 Laboratory Evaluations

Laboratory data, including hematology, biochemistry, coagulation, urinalysis, and thyroid panel, will be listed by participant and summarized for each visit/timepoint by treatment. Observed values and changes from baseline will be presented.

In addition, a shift table representing the categorical change (low, normal, high) from baseline to each post baseline visit/timepoint will be presented.

Abnormal results will be flagged in the listings.

If more than one clinical laboratory is used, a formula that takes into consideration the relative normal ranges of each test of the laboratories will be utilized to normalize these data.[d] The conversion formula used for each test will depend on the typical distribution of the normal range for the test.[e] Prior to applying these formulas, units will be adjusted, as necessary. The laboratory which has the most results for each parameter will be considered primary in the formulas.

10.4 Vital Signs

Vital sign measurements (temperature, blood pressure, pulse rate, and respiratory rate) will be listed by participant and summarized for each visit/timepoint by treatment. Observed values and changes from baseline will also be presented.

In addition, a shift table representing the categorical change (normal, abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline timepoint will be presented.

Abnormal results will be flagged in the listings.

10.5 Electrocardiograms (ECGs)

Electrocardiogram (ECG) values (ventricular heart rate and the PR, RR, QRS, QT, and corrected QT interval using Fridericia's formula [QTcF] intervals) will be listed by participant and summarized for each visit/timepoint by treatment. Observed values and changes from baseline will be presented.

A shift table representing the categorical change in overall interpretation (normal, abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline timepoint will be presented.

Abnormal results will be flagged in the listings.

A frequency table with a QTcF interval reading change from triplicate baseline (average) to any single QTcF interval reading greater than 20 ms, 40 ms, or 60 ms will be presented. Participants will only be counted once in each category.

10.6 12-Lead Telemetry

12-lead telemetry will be conducted for evaluation of cardiac arrhythmias. Abnormal results will be listed by participant.

10.7 Physical Examination

The results of physical and neurological examinations will be listed by participant. Abnormal results will be flagged in the listings.

10.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

The results of C-SSRS assessments will be listed by participant, and the change in responses to questions on suicidal ideation and behavior will be summarized by treatment.

11. Changes from Analysis Planned in the Protocol

No changes were made to planned analyses.

12. Programming Considerations

All TFLs and statistical analyses will be generated using SAS for Windows, release 9.4 (SAS Institute Inc., Cary, NC, USA) software in accordance with Food and Drug Administration (FDA) guidelines. Phoenix WinNonlin, version 8.3.4 (Certara USA, Inc., Princeton, NJ) will be used for all PK analyses. This software was validated by [redacted] in compliance with US 21 CFR Part 11 regulation.

12.1 General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in rich text format that can be manipulated in MS Word.
- Numbering of TFLs will follow International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E3.[f]

12.2 Table, Listing, and Figure Format

12.2.1 General

- TFLs will be produced in landscape format. The orientation may be changed to portrait, as necessary to allow additional rows to be presented.
- TFLs will be produced using the Times New Roman font, size 10. The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all four sides.
- Unless otherwise specified, TFLs will be in black and white (no color).
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used; see below.
- Standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- TFLs will be produced using sentence case, unless otherwise specified.

12.2.2 Headers and Footers

- Times New Roman font, size 10 will be used for TFL headers and footers.
- All outputs will have the following at the top of each page: HanAll Pharmaceutical International Inc. Protocol HL192-PD-CA-P101.
- All outputs will have page x of y at the top or bottom right corner of each page. TFLs are individually paginated in relation to total length (i.e., the page number appears sequentially as page x of y, where y is the total number of pages in the output).
- The date and time the output was generated will appear, along with the program name, at the bottom of each page.

12.2.3 Display Titles

Each display title includes the appropriate designation (“Table”, “Figure”, or “Listing”) and a numeral, along with a descriptive name (e.g., Table 14.1-1 Participant Enrollment and Disposition). ICH E3 numbering is strongly recommended, but Sponsor preferences are obtained for final determination. Display titles are left aligned, single spaced, and presented in title case. A solid line spanning the margins will separate display titles from column headings.

12.2.4 Column and Row Headings

- Column and row headings are presented in title case, with the exception of complete sentences, which will be presented in sentence case.

- In efficacy tables, the variable (or characteristic) column will be on the far left, followed by the group columns and overall column (if applicable). P-values may be presented under the overall column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- Column and row headings will include "Unit" for numeric variables, as appropriate.
- Column and row headings will include the number of participants in the analysis population for each group, presented as (N=xx). This is different from the 'n' used in descriptive statistics, which represents the number of observations.
- The order of treatments in the tables and listings will be placebo first, in placebo-controlled studies, and active comparators first, in active comparator trials, with "overall" (if applicable) last.

12.2.5 Body of the Data Display

12.2.5.1 General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left aligned.
- Whole numbers (e.g., counts) are right aligned.

12.2.5.2 Table Conventions

- Units will be included, where available.
- If the categories of a parameter are ordered, all categories between the maximum and minimum category are presented in the table, even if n=0 for all groups in a category between the minimum and maximum level for that parameter. See the example for the frequency distribution for symptom severity below. If percentages are presented in these tables, 0% will not be presented, therefore, counts of zero will be presented as "0", not "0 (0%)".

Severity Rating	N
Severe	0
Moderate	8
Mild	3

- Where the categories are not ordered (e.g., Reason for Discontinuation), only those categories for which there is at least one participant represented will be included.
- An "Unknown" or "Missing" category will be added to each parameter for which information is unavailable for one or more participants.
- Probability values (p-values) are presented in the format: 0.xxxx, where xxxx is the value. If the p-value is less than 0.0001, it will be presented as "<0.0001." If the p-value is >0.999, it will be presented as ">0.999."

- Percentage values are presented in parentheses with no spaces, one space after the count [e.g., 7 (12.8%), 13 (5.4%)]. Unless otherwise noted, for all percentages, the denominator will be the number of participants in the analysis population for the group that has an observation. Percentages after zero counts are not displayed, and percentages equating to 100% are presented as "100%" (without decimal places).
- Unless otherwise noted, tabular displays of data for medical history, prior/concomitant medications, and AEs data are presented in alphabetical order.
- The percentage of participants is typically calculated as a proportion of the number of participants assessed in the relevant group (or overall) for the analysis population presented; however, careful consideration is required in many instances, due to the complicated nature of selecting the denominator. Details of this will be presented in footnotes or programming notes.
- In categorical summaries where a participant can be included in more than one category, a footnote or programming note will specify whether the participant is included in the summary statistics for all relevant categories or just one category and the criteria for selecting the category.
- Where a category with a subheading (such as SOC) must be split over more than one page, present the subheading followed by "(cont.)" at the top of each subsequent page. The overall summary statistics for the subheading will only be presented on the first relevant page.

12.2.5.3 Listing Conventions

- Unless otherwise noted, listings will be sorted for presentation in order of phase, treatment, and participant number.
- Dates are printed in SAS DATE9.format (e.g., "ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on participant listings as dashes (e.g.,--JUL2000). Dates that are missing because they are not applicable for the participant are presented as "N/A", unless otherwise specified.
- All observed time values are presented using a 24-hour clock HH:MM:SS or HH:MM format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included, where available.

12.2.5.4 Figure Conventions

- For safety figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values will be displayed on the Y-axis, unless otherwise specified.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- Units will be included, where available.

12.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left aligned, with single spacing, immediately below the solid line beneath the data display.
- Informational footnotes begin with “Note:”. Reference footnotes begin with a reference number or letter (e.g., 1, 2, 3 or a, b, c).
- Each new footnote starts on a new line, where possible.
- Participant-specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or data listing. If more than six lines of footnotes are planned, a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

13. Quality Control

SAS programs are developed to produce outputs such as analysis data sets, summary tables, data listings, figures, and statistical analyses. These are developed and undergo quality control in accordance with the latest versions of [redacted].

14. Reference List

[a]Hummel, J., McKendrick, S., Brindley, C., & French, R. (2009). Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion. Pharmaceutical Statistics, 8(1), 38-49. doi:10.1002/pst.326

[b] Kenward, M. G., & Roger, J. H. (1997). Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics, 53(3), 983-997. doi:10.2307/2533558

[c] Kincaid, C., COMSYS Information Technology Services, Inc., Portage, MI. 198-30: Guidelines for Selecting the Covariance Structure in Mixed Model Analysis (sas.com). https://support.sas.com/resources/papers/proceedings/proceedings/sugi30/198-30.pdf

[d]Chuang-Stein, C., PhD, Research Support Biostatistics Unit, 9164–32–2, The Upjohn Company, Kalamazoo, Michigan. (1992). Summarizing Laboratory Data with Different Reference Ranges in Multi-Center Clinical Trials. Drug Information Journal, 26(1), 77-84. doi:10.1177/009286159202600108

[e]Karvanen, J., Signal Processing Laboratory, Helsinki University of Technology, Helsinki, Finland. (2003). The Statistical Basis of Laboratory Data Normalization. Drug Information Journal, 37(1), 101-107. doi:10.1177/009286150303700112

[f]International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (1996). Guideline for Industry, Structure and Content of Clinical Study Reports (ICH E3).

[redacted]

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