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Official Title: A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Vonoprazan (20 mg) and Lansoprazole (30 mg) in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Vonoprazan (20 mg) and Lansoprazole (30 mg) in Healthy Subjects

Sponsor Project No.: VONO-103
Final Protocol Amendment 1 Date: 08 March 2021
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Compound Name: Vonoprazan
US IND Number: 079212

Celerion Project No.: CA32534
Final Version 1.0
Date: 06 July 2021

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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Issue Date: 06 July 2021

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1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the summarization of the data from this study. Any changes made from the planned analysis, after locking of the database, will be documented in the clinical study report (CSR).

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of vonoprazan (20 mg) and lansoprazole (30 mg) following single (Day 1) and multiple doses (Day 7).

Secondary Objective

- To evaluate the safety and tolerability of vonoprazan (20 mg) following single (Day 1) and multiple doses (Day 7).

2.2 Endpoints

Primary Endpoints

- PD parameters: gastric pH >4 holding time ratio (HTR) and mean gastric pH over 24 hours on Days 1 and 7.
- PK parameters as appropriate: following Day 1: AUC0-24, AUC0-inf, Cmax, and Tmax, and following Day 7: AUCtau, Cmax,ss, and Tmax,ss.

Safety Assessments

- Adverse events (AEs), 12-lead electrocardiograms (ECGs), vital signs, clinical laboratory tests, and physical examinations.

3. STUDY DESIGN

This is a Phase 1, open-label, randomized, 2-period, crossover study to evaluate the PK, PD, and safety and tolerability of vonoprazan in comparison to lansoprazole in healthy subjects. The study will be conducted at a single site.

Forty (40), healthy, adult male and female subjects will be enrolled. Subjects will be randomized to 1 of 2 treatment sequences in a 1:1 ratio, either AB or BA, where treatment A and treatment B are vonoprazan 20 mg QD and lansoprazole 30 mg QD, respectively.

Screening of subjects will occur within 28 days prior to the first dosing.

In each period, multiple doses of either vonoprazan or lansoprazole will be administered QD for 7 consecutive days. Gastric pH will be measured continuously over a 24-hour period at Baseline (Day -1 of Period 1 only) and on Days 1 and 7 of Periods 1 and 2. PK samples will be collected at predose and for 24 hours following dosing on Days 1 and 7 of Periods 1 and 2. Gastrin samples will be collected over a 24-hour period at Baseline (Day -1 of Period 1 only), at predose and for 24 hours following dosing on Days 1 and 7 of Period 1 only, and at predose (single sample) on Day 1 of Period 2. Safety will be monitored throughout the study by clinical safety and laboratory evaluations.

Subjects will fast overnight for at least 10 hours prior to each dosing. On Days 1 and 7 of Periods 1 and 2, subjects will continue the fast for 4 hours postdose when they will be given a meal, the next meal will be served at 9 hours postdose, and a snack will be served at 12 hours postdose. On Day -1 of Period 1, subjects will follow a similar time matched (± 15 minutes) food administration schedule as planned for Day 1.There will be a washout period of at least 7 days between the last dose in Period 1 and the first dose in Period 2.

Discontinued subjects may be replaced at the discretion of the Sponsor.

Blood sampling for PK of vonoprazan and lansoprazole in plasma will be obtained at the timepoints specified in Section 7.1.

SAMPLE SIZE

A total of 40 subjects, 20 subjects per sequence group (AB, BA) provides 90% power to detect a difference of at least 10% in the change from baseline in pH>4 HTR on Day 7 between the treatment groups, assuming a common standard deviation of 17% and that the correlation coefficient between periods is 0.5. This sample size allows for 4 dropouts.

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

PD Population

All subjects who received at least one dose of the study drug and have sufficient postdose pH measurements and absence of major protocol violations will be included in the PD analysis.

PK Population

All subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the PK analysis.

Safety Population

All subjects who received at least one dose of the study drug will be included in the safety analysis.

4.2 Preliminary Data and Interim Analysis

There are no interim analyses planned for this study.

5. TREATMENT DESCRIPTIONS

Treatments are described as follows:

Treatment	Short Description (text, tables, figures, listings, SAS output)	Description
A	Vonoprazan	Vonoprazan (1 x 20 mg tablet) administered QD on Days 1 through 7
B	Lansoprazole	Lansoprazole (1 x 30 mg capsule) administered QD on Days 1 through 7

6. PHARMACODYNAMIC ANALYSIS

6.1 Gastric pH Monitoring

Gastric pH will be measured continuously over a 24-hour period at Baseline on Day -1 (Period 1 only) and on Days 1 and 7 of Periods 1 and 2, using a pH and pressure sensitive probe and ambulatory pH recording system (Sleuth/ZepHr™ Software from Sandhill Scientific). A pH recording will be taken every 5 seconds. After each 24-hour recording period, the flashcard will be removed from the recorder and transferred to the computer. It will then be placed back to start the next 24-hour collection, as appropriate. Once the recording is complete for Day -1 of Period 1 and Days 1 and 7 of Periods 1 and 2, the data will be transferred on a SAS data file and sent for analyses.

On Day -2 (Period 1) the lower esophageal sphincter (LES) will be identified and the distance from the upper border of LES to the nares will be recorded to facilitate the placement of the microelectrode probe for pH monitoring.

Prior to pH monitoring, the pH probe will be inserted nasogastrically. The microelectrode will record pH values over a 24-hour time frame.

Baseline pH monitoring will start in the morning of Day -1 of Period 1 and will continue for approximately 24 hours. On Days 1 and 7 of Periods 1 and 2, the continuous pH recording session will commence 30 to 60 minutes prior to treatment administration (Hour 0). Gastric pH will be sampled and recorded every 5 seconds and will conclude at the end of the 24-hour continuous monitoring period. Start time and stop time will be recorded. On Day -1 of Period 1, continuous pH recording will follow a similar time matched (± 15 minutes) scheduled as planned for Day 1. Any interruptions in pH monitoring will be captured.

6.2 Gastric pH Pharmacodynamic Parameters

For each 15-minute interval within a pH collection time interval, the median pH, the mean pH, and the standard deviation of the pH values will be calculated for each subject using the pH values collected every 5 seconds. Nominal times will be used with dosing on Days 1 and 7 of each period being time 0.

Using the 15-minute interval median pH values, the following PD parameters will be assessed (Day - 1 of Period 1 only and Days 1 and 7 for both treatments/periods):

Table 6.1. Method of Determination of pH Parameters

Parameter and Label	Definition	Method of Determination
Integrated gastric acidity (IA): IA0-2 IA0-4 IA12-24 IA0-24 IA4-9 IA9-12	The acid concentration (mM) is calculated as 1000×10^{-pH}. This parameter will be computed over the following time intervals: o Initial 2 hours after the start of each 24-hour monitoring period (IA0-2); o Initial 4 hours after the start of each 24-hour monitoring period (IA0-4); o From 12 hours after the start of each 24-hour monitoring period (IA12-24); o Overall 24-hour monitoring period (IA0-24). To measure Integrated acidity for food intake, Integrated acidity will also be computed over the following intervals: o From 4 hours to 9 hours after the start of each 24-hour monitoring period (IA4-9); o From 9 hours to 12 hours after the start of each 24-hour monitoring period (IA9-12).	The IA is the time-weighted average of the acid concentration expressed as mmol×hr/L. It is also the area under the acid concentration-time curve. The IA will be calculated using the linear trapezoidal with linear interpolation method. In case of missing data for an interval, no extrapolation will be used and the associated IA will be set to missing.
Mean Gastric pH: pH0-2 pH0-4 pH12-24 pH0-24 pH4-9 pH9-12	The average gastric pH is a measure of the immediate effect on gastric pH and the duration of effect on gastric pH. The average gastric pH will be calculated over the following time intervals: o Initial 2 hours after the start of each 24-hour monitoring period (pH0-2); o Initial 4 hours after the start of each 24-hour monitoring period (pH0-4); o From 12 hours after the start of each 24-hour monitoring period (pH12-24); o Overall 24-hour monitoring period (pH0-24). To measure average gastric pH for food intake, gastric pH will also be computed over the following intervals: o From 4 hours to 9 hours after the start of each 24-hour monitoring period (pH4-9); o From 9 hours to 12 hours after the start of each 24-hour monitoring period (pH9-12).	In case of missing data for an interval, no extrapolation will be used and the associated average gastric pH will be set to missing.

Parameter and Label	Definition	Method of Determination
Time pH >4	Calculated time that the gastric pH is >4 over the course of the 24-hour monitoring period within the intervals described above	Taken directly from the data (median values over 15-minute intervals) as the sum of intermittent times that pH > 4
pH >4 HTR	pH >4 holding time ratio: the percentage of time the gastric pH is >4 over the course of the 24-hour monitoring period within the intervals described above	Calculated as: Time pH > 4*100/total actual monitoring period time
Time pH >5	Calculated time that the gastric pH is >5 over the course of the 24-hour monitoring period within the intervals described above	Taken directly from the data (median values over 15-minute intervals) as the sum of intermittent times that pH > 5
pH >5 HTR	pH >5 holding time ratio: the percentage of time the gastric pH is >5 over the course of the 24-hour monitoring period within the intervals described above	Calculated as: Time pH > 5*100/total actual monitoring period time
Time pH >6	Calculated time that the gastric pH is >6 over the course of the 24-hour monitoring period within the intervals described above	Taken directly from the data (median values over 15-minute intervals) as the sum of intermittent times that pH > 6
pH >6 HTR	pH >6 holding time ratio: the percentage of time the gastric pH is >6 over the course of the 24-hour monitoring period within the intervals described above	Calculated as: Time pH > 6*100/total actual monitoring period time

6.3 Gastrin Sampling

For all subjects, blood samples for determination of serum gastrin concentrations will be drawn at 0, 2, 4, 5, 9, 10, 12, 13, and 24 hours on Day -1 of Period 1 for baseline determination and on Days 1 and 7 of Period 1. Sampling times on Day -1 will be time matched to postdose sampling on Day 1 and Day 7. The samples collected at 4, 9, and 12 hours postdose should be collected prior to starting meal/snack consumption. The 0-hour (predose) sample on Day 1 of Period 1 will be the same as the 24-hour sample on Day -1; only one sample will be collected. A single gastrin sample will also be drawn in Period 2 at Day 1 predose.

The 24-hour gastrin sample on Day -1 of Period 1 is to be taken approximately 15 minutes prior to dosing on Day 1 of Period 1, and the 24-hour postdose gastrin sample on Day 1 and Day 7 of Period 1 is to be taken approximately 15 minutes prior to pH probe removal on Day 2 and Day 8 of Period 1, respectively.

6.4 Gastrin Pharmacodynamic Parameters

PD parameters for serum gastrin will be calculated as follows:

Gastrin AUC0-24:	The area under the curve over the 24-hour postdose period (AUC0-24) for Day -1 of Period 1 (Baseline) and Days 1 and 7 of Period 1, as calculated by the linear trapezoidal method.

6.5 PD Data Summarization and Presentation

SAS® software Version 9.4 will be used for all PD data presentation and summarization including statistical analyses, summary tables, and data listings. Descriptive statistics of pH PD parameters, gastrin concentrations, and gastrin PD parameters will be generated using SAS®.

For each 15-minute interval within a pH collection time interval, the median pH, the mean pH, and the standard deviation of the pH values will be calculated and listed for each subject.

Summary statistics, including sample size (n), arithmetic mean (mean), standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum will be calculated for all gastrin serum concentrations.

Summary statistics, including n, mean, SD, CV%, median, minimum, maximum, geometric mean (Geom Mean), and geometric CV% (Geom CV%) will be calculated for all PD parameters (for gastric pH and gastrin). Where a PD parameter cannot be reported, the parameter record will display “NA” for not available. Means will only be calculated based on the available subject data (i.e., if a parameter is “NA”, that result will be excluded from the mean calculation).

Mean gastric pH (based on median pH values of each 15-minute interval) over time on Day 7 will be presented graphically for vonoprazan and lansoprazole on one graph; similar graphs will also be presented for Days -1 and 1.

Mean gastric pH (based on median pH values of each 15-minute interval) versus time for vonoprazan will be presented for baseline, Day 1 and Day 7 on the same graph; a similar graph will be presented for lansoprazole.

In addition, individual plots for gastric pH (based on median pH values of each 15-minute interval) over time will be presented for each subject including Day -1 and Day 1 and Day 7 for both periods.

6.6 Statistical Analysis of PD Parameters

6.6.1 Analysis of Variance

For gastric pH >4, pH >5, and pH >6 HTRs and mean gastric pH on Days 1 and 7, the point estimate of the difference in changes from baseline between the study medications (vonoprazan - lansoprazole) will be calculated along with the 2-sided 95% CI, using an ANOVA with treatment, sequence, and period as fixed effects and subject within sequence as a random effect. The data for these endpoints will be evaluated for gross departures from normality and transformations may be considered.

The statistical analyses will be performed using the following SAS® code:

Proc Mixed data=< >;

By day;

Class subject sequence period treatment;

Model parameter = sequence period treatment/ddfm=KR;

Random subject(sequence);

Estimate “vonoprazan vs lansoprazole” treatment 1 -1/CL alpha=0.05;

LSMeans treatment;

Run;

Gastric pH >4, pH >5, and pH >6 HTRs, mean gastric pH, and their changes from baseline will be summarized with descriptive statistics and 2-sided 95% CIs for each study treatment.

7. PHARMACOKINETIC ANALYSIS

7.1 Measurements and Collection Schedule

Blood samples for the determination of plasma vonoprazan and lansoprazole concentrations will be obtained on Days 1 and 7 of Periods 1 and 2 at the following time points: predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 9, 10, 12, 13, 16, and 24 hours postdose.

All concentration data will be included in the calculation of the individual PK parameters, the individual concentration-time plots (based on actual sample times), and in the mean concentration-time plots (based on nominal sample times). However,

if there are any significant deviations from nominal sample times, some concentration data may be excluded from mean concentration-time plots and/or additional concentration-time plots of the mean data may be provided. All deviations and excluded data will be provided and discussed in the CSR.

7.2 Bioanalytical Methods

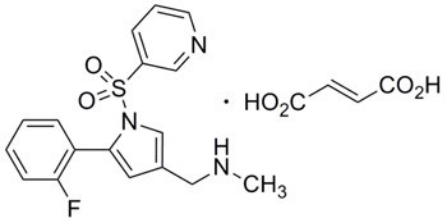
The analyses of vonoprazan and lansoprazole in plasma samples will be performed at [redacted] and [redacted] respectively using validated liquid chromatography-mass spectrometry/mass spectrometry methods. The analytical ranges (lower limit of quantitation [LLOQ] – upper limit of quantitation [ULOQ]) for vonoprazan and lansoprazole are expected to be 0.1 – 100 µg/mL and 2.00 – 2000 ng/mL, respectively.

Samples from all subjects will be assayed even if the subjects do not complete the study. The Bioanalytical Reports for the determinations of vonoprazan and lansoprazole will be included in the CSR.

7.3 Investigational Product and PK Analyte Information

7.3.1 Vonoprazan

The chemical structure of vonoprazan fumarate is shown below.



Chemical name: 1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-*N*-methylmethanamine monofumarate

Molecular formula: $C_{17}H_{16}FN_3O_2S \bullet C_4H_4O_4$

Molecular weight (salt): 461.46

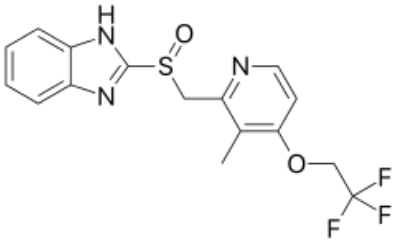
Molecular weight (free base): 345.39

Dose correction for the administered salt formulation will be made for the calculation of dose-dependent parameters if free base is measured, while no correction is needed if the salt is measured.

$Dose_{corrected} = (MW_{freebase}/MW_{saltform}) \times Dose_{administered}$

7.3.2 Lansoprazole

The chemical structure of lansoprazole is shown below.



Chemical name: 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-benzimidazole

Molecular formula: $C_{16}H_{14}F_3N_3O_2S$

Molecular weight: 369.37

7.4 Pharmacokinetic Concentrations

Plasma concentrations of vonoprazan and lansoprazole as determined at the collection times and per the bioanalytical methods described in Section 7.1 and Section 7.2, respectively, will be used for the calculation of the plasma vonoprazan and lansoprazole PK parameters.

7.5 Non-Compartmental Pharmacokinetic Analysis and Parameter Calculation

7.5.1 Plasma Pharmacokinetic Parameters

The appropriate non-compartmental PK parameters will be calculated from the plasma vonoprazan and lansoprazole concentration-time data using Phoenix® WinNonlin® Version 8.1 or higher. Actual sample times will be used in the calculations of the PK parameters. The calculation of the actual time for vonoprazan and lansoprazole will be in respect to the start of the respective dose administration time. All PK parameters included in the protocol are listed in Table 7.1.

Table 7.1. Noncompartmental Pharmacokinetic Parameters to be Calculated

Day 1

Parameter	Definition	Method of Determination
AUC0-t:	The area under the concentration time curve, from time 0 to the last observed non-zero concentration	Calculated using the Linear Trapezoidal with Linear Interpolation Method
AUC0-24:	The area under the concentration time curve, from time 0 to the 24hour time point	Calculated using the Linear Trapezoidal with Linear Interpolation Method
AUC0-inf:	The area under the concentration time curve from time 0 extrapolated to infinity	AUC0-inf = AUC0-t + (Clast/kel) where Clast is the last observed/measured concentration
Cmax:	The maximum observed concentration	Taken directly from bioanalytical data
Tmax:	The time to reach Cmax	Taken from clinical database as the difference in the time of administration and the time of the blood draw which is associated with the Cmax If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.

Parameter	Definition	Method of Determination
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve	Calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations excluding Cmax)
t½:	Apparent first-order terminal elimination half-life	Calculated as 0.693/Kel
CL/F	Apparent total plasma clearance after oral (extravascular) administration	Calculated as Dose/AUC0-inf
Vz/F:	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration	Calculated as Dose/(AUC0-inf x Kel)

Day 7

Parameter	Definition	Method of Determination
AUCtau:	The area under the concentration-time curve during a dosing interval (tau) at steady state	Calculated using the Linear Trapezoidal with Linear Interpolation Method
Cmax,ss:	The maximum observed concentration at steady state	Taken directly from bioanalytical data
Cavg:	Average concentration at steady state	Ratio of AUCtau to the dosing interval, tau
Tmax,ss:	The time to reach Cmax at steady state	Taken from clinical database as the difference in the time of administration and the time of the blood draw which is associated with the Cmax,ss
RA,AUC	AUC accumulation ratio	Calculated at steady-state, as: RA,AUC = AUCtau/AUC0-24 Note: AUC0-24 is from Day 1 dosing.
RA,Cmax	Cmax accumulation ratio	Calculated at steady-state, as: RA,Cmax = Cmax,ss/Cmax Note : Cmax is from Day 1 dosing

Note: Additionally, Kel may be calculated for Day 7.

For the calculation of the PK parameters, plasma concentrations below the limit of quantification (BLQ) prior to the first quantifiable concentration will be set to 0 and plasma concentrations BLQ after the first quantifiable concentration will be treated as missing.

The Kel will be determined using linear regressions composed of least 3 data points. The Kel will not be assigned if 1) the terminal elimination phase is not apparent, 2) if Tmax is one of the 3 last data points, or 3) if the R^2 value is less than 0.8. In cases where the Kel interval is not assigned, the values of t½, AUC0-inf, CL/F, and Vz/F are considered not calculable and will not be reported. Wherever the resulting T½ is more than half as long as the sampling interval, the Kel values and associated parameters (t½, AUC0-inf, CL/F, and Vz/F) may not be presented as judged appropriate and in accordance with Celerion SOPs.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

AUC0-24 will be calculated for plasma vonoprazan and lansoprazole concentration versus time profiles containing measurable concentrations up to 24 hours postdose. If the last measurable concentration occurs prior to 24 hours postdose, or the concentration at 24 hours is missing, the Kel may be used to extrapolate a concentration value at 24 hours postdose in order to calculate AUC0-24h. If the Kel is not reportable, but the actual time of the 24-hour sample is within 1% of the nominal sample time and the sample is not missing or BLQ, the AUC0-24h will be calculated based on the area under the curve from 0 through the actual time of the 24-hour sample. Otherwise, AUC0-24h will not be reported.

7.6 PK Data Summarization and Presentation

SAS® software Version 9.4 will be used for all data presentation and summarization including statistical analyses, summary tables, graphs, and data listings. Plasma concentrations and PK parameters descriptive statistics will be generated using SAS®.

Plasma vonoprazan and lansoprazole concentrations will be presented with the same precision as received from the bioanalytical laboratory based on number of decimal places or significant figures. They will be listed by nominal sample time for each subject, tabulated by treatment, and summarized using descriptive statistics, including sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, maximum and median. Concentrations from excluded subjects will be included in the plasma concentration tables, but will be excluded from the summary statistics and noted as such in the tables. All BLQ values will be presented as “BLQ” in the plasma concentration table listings and footnoted accordingly.

Parameter values for Cmax, Cmax,ss, and Cavg will be presented with the same precision as per the bioanalytical data. Exposure parameters (i.e., AUC0-t, AUC0-24, AUC0-inf, and AUCtau) will be presented with, at maximum, the precision of the bioanalytical data, and, at minimum, 3 significant figures (will be determined by the pharmacokineticist). Values for time-based parameters (i.e., Tmax, Tmax,ss, and t½) will be presented with 2 decimals. All other PK parameters will be presented with 3 significant figures.

PK parameters will be listed by subject, tabulated by treatment, and summarized using summary statistics (n, mean, SD, CV%, SEM, minimum, median, and maximum). In addition, geometric mean (Geom Mean) and geometric mean coefficient of variation (Geom CV%) will be calculated for AUC, Cmax, and Cavg parameters. Excluded subjects will be included in the PK parameter tables and listings, but will be excluded from the summary statistics and noted as such in the tables.

The level of precision for the summary statistics on plasma concentrations and PK parameters will be presented as follows:

- n: no decimal;
- Minimum, Maximum: same precision as in individual values
- Mean, Median, Geom Mean: one more level of precision than the individual values;
- SD, SEM: one more level of precision than the Mean;
- CV% and Geom CV%: one decimal place.

The following graphical presentations will be made for vonoprazan and lansoprazole:

- Linear and semi-log scale of mean plasma concentrations versus nominal time points with all treatments plotted in the same figure. Linear mean plots will be presented with and without ± SD.
- Individual plasma concentration versus time profiles on linear and semi-log scales with all treatments plotted in the same figure.
- Individual plasma concentration versus time profiles on semi-log scale for each treatment showing the points and regression line used to determine Kel.

8. SAFETY

All safety endpoints will be reported for the observed data by treatment group for the Safety Population. No imputation will be made for the missing safety data. All case report form (CRF) safety data will be summarized by treatment group and listed by subject and chronologically by assessment time points including rechecks, unscheduled assessments, and early termination visits.

Continuous variables will be summarized using n, arithmetic mean, SD, minimum, median, and maximum for each treatment. Categorical variables will be summarized by frequencies and percentage by treatment group.

The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer.

8.1 Subject Disposition

Subject disposition will be summarized by number of subjects enrolled, completed, and discontinued the study with discontinuation reasons by treatment sequence and overall. Subjects' dosing status will also be tabulated by treatment and presented with discontinuation reason and date of discontinuation. The total number of subjects exposed to each treatment will also be displayed.

In addition, the number and percentage of subjects who signed the informed consent form and who screen failed will be presented along with the reason for screen failure.

8.2 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, and body mass index [BMI]) by treatment sequence and overall. Age will be derived by subtracting the year of birth from the year of informed consent. If year of informed consent – year of birth is less than the protocol minimum age then the age derivation will be year of informed consent – year of birth +1.

Frequency counts will be provided for categorical variables (race, ethnicity, and sex) by treatment sequence and overall.

8.3 Adverse Events

All AEs occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 23.0.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, MedDRA preferred term, treatment, severity, relationship to study medication, action taken with study drug, and outcome; however, only treatment-emergent AEs (TEAEs) will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration. Each TEAE will be attributed to a treatment based on the onset date and time of the AE.

If the onset time of an AE is missing and the onset date is the same as the treatment dosing date, then the AE will be considered treatment emergent for the current treatment. If onset time of an AE is missing and the onset date does not fall on a dosing date, then the AE will be considered treatment emergent for the last treatment administered. If the onset date of an AE is missing, then the AE will be considered treatment emergent to the treatment of that period.

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number (%) of subjects reporting the AEs by treatment and overall. The number of AEs will be tabulated in a similar manner. Tables which tabulate the

number of TEAEs by severity and relationship to study treatment will also be included.

8.4 Clinical Laboratory Tests (Serum Chemistry, Hematology, and Urinalysis)

Clinical laboratory data will be performed at screening, at Check-in of each period, and Day 8 of Period 2 or upon early termination.

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. Out-of-range values and corresponding recheck results will be listed.

For all numeric laboratory values, descriptive statistics will be presented for each laboratory test by assessment time point and randomized treatment sequence. Change from baseline will be summarized in a similar manner. Baseline is defined as the latest assessments prior to the first dose at Period 1 which may include unscheduled or recheck results. This will typically be the result collected at Day -2 of Period 1. Postdose unscheduled events, rechecks and early termination results will not be included in summaries.

For each laboratory test, a shift table will be developed to compare the frequency of the results at baseline (above normal, normal, or below normal) with the respective postdose results. For urinalysis tests, the categories are normal and outside normal.

8.5 Vital Signs

Vital signs (temperature, heart rate and blood pressure) will be measured at screening, check in, approximately 1 hour before and after pH probe placement on Day -1 (Period 1 only) and on Days 1 and 7 of Periods 1 and 2, and approximately 1 hour prior to each dose on Days 2 through 6 of Periods 1 and 2. The vital signs assessment following removal of the pH probe used for monitoring on Day -1 of Period 1 will be the same as the vital signs assessment prior to dosing on Day 1 of Period 1. Respiration rate will be collected at screening and at the end of Period 2 or prior to early termination from the study only.

Descriptive statistics will be presented for each vital sign measurement by assessment time point and treatment. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first dose at each period which may include unscheduled or recheck results. This will typically be the result collected at Day 1 predose of each period. Postdose unscheduled events, rechecks and early termination results will not be included in summaries.

8.6 Electrocardiogram

Safety ECGs (heart rate, PR, QRS, QT, QTcF [Fridericia correction], and RR) will be measured at screening, at Check-in of each period, and Day 8 of Period 2 or upon early termination.

Descriptive statistics will be presented for each ECG parameter by assessment time point and randomized treatment sequence. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first dose at Period 1 which may include unscheduled or recheck results. This will typically be the result collected at Day -2 of Period 1. Postdose unscheduled events, rechecks and early termination results will not be included in summaries.

QTcF values that are > 450 msec and increase from baseline > 30 msec will be flagged in the data listing.

8.7 Concomitant Medications and Medical History

All concomitant medications recorded during the study will be coded with the WHO Dictionary 01SEP2020-b3 and listed. Medical history will be listed.

8.8 Physical Examination

Physical examination will be performed at screening and Day 8 of Period 2 or upon early termination. Symptom-driven physical examinations may be performed at other times, at the PI's or designee's discretion. Abnormal findings will be reported as medical history or adverse events. All data found in the CRF will be listed.

9. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The analyses described in this SAP are aligned with those analyses described in the protocol.