Statistical Analysis Plan

Client Study Code:	CX842A2107
Study Title:	A phase 1, open label, randomized, parallel-group, single center study to investigate pharmacokinetics and pharmacodynamics (intragastric pH) of linaprazan glurate/linaprazan after single and 14 days repeated oral administration of linaprazan glurate to healthy subjects.

Document Control

Control

Document Name	Statistical Analysis Plan
Based on most recently amended clinical study protocol	CSP CX842A2107 Final V 4.0
EudraCT number	2022-002725-10
Version (Date)	Version 2.0 (04-Oct-2023)
Study statistician	[redacted]
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Status	Final

Signatures

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History

Version	*Modified By*	*Date*	*Description of Changes*
0.1	[redacted]	02-Feb-2023	First draft
1.0	[redacted]	01-June-2023	Changes made after review comments
2.0	[redacted]	27-Sep-2023	Update of sections 2.6 urine metabolites omitted. Section 4.1 clarification on determining the PKAS. Section 5.2.3 added to describe the calculations of the pharmacodynamic data (pH) Section 5.7 updated with more detailed descriptions of presenting the PD related (pH) data and pH in relationship to PK. Minor corrections throughout the document.

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Abbreviations

Abbreviation	Term
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin clotting time
AR	Adverse reaction
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration *vs.* time curve
AUC_{0-t}	AUC from time 0 to time t
$AUC_{0-24,\ 0-12,\ 12-24,\ 24-48}$	AUC from time 0-24, 0-12, 12-24, 24-48 hours, respectively
$AUC_{extrap\%}$	AUC percent extrapolation
AUC_{inf}	AUC from 0 to infinity
AUC	AUC from 0 to time of last measurable plasma concentration
BID	*Bis in die* (twice daily)
BMI	Body mass index
BP	Blood pressure
C_{aver}	Average concentration
CL/F	Apparent total body clearance following extravascular administration
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
C_{trough}	The plasma concentration observed at the start of a dosing interval.
CS	Clinically significant
[redacted]	
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DSUR	Development safety update report

Abbreviation	Term
ECG	Electrocardiogram
eCRF	Electronic Case report form
EDC	Electronic data capture
eGERD	Erosive GERD
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GERD	Gastroesophageal reflux disease
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
HTR	Holding Time Ratio (%)
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IME	Important medical event
IMP	Investigational medicinal product
IR	Immediate release
ISF	Investigator site file
IUS	Intra-uterine system
LLOQ	Lower limit of quantification
MAD	Multiple-ascending dose
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
NCA	Non-compartmental analysis
NCS	Not clinically significant
PD	Pharmacodynamics

Abbreviation	Term
PK	Pharmacokinetics
PK(INR)	Prothrombin complex international normalized ratio
PKAS	PK analysis set
PT	Preferred term
QC	Quality control
QD	*Quaque die* (once daily)
QRS interval	(ECG) The time required for stimulus to spread through the heart's ventricles
QT interval	(ECG) The time from the beginning of the QRS complex to the end of the T wave
QTcF	(ECG) Corrected QT interval by Fredericia
R_{acc}	Accumulation ratio
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial Master File
T_{max}	Time of occurrence of C_{max}
$T_{1/2}$	Terminal elimination half-life
V_z/F	Volume of distribution following extravascular administration
WHO	World Health Organization

1. Introduction

This Statistical Analysis Plan (SAP) provides a detailed and technical description of the planned pharmacokinetic (PK) and pharmacodynamic (PD) analyses and statistical evaluations of Cinclus Pharma AB's study CX842A2107: "A phase 1, open label, randomized, parallel-group, single center study to investigate pharmacokinetics and pharmacodynamics (intragastric pH) of linaprazan glurate/linaprazan after single and 14 days repeated oral administration of linaprazan glurate to healthy subjects.".

The SAP is prepared in compliance with the guidelines for Statistical Principles for Clinical Trials (ICH E9).

A full description of the investigational plan, eligibility criteria, assessments, etc. is given in the Clinical Study Protocol (CSP) CX842A2107 v4.0 dated 10MAR2023.

In case this SAP deviates from the statistical analysis described in the CSP, the reason for the deviation and/or alternative or additional statistical analyses will be documented in amendments to the CSP or in this SAP.

2. Study Objectives and Endpoints

This is a Phase I, single-center, open parallel-group, randomized study designed to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety and tolerability of single and repeated oral doses of linaprazan glurate at 3 dose levels in healthy male and female subjects.

2.1 Primary Objectives

- To characterize the PK and PD of linaprazan glurate and linaprazan after once daily (QD evening dose) and twice (BID) daily dosing after single and repeated administration of linaprazan glurate.

2.2 Secondary Objectives

- To assess the safety and tolerability after single and repeated doses of linaprazan glurate.

2.3 Exploratory Objectives

[redacted]

2.4 Primary endpoints

- Linaprazan glurate and linaprazan PK parameters after single and repeated administration of linaprazan glurate (when applicable):
    - Area under the plasma concentration *vs*. time curve (AUC) at different timepoints: $AUC_{0\text{-}24}$, $AUC_{0\text{-}12}$, $AUC_{12\text{-}24}$, $AUC_{24\text{-}48}$, and $AUC_{0\text{-}t}$.
    - The minimum, end-of dosing interval, maximum and average plasma concentrations C_{trough}, C_{max}, C_{aver}.

- Terminal elimination half-life ($t_{½}$,) and time of occurrence of C_{max} (t_{max}).

- Percentage of time gastric pH >4 at Day 1 and Day 14, over a 24-hour monitoring period following linaprazan glurate administration.

2.5 Secondary endpoints

- Additional PK parameters for linaprazan glurate and linaprazan PK parameters (*e.g.*, but not limited to apparent clearance [CL/F], apparent volume of distribution [V/F], accumulation ratio [R_{Acc}], C_{min}, AUC from 0 to infinity [AUC_{inf}] and AUC percent extrapolation [$AUC_{extrap\%}$]).
- Frequency, intensity and seriousness of adverse events (AEs).
- Clinically significant changes in:
  - Electrocardiogram (ECG)
  - Vital signs
  - Physical examinations
  - Safety laboratory parameters

2.6 Exploratory endpoints

[redacted]

The exploratory endpoints may be reported separately from the clinical study report (CSR).

3. Study Details

3.1 Study Design

This is a Phase I, single-center, open parallel-group, randomized study designed to evaluate the PK, PD, safety, and tolerability of single and repeated oral doses of linaprazan glurate at three dose levels in healthy male and female subjects.

An overview of the study design is shown in

Figure **1**. The overall schedule of events is presented in Appendix Table 1. The detailed schedule of events for individual visits are tabulated in the CSP (see Tables 8.1-2 to 8.1-7 of the CSP for details).

Subjects will be randomized into 1 of 6 dose groups. There will be 6 dose groups as follows:

- No 1: 25 mg linaprazan glurate (1x25 mg oral tablet) QD for 14 days
- No 2: 50 mg linaprazan glurate (2x25 mg oral tablet) QD for 14 days
- No 3: 75 mg linaprazan glurate (3x25 mg oral tablets) QD for 14 days

- No 4: 25 mg linaprazan glurate (1x25 mg oral tablet) BID for 14 days
- No 5: 50 mg linaprazan glurate (2x25 mg oral tablet) BID for 14 days
- No 6: 75 mg linaprazan glurate (3x25 mg oral tablets) BID for 14 days

Subjects participating in the study will attend 7 visits to the clinical research unit (CRU): a screening visit (Visit 1) followed by 6 visits (Visit 2-7). Visit 2, Visit 5 and Visit 7 are residential stays at the CRU and Visit 3, Visit 4, and Visit 6 are outpatient visits. The participants will also be followed by a remote follow-up/end-of-study visit via telephone (Visit 8), 7 days (±2 days) after the final dose.

Figure 1. Overview of study design

3.2 Study population

The subjects participating in this study will be healthy male and female subjects 18–65 (both inclusive) years of age, have with a body mass index (BMI) of 18.5 - 30.0 kg/m^2 (inclusive), and are eligible for the study. More details regarding the study population, including inclusion and exclusion criteria, can be found in the CSP section 9.

3.3 Randomization and Blinding

Block randomization (block size=6) stratified by gender will be used to generate the randomization list, which will show the assignment of subjects to 1 of the 6 dose groups given in Section 3.1.

The randomization list of the study was be prepared by a statistician at CRS Tomaz Vovk, and transferred to the Trial Master File (TMF) for archiving.

As this is an open label study, the dose group to which each subject is allocated will be recorded in the eCRF. A computer-generated randomization list will be created using SAS Proc Plan, SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC) or equivalent program. The randomization list will contain subject number, block, gender, drug holiday period, and dose group.

The randomization list will be generated and kept by CRS.

No blinding procedures will be followed.

3.4 Number of Subjects

3.4.1 Sample Size

Approximately, 116 healthy volunteers are planned to be screened to achieve 72 randomized subjects. An estimated total of 12 subjects will be included per dose level (in total 6 dose groups). If less than 9 subjects are evaluable per dose level, addition of new a subject to replace a discontinued subject can be allowed.

3.5 Subject Replacement

Subjects who consented to study participation but discontinued prior to IMP administration (dosing) may be replaced. Subjects withdrawn after dosing may be replaced at the Sponsor's discretion after consultation with the Investigator.

4. Assessments

The overall Schedule of Assessments is given in Appendix Table 1. Details about each visit and the assessments made during the visit are given in the sections in the CSP that are listed in Appendix Table 1.

4.1 Protocol Deviations

Deviations from the CSP should not occur. If deviations from the CSP occur, the implications and classification (minor or major) of each deviation will be decided and documented at the clean file meeting prior to database lock. If a subject is classified with a major protocol deviation potentially altering the treatment outcome, it will lead to exclusion of data from the PK analysis set and any such case should be clearly justified.

Major protocol deviations include:

- Significant non-compliance with study procedures.
- Any serious unforeseen deviation in dosing of the subjects.
- Vomiting or diarrhea within 6 hours after dosing which could render the plasma concentration-time profile unreliable.
- Intake of prohibited medication that may influence the PK results (i.e., known to interact with the PK of linaprazan glurate).

All protocol deviations will be assessed whether they affect the PK analysis to such an extent that the subject needs to be excluded from the PKAS (see section 5.1.2 for the PKAS definition). This assessment will be performed by the Clinical Pharmacology Specialist and be documented in the final Protocol Deviations Log.

Blood sampling outside of the allowed timeframe will not be considered as a major protocol deviation.

4.2 Demographic and Baseline Characteristics

The demographic and baseline data collected in this trial are gender, age, ethnicity, race, height and weight. BMI will be calculated from height and weight and recorded with 1 decimal point.

4.3 Medical/Surgical History

Medical/surgical history will be obtained by subject interview in order to verify that the eligibility criteria are met. The medical/surgical history will include all relevant diseases and operations within 2 months prior to screening as judged by the Investigator.

4.4 Prior and Concomitant Medications

Prior medications taken within 2 weeks prior to first IMP administration are obtained by subject interview in order to verify that the eligibility criteria are met.

Medications are classified as prior if the stop date was before or on the day of the first dose administration (pre-dose) and as concomitant if ongoing on the day of the first dose administration, stopped after the first dose administration or started after the first dose administration.

Any use of concomitant medication from screening until the end-of-study visit will be documented appropriately. Relevant information (i.e., name of medication, dose, unit, frequency, dose form, route, start and stop dates, reason for use) will be recorded.

4.5 Safety Variables

4.5.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Definitions for the different types of AE including the definition for Serious Adverse Events (SAEs), Adverse Reaction (AR), Serious Adverse Reaction (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR) are given in section 11.4 of the CSP.

The following variables will be collected for each AE and SAE:

- Start date and time
- Stop date and time
- Whether the AE is serious
- Intensity (Grading using CTCAE v5.0)
- Causal relationship to IMP (Probable, Possible, Unlikely)
- Assessment of outcome (Recovered/resolved, Recovering/resolving, Recovered/resolved with sequelae, Not recovered/not resolved, Fatal, Unknown)
- Action taken with study treatment (Dose increased, Dose not changed, Dose reduced, Drug interrupted, Drug withdrawn, Not applicable, Unknown)

An AE is considered causally related to the use of the IMP when the causality assessment is probable or possible.

AEs will be followed up until resolution or end-of-study visit, whichever comes first.

4.5.2 Laboratory Evaluations

Blood and urine samples for the assessment of safety and eligibility will be collected as shown in Table 3. Safety laboratory values will be specified and documented as Normal, Abnormal NCS (not

clinically significant), or Abnormal CS (clinically significant). Abnormal post-dose findings assessed by the Investigator as CS will be reported as AEs.

Table 3. Safety Laboratory Parameters

Category	Parameter
Clinical chemistry	Alanine aminotransferase (ALT)
	Albumin
	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
	Bilirubin (total and conjugated)
	Calcium
	Creatinine
	Glucose
	Phosphate
	Potassium
	Sodium
	Urea
Hematology	Erythrocyte count
	Leukocyte count with differential count
	Hematocrit (B-EVF)
	Hemoglobin (Hb)
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Platelet count
Coagulation	Activated Partial Thromboplastin Time (APTT)
	Prothrombin Complex International Normalized Ratio (PK[INR])
Urinalysis (dip stick)	Erythrocytes
	Glucose
	Ketones
	Leukocytes
	Nitrite
	pH
	Protein
	Specific gravity
	Urobilinogen

Category	Parameter
FSH -test (at screening, postmenopausal females only)	Follicle stimulating hormone (FSH)
Pregnancy test (female subjects of childbearing potential only)	Urine pregnancy test.

4.5.3 Physical Examination

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities.

Any abnormalities will be specified and documented as CS or NCS. Abnormal post-IMP administration findings assessed by the Investigator as clinically significant will be reported as AEs.

4.5.4 Vital Signs

Vital signs will include systolic and diastolic blood pressure, pulse rate and body temperature. Any vital signs outside of normal ranges will be specified and documented as CS or NCS. Abnormal post-dose findings assessed by the Investigator as CS will be reported as AEs.

4.5.5 ECGs

A 12-lead ECG will be recorded pre-IMP administration and at 24 hours post IMP-administration during visits 1, 2, 5 and 7.

The following variables will be recorded:

- Resting Heart Rate (HR)
- PQ/RR
- QRS
- QT
- QTcF

Any abnormalities will be specified and documented as CS or NCS. Abnormal post-IMP findings assessed by the Investigator as CS will be reported as AEs.

4.6 Pharmacokinetic Assessments

Blood sampling time points for PK analyses and their allowed sampling time windows are detailed in section 11.3.1 of the CSP. The actual blood sampling time points will be recorded in the CRFs.

Plasma samples for determination of plasma concentrations and PK characterization of linaprazan glurate and linaprazan will be analyzed by [redacted] by means of a [redacted] The PK parameters to be determined are listed and defined below. For further details regarding the calculation of these parameters, see section 5.6.

4.6.1 Primary and secondary analyses

PK parameters:

When applicable, the following PK parameters will be obtained or calculated from the plasma concentration-time data of linaprazan glurate and linaprazan after QD or BID dosing with linaprazan glurate:

- AUC_{inf} (the area under the concentration–time curve from time zero extrapolated to infinity)
- $AUC_{extrap\%}$ (% extrapolated AUC)
- AUC_{0-t} (area under the concentration-time curve from time zero to t=last)
- Partial AUC (area under the concentration-time curve from time zero to t=12h and 24h, from 12h to 24h, and from 24h to 48h)
- C_{max} (maximum observed concentration)
- C_{min} (minimum observed concentration)
- C_{trough} (Concentration before next dose)
- C_{aver} (average concentration in a 12 or 24 h dose interval)
- T_{max} (time to maximum observed concentration)
- $T_{1/2}$ (terminal half-life)
- CL/F (apparent total clearance)
- V/F (apparent volume of distribution)
- R_{acc} (accumulation ratio for C_{max} and AUC in a 12 or 24 h dose interval)

Additional PK parameters may be determined, such as:

- λ_z (elimination rate constant)
- T_{lag} (Delay between the time of dosing and the time of appearance of plasma concentration)
- AUC_{tau} (the area under the concentration–time curve in a dosing interval)

4.6.1 Exploratory analyses

[redacted]

5. Analysis Methods

All statistical analyses will be performed using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

All PK analyses will be performed on individual plasma concentration-time data by non-compartmental analysis (NCA) using the software Phoenix WinNonlin® 8.3 or higher (Certara Inc, Princeton NJ, United States).

All statistical and PK analyses will be performed after this SAP is finalized and approved, the Clean File Report including decisions on analysis sets has been signed, and the database has been locked.

5.1 Analysis Sets

5.1.1 Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all subjects who have been randomized and received at least 1 dose of IMP and who provided at least 1 post-baseline assessment of data.

The FAS will also be used for all safety analyses.

5.1.2 PK Analysis Set (PKAS)

The PK analysis set (PKAS) will consist of all subjects who received at least 1 dose of linaprazan glurate and provided an evaluable plasma concentration profile, and who have no AEs or protocol deviations judged to affect the PK analysis. Individual PK values may be excluded from the analysis as specified in section 5.6.

5.1.3 PK/PD Analysis Set (PK/PDAS)

The PK/PD Analysis set (PK/PDAS) is a subset of the PK Analysis Set, excluding subjects without an evaluable and appropriate pH profile.

5.2 General Principles for Presenting Study Data

5.2.1 Presentation of Data

Continuous data will be summarized using descriptive statistics where the following statistics will be reported:

- Number of observations (n),
- Arithmetic Mean
- Arithmetic Standard deviation (SD),
- Median,
- Min. and Max.
- Geometric Mean for log-normal PK parameters
- Geometric Coefficient of Variation (CV%) for log-normal PK parameters

Categorical data will be presented as the number and percentage of subjects or observations in each category.

Percentages will be based on number of subjects with data at a certain time point in the analysis set of interest except for presentations of medical history, medications, and AEs where the percentages will be based on the number of subjects in the study population.

In general, all data will be listed. All summary tables will be structured with a column for each dose group and will be annotated with the total population size relevant to that table/dose group, including any missing observations.

A separate TLF plan will be prepared by the study statistician.

5.2.2 Calculation of PK Data

Individual and mean PK profiles for concentrations of linaprazan glurate and linaprazan will be plotted in Phoenix® WinNonlin® and reported for all subjects in the PK analysis sets. Mean concentration data will be plotted against scheduled (nominal) sampling times while individual concentration data will be plotted against actual sampling times.

PK concentration data

All individual PK concentrations will be presented in listings included in the appendices of the CSR. These data will be presented and analyzed with the same precision as the source data provided by the bioanalytical laboratory.

PK parameters

The derived parameters will be listed individually by subject and summarized by treatment using descriptive statistics. PK parameters and actual elapsed sample collection times will be rounded for reporting purposes in by-subject listings.

PK data will be presented by treatment using summary statistics with number of measurements, arithmetic mean, SD, as well as median, minimum and maximum values. For the PK parameters AUC_{inf}, $AUC_{0\text{-}t}$, partial AUCs, C_{max}, C_{aver}, C_{trough}, and C_{min} the geometric mean and geometric coefficient of variation (CV%) will also be presented. For the PK parameters T_{lag} and T_{max}, only the median, minimum, and maximum values will be presented. For the PK parameter R_{acc} and $AUC_{extrap\%}$, the geometric mean and CV% will also be presented. All data will be listed by treatment and subject.

Individual and mean linaprazan glurate and linaprazan plasma concentrations will be plotted against time for each dose group.

In export datasets, PK parameters will be provided with full precision, and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values and rounded for reporting purposes only.

5.2.3 Calculation of PD data (intragastric pH)

The raw pH-data presents pH values for each second of the patient's pH recording period. In the derivations, subject specific time windows based on subject's first dose of the day were used.

For the calculation of Holding Time Ratio (HTR), both raw pH-data (every second measurements) and the raw data compressed into 10-minute periods by calculating the median for each 10-minute period, were used. For all other analyses described in section 5.7 the 10-minute median values were used.

Before the described derivations, the raw pH-data was processed according to the rules defined in the SAP addendum ("Process to manage issues associated with the pH-metry recordings and data").

5.3 Statistical/Analytical issues

5.3.1 Calculation of PD data (intragastric pH)

All available data, except as described in 8. Addendum to SAP on handling of pH-metry data will be used in the statistical analysis. A subject who withdraws prior to the last planned visit in the study will be included in the analyses up to the time of discontinuation. No imputation of missing data will be performed.

The addendum attached to the SAP provides guidance on how to handle pH-metry recordings and data for analysis and reporting.

5.3.2 PK drug concentration data

Concentration results that are below the lower limit of quantification (LLOQ) will be identified as below limit of quantification or not quantifiable (NQ) by the Bioanalysis lab.

For the PK analysis and plots of data, values <LLOQ before the first observed concentration will be entered as zero and values <LLOQ at any other time point will be excluded from the analysis (i.e., handled as missing data). The handling of these values will be justified and documented. Not quantifiable samples will be treated as missing data. In plots, the method used for handling values <LLOQ will be described in a footnote.

5.3.3 Outliers

In general, no outliers will be removed from analyses. However, if an outlier is identified in the PK analysis sets, an outlier analysis will be performed to determine the outlier effect on study results.

5.3.4 Multicentre Studies

The study will be performed at a single center.

5.4 Disposition and Background Information data

Descriptive summaries for continuous data and for categorical data will be provided in accordance with Section 5.22.

5.4.1 Subject Disposition

Number of subjects screened, screening failures, randomized, randomized and not taken IMP, randomized and taken IMP, completing the study, withdrawals (including withdrawal reason) and number of subjects in each analysis set will be summarized by dose group.

5.4.2 Protocol Deviations

Protocol deviations will be presented in listings.

5.4.3 Demographic and Baseline Characteristics

Demographic and baseline data will be summarized as appropriate depending on the data type (continuous or categorical), dose group and total.

5.4.4 Medical History

Medical coding will be performed by trained personnel at the Consultinc Oy. AEs and medical/surgical history verbatim terms are coded using the medical dictionary of regulatory activities (MedDRA, latest version available at eCRF setup) and will be presented in listings.

5.4.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the World Health Organization (WHO) drug dictionary classification system (WHODrug).

5.4.6 Treatment Compliance

During residential visits at the clinic (visits 2, 5 and 7), IMP will be administered at the clinic under medical supervision and entered in the eCRF by study personnel. On other days, subjects will self-administer IMP at home and register each intake of study drug in a paper diary. Text reminders to mobile phones will be sent to the subjects each day. At visit 5 (day 14) to the clinic, subjects will be asked to return any unused study drugs and all empty containers. Percent compliance will be calculated for the home administration period as:

% Compliance = 100 × (# tablets dispensed – # of tablets returned) / Expected # of tablets taken

The subjects in each dose level and dose group and their individual doses will be listed.

5.4.7 Subject Discontinuation

Subjects who discontinue the study will be summarized by reason for discontinuation and dose group and total.

5.5 Safety Analyses

No formal analyses will be performed for safety endpoints. Descriptive summaries for continuous and categorical safety data will be provided in accordance with Section 5.2 if not otherwise stated. Complete listings of all subject safety evaluations will be provided to support each summary table.

All presentations will be based on the full analysis set.

5.5.1 Adverse Events

All adverse events (Aes) occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), latest version available at the time of eCFR setup.

Aes will be tabulated by System Organ Class (SOC) and Preferred Term (PT). Summary tables will include number of subjects reporting the AE and as percentage of number of subjects by dose group and total. Event counts will be tabulated together with the subject counts.

Aes will be counted as follows:

- In summaries of number of subjects experiencing Aes, subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT.
- In summaries of number of subjects experiencing Aes, subjects reporting an AE more than once within that SOC/PT, but with different severities or different relationships, the worst category of severity/relationship will be used.

All Aes will be listed in by-subject data listings including verbatim term, MedDRA coded term, treatment, severity, relationship to IMP and action taken with respect to IMP.

SAEs will be summarized and listed separately.

5.5.2 Laboratory Evaluations

Descriptive summaries for clinical chemistry, hematology, coagulation, and urinalysis including absolute and relative (%) change from their baselines will be presented by dose group.

All laboratory parameters for individual subjects will be listed and subjects with clinically significant (according to the Investigator's criteria) abnormal values (out of normal range reported by the laboratory) will be flagged and listed separately. The categorization of laboratory parameter observations into 'Normal', 'Abnormal (Not Clinically Significant)', or 'Abnormal (Clinically Significant)' will be summarized using shift-tables (baseline category versus the worst observed categorization over time points post-baseline) by dose group.

5.5.3 Concomitant Medications

Concomitant medications will be summarized using WHO Drug preferred names and show number and percentage of subjects per preferred name.

All data will be presented by dose group and summarized overall, as well as presented in listings by dose group and subject.

5.5.4 Physical Examination

Physical examination will be presented as the number and percentage of subjects with Normal, Abnormal (not Clinically Significant) and Abnormal (Clinically Significant) result over time by Body System, dose group and total.

5.5.5 Vital Signs

Vital signs will be summarized by dose group and total. The summary will include absolute and percent change from baseline at each visit.

5.5.6 Electrocardiogram

Summaries of ECG results and change from baseline over time will be presented by dose group and total.

5.6 Pharmacokinetic Analyses

The PK analysis will be performed based on the PK analysis set. All PK analyses will be performed according to the actual treatment and dose received. Actual sampling time points relative to dosing will be used in the calculations. Pre-dose concentration values will be excluded from the NCA and set to 0.

The parameters to be determined in the study are presented in section 4.6. Parameters directly derived from the plasma concentration – time plot are not further described (i.e., C_{max}, C_{min}, t_{max}, C_{trough}), but all other calculations to be performed are described in detail below. Missing sample around the anticipated T_{max} may be flagged as "not accepted" upon decision by the Pharmacokineticist.

Estimation of the terminal elimination rate constant (λ_z)
The terminal elimination rate constant (λ_z) is calculated by log-linear regression of the terminal portion of the plasma concentration time profile. At least three observations will be used to estimate λ_z and the data points used in each estimation are indicated in the individual PK profiles. Data points for calculation of $T_{1/2}$ via λ_z are selected based on visual inspection of log-concentration-time plots of individual profiles and adjusted if needed. Any exclusion of data points in the terminal phase for this estimation should be clearly justified in the PK analysis log.

The adjusted R^2 should be considered in the selection of samples for calculation of λ_z and preferably exceed a value of 0.8. If λ_z cannot be reliably estimated, because of a low value of R^2, it will be flagged as "not accepted" and the associated parameters may be reported as "not determined". Use

of λ_z values obtained from data spanning less than three half-lives is permissible on the judgement of the Pharmacokineticist.

For subjects with insufficient PK data available leading to an extrapolated AUC ($AUC_{extrap\%}$) exceeding 20%, the parameters depending on λ_z will not be reported. The % of extrapolated AUC will be presented for all subjects.

Area under the plasma concentration-time curves (AUCs)
The area under the plasma concentration-time curves (AUCs) are calculated using the linear up -log down method (i.e., linear trapezoidal rule is used when concentration data is increasing and the logarithmic trapezoidal rule is used when concentration data is decreasing) using uniform weighing.

AUC_{inf} is calculated based on the AUC_{0-t} (AUC from time of dosing to the time point of the last quantifiable plasma concentration) and then extrapolated to infinity using the concentration in the last quantifiable sample (C_{last}) and the estimated terminal elimination rate constant (λ_z), as follows:

$AUC_{inf} = AUC_{0-t} + (C_{last}/\lambda_z)$

Accumulation ratio (R_{acc})
Accumulation index will be calculated for the observed accumulation ratio:
R_{acc} AUC = AUC_{tau} last dose / AUC_{tau} first dose
R_{acc} C_{max} = C_{max} last dose / C_{max} first dose

terminal half-life ($T_{1/2}$)
The half-life is calculated by $\ln 2/\lambda_z$.

Apparent total clearance (CL/F)
Total body clearance for extravascular administration, $CL/F = Dose/AUC_{inf}$, or $CL/F = Dose/AUC_{tau}$ at steady state

Apparent volume of distribution (V/F)
Volume of distribution based on the terminal elimination phase, $V/F = Dose/(\lambda z * AUC_{inf})$, or $V/F = Dose/(\lambda z * AUC_{tau})$ at steady state

Average concentration during a dosing interval (C_{aver})
C_{aver} will be calculated for repeated dosing, as follows: $C_{aver} = AUC_{tau}/_{tau}$

5.7 Summaries of Intragastric pH-metry

The Full Analysis Set for pH measurements is defined in the SAP addendum. pH measurements will be analyzed as per SAP addendum Full Analysis Set #2 “Statistical analysis of either channel 1 or 2 depending on which is deemed to be showing intragastric pH. Exclusion of “air measurements” is applied.”

Exploratory analyses will be performed based on Full Analysis Sets #1 and #3 in the SAP addendum.

Descriptive statistics of HTR pH >4, pH >5, and pH >6 over a 24-hour period during baseline, day 1, day 14 and day 15, will be presented by dose group.

A Mixed Model for Repeated Measurements (MMRM) will be utilized to analyze the percentage of time with intragastric pH >4, pH >5, and pH >6 (each pH cut-off separately), from now on referred to as Holding Time Ratio (HTR). The model will include the dose group, day (day 1, day 14) and the interaction between the dose group and day as fixed effects, the corresponding baseline HTR as a covariate and subject as a random effect. Least Squares Means (LSMs) , together with their corresponding 95% confidence intervals (CI) will be used to estimate the HTR for each dose group and day.

The LSMs of HTR pH >4, pH >5, and pH >6 will also be graphically displayed together with their corresponding 95% CIs by visit (day 1 and day 14) for each dose group. As a sensitivity analysis a MMRM-model (separately for the three pH cutoffs) excluding the baseline covariate will also be fitted to support the results from the primary statistical model.

The trajectories (profiles) for the average 24-hour intragastric pH (pH values averaged over subjects for each 10-minute median value) will be plotted for day 1 and day 14 separately. The plot for each day will show the mean 24-hour intragastric pH for the six dose groups and baseline.

Bar plots for the frequencies of subjects showing the HTR (0-60, 60-80, 80-85, 85-90, 90-95, 95-100) with gastric pH >4, pH >5, and pH >6 over a 24-hour period during baseline, day 1, day 14 and day 15, will be presented by dose group. The horizontal axis of the bar plot will represent categorized HTR with gastric pH >4, pH >5 or pH >6 over a 24-hour period.

Descriptive statistics will be presented for the mean intragastric pH 0-12 hours and 12-24 hours and 0-24 hours after dose (mean within individuals over 0-12 hours, 12-24 hours and 0-24 hours after dose morning dose for BID, evening dose for QD) for days 1 and 14 by dose group.

The mean intragastric pH 0-12 hours, 12-24 hours and 0-24 hours after dose (morning dose for BID, evening dose for QD) for day 1 and 14 will be plotted together and separately, with their corresponding 95% confidence intervals in a graph displaying the mean values by visit for each dose group.

5.7.1 Relationship between plasma concentration of Linaprazan and intra gastric acid secretion (pH)

To illustrate the association between pH and the linaprazan concentration, scatterplots with pH on the y-axis and a horizontal line to illustrate pH >4, and linaprazan concentration in the x-axis will be plotted. These scatterplots will be presented as follows: i) QD dosing groups, ii) BID dosing groups, iii) all dosing groups. All dosing groups in one scatterplot will be presented for Day 1, Day 14 and together. All measurements from within <2h after first dose on Day 1 will be omitted from the scatter plots.

Line plots with two y-axes (primary y-axis: pH, and secondary y-axis: plasma concentration of linaprazan) against time will be presented for the average pH and average concentration data added with error bars for the standard errors of the means. Three separate plots will be generated, i) QD dosing groups, ii) BID dosing groups, iii) all dosing groups. In the plots both the means pooled over the mentioned dosing groups and the mean for individual dosing groups will be presented for Day 1, Day 14 and together.

Also, scatterplots relating HTR for pH >4 and pH >5 versus linaprazan exposure parameters (AUC, Cmax and Cmin) (ref: Scarpignato et al 2023) will be produced, to explore which PK-parameter would be most relevant. The HTR response within each subject will be explored as well. Three separate plots will be generated, i) QD dosing groups, ii) BID dosing groups, iii) all dosing groups. All plots will be presented for Day 1, Day 14 and together. . All measurements from within <2h after first dose on Day 1 will be omitted from the scatter plots.

5.8 Changes to Planned Analysis

No changes for the main protocol planned analysis have been made. The formal analysis of the pH data and the association between the concentration and pH data was not defined in the protocol but introduced only in the SAP. Also, the PK/PD analysis set is a new analysis dataset defined only in the SAP.

6. References

1. Clinical Study Protocol CX842A2107. Final version 4.0 dated 10MAR2023.

2. Statistical Principles for Clinical Trials (ICH Topic E 9). EMEA. September 1998, CPMP/ICH/363/96.

7. Appendix

Table 1. Overall schedule of events

Visit → Assessment↓	**CSP Section**	**Visit 1 Screening**	**Visit 2 Residential**	**Visit 3 and Visit 4 Outpatient**	**Visit 5 Residential**	**Visit 6 Outpatient**	[redacted]	**Visit 8 Telephone follow-up**
Day→		**Day -28 to Day -2**	**Day -2 to 2**	**Day 5 and Day 10**	**Day 14 to Day 15**	**Day 16**		**7 days (±2 days) post-last dose[1]**
Informed consent	11.2.1	X						
Eligibility criteria	9.4, 9.5	X	X[2]					
Demographics	11.2.3	X						
Weight/height (BMI)	11.2.4	X						
Medical/surgical history	11.2.5	X						
HIV, Hep B and C test	11.2.7	X						
FSH test[3]	11.2.8	X						
Pregnancy test	11.2.9	X	X					
Urine drug screen	11.2.10	X	X[4]					
Alcohol test	11.2.11	X	X[4]					
Screening for Helicobacter Pylori	11.4.5	X						
Safety laboratory profile	11.4.3	X	X	X	X	X		
Vital signs[5]	11.4.4	X	X		X			

Visit → Assessment↓	CSP Section	Visit 1 Screening	Visit 2 Residential	Visit 3 and Visit 4 Outpatient	Visit 5 Residential	Visit 6 Outpatient	[redacted]	Visit 8 Telephone follow-up
Physical examination	11.4.2	X	X		X			
12-lead safety ECG	9.9	X	X		X			
Randomization	10.5	X[6]						
IMP administration[7]	11.3.1		X	X	X			
PK blood sampling[8]	11.3.2		X	X	X	X		
Intragastric pH measurement	9.6.1		X		X			
Standardized meals	10.5		X		X			
Hand-out of linaprazan glurate[9]	10.7		X					
Compliance check	N/A				X			
Overnight stay in clinic	11.2.12		X		X			
Baseline symptoms[10]	11.4	-------- X --------						
AEs[11]	9.6.2		---------- X ----------					
Prior and concomitant medications	11.2.1	---------- X ----------						

BMI: Body mass index. CSP: Clinical study protocol. FSH: follicle stimulating hormone. HIV: Human immunodeficiency virus. IMP: Investigational medicinal product. PK: Pharmacokinetic.

1. A final remote follow-up visit (Visit 8) will be conducted via telephone 7 days (±2 days) after the final dose of IMP, or after early withdrawal, to follow-up on AEs and concomitant medications.
2. Confirmation of eligibility prior to start of baseline pH-measurement.

3. Confirmation of menopause. Only in questionable cases at the discretion of the Investigator.
4. Additional random alcohol and drug tests can be performed at subsequent visits at the discretion of the Investigator.
5. Resting systolic and diastolic blood pressure, pulse and body temperature. Blood pressure and pulse should be measured with the subject in a supine position, after 10 minutes of rest.
6. Randomization will take place after confirmation of all eligibility criteria evaluated at the screening visit and prior to the start of Visit 2.

[redacted]

[redacted]

9. The subjects will administer linaprazan glurate at home from Day 3 to Day 13.
10. Baseline symptoms will be recorded from the signing of the informed consent form (ICF) up until first dose on Day 1.
11. AEs will be recorded from (first) dosing on Day 1 up until the follow-up visit (Visit 8), or early withdrawal.