Statistical Analysis Plan

Sponsor Name: GSK Consumer Healthcare

Protocol Number: 218246

Protocol Title: A randomized, single blind, single center, single dose, two period, two sequence crossover bioequivalence study of esomeprazole 20 mg delayed-release capsules (Catalent, Guayama) compared to the esomeprazole 20 mg delayed-release capsules (Nexium 24HR, AstraZeneca Södertälje) in healthy adult subjects under fasted conditions

Protocol Version and Date: 1.0, 25-Nov-2021

PPD **Project Code:** CCI

Author: PPD **, Senior Biostatistician**

This document contains confidentiality statements that are not relevant for this publicly available version.

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	11-Feb-2022	PPD	Initial Version
0.2	01-Mar-2022	PPD	Address Comments
1.0	11-Mar-2022	PPD	Finalize SAP

Signature Approvals

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

PPD Approval		
PPD, Sr. Biostatistician Name, Title Lead Biostatistician	PPD Signature	PPD Date (DD-Mmm-YYYY)
PPD Principal Statistician Name, Title Senior Reviewing Biostatistician	PPD Signature	PPD Date (DD-Mmm-YYYY)
PPD, Pharmacokineticist Name, Title Lead Pharmacokineticist	PPD Signature	PPD Date (DD-Mmm-YYYY)
PPD Sr Medical Writer Name, Title Lead Medical Writer	PPD Signature	PPD Date (DD-Mmm-YYYY)
GSK CH Approval		
PPD, Manager Biostatistics Name, Title Sponsor Contact	PPD Signature	PPD Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation	Description
λz	The terminal elimination rate constant
Abs	absolute
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the curve
AUC_{0-t}	area under the concentration-time curve from time 0 to the time of the last measurable sampling time point, t
AUC_{0-inf}	area under the concentration time curve from time 0 to infinity
AZ	AstraZeneca
BDR	blinded data review
BLOQ	below the lower limit of quantification
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CG	Catalent Guayama
CI	confidence interval
C_{max}	peak or maximum observed concentration
CRF	case report form
CSR	clinical study report
EC	ethics committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
HIV	human immunodeficiency virus

Abbreviation	Description
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	institutional review board
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
N/A	not applicable
PCR	polymerase chain reaction
PK	pharmacokinetics
PR	pulse rate
PT	preferred term
QC	quality control
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SOC	system organ class
SOP	standard operating procedure
$t_{½}$	terminal half-life
TLFs	tables, listings and figures
THC	tetrahydrocannabinol
t_{max}	time to reach maximum concentration
WBC	white blood cell

2. 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 conclusion regarding the study objectives. Safety and pharmacokinetic (PK) analyses will all be described.

This SAP is based on the following documents:

- Protocol No. 218246, Version 1.0 dated 25-Nov-2021 (PPD Project No. CCI
- Electronic Case Report Form (eCRF) Draft 1.0, dated 10-Feb-2022

The plan may change due to unforeseen circumstances and any changes made after the plan has been finalized will be documented. 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 clinical study report (CSR). No change will be made without prior approval of the study sponsor. No revision to the SAP is required for changes which do not affect the statistical analysis methods, definitions, or rules defined in this document.

When applicable, all methodologies and related processes will be conducted according to PPD Standard Operating Procedures (SOPs) as appropriate. Shells for all statistical tables, listings, and figures referred to in this SAP will be displayed in a separate document.

2.1 Responsibilities

PPD will perform the statistical analyses and are responsible for the production and quality control of all tables, listings and figures (TLFs) and PK analysis.

2.2 Timings of Analyses

No Interim analysis is planned for this study.

Dry-run Analysis:

A Dry-run analysis is planned for this study using dummy or available data before database softlock. This dry-run analysis will include a set of all unique tables, figures, and listings and are denoted in the accompanying SAP Shells.

Blinded Data Review (BDR):

After completion of database softlock, a BDR will be conducted. The details of the BDR will be compiled in a separate document. The purpose of the BDR is to assign the study populations outlined in Section 6 of this SAP. As this study is single blind, the term "blind" is used to denote that the population determination will be done without respect to treatment.

Topline TLFs:

After completion of database hardlock, a subset of all TLFs will be generated intended to identify key results of the study (i.e. bioequivalence and safety).

The final analysis of safety and PK is planned to be completed after completion of Topline TLFs. The final analysis will include the Topline TLF.

3. Study Objectives

3.1 Primary objective

- Demonstrate the bioequivalence of esomeprazole 20 mg delayed-release capsules from Catalent Guayama (CG) compared to esomeprazole 20 mg delayed-release capsules from AstraZeneca Södertälje (AZ) under fasted conditions.

3.2 Secondary objective

3.2.1 PK objective

- Assess the pharmacokinetic profile

3.2.2 Safety objective

- Assess the safety profile (local and systemic) of both products

4. Endpoints

4.1 Pharmacokinetic Endpoints

- Primary
  - C_{max} (The maximum observed post-dose concentration; obtained without interpolation)
  - AUC_{0-t} (The area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t, computed using the linear trapezoidal rule)
- Secondary
  - AUC_{0-inf} (The area under the plasma concentration versus time curve calculated from time 0 to infinity $AUC_{0-inf} = AUC_{0-t} + C(t)/\lambda_z$ where C(t) is the concentration at the last measurable sampling time point and λ_z is the terminal elimination rate constant)
  - $\%AUC_{ex}$ (Percentage of AUC_{0-inf} obtained by extrapolation, calculated as $(1-[AUC_{0-t}/AUC_{0-inf}])\times 100$)
  - λ_z (The terminal elimination rate constant computed as the slope of the regression line of ln (C(t)) on time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time)
  - t_{max} (The time of the maximum observed post-dose concentration)
  - $t_{1/2}$ (The elimination half-life computed as $t_{1/2} = \ln(2)/\lambda_z$)

All PK parameters, calculated using plasma concentration data, are referred to in Section and 9.4.

4.2 Safety Endpoints

Safety will be assessed by:

- Monitoring and recording of adverse events
- Physical examination
- Vital signs
- Laboratory tests

5. Study Design

This is a single center, single dose, single-blind, randomized, two-sequence, two-period crossover, bioequivalence study in healthy adult subjects with at least a 7-day washout period.

The study is intended to dose in more than one group; all groups will be dosed at the same clinical site and the same protocol requirements and procedures will be followed within each group.

Subjects will be randomly assigned to one of 2 treatment sequences and receive a single dose of one of the following treatments in each period following a crossover design:

Treatment A: esomeprazole 20 mg capsules from CG in the fasted state (Test)

Treatment B: esomeprazole 20 mg capsules from AZ in the fasted state (Reference).

5.1 Subject Selection

Healthy non-smoking adult subjects between the ages of 18 to 55 years of age, inclusive, at the signing of informed consent with a Body Mass Index (BMI) between 18.5 to 30 kg/m^2 and a total body weight $\geq$ 50.0 kg for males and $\geq$ 45.0 kg for females are to be included in this study. Detail all of the inclusion and exclusion criteria may be found in study protocol, Sections 5.2 and 5.3.

5.2 Determination of Sample Size

A sufficient number of subjects will be screened to randomize approximately 49 to ensure at least 41 evaluable subjects complete the entire study.

According to previous GSK CH study CCI [redacted] it is estimated a sample of 41 subjects will provide at least 90% power to establish bioequivalence. Considering a drop out discontinuation rate of 15%, approximately 49 subjects will need to be enrolled.

5.3 Randomization and Blinding

5.3.1 Randomization

Randomization will occur prior to first dosing. Since enrollment into the study is based on the results of inclusions/exclusion and Randomization is prior to dosing, it is possible that a subject is enrolled in the study, but not randomized. Hence, randomization will be considered the time at which the subject identifier is assigned to a subject which is tied to a randomized treatment sequence.

Computer generated randomization schedules will be prepared prior to the start of the study. The schedules will be generated through the statistical analysis system (SAS) software, version 9.4. Block randomization will be used. Subjects will be randomly assigned a 3-digit subject number

beginning with 0 with the last two numbers being 01-60.

5.3.2 Blinding

Blinding is required as per Canadian regulation. This will be a single-blind study.

PPD will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the subject will receive the study treatment regimen assigned to the corresponding randomization number.

Treatments will be provided in a blind manner. Personnel involved in the collection, monitoring, revision, or evaluation of adverse events, personnel of the bioanalytical department, and personnel who could have an impact on the outcome of the study, including GSK/PPD statisticians, programmers, scientists, DM study managers, clinical study team except Global supply, and PPD PK analyst, will not have prior access to the randomization code.

5.4 Subject Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures.

The following circumstances require discontinuation of study product and/or premature subject withdrawal:

- Protocol violation that may impact the subject's safety
- Positive test for COVID-19, conducted during the study, at times deemed necessary by Investigator
- Emesis within 5 hours post dosing
- Diarrhea (defined as one episode of loose stools) within 10 hour post dosing
- Withdrawal of informed consent
- Subject lost to follow-up
- Unblinding of the subject
- Pregnancy

If a subject is discontinued or prematurely withdraws from the study, the reason(s) for discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the CRF. Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded on the appropriate AE CRF page.

6. Analysis Populations and Sets

Subjects who deviate from the protocol will be identified and excluded from the pharmacokinetic analyses as agreed by the biostatistician and medical director or designee. Exclusion of any data from the analyses will be determined during a BDR meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

The analysis of safety parameters will be based on the Safety Population detailed in Section 6.2. Summaries statistics of PK (concentration and parameters) will be based on the PK Analysis Set detailed in Section 6.4. All collected data will be included in the listing, including any data captured and entered into the database of screen failures.

6.1 Screened Population

The Screened Population is defined as all who were screened to potential receive at least one dose of the study medication. Listings which include screen failure subjects or eligible subjects who were not randomized will used the Screened Population.

6.2 Safety Population

The Safety Population is defined as all randomized subjects who receive at least one dose of study medication. The Safety Population will be used for all listings unless stated otherwise.

6.3 Pharmacokinetic Population

The PK population is defined as all randomized subjects who have at least one post-dose concentration value, and who have no major protocol deviations concerning pharmacokinetics. The PK population will be used to list all concentration data for every subject.

6.4 Pharmacokinetic Analysis Set

The following PK analysis set is defined to address the PK objectives and further PK considerations within this study:

PK analysis set includes all subjects of the PK population who complete both treatment periods, and for which the relevant PK parameters (at least AUC_{0-t} or C_{max}) can be derived. Subjects with baseline concentration >5% of the individual C_{max} for either period will be excluded from the PK analysis set. This analysis set will be used in summaries, the primary PK analysis, and the secondary PK analysis.

7. General Aspects for Statistical Analysis

7.1 General Methods

SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA) software will be used to perform all data analyses.

Unless otherwise stated, all listings will be sorted by subject number and assessment date/time, when applicable.

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

- Esomeprazole CG (Test) [A]
- Esomeprazole AZ (Reference) [B]

7.2 Summary Statistics

Unless otherwise stated, continuous variables will be summarized using the number of observations (n), and the statistics arithmetic mean, standard deviation (SD), geometric mean, coefficient of variation (CV%), median, minimum, and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the CRF, arithmetic 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. Categorical variables will be summarized with frequency counts and percentages. Percentages (other than PK parameters) will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population, unless otherwise stated.

For the plasma PK data, the data will be rounded to two decimal places in the listings. The following rules will be applied to following situations:

- λ_z data: Presentation of data in listings and calculated means (arithmetic and geometric), minimum, and maximum - rounded off to 4 decimal digits. Calculated SD will be presented to 5 decimal places.
- Pharmacokinetic parameters related to time such as T_{max}, $K_{el\ Lower}$, and $K_{el\ Upper}$ must be reported with the same precision as the actual sampling time: rounded off to 3 decimal digits. This applies to presentation in listings and calculated means (arithmetic and geometric), minimum, and maximum. SD will be presented to 4 decimal places.
- Concentration data as well as C_{max}: reported as they appear in the corresponding dataset.

Note: these rules are only intended as a guide and may be changed based on available data for the study and are not meant to override the number of decimal places in the data used as input for analysis. The full unrounded precision will be used for all calculation prior to rounding for display as applicable.

Summary statistics including the geometric mean will be displayed to the same number of decimal places as the arithmetic mean and the coefficient of variation (CV) (%) will be rounded to 1 decimal place.

Only data from nominal protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the listings.

All assessments will be presented in the listings.

7.3 Key Definitions

Study Day:
Study day will be calculated using first study drug administration (either Test or Reference) 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.

Prior medication:

Medication/treatments taken within 90 days of signing the informed consent form will be documented as a prior medication/treatment.

Concomitant medication:

Medications/treatments taken after the first study drug administration will be documented as concomitant medication/treatments.

Treatment: Treatment is assigned as the last received treatment, except in the case of pre-dose measurements. Any non-adverse event assessment occurring on the same calendar date as a given treatment before dosing would be attributed to the same treatment given on that calendar day. If no treatment was applied on the same calendar day then any measurements pre-dose will not be summarized by treatment. Adverse events will be summarized only by the last received treatment.

Height:
Height (in cm) = height (in inches) * 2.54

Weight:
Weight (in kg) = weight (in lbs) * 0.4536

BMI:
BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

7.4 Handling of Dropouts and Missing Data

All data from subjects who withdraw from the study will be included in the summaries up to the time of withdrawal.

For safety,

- If an AE is recorded with an onset date corresponding to a study drug administration day, but the time is missing, then the AE will be assigned to the actual treatment with study drug administration that day and considered treatment-emergent.
- If an AE is recorded with an onset date that does not correspond to a study drug administration day, but the time is missing, then the AE will be assigned to actual

treatment that covers the AE onset day and considered treatment-emergent if appropriate.

- If an AE is recorded with an onset date where day and time are both missing, then the AE allocation to a treatment will be done on a case by case basis considering available information (e.g. AE onset date, AE end date, AE comments, subject disposition) in raw data. It will be considered treatment-emergent if appropriate.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate

- Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

For PK analysis, only observed concentration data will be used in the data analysis except for concentration values BLQ as described in Section 9.1 and Section 9.2. No attempt will be made to extrapolate or interpolate estimates for missing data.

8. Demographic, Other Baseline Characteristics and Medication

8.1 Inclusion and Exclusion Criteria

All recorded inclusion/exclusion criteria status will be presented in a data listing. Each subject's inclusion or exclusion from each population will also be presented in a data listing.

8.2 Demographics and Body Measurements

The demographic characteristics will consist of age (years), sex (female or male), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other, Not Reported, and Unknown). The body measurements consist of height (cm), weight (kg), and body mass index (BMI) (kg/m^2).

Descriptive statistics (n, mean, SD, Min, median, and Max) will be calculated for body measurements using the last results obtained prior to first study drug administration. Frequency counts and percentages will be tabulated for categorical variables. All demographic characteristics will be summarized overall and listed by subject for the Safety Population and PK Population. If the Safety Population and PK Population are the same, the table for the PK Population will not be generated.

8.3 Medical History

Details of relevant medical and surgical history in the last 5 years, including allergies or drug sensitivity will be recorded. This data will be included in a data listing. Any abnormal findings from the physical exam occurring before the first study drug administration will be included in the Medical History. The Medical Dictionary for Regulatory Activities (MedDRA®) Version 24.1 will be used to classify all medical history findings by System Organ Class (SOC) and Preferred Term (PT).

8.4 Urine Drug Screen, Urine Cotinine Test, and Alcohol breath test

A urine drug screen will be performed at screening and Day -1 of each period. Testing includes: Amphetamine, Methamphetamine, Barbiturates, Benzodiazepine, cocaine, 3,4-methylenedioxymethamphetamine, Methadone, Opiate, Phencyclidine, and Tetrahydrocannabinol.

A urine cotinine test will be performed at screening and Day -1 of each period.

An alcohol breath test will be performed at screening and Day -1 of each period.

The urine drug screen, urine cotinine test, and alcohol breath test and restriction assessments will be presented in separate listings.

8.5 Virology

Virus serology will be performed at screening for Hepatitis B Surface Antigen, Hepatitis B Core Antibody, Hepatitis C Virus Antibody, HIV Antigen/Antibody. Findings from Virology results

will be included in a data listing.

8.6 Pregnancy Testing and Follicle Stimulating Hormone (FSH) Levels

For all female subjects of childbearing potential, a urine pregnancy test, will be performed at screening and end of study and a serum pregnancy test will be performed on Day -1 of each period. Results will be obtained prior to dosing during each period. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active study period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of IRBs/ECs or if required by local regulations.

FSH will be performed at the screening visit for females who have been amenorrhoeic for 12 months.

Results from the pregnancy testing and FSH Levels will be listed, separately.

8.7 COVID-19 Testing

Nasal/Nasopharyngeal swab will be collected to test for COVID-19 using PCR or antigen test, at screening, Day -1 of each period, at Day 2 of Period 1, during the washout period, early discontinuation or end of study, and at any time during residential period in the study when subjects report symptoms suggestive of COVID-19. A listing including all results from COVID-19 testing will be created.

8.8 Electrocardiogram

A standard 12-lead ECG will be performed at screening. Results of any clinically significant abnormalities should be reported in the CRF. Clinically significant abnormalities should also be recorded on the Adverse Event CRF. All findings will be listed.

8.9 Prior and Concomitant Medications

Concomitant medication use will be recorded from the time the subject signs the ICF until the EOS visit. Subjects will abstain from all concomitant treatments, except for contraceptives and hormone replacement therapy, and those used for the treatment of adverse events unless they jeopardize the integrity of the study.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD), Version B3, Mar 2021 or later. Data as recorded in the CRF (i.e. with incomplete dates) will be listed. For the purpose of inclusion in Prior and concomitant medication tables, incomplete medication start and stop dates on CRF 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, month, and year: Assume that the medication is continuing;

- In the case of the death of a subject, 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 drug administration lie within the same month and year and the date of drug administration is not after the stop date of the medication, set to the date of drug administration. Otherwise, set to stop date of the medication.
  - Missing day and month: Assume January 1st.
- However, if the partial date and the date of drug administration lie within the same year and the date of drug administration is not after the stop date of the medication, set to the date of drug administration. Otherwise, set to stop date of the medication.
  - Missing day, month, and year: Assume date of drug administration if it's not after the stop date for the medication. Otherwise, set to stop date for the medication.

For the missing day imputation, the following examples should be used for reference:

- Example 1:

  Medication start: UNJUN2019

  Medication end: 20OCT2019

  Date of administration: 16OCT2019

  Medication start imputed: 01JUN2019

  Tabular results: Concomitant

- Example 2:

  Medication start: UNOCT2019

  Medication end: 20OCT2019

  Date of administration: 16OCT2019

  Medication start imputed: 16OCT2019

  Tabular results: Concomitant

- Example 3:

  Medication start: UNOCT2019

  Medication end: 20OCT2019

  Date of administration: 24OCT2019

Medication start imputed: 20OCT2019

Tabular results: Prior

Relative start day or end day with respect to the dose date of the study drug administration will not be calculated if the medication start date or end date is incomplete.

All prior and concomitant medications will be presented in data listings.

8.10 Study Drug Administration

The study drug administration details including date and time of administration, Treatment Description (frequency, route, formulating, dose (units)), Fasting status at time of administration, and if a medication/dosing error occurred will be listed by Subject.

8.11 Subject Disposition

The number of subjects screened, enrolled, subjects not randomized (and reason), subjects randomized in Period 1 or 2 (including number of subject starting, completing period, and not completing (and reason)) will be tabulated for the safety population. Medication errors and reason for discontinuation for individual subjects will be listed and summarized.

9. Pharmacokinetic Analyses

All plasma concentration and PK parameter summaries and analysis will be conducted on the PK Analysis Set. All concentration and PK data will be listed on the PK population. This includes any data for subjects who are not included in the analysis (e.g. subjects withdrawn from the study due to adverse events). The listing for plasma concentration will include planned timepoint, sample collection (yes or no), date and times of collection, and the calculated time deviations from the planned timepoint.

9.1 Handling of Concentrations Below the Lower Limit of Quantification (BLOQ), No Reportable Concentration Values, and Missing Data

For the analysis of all individual plasma concentrations and all secondary PK parameter, all concentration BLOQ values that occur before the first measurable concentration (i.e. non-BLOQ) will be treated as zero (0). Any BLOQ values after the first measurable concentration will be treated as "Not Detectable" (ND), which will be shown as missing for plasma PK concentrations and PK parameter estimation.

Samples with invalid concentration (due to bioanalytical or clinical issue) will be replaced by "0.00" when it occurs prior to study drug administration. Otherwise, they will be set to missing for tabulation, graphical representation and calculation purposes if it occurs after study drug administration.

Listings will show the actual value of concentration at the timepoint. The value of BLOQ will be displayed as applicable in the listings.

If any concentration data is missing or deviates from the planned time of collection, then the pharmacokineticist may calculate the PK parameters using the available data.

9.2 Handling of the Difference between the Scheduled and the Actual Sampling Times

The actual clock time for study drug administration and each collection time for the PK samples will be recorded. For all sampling times, the actual sampling times relative to study drug administration will be calculated as the difference between the actual clock time of sampling and the actual clock time of study drug administration. The actual post-dose sampling times relative to study drug administration expressed in hours and rounded off to three decimal digits will be used to calculate the PK parameters, except for pre-dose samples occurring prior to study drug administration, which will always be reported as zero (0.000), regardless of the time difference. Scheduled sampling times (presented as 3 numbers [i.e. 0.50, 0.75, 1.00 or 24.0]) will be presented in concentration tables and mean graphs, while actual sampling times will be presented in the individual graphs.

9.3 PK Sampling Schedule

Blood samples will be collected from each subject during this study for the determination of the PK of esomeprazole.

PK blood samples of esomeprazole will be drawn according to the following schedule:

Pre-dose (within 1 hour before study drug administration) and at 0.5-, 0.75-, 1-, 1.25-, 1.5-, 1.75-, 2-, 2.25-, 2.5-, 2.75-, 3-, 3.5-, 4-, 4.5-, 5-, 5.5-, 6-, 8-, 10-, 12-, 16-, and 24-hours following dosing in each treatment period. The time tolerance window for blood samples will be ±1 minute for all samples collected before 8 hours post-dose and ±3 minutes for subsequent samples.

Samples obtained outside the pre-defined time windows will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (e.g. CRF).

9.4 Plasma Pharmacokinetic Parameters

Plasma concentrations from esomeprazole will be used to calculate the following PK parameters by standard non-compartmental methods:

PK Parameter	Definition
	Primary PK Parameters
AUC_{0-t}	Area under the plasma concentration versus time curve from time zero to time t, where t is the time of the last measurable plasma concentration of esomeprazole, computed using the linear trapezoidal rule
C_{max}	The maximum observed post-dose concentration; obtained without interpolation
	Secondary PK Parameters
AUC_{0-inf}	Area under the plasma concentration versus time curve calculated from time zero to infinity. $AUC_{0-inf} = AUC_{0-t} + C(t)/\lambda_z$ where C(t) is the concentration at the last measurable sampling time point and λ_z is the terminal elimination rate constant
$\%AUC_{ex}$	Percentage of AUC_{0-inf} obtained by extrapolation, calculated as $(1-[AUC_{0-t}/AUC_{0-inf}])\times 100$
t_{max}	Time of the maximum observed post-dose concentration
$t_{½}$	Elimination half-life computed as $t_{1/2} = \ln(2)/\lambda_z$
λ_z	Terminal elimination rate constant computed as the slope of the regression line of ln (C(t)) on time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time.

The adjusted coefficient of determination (R^2 adjusted) in general should be greater than 0.80. All the derived parameters (e.g., λ_z, $t_{½}$, AUC_{0-inf}) will be flagged accordingly for exclusion from summary statistics and statistical modeling as appropriate. The time point where ln-linear λ_z calculation begins ($\lambda_{z\ lower}$), the actual sampling time of the last quantifiable concentration used to estimate the λ_z ($\lambda_{z\ upper}$) as well as the R^2 adjusted for the ln-linear regression for the calculation of the elimination rate constant calculation will be reported.

9.5 Statistical Analyses

The following statistical analysis will be based on the PK Analysis Set.

Individual plasma concentrations will be summarized descriptively at each time point; the concentration vs. time profile will be graphed by formulation for individual subjects and for the arithmetic mean (±SD) on both original and logarithmic scales for the safety population. For ease of presentation, actual and scheduled sampling times will be used to present results for individual and mean figures respectively. Individual subject data will also be listed.

The PK parameters (AUC_{0-t}, and C_{max}) will be summarized for each treatment by descriptive statistics.

The PK parameters (AUC_{0-inf}, $\%AUC_{ex}$, λ_z, t_{max}, and $t_{1/2}$) will be summarized for each treatment using descriptive statistics same as for the primary PK parameters.

9.6 Assessment of Bioequivalence

The primary objective will be evaluated based on the following comparison:

Esomeprazole CG (Test) versus esomeprazole AZ (Reference), in terms of esomeprazole AUC_{0-t} and C_{max}.

A linear mixed effects model will be fitted to the log-transformed PK variables (AUC_{0-t} or C_{max}), as the dependent variable, and treatment, sequence, and period as fixed effects. Subject nested within sequence will be a random effect. Least squares estimates of treatment effects will be calculated and a 90% confidence interval (CI) for the treatment difference will be computed. The treatment difference and its CI will be exponentiated to obtain the ratio of the geometric means between the test and reference products (test/reference) and its CI.

Bioequivalence will be declared for AUC_{0-t} if the 90% 2-sided CI for the ratio lies completely within the range of 0.8-1.25 and for C_{max} if the point estimate for the ratio lies completely within the range of 0.8-1.25. No further adjustments for multiplicity of the co-primary endpoints are necessary as both endpoints must be met in order to achieve study success.

The SAS code for the analysis model will follow the format given below (The input variables (or datasets) are depicted in slanted red text and have been given generic names).

9.6.1 Group Effect Analysis

This study is planned to dose in more than 1 groups. The group effect will be added to the model

as described in Section 9.6 based on the following criteria:

- If the two groups are dosed more than 4 weeks (28 days) apart the group
    a. All subjects have been recruited from the same enrollment pool (The enrollment pool will be considered the same if all subjects from the second group are not screened after dosing of the first group).
    b. All subjects have similar demographics.
    c. The clinical study takes place at one site.
    d. All enrolled subjects are randomly assigned treatment groups at study outset.

Because this is a single center study with well-defined enrollment criteria for subject in respects to demographics, points B and C are met by definition of the study. A single randomization was also provided for all subjects before any dosing for the study was performed, including 49 subjects. If additional randomization is required after dosing 2 groups due to a larger than expected drop out rate, this point will not be met and the effect of group would be included in the statistical model. Otherwise, the primary criteria for the decision of adding the group effect will be based on the time between the two groups and the screening period of all subjects.

If the group effect is determined to be necessary, the following fixed terms will be included in the model: group, sequence, group by sequence, period within group, and treatment. The ratio and 90% CI will be calculated for AUC_{0-t} and C_{max} as applicable.

The SAS code for the analysis model will follow the format given below (The input variables (or datasets) are depicted in slanted red text and have been given generic names).

10. Safety

All safety analyses will be based on the Safety Population. Safety will be assessed on the basis of adverse event (AE), clinical laboratory data, vital signs, and physical examination.

10.1 Adverse Events

The assessment of safety will be based on the frequency and severity of AEs that are collected immediately after a subject provides consent to participate in the study by the completion (signature) of the ICF and until 5 days following last administration of the study product.

Treatment-emergent AEs (TEAEs) and non-TEAEs will be listed by subject and treatment.

TEAEs will be defined as any AEs that first occurs on or after the date and time of first drug administration. Any AE that first occurs pre-dose but worsens in severity after the first study drug administration will also be considered a TEAE. Non-TEAEs are those that occur prior to the first administration of the study medication and resolved prior to study drug administration or that first occur prior to the first study drug administration but do not worsen in severity after study drug administration. AEs will be captured during the study until study exit. All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. .

Adverse events will be coded using the MedDRA® dictionary Version 24.1. The incidence of AEs will be tabulated (for each treatment) after grouping by preferred term within System Organ Class (SOC). AEs will be summarized as the number and percentage of subjects having any AE, an AE by SOC, and AE by preferred term within SOC. Treatment-emergent AEs will also be summarized by SOC, PT, and maximum severity. The subset of AEs suspected of a relationship to study drug administration (related: probable, possible, remote, or not related: unrelated) will be summarized similarly. All AEs will also be tabulated by severity (mild, moderate, or severe). AEs will be assigned to the treatment administered immediately prior to the onset. Adverse events due to COVID-19, if any, will be listed and tabulated separately.

The relationship of TEAEs will be classified according to the study protocol as unrelated or related (remote, possible, or probable) to esomeprazole. The severity of TEAEs will be classified according to the study protocol as mild, moderate or severe.

Incidence of subjects who experienced TEAEs (frequency and the percentage of subjects) will be presented for each treatment and overall by:

- Overall summary of TEAEs;
- TEAEs by SOC
- TEAEs by SOC and PT;
- TEAEs by SOC, PT, and severity;
- TEAEs by SOC, PT, and relationship to the study drug;

All AEs will be listed. AE's that are serious, leading to death, leading to study discontinuation, or Treatment Emergent will be flagged.

For the purpose of inclusion in TEAE tables, the CRF question "Onset Date and Time" on "Adverse Events" page will be compared to the date and time of study drug administration, if the answer is not available, the imputed AE onset date will be used. Incomplete AE onset and end dates will be imputed similar to those rules as presented in Section 8.9. Additional rules are as follows:

If an AE is recorded with an onset date corresponding to a study drug administration day, but the time is missing, then the AE will be assigned to the treatment as a TEAE.

If an AE is recorded with an onset date that does not correspond to the study drug administration day, but the time is missing, then the AE will be assigned to the treatment as a TEAE if AE onset date is after study drug administration date.

If an AE is recorded with an onset date where day and time are both missing, then the AE allocation to the treatment will be done on a case by case basis considering available information (e.g., AE end date, AE comments, subject disposition).

10.2 Clinical Laboratory Parameters

Laboratory analyses of blood and urine samples will be performed by the local laboratory.

The following clinical laboratory assessments will be performed:

Chemistry:	Standard serum chemistry will be collected. These include: Albumin, ALP, ALT, AST, Calcium, Chloride, Creatine kinase, Creatinine, GGT, Glucose, Phosphorus, Potassium, Sodium, Total bilirubin, Total protein, Urea (BUN)
Hematology:	Standard blood Hematology will be collected. These include: Hematocrit, Hemoglobin, Platelet count, RBC count, WBC count and differential (Basophils, Eosinophils, Lymphocytes, Monocytes, and Neutrophils)
Urinalysis:	Standard Urinalysis will be collected. This includes: Bilirubin, Blood (occult), Color and appearance, Glucose, Ketones, Leukocyte esterase, Nitrite, pH, Protein, Specific gravity, and Urobilinogen
Local Urinalysis (Microscopic)	Urine samples for Microscopic inspection will be performed only in the event of abnormal findings. This will include: Leukocytes, Erythrocytes, Epithelial cells, and the results, interpretation, and clinical significance of (Bacteria, Mucus, or other)

Clinical laboratory testing (hematology, chemistry, and urinalysis) will be performed at screening and at the End of Study visit.

Clinical laboratory values will be flagged as either high or low based on the reference ranges provided by the local laboratories for each laboratory parameter.

Individual clinical laboratory results and reference ranges will be presented in data listings.

10.3 Vital Sign Measurements

Vital signs measurements will include systolic and diastolic blood pressures (BPs), pulse rate (PR), respiratory rate (RR), and oral body temperature (BT).

Vital sign measurements will be performed at screening, BT on Day -1 of each period, Day 1

(within 1 hour before drug administration) of each treatment period, BT on Day 2 of each treatment period (Note: oral body temperature performed on Day 2 of Period 2 can be used as the oral body temperature required at End of Study), and at the end of Study Visit.

Vital signs will be summarized by time-point (Overall). Summary statistics will include mean, SD, minimum, median, and maximum. No inferential statistics will be presented. Data will be listed with abnormal values flagged.

10.4 Physical Examination

A full physical examination will be performed at screening. A brief physical examination will be performed on Day -1 of each period and the End of Study visit.

A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, vascular and neurological systems. A brief physical examination will be focused on general appearance, heart (Cardiovascular), and lung (Respiratory) findings, as well as towards subject reported symptoms.

Any untoward findings identified on physical exams conducted after the administration of the first study drug administration will be captured as an adverse event, if those findings meet the definition of an adverse event.

11. Changes from the Protocol

The following text from the protocol was included by error and was not considered for this SAP as baseline corrections for plasma concentrations is not planned:
"Missing values of λ_z can be estimated from the subject's λ_z value from the other treatment. If a λ_z value cannot be calculated from the other treatment, then the λ_z will be obtained from the treatment mean value for subjects with non-missing values of λ_z in the period in which it is not available. This estimated λ_z can be used to calculate other λ_z dependent variables. This λ_z value derivation is only applied for pre-dose concentration adjustments.".

12. Reference List

None

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13. Quality Control

SAS programs are developed to produce outputs such as analysis data sets, summary tables, data listings, figures or statistical analyses. These will be developed and undergo quality control as per SOPs CCI and CCI

14. Appendices

None