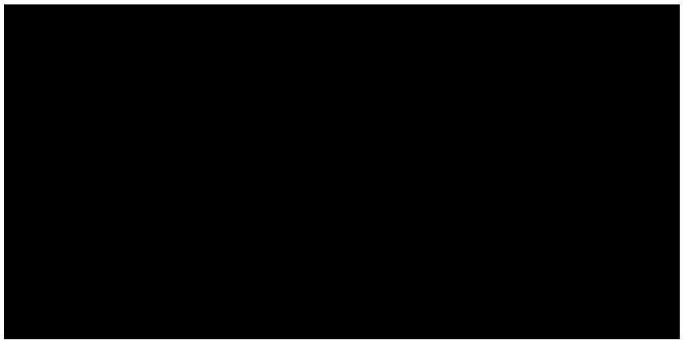

Statistical Analysis Plan

Client Study Code:	CX842A2106
Study Title:	A randomized, single dose, crossover study in healthy volunteers to investigate the relative bioavailability of linaprazan for a new oral tablet formulation of linaprazan glurate, and to assess the effect of food on the pharmacokinetics of linaprazan
SDS Project Code:	

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Document Control

Control

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Study statistician	[redacted]
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Authors	[redacted]
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Signatures

Prepared at SDS by:

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[redacted] (Statistician, [redacted] Date

[redacted]

[redacted] (Consultant, Clinical Pharmacology and DMPK) Date

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[redacted] (Statistician, [redacted] Date

[redacted]

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[redacted] (Biostatistician and Pharmacokineticist, [redacted] Date

Approved at Cinclus Pharma by:

[redacted]

[redacted] (Chief Medical Officer, Cinclus Pharma) Date

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0.1	[redacted]	2022-11-18	First draft
1.0	[redacted]	2023-01-16	Final version following review by [redacted] Statistician [redacted] Cinclus and [redacted]

[redacted]

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[redacted]

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
$AUC_{extrapol\%}$	AUC percent extrapolation
AUC_{inf}	AUC from 0 to infinity
AUC_{last}	AUC from 0 to time of last measurable plasma concentration
BMI	Body mass index
CL/F	Apparent total body clearance following extravascular administration
C_{max}	Maximum observed concentration
CS	Clinically significant
CSP	Clinical study protocol
CSR	Clinical study report
[redacted]	
CV	Coefficient of variation
DMP	Data management plan
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EPKAS	Exploratory PK analysis set
FAS	Full analysis set
GCP	Good clinical practice
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form

[redacted]

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IME	Important medical event
IMP	Investigational medicinal product
ISF	Investigator site file
IUD	Intra-uterine device
IUS	Intra-uterine system
[redacted]	
LLOQ	Lower limit of quantitation
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
NCA	Non-compartmental analysis
NCS	Not clinically significant
PI	Principal Investigator
PK	Pharmacokinetics
pK_a	Acid dissociation constant at a Log scale (negative Log base 10 of the acid dissociation constant K_a)
PKAS	PK analysis set
PR interval	(ECG) The time from the onset of the P wave to the start of the QRS complex
PT	Preferred term
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
RSI	Reference safety information
SAD	Single-ascending dose
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

[redacted]

$T_{1/2}$	Terminal elimination half-life
T_{lag}	Delay between the time of dosing and the time of appearance of plasma concentration
T_{max}	Time of occurrence of C_{max}
V_z/F	Volume of distribution following extravascular administration
WHO	World Health Organization
WHODrug	WHO drug dictionary

[redacted]

1. Introduction

This Statistical Analysis Plan (SAP) provides a detailed and technical description of the planned pharmacokinetic (PK) analyses and statistical evaluations of Cinclus Pharma AB's study CX842A2106: "A randomized, single dose, crossover study in healthy volunteers to investigate the relative bioavailability of linaprazan for a new oral tablet formulation of linaprazan glurate, and to assess the effect of food on the pharmacokinetics of linaprazan".

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) CX842A2106 v2.0 dated 12 Oct 2022.

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 single-center, open-label, randomized, single dose, 3-way crossover study in healthy volunteers designed to evaluate the relative bioavailability of a new oral tablet formulation of linaprazan glurate in comparison to a previously studied oral tablet formulation under fasting conditions, and to assess the effect of a high-fat, high-calorie meal on the pharmacokinetics (PK) of linaprazan glurate and the active metabolite linaprazan after the administration of the new oral tablet formulation.

2.1 Primary Objectives

- To evaluate the relative bioavailability of linaprazan between the test formulation of linaprazan glurate and the previously studied reference formulation after the administration of single 100 mg doses in fasting conditions.
- To assess the effect of a high-fat, high-calorie meal, in comparison to fasting conditions, on the PK of linaprazan after the administration of single 100 mg doses of the test formulation.

2.2 Secondary Objectives

- To evaluate the relative bioavailability of linaprazan glurate between the test formulation of linaprazan glurate and the previously study reference formulation after the administration of single 100 mg doses in fasting conditions.
- To assess the effect of a high-fat, high-calorie meal, in comparison to fasting conditions, on the PK of linaprazan glurate after the administration of single 100 mg doses of the test formulation.
- To collect additional PK data on linaprazan glurate and linaprazan after single 100 mg doses of the test formulation.
- To assess the safety and tolerability of single oral doses of 100 mg of linaprazan glurate.

2.3 Primary endpoint

- Relative bioavailability of linaprazan for the test formulation vs. reference formulation of linaprazan glurate, based on the means ratios for the following PK parameters:
    - Area under the plasma concentration vs. time curve (AUC) from time 0 to infinity (AUC_{inf})
    - AUC from time 0 to the last measurable concentration (AUC_{last})

[redacted]

- Maximum plasma concentration (C_{max})

- Relative bioavailability of linaprazan under fed conditions vs. fasting conditions, based on the means ratios for AUC_{inf}, AUC_{last} and C_{max}.

2.4 Secondary endpoints (PK)

- Relative bioavailability of linaprazan glurate for the test formulation vs. reference formulation of linaprazan glurate, based on the means ratios for AUCinf, AUClast and Cmax.
- Relative bioavailability of linaprazan glurate under fed conditions vs. fasting conditions, based on the means ratios for AUCinf, AUClast and Cmax.
- Additional linaprazan glurate and linaprazan PK parameters after single 100 mg doses of the linaprazan glurate test formulation in fasting and fed conditions:
  - Time to Cmax (Tmax)
  - Delay between the time of dosing and the time of appearance of plasma concentration (Tlag)
  - Terminal elimination half-life (T1/2)
  - AUC percent extrapolation (AUCextrapol%)
  - Apparent clearance (CL/F)
  - Apparent volume of distribution (Vz/F)

2.5 Secondary endpoints (Safety)

- Frequency, seriousness, and intensity of adverse events (AEs).
- Clinically significant changes in electrocardiograms (ECGs), vital signs, safety laboratory measurements (clinical chemistry/hematology/coagulation) and physical examination findings.

3. Study Details

3.1 Study Design

The study will follow a 3-treatment, 3-period cross-over design where eligible study participants will be randomly allocated to one of six different treatment sequences. The participants will receive single doses of the Test and Reference formulations as given below:

- Treatment A: [redacted]
- Treatment B: [redacted]
- Treatment C: [redacted]

The six treatment sequences are given in Table 1.

Table 1. Treatment sequences

Sequence no.	Sequence
1	ABC
2	ACB
3	BAC
4	BCA
5	CAB
6	CBA

[redacted]

3.2 Study population

The subjects participating in this study will be healthy male and female subjects 18–65 (both inclusive) years of age. More details regarding the study population, including inclusion and exclusion criteria, can be found in the CSP section 9.

3.3 Randomisation and Blinding

Block randomization (block size=6) will be used to generate the randomization list, which will show the assignment of subjects to 1 of the 6 treatment sequences shown on Table 1.

Randomisation lists for both parts of the study will be prepared by the DM provider and transferred to the Trial Master File (TMF) for archiving.

As this is an open label study, the treatment sequence 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, treatment sequence, period, and treatment.

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, 84 healthy volunteers are planned to be screened to achieve 54 randomized subjects (assuming a screening failure rate of approximately 37%), and at least 42 evaluable subjects. The number of subjects included in the trial is considered sufficient to describe and compare the PK of the Test formulation in relation to the Reference formulation.

3.5 Subject Replacement

Subjects who consent to study participation but discontinue study prior to IMP administration (dosing) may be replaced. If subjects are withdrawn after dosing, additional subjects may be included to obtain at least 42 evaluable subjects at the Sponsor's discretion after consultation with the Investigator.

4. Assessments

The overall schedule of assessments is given in Table 2. Details about each visit and the assessments made during the visit are given in the sections in the CSP that are listed in Table 2.

Table 2. Overall schedule of assessments

Visit → Assessment↓	**CSP Section**	**Visit 1 Screening**	**Visit 2-4 Treatment visits**			**Visit 5 Telephone follow-up[1]**
Day→		**28-1 days prior to first dose**	**Day -1 to 2 Residential**	**Day 3 Return to clinic**	**Day 4 Return to clinic**	**7 days (±2 days) post-last dose**
Informed consent	11.2.1	X				

[redacted]

Visit → Assessment↓	CSP Section	Visit 1 Screening	Visit 2-4 Treatment visits			Visit 5 Telephone follow-up[1]
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		X	X[4]			
Urine drug screen	11.2.9	X	X[4]			
Alcohol test	11.2.10	X	X[4]			
Safety laboratory profile	11.4.3	X	X		X	
Vital signs[5]	11.4.4	X	X		X	
Physical examination	11.4.5	X	X		X	
12-lead safety ECG[6]	11.4.2	X	X		X	
Randomization	9.9		X[7]			
High-fat, high-calorie breakfast (fed condition)	10.5.2		X			
IMP administration	10.5		X			
PK blood sampling[8]	11.3.1		X	X	X	
Standardized meals	9.6.1		X			
Overnight stay in clinic			X			
Baseline symptoms[9]	11.2.11	---------- X ----------				
Adverse events (AEs)[10]	11.4.1		---------- X ----------			
Prior and concomitant medications	11.2.6	---------- X ----------				

BMI: Body mass index. CSP: Clinical study protocol. ECG: electrocardiogram. FSH: Follicle stimulating hormone. HIV: Human immunodeficiency virus.

1. Or after early withdrawal.
2. Confirmation of eligibility. Visit 2 only. Can be done on Day -1 or Day 1 prior to randomization.
3. Confirmation of menopause. Only in questionable cases at the discretion of the Investigator.
4. At Visit 2 only. 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. ECG time window between 4h and 4h30min after dosing.

[redacted]

7. At Visit 2 only.
8. Collected within -01:00 hh:mm prior to IMP administration (pre-dose) and at 00:15, 00:30, 01:00, 01:15, 01:30, 02:00, 03:00, 04:00, 06:00, 08:00, 12:00, 14:00, 20:00, 24:00, 36:00, 48:00 and 72:00 hh:mm post-dose. Actual time for PK blood sampling must not deviate more than ±10% from the planned times.
9. Baseline symptoms will be recorded from the signing of the informed consent form (ICF) up until first dose on Day 1.
10. AEs will be recorded from dosing on Day 1 up until the follow-up visit (Visit 5), or early withdrawal.

4.1 Disposition and Other Supporting Assessments

4.2 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, 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 diarrhoea 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)

Subjects with minor protocol deviations may be included in the PK analysis set. If so, handling of minor protocol deviations in the PK analyses will be documented.

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

4.3 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.

4.4 Medical/Surgical History

Medical/surgical history will include all relevant diseases and operations within 2 months prior to screening as judged by the Investigator.

4.5 Prior and Concomitant Medications

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.

4.6 Safety Variables

4.6.1 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

[redacted]

be any unfavourable 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 Serious Unexpected Adverse Reaction (SUAR) 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 (Mild, Moderate, Severe)
- Causality (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 decreased, 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.

4.6.2 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, or Abnormal CS. 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

[redacted]

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

4.6.3 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-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

4.6.4 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.

4.6.5 ECGs

A 12-lead ECG will be recorded at admission (day -1), after 4 hours (with a time window of 30 min) on Day 1 and at discharge from the study i.e., 72 hours after dosing (which is on day 4 of the study). The ECG measurements must occur after the PK and safety blood samples have been collected.

The following variables will be recorded:

[redacted]

- Resting Heart Rate
- PQ/RR
- QRS
- QT
- QTcF

Any post-dose abnormalities will be specified and documented as CS or not NCS. Abnormal post-dose findings assessed by the Investigator as CS will be reported as AEs.

4.7 Pharmacokinetic Assessments

Blood sampling time points for PK analyses and their allowed sampling time windows are detailed in section 8.1, 11.1 and 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 [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.

PK parameters:

The following PK parameters will be obtained or calculated from the plasma concentration-time data of linaprazan glurate and linaprazan, after dosing with Treatment A (Reference formulation, fasting condition), B (Test formulation, fasting condition) and C (Test formulation, fed condition) if sufficient data is available:

- AUCinf (the area under the concentration–time curve from time zero extrapolated to infinity)
- AUClast (area under the concentration-time curve from time zero to time of last measurable observed concentration)
- Cmax (maximum observed concentration)
- T_{lag} (Delay between the time of dosing and the time of appearance of plasma concentration), if applicable
- T_{max} (time to maximum observed concentration)
- λ_z (elimination rate constant)
- $T_{1/2}$ (terminal half-life)
- CL/F (apparent total clearance)
- V/F (apparent volume of distribution)

Additional PK parameters may be determined if deemed appropriate.

How the PK parameters are determined are further described in section 5.6

[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). An interim evaluation of PK and safety data will be performed when all subjects finalized sampling after their first dose.

All final 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. Relative bioavailability will be estimated for individuals who have provided at least two PK profiles for the comparison of interest (A and B) or (B and C).

5.1.3 Exploratory PK Analysis set (EPKAS)

[redacted]

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 parameters 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).

[redacted]

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 treatment and will be annotated with the total population size relevant to that table/treatment, including any missing observations. Summary by treatment corresponds to summary by treatment ignoring period (treatment sequence), i.e., linaprazan glurate fasted (Reference formulation), x linaprazan glurate fasted (Test formulation), and linaprazan glurate fed (Test formulation).

TLF mock shells will be shown in a separate TLF plan.

5.2.2 Presentation 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 listing tables included in the appendices of the CSR. These data will be presented and analysed 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 summarised 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 AUCinf, AUClast, and Cmax, the geometric mean and geometric coefficient of variation (CV%) will also be presented. For the PK parameters T_{max} and $T_{1/2}$, only the median, minimum, and maximum values will be presented. For the PK parameter $AUC_{extrapol\%}$, 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 treatment (A, B and C).

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.

5.3 Statistical/Analytical issues

5.3.1 Missing Data and Handling of Dropouts

All available 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.

[redacted]

5.3.1.1 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.

No value of AUC_{inf}, $t_{1/2}$, CL/F and V/F will be reported for cases that do not exhibit a good estimate for the terminal log-linear phase in the concentration versus time profile (for details see 5.6).

5.3.2 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.

5.3.3 Data Transformations and Derived Variables

The natural-log (ln) transformation will be made for the PK parameters AUC_{last}, AUC_{inf} and C_{max} prior to calculating the ratios of these parameters for the Test and Reference products and obtaining the confidence intervals for the ratios.

[redacted]

5.3.5 Multicentre Studies

The study will be performed at a single centre.

[redacted]

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 treatment sequence.

5.4.2 Protocol Deviations

Protocol deviations, and implications of the 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 by treatment sequence.

5.4.4 Medical History

Medical history will be coded by system organ class (SOC) and preferred term (PT) using MedDRA and presented as number and percentage of subjects in each SOC and PT by treatment sequence and will be presented in listings.

5.4.5 Prior and Concomitant Medications

Prior medications will be coded in the electronic data capture (EDC) system using WHODrug preferred terms.

5.4.6 Treatment Compliance

IMP administered will be listed by subject and sequence.

5.4.7 Premature Discontinuation

Subjects who discontinue the study prematurely will be summarized by reason for early discontinuation and treatment sequence.

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) version 24 or later.

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 percent of number of subjects dosed by treatment.

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 a TEAE more than once within that SOC/PT, but with different severities or different relationships, the worst category of severity/relationship will be used.
- If the severity or relationship is missing for a TEAE, it will be considered as missing in the summary tables.

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 summarised and listed separately. The summary will include number of SAEs as well as the number and percentage of subjects reporting any SAE by SOC and PT for each treatment.

5.5.2 Laboratory Evaluations

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

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 treatment).

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 treatment and summarized overall, as well as presented in listings by treatment sequence 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, abnormal clinically significant result over time by Body System and treatment.

5.5.5 Vital Signs

Vital signs will be summarised by treatment. The summary will include change from baseline at each visit.

5.5.6 Electrocardiogram

Summaries of ECG results and change from baseline over time will be presented by treatment.

The last measurement taken before dose intake.

5.6 Pharmacokinetic Analyses

The PK analysis will be performed based on the PK analysis set and Exploratory 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.

[redacted]

The parameters to be determined in the study are presented in section 4.7. Parameters directly derived from the plasma concentration – time plot are not further described (i.e. C_{max}, t_{max}), but all other calculations to be performed are described in detail below. Missing sample around the anticipated tmax may be flagged as "not accepted" upon decision by the pharmacokineticist.

For subjects with insufficient PK data available leading to an extrapolated AUC (%Extrap AUC) exceeding 20%, the parameters depending on λ_z (AUC_{inf}, $t_{1/2}$, CL/F, and V/F) will not be reported.

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, resulting in a low value of R^2, it will be flagged as "not accepted" and the associated parameters (AUC_{inf}, $t_{1/2}$, CL/F, and V/F) 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 provided that the resulting extrapolated area is not more than 20% of the total AUC determined. 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_{last} (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 (Clast) and the estimated terminal elimination rate constant (λ_z), as follows:

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

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, $CL/F = Dose/AUC_{inf}$

Apparent volume of distribution (V/F)
Volume of distribution based on the terminal elimination phase, $V/F = Dose/(\lambda z * AUC_{int})$

Relative Bioavailability (F)

The assessments of relative bioavailability will be based upon 90% confidence intervals for the ratios of the population geometric means (Treatment B [Test]/Treatment A [Reference]) for AUC_{inf}, AUC_{last}, and C_{max}, which will be obtained from the Linear Fixed Effects model described in Section 5.6.1.

The food effect evaluation will be based upon 90% confidence intervals for the ratios of the population geometric means (Treatment C [Test, fed] /treatment B [Test, fasted]) for AUC_{inf}, AUC_{last}, and C_{max}.

[redacted]

5.6.1 *Statistical Analysis of PK Parameters*

The statistical analysis of the PK data will be performed on the PK analysis set. A comparison of natural-log (ln)-transformed PK parameters $AUC_{inf,}$ $AUC_{last,}$ and C_{max} will be made to evaluate the relative bioavailability of the Test versus Reference formulations, by performing a linear fixed effects model analysis using PROC MIXED of SAS®. The model will include SEQUENCE, TREATMENT (A, B or C), and PERIOD (1, 2, or 3) and SUBJECT as fixed effects, with SUBJECT nested within SEQUENCE. The inferential results (least-squares [LS] means, difference between LS means, and 90% CIs of the difference) will be exponentiated to the original scale. Geometric LS means, geometric mean ratios (GMR) and 90% CIs will be presented.

From the Linear Model the following comparisons will be evaluated:

- Treatment B (Test, fasted) compared with Treatment A (Reference, fasted)
- Treatment B (Test, fasted) compared with Treatment C (Test, fed)

The first comparison is used to evaluate the relative bioavailability of single doses (100 mg) of the two formulations of linaprazan glurate under fasted conditions. The second comparison is used to assess the food effect on the PK of the Test formulation.

The Linear Fixed Effects Model analysis will be performed using the following example SAS® code:

```
PROC MIXED DATA=BA;
CLASS TREATMENT SUBJECT PERIOD SEQUENCE;
        MODEL LN_PK_PARAMETER = TREATMENT PERIOD SEQUENCE SUBJECT(SEQUENCE) /
        DDFM=SATTERTH;
ESTIMATE "TREATMENT B VERSUS TREATMENT A" TREATMENT -1 1 0 / CL ALPHA = 0.1;
ESTIMATE "TREATMENT C VERSUS TREATMENT B" TREATMENT 0 -1 1 / CL ALPHA = 0.1;
LSMEANS TREATMENT;
RUN;
```

This Fixed Effects Model is the primary method of analysis and is consistent with the EMA recommended methodology of analysis and will involve only study completers.

In addition, the Random Effects Model given by the SAS code below (which is consistent with the FDA recommended methodology of analysis) will be used as a supplementary analysis. The method uses all available data. The within- and between-subject variability is estimated directly for the model for all AUC and C_{max}.

The Linear Mixed Effects Model analysis will be performed using the following example SAS® code:

```
PROC MIXED DATA=BA;
CLASS TREATMENT SUBJECT PERIOD SEQUENCE;
        MODEL LN_PK_PARAMETER = TREATMENT PERIOD SEQUENCE / DDFM=KR;
        RANDOM SUBJECT(SEQUENCE);
        ESTIMATE "TREATMENT B VERSUS TREATMENT A" TREATMENT -1 1 0 / CL ALPHA = 0.1;
ESTIMATE "TREATMENT C VERSUS TREATMENT B" TREATMENT 0 -1 1 / CL ALPHA = 0.1;
LSMEANS TREATMENT;
RUN;
```

[redacted]

5.7 Changes to Planned Analysis

No changes for the main protocol planned analysis have been made. [redacted]

6. References

1. Clinical Study Protocol CX842A2106. Final version 2.0 dated 12 Oct 2022.
2. Statistical Principles for Clinical Trials (ICH Topic E 9). EMEA. September 1998, CPMP/ICH/363/96.

Statistical Analysis Plan CX842A2106 v1.0

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