Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, 3-Period, Incomplete Block Design Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-954 in Healthy Adult Participants.

NCT Number: NCT03870555

SAP Approve Date: 18 March 2019

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-954-1009
CELERION STUDY NUMBER: CA27260

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, 3-Period, Incomplete Block Design Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-954 in Healthy Adult Participants

Version: Final

Date: 18 March 2019

Prepared by:

PPD

Based on:

Protocol Dated: 07 February 2019
Protocol Amendment 1 Dated: 08 March 2019

1.1 Approval Signatures

Study Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, 3-Period, Incomplete Block Design Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-954 in Healthy Adult Participants

PPD

Date

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

Ae	Amount of drug excreted in urine
AE	adverse event
AUC	area under the curve
AUC0-24	area under the plasma concentration-time curve from time 0 to 24 hours postdose
AUC0-inf	area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC0-t	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
BLQ	below the limit of quantitation
BMI	body mass index
Ceoi	Concentration at the end of infusion
CI	confidence interval
CL	total plasma clearance of drug after IV administration (parent only)
CLR	renal clearance calculated as CLR = Ae/AUC where both Ae and AUC are determined over matched time interval
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CRU	clinical research unit
CS	clinically significant
CSR	clinical study report
CV	coefficient of variation
DMP	Data Management Plan
ECG	electrocardiogram
eCRF	electronic case report form
fe	fraction of IV dose excreted in urine
Geom CV	geometric coefficient of variation
Geom Mean	geometric mean
ICF	informed consent form
ICH	International Conference on Harmonisation
λz	Terminal disposition phase rate constant
ln	natural log
LSM	least-square means
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities

PD	pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetics
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
t½	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	tables, figures and listings
Tmax	time of maximum observed plasma concentration
Vz	volume of distribution during the terminal elimination phase after IV administration (parent only)
WHO	World Health Organisation

Note: The words 'subject' and 'participant' are used interchangeably in this statistical analysis plan.

4.0 OBJECTIVES

4.1 Hypothesis

TAK-954 1 and 2 mg by IV infusion will be sufficiently safe and well-tolerated to permit use for clinical investigation.

4.2 Primary Objectives

- To evaluate the safety and tolerability of single ascending IV doses of TAK-954.
- To evaluate the PK of single ascending IV doses of TAK-954.

4.3 Secondary Objective

To evaluate the PD effect of single ascending IV doses of TAK-954 on the GI motility in healthy participants while in confinement.

4.4 Exploratory Objectives

CCI [redacted]

4.5 Study Design

This is a double-blind, placebo-controlled, single ascending IV dose, 3-period, incomplete block design study to investigate the safety, tolerability and PK, and PD of TAK-954 at higher IV doses than those previously studied. In this Phase 1 study, healthy adult participants will attend a screening visit within 28 days prior to the first dose.

Participants will be randomized to one of 3 treatment sequences as detailed in the Table 4.a below. In each sequence, each participant will receive 2 doses of the active drug (out of 3 evaluated dose levels) in an ascending order and 1 dose of placebo. A sample size of 6 participants is proposed based on empirical considerations.

Table 4.a Sequence Groups for the Planned Doses of TAK-954 and Placebo

	Period 1		Period 2		Period 3	
Sequence	**Day 1 (Lead-in)**	**Day 2 (Treatment)**	**Day 1 (Lead-in)**	**Day 2 (Treatment)**	**Day 1 (Lead-in)**	**Day 2 (Treatment)**
Sequence 1 (n=2)	Placebo	Placebo	Lead-in TAK-954	Treatment B	Lead-in TAK-954	Treatment C
Sequence 2 (n=2)	Lead-in TAK-954	Treatment A	Placebo	Placebo	Lead-in TAK-954	Treatment C
Sequence 3 (n=2)	Lead-in TAK-954	Treatment A	Lead-in TAK-954	Treatment B	Placebo	Placebo

Lead-in TAK-954: 0.1 mg (100 mL x 0.001 mg/mL) TAK-954 IV infusion.
Treatment A: 0.5 mg (100 mL x 0.005 mg/mL) TAK-954 IV infusion.
Treatment B: 1 mg (100 mL x 0.01 mg/mL) TAK-954 IV infusion.
Treatment C: 2 mg (100 mL x 0.02 mg/mL) TAK-954 IV infusion.
Placebo: 100 mL.

On Day 1 of each period, each participant will receive a lead-in dose of 0.1 mg TAK-954 (if scheduled to receive a dose of active drug on Day 2 of that period as per the randomization schedule) or placebo (if scheduled to receive a placebo on Day 2 of that period as per the randomization scheme) as a 60 min IV infusion. On Day 2 of each period, participants will receive either a single dose of 0.5 mg, 1 mg, or 2 mg TAK-954 or placebo as a 60-minute infusion as per the randomization schedule.

The starting dose of TAK-954 on Day 2 (Period 1) will be 0.5 mg, which is the highest dose previously used in a completed study following IV administration. Subsequent doses will be chosen based on emerging data; the currently proposed doses are 1 mg and 2 mg. Dose escalation to the next dose level (ie, next period) will not take place until the Investigator and the Sponsor have determined that adequate safety/tolerability from the previous period has been demonstrated to permit proceeding to the next dose level. Additional cohorts (approximately 6 participants per cohort) may be enrolled if it is deemed appropriate by the Investigator and the Sponsor to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort. The last dose in the previous period and the first dose of the next period will be separated by a minimum of 16 days.

In each treatment period, participants will be housed on Day -1, at the time indicated by the clinical research unit (CRU) until after the 36-hour blood draw and/or study procedures on Day 3. At all times, a participant may be required to remain at the CRU for longer at the discretion of the Investigator or designee. As per site preference, participants may be confined throughout the washout period.

Day 16 of Period 3 will also be considered as the follow-up visit for participants who complete the study. All participants who received at least 1 dose of study drug or placebo and withdraw from the study early will return for a follow-up visit, 10-14 days after the last dose administration.

When confined to the CRU, water will be allowed *ad libitum*. Participants will fast overnight for at least 8 hours prior to each dose and will remain fasted until at least 4 hours postdose. When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in CRU, participants will be required to fast from all food and drink except water between meals and snacks. Participants will remain seated or semi-reclined for the duration of the infusion and for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures. Participants will then resume normal activity.

Blood samples for assessment of plasma TAK-954 concentrations will be collected at selected times from predose through to 9 hours after each lead-in dose (Day 1). Blood samples for assessment of plasma TAK-954 concentrations will also be collected at selected times from predose through 336 hours (Day 16) after each Day 2 dose. Urine samples for assessment of urinary TAK-954 concentrations will also be collected at selected times from predose through 24 hours (Day 2) after each lead-in Day 1 dose and from predose through 36 hours (Day 3) after each Day 2 dose. CCI [redacted] The time to first stool will be recorded after dosing on Day 1 until prior to Day 2 dosing and postdose Day 2. The number of stools per day and stool form (Bristol Stool Form Scale) will be recorded after dosing on Day 1 until prior to dosing on Day 2 and for 36 hours postdose on Day 2.

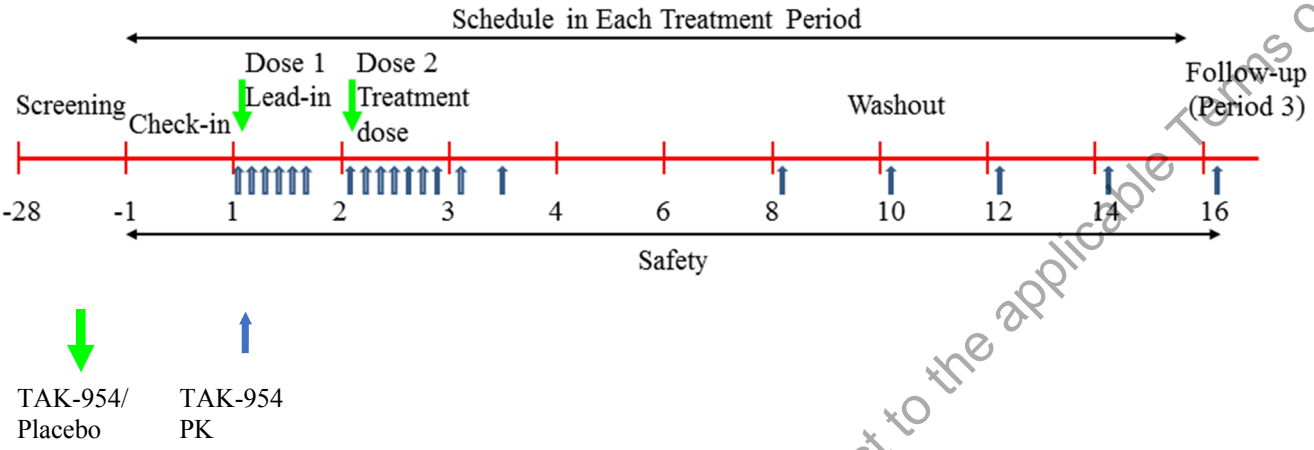
A schematic of the study design is included as Figure 4.a and Figure 4.b.

Figure 4.a Study Schematic

Pretreatment	**Treatment Periods 1-3**						
Screening	**Check-in and Predose Assessments**	**Lead-in Dose and Study Assessments**	**Treatment Dosing and Study Assessments**	**Safety and PK Assessments**		**Study Exit (a)**	**Follow Up (b)**
Within 28 days prior to first dosing	Day -1	Day 1	Day 2	Day 3	Days 4-16	Day 16 of Treatment Period 3	14 days after last dose
Outpatient Visit	◄- - - - - - - - Confinement (a) (c) - - - - - - - - ►				Outpatient Visits (c)		

(a) At all times, a participant may be required to remain at the clinical research unit for longer at the discretion of the Investigator or designee.
(b) Day 16 of Period 3 will also be considered as the follow-up visit for participants who complete the study. All participants who received at least 1 dose of study drug or placebo and withdraw from the study early will return for a follow-up visit 10-14 days after the last dose administration.
(c) Participants will start the confinement on Day -1 and be released from confinement after Day 3 study assessments are complete and will return to the study site for subsequent safety and PK assessments as per the scheduled of study procedures. There will be a washout period of at least 16 days between the last dose in the previous period and the first dose of the next period.

Figure 4.b Schematic of Study Design



Safety will be assessed by monitoring for AEs, vital signs, orthostatic vital signs, ECGs, safety laboratory assessments, and physical examinations throughout each dosing period.

A decision to proceed to the next higher dose administration (next period) will be made by the Investigator and Sponsor representative(s) who will review all pertinent blinded safety/tolerability (eg, physical examinations, vital signs assessments, orthostatic vital signs, 12-lead ECGs, clinical laboratory tests, and AEs) data through at least 10 days following Day 2 dosing in each period for at least 75% of participants from the current period and those from all previous periods, as applicable.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoints of the study are the following safety parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period:

- Treatment-emergent adverse event (TEAE) assessments.
- Vital signs and orthostatic vital signs.
- 12-lead ECG.
- Clinical laboratory testing (hematology, serum chemistry, and urinalysis).

The following plasma PK parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period:

- AUC0-t: Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
- AUC0-inf: Area under the plasma concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.

- Ceoi: Observed plasma concentration at the end of infusion.
- CL: Total clearance after intravenous administration, calculated using the observed value of the last quantifiable concentration.
- Vz: Volume of distribution during the terminal disposition phase after intravenous administration, calculated using the observed value of the last quantifiable concentration.

The following urine PK parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period:

- Ae: Amount of unchanged drug excreted in urine.
- Fe: Fraction of IV dose excreted in the urine.
- CLR: Renal clearance.

5.2 Secondary Endpoints

The secondary endpoints of the study are the following PD parameters derived after a single dose of TAK-954 on Day 2 of each treatment period:

- Time to first stool.
- Number of stools per day.
- Stool from (Bristol Stool Form Scale).

5.3 Exploratory Endpoints

CCI

[redacted]

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The sample size of 6 healthy male and female participants is empirical, was selected without statistical considerations, and is deemed adequate to meet the study objectives. Additional cohorts (approximately 6 participants per cohort) may be enrolled if it is deemed appropriate by the Investigator and the Sponsor to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All PK analyses will be conducted using Phoenix® WinNonlin® Version 7.0, or higher. All statistical analyses will be conducted using SAS® Version 9.3, or higher. All data recorded on the CRF will be listed by participant. All tables, figures and listings (TFLs) shells and numbering list specified in the Clinical Pharmacology Analysis Plan (CPAP) will be included.

The concentration data will be used as reported by the respective bioanalytical groups without rounding for all analyses. Arithmetic mean (mean), median, and geometric mean (Geom Mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values. Minimum and maximum values will be presented to the same precision as the individual values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (Geom CV%) will be presented to 1 decimal place.

Dose proportionality will be assessed graphically.

Concentration values below the limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK parameters, unless they are obvious outliers (eg, BLQ value between 2 measurable values), in which case they will be treated as missing. In the tables presenting summary statistics of concentration-time series, the total number of values (n) and the number of values that are above the level of quantification (LOQ) will be presented to allow appropriate interpretation of the data. A statement similar as "all values reported BLQ have been replaced with zero" will be included as footnote to the appropriate figures.

For the calculation of PK parameters, if actual times are missing, nominal times will be used instead.

A participant's PK parameter data will be included in the listings but excluded from the descriptive statistics and dose proportionality plots if one or more of the following criteria are met:

- A predose (0 hr) concentration is greater than 5% of that participant's maximum concentration value in that period.
- A participant did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist).
- A participant deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist).

The details on PK parameter calculations will be outlined in the CPAP including specifics on the following:

- Insufficient data to determine a reliable t½ value and other terminal disposition phase rate constant dependent parameters.
- PK parameters presented by treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables.
- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables.
- Concentration data file used for PK analysis.
- PK parameter WinNonlin® output file used to generate the TFLs.
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures.
- Individual concentration-time figures presented in Appendix 16.2.6.

For PD data, descriptive statistics (mean, SD, minimum, median, and maximum) will be provided by treatment and time point for continuous data. Listing will be provided for categorical data.

For demographic data where appropriate, variables will be summarized descriptively by treatment sequence and overall. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment sequence, and overall, where applicable. The denominator for the proportion will be based on the number of participants who provided non missing responses to the categorical variable. For continuous variables, the number of participants with non-missing values, mean, SD, minimum, median, and maximum values will be tabulated.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Day 1 (lead-in) for each period is defined as the date on which a participant is administered their first dose of the study drug(s) in each period. Other study days are defined relative to Day 1 with Day -1 being the day prior to Day 1 of each period. Study day prior to the first dose of each treatment will be calculated as: date of assessment/event - date of treatment (Day 1); study day on or after the date of first dose will be calculated as: date of assessment/event - date of treatment (Day 1) + 1.

7.2 Analysis Sets

Safety Set:

All participants who received at least one dose of the study drug(s) (active or placebo) will be included in the safety set. Participants in this analysis set will be used for demographic, baseline characteristics and safety summaries.

PK Set:

Samples from all participants will be assayed even if the participants do not complete the study. All participants who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to active treatment, availability of measurements and absence of major protocol violations) will be included in the PK statistical summaries. In terms of criteria for evaluable participants, please see CPAP.

PD Set:

All participants who received at least one dose of the study drug(s) (active or placebo) and have at completed at least 1 PD sampling period and/or have at least 1 evaluable parameter will be included in the PD summaries.

7.3 Disposition of Subjects

Disposition of participants (number of participants dosed, completed the study, discontinued from the study, and reason(s) for discontinuation) will be summarized for each treatment sequence and overall. Study completion status, including reason for discontinuation, will also be listed by participant.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment sequence and overall. Summary statistics (number of participants [n], mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [calculated from the date of signed Informed Consent Form [ICF], weight, height and body mass index [BMI]) and the number and percentage of participants within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI collected at screening will be used in the baseline

summaries. Demographics data will also be listed as recorded on the CRF, including the date of informed consent.

7.5 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include any significant conditions or diseases relevant to the disease under study that resolved at or before signing the ICF. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each participant's medical history and concurrent medical conditions will be listed. Any medical condition started after taking the study drug will be classified as an adverse event. The medical history listing will include whether the event was medical or surgical, the body system or organ class involved, start date (if known) and end date or whether the condition was ongoing, and a description of the condition or event. There will be no statistical analysis of medical history.

7.6 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 28 days prior to signing the ICF. Concomitant medication includes any medication other than study drug taken at any time between time of signing the ICF through the end of the study (including follow-up visit). All medication history and concomitant medications recorded during the study will be coded with the World Health Organization (WHO) Dictionary, as described in the Data Management Plan (DMP), and listed. If appropriate, the listing will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time, or whether it continued after study completion, and indication for use.

7.7 Study Drug Exposure and Compliance

Not applicable.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Blood and urine samples for PK analysis of TAK-954 will be collected as specified in Table 7.a following administration of different treatments on Days 1 and 2 of each period under fasted conditions.

Table 7.a Collection of Blood and Urine Samples for Pharmacokinetic Analysis

Sample Type	Dosing Day (Periods 1, 2 and 3)	Time (hours)
Plasma	1	Predose and at 1, 1.083, 1.25, 3, and 9 hours postdose.
Plasma	2	Predose and at 0.5, 1, 2, 4, 6, 12, 24, 36, 144, 192, 240, 288, and 336 hours postdose.
Urine	1	Predose (spot sample), 0-12 and 12-24 hours
Urine	2	0-12, 12-24, and 24-36 hours

The actual date and time of sample collection will be recorded on the source document and electronic case report form (eCRF).

Placebo data will be listed (if provided) and will not be included in any summary analyses.

The PK parameters of TAK-954 will be listed in the CPAP for this study and will be determined from the concentration-time profiles for participants in the PK set using a noncompartmental analysis method. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If actual sample times are missing, nominal times may be used.

Concentrations will be listed and summarized descriptively by PK sampling time. Summary will be done by treatment using the summary statistics listed in the CPAP. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive summary statistics. Individual participant and arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear (with and without SD) and semi-log scales. For summary statistics and arithmetic mean plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used.

PK parameters will be summarized descriptively by treatment using the summary statistics listed in the CPAP. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from the descriptive summary statistics. Dose proportionality will be assessed graphically by plotting the natural-log (ln)-transformed PK parameters (AUC0-t, AUC0-inf, AUC0-24, and Ceoi) against the ln-transformed dose levels. Excluded parameters will not be included in the dose proportionality plots.

No inferential statistical analysis will be performed to assess period or sequence effects.

7.9.2 Pharmacodynamic Analysis

Stool samples for PD analysis of TAK-954 will be collected as specified in Table 7.b following administration of different treatments on Days 1 and 2 of each period under fasted conditions.

Table 7.b Collection of Stool Samples for Pharmacodynamic Analysis

Sample Type	Dosing Day (Periods 1, 2 and 3)	Time (hours)
Stool	1	Day 1 postdose through Day 2 predose
Stool	2	Day 2 dosing through 36 hours postdose.

The time to first stool will be recorded after dosing on Day 1 until prior to Day 2 dosing and postdose Day 2. The number of stools per day and stool form (Bristol Stool Form Scale) will be recorded after dosing on Day 1 until prior to dosing on Day 2 and for 36 hours postdose on Day 2. Descriptive statistics will be provided for time to first stool and number of stools as recorded in the CRF by treatment and dosing day. Stool form type will be listed by subject and time point.

Additional analyses may be performed, if deemed appropriate.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and type of TEAEs, changes from baseline in the participants' clinical laboratory results, vital signs, orthostatic vital signs, and ECG's using the safety set. Reasons for discontinuation will be tabulated. All clinical safety data will be listed by participant and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.11.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity (mild, moderate or severe), relationship to study drug (related or not related), action relative to the study drug, and procedures. All AEs occurring during this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), as described in the DMP. However, only TEAEs occurring after administration of the first dose of study drug and through the follow-up visit (Day 16 of Period 3 or 10 – 14 days after the last dose of investigational product administration for participants who withdraw from the study early) will be summarized. A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration.

For each treatment, TEAEs will be coded using MedDRA® and tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of participants reporting the AE

and as percent of safety set by treatment. The most commonly reported TEAEs (ie, those events reported by >5% of all participants in each treatment, excluding SAEs) will also be summarized. For the list of all AE summary tables see CPAP.

In addition, TEAEs will be summarized as number of AEs and percentage of AEs for each treatment for the overview of TEAEs.

Additional TEAE summary tables will be presented by severity and relationship to study drug. If a participant has multiple AEs with different severity levels within the same term, the participant will be counted in the most severe category only. If a participant has both related and unrelated AEs with the same term, the participant will be counted as having related TEAEs only.

Should any SAEs occur they will be summarized the same way as TEAE. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the study report.

7.11.2 Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1), Day 2 Predose and 24 hours post-Day 2 dosing in each period. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Principal Investigator (PI).

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by treatment and assessment time points. Change from baseline will be summarized in a similar way. Baseline is defined as the last assessment including rechecks taken prior to dosing on Day 1 in each period (Day -1 Check-in).

For each laboratory test, a shift table will be developed comparing the frequency of the results at treatment baseline (above normal (H), normal (N), or below normal (L)) with those postdose time points for each regimen. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a clinically significant (CS) range. If the value falls within the CS range, it will be noted as “N” for not clinical significant. If the value fails the CS range, it will be flagged with a “Y” which prompts the PI to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. All clinically significant laboratory tests, as indicated by the PI (either in the PI flag or in PI comments), and the corresponding values will be listed by participant. All clinical laboratory data will be presented in by-subject data listings.

7.11.3 Vital Signs

Single measurements and orthostatic vital signs will be collected as outlined in Table 7.c.

Table 7.c Collection of Vital Signs and Orthostatic Vital Signs

Measurement Type	Period	Day	Time Point
Orthostatic Vital Signs (Heart Rate and Blood Pressure)	Screen		
	1, 2, 3	-1	
		1	1 and 3 hours postdose
		2	Predose and 1, 2, 6, 24 hours postdose
		8, 10, 12, 14	
	3	16 or ET*	
Vital Signs (Heart Rate and Blood Pressure)	1, 2, 3	1	Predose
	3	16 or ET*	
Vital Signs (Respiratory Rate and Temperature)	Screen		
	1, 2, 3	1	Predose
		2	Predose and 24 hours postdose
	3	16 or ET*	

* ET = Early termination.

Additional unscheduled vital signs measurements may be taken at other times, if deemed necessary by the PI.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for vital sign results (seated and standing measurements will be reported separately) and orthostatic change in blood pressure and heart rate by treatment and time point of collection. Change from baseline will be summarized in a similar way. Orthostatic change in vital signs (ie, seated and standing blood pressure and pulse rate) is defined as the difference between the measurement collected in the standing position and the measurement collected in the seated position (ie, Standing – Seated). Baseline is defined as the last assessment including rechecks taken prior to Day 1 dosing in each period (Day 1 Predose for seated vital signs and Day -1 check-in for orthostatic vital signs). Vital signs will also be displayed in a data listing by participant.

7.11.4 12-Lead ECGs

Standard 12-lead ECGs will be recorded as outlined in Table 7.d.

Table 7.d Collection of Electrocardiograms

Measurement Type	Period	Day	Time Point
12-Lead ECG	Screen		
	1, 2, 3	-1	
		1	Predose and 1, 3 hours postdose
		2	Predose and 1, 2, 6, 24 hours postdose
		8, 10, 12, 14	
	3	16 or ET*	

* ET = Early termination.

Additional unscheduled ECGs may be recorded at other times if deemed necessary by the PI.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG results and change from baseline by treatment and time point of collection. Baseline is defined as the last assessment including rechecks taken prior to Day 1 dosing in each period (Day 1 Predose). ECG data will also be displayed in a data listing by participant.

7.11.5 Physical Exams

A full physical exam will be performed at screening and Day 16 of Period 3 or upon early termination. Abbreviated physical examinations will be performed at check-in (Day -1) and 24 hours post-Day 2 dosing in each period. Symptom driven physical exams may be performed at other times at the discretion of the PI. Physical exam findings, as recorded on the CRF, will be presented in a data listing by participant. Reproductive system findings will also be listed by participant.

7.11.6 Overdose

All cases of overdose will be presented in a data listing by participant. Any AEs associated with overdose will be documented as AEs.

7.12 Interim Analysis

A blinded safety and tolerability assessment will be conducted by the Investigator and sponsor representative(s) prior to proceeding to the next higher dose level (next period) according to the dose escalation and stopping rules.

7.13 Preliminary Analysis

CCI

CCI

[redacted]

7.14 Changes in the Statistical Analysis Plan

There are no changes in the statistical analysis plan from the protocol analysis.

8.0 REFERENCES

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	19-Mar-2019 15:46 UTC