Clinical Study Protocol	
EudraCT no.	2022-002273-29
Investigational medicinal product	Linaprazan glurate
Study code	CX842A2106
Protocol version and date	Final V2.0, 12OCT2022

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

Phase	I
Test product and dose	Linaprazan glurate (formerly X842) 100 mg
International non-proprietary name (INN)	Linaprazan glurate
Unique ingredient identifier (UNII)	3VG4D399DT
Sponsor signatory	[redacted] PhD, CMO Cinclus Pharma Holding AB World Trade Center, Kungsbron 1 SE-111 22 Stockholm, Sweden
Principal Investigator	[redacted] MD [redacted]
Clinical study conduct and management	[redacted]

1 STUDY SYNOPSIS

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

Study code	**EudraCT no.**
CX842A2106	2022-002273-29
Planned study period	**Phase of development**
Q3 2022 – Q4 2022	Phase I

Principal Investigator

[redacted]

Study design

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 substance linaprazan after the administration of the new oral tablet formulation.

Objectives

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.

Secondary objectives

- To evaluate the relative bioavailability of linaprazan glurate between the test formulation on 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.

Endpoints

Primary endpoints

- 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})

- 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}.

Secondary endpoints (PK)

- Relative bioavailability of linaprazan glurate for the test formulation *vs.* reference formulation of linaprazan glurate, based on the means ratios for AUC_{inf}, AUC_{last} and C_{max}.
- Relative bioavailability of linaprazan glurate under fed conditions *vs.* fasting conditions, based on the means ratios for AUC_{inf}, AUC_{last} and C_{max}.
- 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 C_{max} (T_{max})
  - Delay between the time of dosing and the time of appearance of plasma concentration (T_{lag})
  - Terminal elimination half-life (T1/2)
  - AUC percent extrapolation ($AUC_{extrapol\%}$)
  - Apparent clearance (CL/F)
  - Apparent volume of distribution (V_z/F)

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.

Number of subjects

Approximately 84 healthy volunteers are planned to be screened to achieve 54 randomized subjects and at least 42 evaluable subjects, *i.e.* subjects that complete all treatment visits.

Diagnosis and eligibility criteria

Healthy male and female subjects, 18-65 years of age (inclusive), with a body mass index (BMI) of 18.5-30.0 kg/m2 (inclusive), who are willing to comply with study procedures and who have given written informed consent are considered to be eligible for the study. Subjects with a history or presence of any clinically significant disorders, as judged by the Investigator, will not be included in the study. Both male and female study participants must agree to use highly effective methods of contraception to prevent pregnancy.

Methodology

Subjects participating in the study will attend 4 in-person visits to the study clinic, a screening visit (Visit 1) followed by 3 treatment visits (Visits 2, 3 and 4). The treatment visits are separated by wash-out periods of a minimum of 5 days, which corresponds to approximately 5 half-lives of the active substance linaprazan. The treatment visits will be followed by a remote follow-up/end-of-study visit via telephone (Visit 5), 7 days (±2 days) after the final dose.

Screening (Visit 1) will take place within 28 days prior to the start of treatment and will include an eligibility check, collection of demographic and medical history data as well as a review of health status, including a physical examination and collection of ECGs, vital signs and safety laboratory blood samples.

Eligible subjects will be admitted to the study clinic on Day -1 of Visit 2 and will remain at the study clinic until Day 3 (residential period). After admission, each subject's eligibility will be confirmed, and baseline safety laboratory blood samples, 12 lead safety ECGs, and vital signs will be collected. Study clinic admission on Visits 3 and 4 will follow the same procedure, without the confirmation of eligibility.

Subjects will be randomized into one of 6 treatment sequences. There will be 3 treatments as follows:

- Treatment A: 100 mg linaprazan glurate reference formulation (4x25 mg oral tablets) in fasting conditions.
- Treatment B: 100 mg linaprazan glurate test formulation (1x100 mg oral tablet) in fasting conditions.
- Treatment C: 100 mg linaprazan glurate test formulation (1x100 mg oral tablet) in fed conditions.

During fasting conditions (Treatments A and B), subjects must fast for at least 10 hours before the anticipated dosing time and 4 hours post-dose. During the fed conditions (Treatment C), a high-fat, high-calorie breakfast will be served 30 minutes prior to the anticipated dosing time. Subjects must consume this meal in 30 minutes or less. Water, but no other drinks will be allowed ad libitum except for 1 hour before dosing to 30 minutes after dosing. Subjects will be served standardized meals during the residential period in the study clinic.

On dosing day (Day 1) of Visits 2, 3 and 4, following randomization (during Visit 2) and at corresponding time-points during Visits 3 and 4, subjects will be administered single doses of investigational medicinal product (IMP) (dosing). Subjects will be carefully monitored by clinical staff during and after dosing. Vital signs and 12 lead safety ECGs will be assessed at 4 hours post-dose, and AEs will be recorded from first dose on Day 1. There is immediate access to emergency equipment, qualified staff, and the nearby intensive care unit (ICU) of [redacted] in case of an emergency.

Subjects will remain in the study clinic for at least 36 hours for continuous PK blood sampling. PK blood samples will be collected pre-dose (within -01:00 hh:mm prior to dosing) 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. Subjects will be temporarily discharged from the study clinic after the 36-hour PK blood sample on Day 2. Subjects will return to the study clinic in the morning of Day 3 and again in the morning of Day 4 for PK blood sampling at 48 and 72 hours post-dose, respectively. On Day 4, formal discharge procedures will take place, including safety laboratory, physical examination, vital signs and 12-lead safety ECG assessments as well as the collection of AEs and uses of concomitant medications.

A final remote follow-up visit (Visit 5) 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. Visit 5 will count as each subject's end-of-study visit, and the date of last subject's end-of-study visit will count as the overall end-of-study date.

Investigational medicinal product

- **Test formulation:** [redacted]
- **Reference formulation:** [redacted]

Duration of treatment

The participating subjects will receive single 100 mg doses of IMP on 3 occasions.

Duration of each subject's involvement in the study

Each subject is expected to participate in the study for approximately 49 days. This includes the up to 28-day screening period and approximately 3 weeks of treatment and follow-up.

PK assessments

Blood samples for the analysis of the PK of linaprazan glurate and linaprazan will be collected 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, 36:000, 48:00 and 72:00 hh:mm post-dose.

Safety assessments

AE reporting, resting 12-lead ECG, vital signs (blood pressure, pulse and body temperature), physical examination, use of concomitant medications, and blood sampling for clinical chemistry, hematology and coagulation parameters.

Statistical methods

All data will be listed by treatment and subject.

All descriptive summaries and statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary NC, United States). PK parameters will be calculated using Phoenix WinNonlin® version 8.3 or later (Certara, United States).

Continuous data will be presented in terms of evaluable observations, arithmetic mean, standard deviation (SD), as well as median, minimum, and maximum value. In addition, for the parameters AUC and C_{max} the geometric mean and geometric coefficient of variation (CV%) will be presented.

Categorical data will be presented as counts and percentages.

When applicable, summary data will be presented by treatment and by assessment time. Individual subject data will be listed by subject number, treatment sequence and, where applicable, by treatment and assessment time.

The PK parameters will be calculated by non-compartmental analysis (NCA). 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 T_{max} and $T_{1/2}$, only the median, minimum, and maximum values will be presented. For the PK parameters AUC_{inf}, AUC_{last}, $AUC_{extrapol\%}$ and C_{max}, the geometric mean and CV% will also be presented. Additional PK parameters may be determined if deemed appropriate.

The analyses performed on the PK parameters will also include equivalence testing of AUC_{inf}, AUC_{last}, and C_{max} between the reference formulation (Treatment A) and the test formulation (Treatment B) in fasting conditions, as well as between the test formulation in fasting conditions (Treatment B) and in fed conditions (Treatment C).

AEs will be summarized by Medical Dictionary of Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by treatment and overall. All AE data will be listed by treatment and subject and include the verbatim term entered by the Investigator as well as PT.

Study reporting

After completion of the study, an International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 guideline-compliant clinical study report (CSR) will be prepared.

2 TABLE OF CONTENTS

List of tables

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
ADL	Activities of daily living
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
BID	Twice daily (from Lat. *bis in die*)
BMI	Body mass index
CA	Competent authority
C_{avg}	Steady-state average concentration
CHL	Chinese hamster lung (cells)
CIOMS	Council for International Organizations of Medical Sciences
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
DMSO	Dimethyl sulfoxide
DSUR	Development safety update report
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
eGERD	Erosive gastroesophageal reflux disease

Abbreviation	Explanation
EU	European Union
FAS	Full analysis set
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GDPR	General data protection regulation
GERD	Gastroesophageal reflux disease
GMP	Good manufacturing practice
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent ethics committee
IME	Important medical event
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
INN	International non-proprietary name
IR	Immediate release
ISF	Investigator site file
IUD	Intra-uterine device
IUS	Intra-uterine system
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LLOQ	Lower limit of quantitation
MAD	Multiple-ascending dose
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MPA	Medical Products Agency
MTD	Maximum tolerated dose
MOH	Ministry of Health Republic of Slovenia

Abbreviation	Explanation
NCA	Non-compartmental analysis
NCS	Not clinically significant
NIJZ	National Institute of Public Health
NOAEL	No observed adverse effect level
P-CAB	Potassium-competitive acid blockers
PI	Principal Investigator
PII	Personally identifiable information
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
PPI	Proton pump inhibitor
PR interval	(ECG) The time from the onset of the P wave to the start of the QRS complex
PT	Preferred term
QA	Quality assurance
QC	Quality control
QP	Qualified person
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
SDV	Source data verification
SOC	System organ class
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal elimination half-life

Abbreviation	Explanation
T_{lag}	Delay between the time of dosing and the time of appearance of plasma concentration
T_{max}	Time of occurrence of C_{max}
TMF	Trial master file
UNII	Unique ingredient identifier
V_z/F	Volume of distribution following extravascular administration
WHO	World Health Organization
WHODrug	WHO drug dictionary

4 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

4.1 Medical emergencies contact

The Principal Investigator (PI) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such. Detailed SAE reporting procedures are described in Section 11.4.1.13.

In the case of a medical emergency, the Investigator may contact the Sponsor's medical representative person (Table 4.1-1).

Table 4.1-1 Medical emergencies contact

Name	Function in the study	Telephone number	E-mail
[redacted] MD, PhD, CMO	Sponsor's medical representative	[redacted]	[redacted]

5 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor

Cinclus Pharma Holding AB

World Trade Center, Kungsbron 1
SE-111 22 Stockholm, Sweden

Sponsor's medical representative

[redacted]

Sponsor's project manager

[redacted]

Clinical conduct

[redacted]

Principal investigator

[redacted]

Study management

[redacted]

Clinical research manager

[redacted]

Biostatistician

[redacted]

Pharmacokineticist

[redacted]

Medical writer

[redacted]

Medical monitor

[redacted]

Laboratory (safety)	[redacted]
Laboratory (bioanalysis)	
Investigational Medicinal Product (IMP) manufacturing, packaging and labelling (test formulation)	
IMP import and qualified person (QP) release (test formulation)	
IMP manufacturing (reference formulation)	
IMP packaging, labelling and QP release (reference formulation)	
Pharmacy	
Electronic data capture (EDC) system provider	

Signatures are provided in Section 19.

6 INTRODUCTION

6.1 Background

Gastroesophageal reflux disease (GERD) is a common chronic disorder with high prevalence in North America and Europe, where at least weekly reflux symptoms range from 10% to 30%. Epidemiologic data are limited but suggest a lower prevalence in Asia [1], although prevalence is increasing in this region and other developed countries [2]. A universally accepted definition of treatment success in GERD is not available [1].

A new class of molecules, potassium-competitive acid blockers (P-CABs), present a new mode of action, that, in principle, allows full intragastric acid control both day and night. Such acid inhibitory properties in humans are likely to allow for the successful treatment of subjects with erosive GERD (eGERD), the most acid-sensitive GERD sub-population. Linaprazan, the main metabolite of the study drug of the present study, linaprazan glurate (previously designated X842), has been shown to provide a modest duration of effective acid control in humans [3, 4]. In contrast, linaprazan glurate shows a slower uptake after oral administration compared to orally administered linaprazan. This results in a lower maximum concentration (C_{max}) and longer plasma residence time of linaprazan after the administration of linaprazan glurate. This is thought to translate into a lower load of linaprazan to the liver and a prolonged control of intragastric acidity. Previous studies have shown a lower C_{max} and area under the plasma concentration *vs.* time curve (AUC) for linaprazan after repeated dosing with linaprazan glurate [5].

The first-in-human (FIH) study of linaprazan glurate (single ascending dose [SAD] and multiple ascending dose [MAD]), CX842A2101 (EudraCT no. 2016-002506-39) [6], was performed with a suspension formulation to allow dosing per kg. [redacted] was developed for use in the Phase II development. This is the formulation that will be used as a reference in the present study. The pharmacokinetic (PK) and pharmacodynamic (PD) properties of this formulation have been evaluated in 2 Phase I studies: A 2-period crossover relative bioavailability study [7] and an exploratory PK/PD parallel-group study [8]. Both studies were designed to support the dose selection for Phase II studies of linaprazan glurate. One (1) Phase II active comparator-controlled dose-finding study, CX842A2201 (EudraCT no. 2020-003319-91) [9], is currently ongoing using this tablet formulation.

A new IR oral tablet formulation of [redacted] intended therapeutical dose, has been developed for use in the Phase III development. This is the test formulation that will be used in the present study.

6.1.1 Clinical experience

In the FIH SAD/MAD study CX842A2101, the safety, tolerability and PK properties of linaprazan glurate and linaprazan were evaluated [6]. The study concluded that linaprazan glurate was well tolerated in single doses up to 4.0 mg/kg and multiple doses up to 2.0 mg/kg, and that the intragastric pH correlated with the plasma concentration of linaprazan during the time interval 0-24h after dose.

In the relative bioavailability study of the reference formulation CX842A2102 (EudraCT no. 2019-001231-31) [7], the anticipated target trough plasma concentration of linaprazan for optimal intragastric acid control could not be achieved with once daily dosing and the primary endpoint could not be calculated from the collected study data. It was therefore needed to explore the PK and PD properties of linaprazan glurate oral tablets given twice daily (BID) for 3 consecutive days to support the dose selection for Phase II studies. In the exploratory PK/PD study CX842A2103 (EudraCT no. 2019-003963-24) [8], an increase in exposure to linaprazan after the administration of linaprazan glurate produced an increase in PD effect with respect to elevated control of intragastric pH (evaluated as the time and percentage of time with an intragastric pH >4).

In both studies, linaprazan glurate was found to be safe and well-tolerated as assessed by the evaluation of adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs) and safety laboratory parameters.

There have been no SAEs nor any AEs that led to subject withdrawal after the administration of linaprazan glurate in any of the 3 completed clinical studies. The number of subjects experiencing AEs assessed as related to the IMP show no increase with larger doses of linaprazan glurate, and there have been no clinically relevant findings or dose-dependent mean changes over time in physical examinations, vital signs, ECGs, or laboratory parameters.

6.1.2 Pharmacokinetic summary

In the SAD/MAD study with the oral suspension, plasma concentrations of the parent compound linaprazan glurate [6] were below the lower limit of quantitation (LLOQ) so PK parameters and dose linearity could not be calculated. For the active metabolite linaprazan, the exposure after a single administration of linaprazan glurate showed a less than dose proportional increase in exposure, with regard of both C_{max} and AUC, in the dose range 0.08 mg/kg to 4.0 mg/kg. Dose linearity was shown for linaprazan for SAD Cohort 1-5, but not for SAD Cohort 6-7. The exposure after a single administration of the highest dose (4.0 mg/kg) was lower than expected, and the variability among subjects was high. No indication of food interaction was seen, however there was a high variability for both C_{max} and AUC under fed conditions.

The plasma exposure to linaprazan in the MAD part of the study was lower than expected after the first dose as compared to the corresponding SAD doses. In MAD Cohorts 2 and 3 given multiple 2.0 mg/kg doses of linaprazan glurate, the exposure was lower than after the first dose as compared to SAD Cohort 5 (2.0 mg/kg) and MAD Cohort 1 (1.0 mg/kg). High variability was also seen among subjects. The exposure was also lower on Day 5 as compared to Day 1 at both dose levels (1.0 and 2.0 mg/kg). High variability was again seen among subjects.

In the relative bioavailability study of the reference formulation [7], linaprazan glurate was detectable but plasma concentrations were low and variable. There was an approximately linear increase in linaprazan glurate plasma exposure between 50 mg and 150 mg on Day 1. The 50 mg dose resulted in comparable mean C_{max} and AUC on Day 1 and Day 2. For the 150 mg dose, mean exposure (C_{max} and AUC) was lower on Day 2 compared to Day 1. There was [redacted]

[redacted]

6.1.3 Drug description

[redacted]

6.1.4 Indication

Linaprazan glurate is under development for the treatment of [redacted]

6.1.5 Dosage

The dose level of linaprazan glurate to be tested in this study is 100 mg (3 single doses). This [redacted]

6.1.6 Mechanism of action

The active substance linaprazan is a member of the class of compounds that inhibit gastric H^+, K^+-ATPase by K^+-competitive binding [10]. Based on the results of clinical studies with linaprazan, a series of new compounds with improved properties has been developed [3, 4].

[redacted]

6.1.7 Non-clinical toxicology

Male and female Sprague-Dawley rats were administered linaprazan glurate in single oral doses of up to 250 mg/kg and repeated oral doses of up to 150 mg/kg for 28 consecutive days followed by a 4-week recovery period. Male and female beagle dogs were administered linaprazan glurate in single oral doses of up to 120 mg/kg and repeated oral doses up to 48 mg/kg for 28 consecutive days followed by a 28-day recovery phase.

No signs of treatment-related toxicity have been noted following single oral administration of linaprazan glurate at dose levels of up to 250 mg/kg in rats. Some emesis has been seen at all dose levels investigated in dogs. However, this is a common clinical sign in toxicity studies in dogs and is not regarded as having any toxicological relevance unless it is very pronounced and/or frequent. The maximum tolerated dose (MTD) following a single dose of linaprazan glurate was above the maximum given doses of 250 mg/kg in rats and 120 mg/kg in dogs. In the 28-day repeat-dose study in rats, and a study of fertility and early embryonic development also in rats, the no observed adverse effect level (NOAEL) was considered to be 150 mg/kg in both males and females. In the 28-day repeat-dose study in dogs, the NOAEL was considered to be 48 mg/kg in both males and females. In all instances, these were the highest doses given in each study.

In vitro (Ames test and chromosome aberrations in Chinese hamster lung [CHL] cells) and *in vivo* (micronucleus test in rats) genotoxicity studies showed that linaprazan glurate did not show mutagenic activity either with or without metabolic activation.

For detailed information, refer to the investigator's brochure (IB) for linaprazan glurate.

6.2 Study rationale

[redacted]

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

The overall study design and schedule of events is described in Section 8.1 and the rational for the study design is outlined in Section 8.2.

6.3 Risk/benefit assessment

6.3.1 General risk/benefit assessment

As the healthy subjects in this study are unlikely to experience any medical benefit from their participation, their safety and wellbeing is of the utmost importance. Toxicology studies and previous clinical studies on linaprazan and linaprazan glurate have indicated a low toxicity with no major concerns at the studied dose levels, nevertheless there is a clear need for attention to risk mitigation.

No treatment-related changes were observed in studies on embryo-fetal development in rats and rabbits (GLP compliant), or in fertility mating behavior and early embryonic development in rats (not GLP compliant). Contraception requirements will be applied to both male and female study participants to prevent pregnancy.

Each volunteer will be provided with a subject information card with information about participation in the study, including known and expected benefits and risks.

Based on the results from previous studies with linaprazan glurate (refer to Section 6.1.1), together with published data on administration of linaprazan going back nearly 2 decades, linaprazan has been considered safe and well tolerated at exposures higher than the exposures estimated for the present study. The overall evaluation is that the proposed linaprazan glurate single doses of 100 mg will be safe and well tolerated, based on the linaprazan exposure noted clinically in the previous single- and repeat-dose studies after administration of both linaprazan glurate (refer to Section 6.1.1) and linaprazan (public data) in healthy volunteers. More detailed information about the known and expected benefits and risks and reasonably expected ARs of linaprazan glurate are found in the current version of the linaprazan glurate IB.

The medical staff at [redacted] experience from Phase I studies. The PI at the study clinic will ensure that adequate resources, facilities and procedures are available to manage emergency situations should they occur during the study, including medications to address any expected or unexpected adverse reactions (ARs) in the unlikely event of a linaprazan glurate overdose (refer to Section 11.4.1.17). [redacted] shall contact call center of Regional Information Centre - Administration of the Republic of Slovenia (112) for support in case of emergencies.

Aside from any risks related to the study drug linaprazan glurate, there may also be risks related to the medical devices used in the study (*e.g.*, indwelling venous catheters), as well as study assessments and sampling procedures (*e.g.*, blood-pressure measurements using a blood pressure cuff and frequent blood-sampling). However, these devices and procedures are used in routine medical care and the risk associated with their use is considered low.

6.3.2 Risk assessment with regard to the COVID-19 pandemic

Applicable recommendations from the European Medicines Agency (EMA) [11, 12] related to the COVID-19 pandemic, as well as local guidelines from the Ministry of Health Republic of Slovenia and National institute of Public Health (NIJZ) [13], [14], have been taken into consideration to safeguard the study conduct and the safety of the study subjects. Ongoing risk evaluation assessment sessions with Sponsor representatives, Investigators and representative members of [redacted] and/or external vendors will be carried out to align on local restrictions, impact assessments, contingency plans, and study-specific risk mitigation strategies.

This study is a short-term study including a healthy population. Study visits will include 3 residential visits each comprising 4 days (Day -1 to Day 3). Participation in the study is thus not expected to confer increased risks to the study subjects in terms of exposure to the novel coronavirus (Sars-CoV-2) or development of coronavirus disease (COVID-19). A risk assessment has been performed and risks related to subject safety, study performance and data quality/integrity have been identified. These will be re-assessed on an ongoing, day-to-day basis over the course of the study, and mitigating actions will be updated as applicable. The risks and mitigating actions are documented in a risk log as part of the Sponsor's trial master file (TMF).

6.3.3 Risk/benefit conclusion

As a final, commercial pharmaceutical product, linaprazan glurate has the potential to confer significant benefits over the currently available treatments for severe GERD. Specifically, linaprazan glurate is expected to result in a prolonged control of intragastric acidity.

The combined safety data from previous pre-clinical and clinical studies have not revealed safety issues that would outweigh the expected benefits of the present study. While keeping the identified risk factors at a minimum level, in order to not expose the subjects participating in the study to risks that would not be ethically justifiable, it is concluded that the planned study assessments are considered sufficient to meet the scientific and medical goals for the study. It is therefore concluded that the potential benefits from the study will outweigh the potential risks for the treated subjects.

7 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are included below. Study assessments are described in Section 11 and statistical analyses are described in Section 17.

7.1 Study objectives

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.

Secondary objectives

- To evaluate the relative bioavailability of linaprazan glurate 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 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.

7.1.1 Study endpoints

Primary endpoints

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

Secondary endpoints (PK)

- Relative bioavailability of linaprazan glurate for the test formulation *vs.* reference formulation of linaprazan glurate, based on the means ratios for AUC_{inf}, AUC_{last} and C_{max}.
- Relative bioavailability of linaprazan glurate under fed conditions *vs.* fasting conditions, based on the means ratios for AUC_{inf}, AUC_{last} and C_{max}.
- 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 C_{max} (T_{max}).

- Delay between the time of dosing and the time of appearance of plasma concentration (T_{lag}).
- $T_{1/2}$.
- AUC percent extrapolation ($AUC_{extrapol\%}$).
- Apparent clearance (CL/F).
- Apparent volume of distribution (V_z/F).

Secondary endpoints (safety)

- Frequency, seriousness, and intensity of AEs after a single dose of linaprazan glurate.
- Clinically significant changes in ECGs, vital signs, safety laboratory measurements (clinical chemistry/hematology/coagulation) and physical examination findings after a single dose of linaprazan glurate.

8 STUDY DESIGN

8.1 Overall study design and schedule of events

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 test formulation of linaprazan glurate in comparison to a previously studied reference formulation under fasting conditions, and to assess the effect of a high-fat, high-calorie meal on the PK of linaprazan glurate and the active substance linaprazan after the administration of the test formulation.

The overall schedule of events is presented in Table 8.1-1 and the detailed schedule of events for the 3 treatment visits (Visits 2, 3 and 4) is presented in Table 8.1-2. Study assessments are described in Section 11.

Subjects participating in the study will attend 4 in-person visits to the study clinic, a screening visit (Visit 1) followed by 3 treatment visits (Visits 2, 3 and 4). The treatment visits are separated by wash-out periods of a minimum of 5 days, which corresponds to approximately 5 half-lives of the active substance linaprazan (conservative estimation, see Section 6.1.2). The treatment visits will be followed by a remote follow-up/end-of-study visit via telephone (Visit 5), 7 days (±2 days) after the final dose.

Screening (Visit 1) will take place within 28 days prior to the start of treatment and will include an eligibility check, collection of demographic and medical history data as well as a review of health status, including a physical examination and collection of ECGs, vital signs and safety laboratory blood samples.

Eligible subjects will be admitted to the study clinic on Day -1 of Visit 2 and will remain at the study clinic until Day 2 (residential period). After admission, each subject's eligibility will be confirmed, a physical examination will take place, and baseline safety laboratory blood samples, 12-lead safety ECGs, and vital signs will be collected. Study clinic admission on Visits 3 and 4 will follow the same procedure, without the confirmation of eligibility.

Subjects will be randomized on Day 1 of Visit 2 into one of 6 treatment sequences, as detailed in Section 9.9. There will be 3 treatments as follows:

- Treatment A: 100 mg linaprazan glurate reference formulation (4x25 mg oral tablets) in fasting conditions.
- Treatment B: 100 mg linaprazan glurate test formulation (1x100 mg oral tablet) in fasting conditions.
- Treatment C: 100 mg linaprazan glurate test formulation (1x100 mg oral tablet) in fed conditions.

During fasting conditions (Treatments A and B), subjects must fast for at least 10 hours before the anticipated dosing time and 4 hours post-dose. During the fed conditions (Treatment C), a high-fat, high-calorie breakfast will be served 30 minutes prior to the anticipated dosing time. Subjects must consume this meal in 30 minutes or less (see Section 10.5.2). Water, but no other drinks will be allowed *ad libitum* except for 1 hour before dosing to 30 minutes after dosing. Subjects will be served standardized meals during the residential period in the study clinic, as detailed in Table 8.1-1.

On dosing day (Day 1) of Visits 2, 3 and 4, following randomization during Visit 2 and at corresponding time-points during Visits 3 and 4, subjects will be administered single doses of IMP (dosing). Subjects will be carefully monitored by clinical staff during and after dosing. Vital signs and 12-lead safety ECGs will be assessed at 4 hours post-dose. AEs and the use of concomitant medications will be recorded from first dose on Day 1, as detailed in Table 8.1-2. There is immediate access to emergency equipment, qualified staff, and the nearby ICU of the [redacted] in case of an emergency.

Subjects will remain in the study clinic for at least 36 hours for continuous PK blood sampling. PK blood samples will be collected pre-dose (within -01:00 hh:mm prior to dosing) 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 (Table 8.1-2). Subjects will be temporarily discharged from the study clinic after the 36-hour PK blood sample on Day 2. Subjects will return to the study clinic in the morning of Day 3 and again in the morning of Day 4 for PK blood sampling at 48 and 72 hours post-dose, respectively. On Day 4, formal discharge procedures will take place, including safety laboratory, physical examination, vital signs and 12-lead safety ECG assessments as well as the collection of AEs and uses of concomitant medications.

A final remote follow-up visit (Visit 5) 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. Visit 5 will count as each subject's end-of-study visit, and the date of last subject's end-of-study visit will count as the overall end-of-study date.

Subjects are expected to participate in the study for approximately 49 days. This includes the up to 28-day screening period and approximately 3 weeks of treatment and follow-up.

Table 8.1-1 Overall schedule of events

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				
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.
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.

Table 8.1-2 Detailed schedule of events Visit 2-5

	Residential period Day -1 to Day 2[1]																			
	Day -1		Day 1														Day 2		Day 3	Day 4
Assessment↓/Time→	**Admission**	**Pre-dose**	**00:00**	**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**	**72:00**
Eligibility criteria (Visit 2)	X[2]																			
Pregnancy test (Visit 2)	X																			
Urine drug screen	X																			
Alcohol test	X																			
Safety laboratory profile	X																			X[3]
Physical examination	X[4]																			X[3]
Vital signs	X[5]										X									X[3]
12-lead safety ECG	X[5]										X[6]									X[3]
Randomization (Visit 2)		X[7]																		
High-fat, high-calorie breakfast (fed condition)		X[8]																		
IMP administration			X																	
PK blood sampling[9]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standardized meals[10]	X										---------- X ----------									
Baseline symptoms (Visit 2)	---------- X[11] ----------																			
Adverse events (AEs)[12]		---------- X ----------																		
Prior and concomitant medications		---------- X ----------																		

BMI: Body mass index. ECG: Electrocardiogram. HIV: Human immunodeficiency virus.

1. Subjects will be temporarily discharged from the study clinic after PK blood sampling at 36:00 hh:mm post-dose (Day 2). Subjects will return to the study clinic on Day 3 for PK blood sampling at 48 hh:mm post-dose. Subjects will return to the study clinic on Day 4 for PK blood sampling at 72:00 hh:mm post-dose as well as formal discharge procedures, including safety laboratory, physical examination, vital signs and 12-lead safety ECG assessments.
2. Confirmation of eligibility. Visit 2 only. Can be done on Day -1 or Day 1 prior to randomization.

3. At discharge from the study clinic on Day 4, after PK blood sampling at 72:00 hh:mm post-dose.
4. Can be done on Day -1 or Day 1 prior to randomization.
5. Can be done on upon admission to the study clinic on Day -1 or on Day 1 prior to randomization (Visit 2) or dosing (Visit 3 and 4).
6. ECG time window between 4h and 4h30min after dosing.
7. Randomization can be done at any timepoirt after the confirmation of eligibility and before dosing on Day 1.
8. During fed conditions, a high-fat, high-calorie breakfast will be served 30 minutes prior to dosing. Subjects must consume this meal in 30 minutes or less.
9. Pre-dose PK blood sampling should be done within -1 hour of dosing on Day 1. Subjects will be resting in a supine position for at least 10 minutes prior to and 5 minutes after PK blood sampling. When PK blood sampling, safety laboratory blood sampling, safety ECGs, and vital signs assessments coincide, procedures should be conducted in that order. Actual times for PK blood sampling must not deviate more than 10% from the planned times.
10. During fasting conditions, subjects must fast for at least 10 hours before dosing and 4 hours following dosing. Meals Day -1: optional evening snack. Meals Day 1 during fasting conditions: lunch, mid-day snack, dinner, and optional evening snack. Meals Day 1 during fed conditions: high-fat, high-calorie breakfast, lunch, mid-day snack, dinrer, and optional evening snack. Meals Day 2: breakfast, lunch, mid-day snack, dinner, and optional evening snack. Lunch, the mid-day snack, dinner and optional evening snack will be served approximately 4 hours, 6 hours, 9 hours, and 12 hours after dosing, respectively, or at corresponding times on non-dosing days. Breakfast will be served approximately 2 hours before lunch on Day 2.
11. Baseline symptoms will be recorded from the signing of the informed consent form (ICF) up until dosing on Day 1.
12. AEs will be recorded from dosing on Day 1 up until end-of-study (Visit 5) or on early withdrawal.

8.2 Rationale for study design

The European Medicines Agency (EMA) guideline EMEA/CHMP/SWP/28367/07 Rev. 1 on strategies to identify and mitigate risks in FIH studies and early clinical trials [5] was considered when designing this study.

The $T_{1/2}$ of linaprazan is [redacted] and the T_{max} is estimated to be reached after 0.5-2 hours for linaprazan glurate and after 2-3 hours for linaprazan, based on previous studies (refer to Section 6.1.1). Thus, the 72 hour observation period is considered long enough to provide a reliable estimate of the extent of exposure. The sampling schedule around the predicted T_{max} of linaprazan glurate and linaprazan has been chosen to provide a reliable estimate of peak exposure.

A cross-over design was chosen to yield a more efficient comparison of treatments than a parallel study design, *i.e.*, fewer subjects are required since each subject will serve as its own control. To avoid carryover effects, washout periods of at least 5 days will be employed between treatment visits. The planned wash-out period is considered sufficient based on the half-life of the active substance linaprazan.

Randomization will be used to minimize bias in the assignment of subjects to a treatment sequence and to increase the likelihood that known and unknown subject attributes (*e.g.*, demographic and baseline characteristics) are evenly balanced across treatment sequences.

The sample size of 54 randomized and at least 42 evaluable subjects was calculated to provide 81% power based on the approach used in bioequivalence studies for guidance (refer to Section 17.2).

8.3 Justification of dose level

The planned dose to be used in this study is 100 mg. [redacted]

In the FIH (SAD/MAD) study of linaprazan glurate [6], multiple daily doses close to 300 mg were administered to some study subjects at the 4 mg/kg body weight dose level without any safety concerns. In an ongoing Phase 2 study of linaprazan glurate, similar doses of 100 mg BID were administered for 4 weeks without safety concerns.

The extrapolated mean C_{max} of linaprazan glurate after a single 100 mg dose of the reference formulation is predicted to be approximately 120 nmol/L, assuming linear PK, well below C_{max} at NOAEL observed in non-clinical toxicity studies. In the 28-day repeat-dose toxicity study of linaprazan glurate in rats, the mean C_{max} at NOAEL (150 mg/kg) was 1708 nmol/L for male rats and 186 nmol/L for female rats. In male and female dogs, the corresponding C_{max} data at NOAEL (48 mg/kg) was 801 nmol/L and 1860 nmol/L, respectively.

It is not known how food intake will affect the PK of linaprazan glurate and linaprazan after single doses of 100 mg of the test formulation. However, food intake had no effect on linaprazan PK in the FIH study using a linaprazan glurate oral suspension at the 1 mg/kg dose level. Thus, no or only modest food effects are expected in the present study.

9 STUDY POPULATION

Prospective approval of deviations from the eligibility criteria, also known as protocol waivers or exemptions, will not be allowed.

9.1 Recruitment

Subjects will be recruited from [redacted] database of healthy volunteers, as well as from strategic marketing campaigns. Advertisements in social media and other media (newspapers, internet, radio, local distribution of flyers et c.) will be used to reach the target audience. The advertisement texts approved by the independent ethics committee (IEC) will be used to create all materials (digital, radio and/or print) for recruitment.

9.2 Screening and enrolment log

Investigators must keep a record of all screened subjects even if they were not subsequently included in the study. This information is necessary to verify that subjects were selected without bias. The reason for screen failure should be stated for all subjects screened but not included. The reason for withdrawal should be stated for all subjects included but not completed.

A screening number will be allocated to each subject in connection to the informed consent process at the Screening visit. The screening number is generated automatically in the electronic case report form (eCRF). The screening number will allow identification of subjects irrespective of their possible eligibility for the study.

If a subject cannot receive the planned dose of IMP within 28 days after screening (*i.e.*, the time interval between signing informed consent until dose administration) the subject should be rescreened before proceeding in the study.

9.3 Number of subjects

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. Evaluable subjects are subjects that have received all doses and completed all study visits.

For the replacement of subjects who discontinue the study, see Section 9.8.3.

9.4 Inclusion criteria

For inclusion in the study, subjects must fulfil the following criteria:

1. Willing and able to give written informed consent for participation in the study.
2. Healthy male or female aged 18 to 65 years, inclusive.
3. Body mass index $\geq$18.5 and $\leq$30.0 kg/m^2.

4. Medically healthy, without abnormal clinically significant medical history, physical findings, vital signs, ECGs, or laboratory values at the time of screening, as judged by the Investigator. Discussion between the Investigator and the Sponsor's medical representative regarding the clinical relevance of any abnormal laboratory values obtained during the pre-dose period will be encouraged.
5. Prospective subjects, as well as their partners, must agree to the contraception requirements described in exclusion criteria 1 and 2. Prospective female subjects who are already on a stable regimen of oral, implantable, injectable or transdermal hormonal contraceptives (combined estrogen- and progestogen-containing contraceptives or progestogen-only contraceptives) prior to study enrolment may continue this regimen during the study but must agree to add an additional method of contraception as described in exclusion criterion 1 from the first administration of IMP (dosing) until the end-of-study visit.
6. Willing and able to consume the high-fat, high calorie breakfast as described in Section 10.5.2.

9.5 Exclusion criteria

Subjects will be excluded from the study if any of the following criteria apply:

1. Female subjects of childbearing potential (defined as all subjects physiologically capable of becoming pregnant) unless they agree to use 1 of the following highly effective methods of contraception (failure rate of <1%) from 2 weeks prior to dosing until the end-of-study visit:
    - Total abstinence from sex with a male partner (only allowed when this is the preferred and usual lifestyle of the subject). Periodic abstinence (*e.g.*, calendar, ovulation, symptothermal and/or post-ovulation methods) or the withdrawal method (*coitus interruptus*) are not acceptable methods of contraception.
    - Sterilization of a male partner, defined as vasectomy at least 6 months prior to screening. The vasectomized male partner must be the sole male sexual partner of the prospective female subject for this to apply.
    - Intrauterine devices (IUDs).
    - Intrauterine hormone-releasing systems (IUSs).
    - Double-barrier methods of contraception, *i.e.*, condoms in combination with occlusive cap (diaphragm or cervical vault/cap) with contraceptive gel.

    Female subjects of non-childbearing potential who are not required to use contraception are defined as pre-menopausal females who are sterilized or post-menopausal females. Sterilization is defined as hysterectomy, surgical bilateral oophorectomy with or without hysterectomy, tubal ligation, or bilateral occlusion of fallopian tubes at least 6 weeks prior to dosing. Menopause is defined as at least 12 months of amenorrhea without an alternative medical cause. In questionable cases, a blood sample with detection of follicle stimulating hormone (FSH) ≥25 IE/L at screening will be confirmatory.
2. Male subjects with a partner of childbearing potential, unless they agree to use 1 of the following methods of contraception from the first administration of IMP (dosing) until the end-of-study visit:

- Total abstinence (only allowed when this is the preferred and usual lifestyle of the subject). Periodic abstinence or withdrawal methods as described in exclusion criterion 1 are not acceptable methods.
- Vasectomy at least 6 months prior to screening.
- Condoms. Female partners of childbearing potential must then agree to concurrently (from first dosing until end-of-study) use a highly effective method of contraception, *i.e.*, combined estrogen- and progestogen-containing hormonal contraceptives or progestogen-only hormonal contraceptives (oral, implantable, injectable, intravaginal or transdermal), IUDs and IUSs.

3. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.
4. History of GERD or clinically significant acid reflux, as judged by the Investigator.
5. History of diabetes, metabolic disorder and/or gastrointestinal disease for which the planned high-fat, high-calorie breakfast might be contraindicated, as judged by the Investigator.
6. Any clinically significant medical/surgical procedure or trauma within 4 weeks of the first administration of IMP, as judged by the Investigator.
7. Malignancy within the past 5 years, with the exception of *in situ* removal of basal cell carcinoma.
8. Any planned major surgery within the duration of the study (*i.e.*, from screening to end-of-study visit).
9. Subjects who are pregnant, currently breastfeeding, or intend to become pregnant (female subjects) or father a child (male subjects) during the course of the study (*i.e.*, from screening to end-of-study visit).
10. Any positive result on screening for serum hepatitis B surface antigen (not explained by hepatitis B vaccination in the subject's medical history), hepatitis C antibodies and/or human immunodeficiency virus (HIV).
11. Subjects with swallowing disorders which may affect the subject's capability to swallow the IMP, as judged by the Investigator.
12. After 10 minutes supine rest at the time of screening, any vital signs outside the following ranges:
    - Systolic blood pressure: <90 or ≥140 mmHg
    - Diastolic blood pressure <50 or ≥90 mmHg
    - Pulse <40 or >90 bpm
13. Prolonged QTcF of >450 ms, cardiac arrhythmias or any clinically significant abnormalities in the resting ECG at the time of screening, as judged by the Investigator.
14. History of severe allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to linaprazan glurate.
15. Use of prohibited medications as detailed in Section 9.6.2.
16. Planned treatment or treatment with another investigational drug within 3 months prior to Day -1. Subjects consented and screened but not dosed in previous Phase I studies will not be excluded.

17. Current smokers or users of nicotine products. Irregular use of nicotine (*e.g.*, smoking, snuffing, chewing tobacco) less than 3 times/week before the screening visit will be allowed.
18. Positive screen for drugs of abuse or alcohol at screening or on admission to the study clinic prior to first administration of the IMP. Positive results that are expected given the subject's medical history and prescribed medications can be disregarded as judged by the Investigator.
19. History of or current alcohol abuse or excessive intake of alcohol, as judged by the Investigator.
20. History of or current use of drugs of abuse and/or anabolic steroids, as judged by the Investigator.
21. Excessive caffeine consumption defined by a daily intake of > 5 cups (1 cup = approximately 240 mL) of caffeine-containing beverages, as judged by the Investigator.
22. Plasma donation within 1 month of screening or blood donation (or corresponding blood loss) during the last 3 months prior to screening.
23. The Investigator considers the subject unlikely to comply with study procedures, restrictions, and requirements.

9.6 Restrictions during the study

The subjects must be willing to comply to the following restrictions during the entire study duration *i.e.*, from screening to the end-of-study visit.

9.6.1 General restrictions

- Contraception requirements: Subjects will be expected to practice abstinence (only when this is the preferred and usual lifestyle of the subject) or use highly effective methods of contraception from 2 weeks prior to IMP administration until the end-of-study visit to prevent pregnancy, as detailed in exclusion criteria 1 and 2.
- Fasting: During fasting conditions, subjects must fast overnight for at least 10 hours before dosing and until 4 hours post-dose on dosing days. For details on IMP administration during fasted and fed conditions, refer to Section 10.5.
- Meals and dietary restrictions: Standardized meals (excluding the high-fat, high-calorie breakfast) will be served while the study subjects are in the research clinic. Meals will be standardized regarding the nutritional contents and the times at which they are served. Lunch, a mid-day snack, dinner, and an optional evening snack will be served approximately 4 hours, 6 hours, 9 hours, and 12 hours after dosing, respectively, or at corresponding times on non-dosing days. A standardized breakfast will be served approximately 2-3 hours before lunch on non-dosing days. Water, but no other beverages, will be allowed *ad libitum* at the study clinic except from 1 hour before dosing to 30 minutes after dosing.
- Alcohol: Consumption of alcohol is not allowed within 48 hours prior to screening (Visit 1) and treatment visits (Visits 2, 3 and 4).
- Coffee: Consumption of up to 5 cups of coffee per day will be allowed during the residential periods in the study clinic (Visits 2, 3 and 4).

- Xanthine and/or taurine containing products/beverages: Energy drinks (*e.g.*, Red Bull, Celsius, Monster Energy) are not allowed during the study within 48 hours prior to screening (Visit 1) and treatment visits (Visits 2, 3 and 4).
- Nicotine: Smoking or use of nicotine-containing products, including non-tobacco oral nicotine products, is not allowed from screening (Visit 1) until the end of Visit 4.
- Grapefruit and grapefruit containing products: The consumption of grapefruit and/or grapefruit-containing products such as jams, jellies, preserves and fruit juices is not allowed from screening (Visit 1) until the end of Visit 4.
- Exercise: The subjects must refrain from strenuous exercise (defined as greater than 70% of the maximal pulse rate for 1 hour or more) from screening (Visit 1) until the end of Visit 4.
- Blood donation: The subjects must not donate blood or plasma during the study and until 3 months after the final medical examination at the end of Visit 4.
- Participation in other clinical studies: Study subjects are not allowed to participate in any other interventional clinical study during the study period, *i.e.*, from screening (Visit 1) until the end-of-study visit (Visit 5).

9.6.2 Prior and concomitant therapy

Prohibited medication:

- Regular use of any prescribed or non-prescribed medication, including analgesics, herbal remedies, vitamin supplements and minerals, from 2 weeks prior to IMP administration (dosing), as judged by the Investigator at screening, and until the end-of-study visit (Visit 5).
- Any use of prescribed on non-prescribed antacid medication from 2 weeks prior to dosing and until the end-of-study visit (Visit 5).

Allowed medication:

- Paracetamol in doses up to 2000 mg/day for a maximum of 3 consecutive days. If this amount of paracetamol is not sufficient for treatment of the subjects, withdrawal should be considered.
- Nasal decongestants without cortisone, antihistamine, or anticholinergics for a maximum of 10 days.

Other medications considered necessary for the subject´s safety and wellbeing may be given at the discretion of the Investigator during the residential period. Following consultation with the Sponsor, the Investigator will determine whether or not the subject should continue in the study.

9.7 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects. Minimal information includes documentation of signed and dated informed consent form (ICF), demographic data and reason(s) for screening failure.

Re-screening can be performed if any of the following were reasons for screening failure or non-randomization (as judged by the Investigator):

- Practical reasons.
- Non-significant medical conditions (*e.g.*, influenza, nasopharyngitis).
- Reserve subjects.
- Plasma or blood donation outside allowed time windows.

For subjects who are re-screened, a new screening number will be assigned and a new, signed ICF will be collected.

9.8 Subject withdrawal

9.8.1 General discontinuation/withdrawal criteria

Subjects are free to withdraw their participation in the study at any time and for whatever reason without affecting their right to an appropriate follow-up investigation or their future care. If possible, the reason for withdrawal of consent should be documented.

Subjects may be discontinued from the study at any time at the discretion of the Investigator.

Potential reasons for discontinuation include:

- Subject decision
- Severe non-compliance to study protocol procedures, as judged by the Investigator and/or Sponsor
- Subject is lost to follow-up.
- Significant AEs posing a risk for the subject, as judged by the Investigator and/or Sponsor
- Withdrawal of informed consent to the use of biological samples
- Pregnancy
- Death
- Meeting of an exclusion criterion during the study, which, in the opinion of the Investigator, may pose a risk for the subject
- Use of prohibited medication

9.8.2 Procedures for discontinuation of a subject from the study

A subject who prematurely discontinues participation in the study will always be asked about the reason(s) for discontinuation and the presence of any AEs. If a subject withdraws consent, the Investigator must ask the subject if he/she is willing, as soon as possible, to be assessed according to the procedures scheduled for the end-of-study visit. Any ongoing AEs will be followed as described in Section 11.4.1.15.

The primary reason for discontinuation/early withdrawal must be specified in the eCRF and final drug accountability must be performed.

9.8.3 Subject replacement

Subjects who consented to study participation but discontinued 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.

9.9 Randomization

Block randomization (block size=6) will be used to generate the randomization list, which will show the assignment of subjects to 1 of 6 treatment sequences. On Day 1 (Visit 2), the subjects will be randomized to treatment sequences using the following treatment nomenclature:

- A: 100 mg linaprazan glurate reference formulation (4x25 mg oral tablets) in fasting conditions.
- B: 100 mg linaprazan glurate test formulation (1x100 mg oral tablet) in fasting conditions.
- C: 100 mg linaprazan glurate test formulation (1x100 mg oral tablet) in fed conditions.

The 6 treatment sequences are given as follows:

1. A B C
2. A C B
3. B A C
4. B C A
5. C A B
6. C B A

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 by [redacted] The original randomization list will be kept by the randomizer.

Because this is an open-label study, *i.e.* the Investigator, study staff and study subjects will know which treatment the subjects will receive at all times, no blinding procedures will be followed.

10 STUDY TREATMENTS

10.1 Identity of investigational medicinal products

- **Test formulation:** [redacted]
- **Reference formulation:** [redacted]

[redacted] The composition of both test formulation and reference formulation tablets is provided in the investigational medicinal product dossier (IMPD).

[redacted]

10.2 Manufacturing, packaging, labelling and release

All manufacturing, packaging, labelling and release of IMP will comply with applicable good manufacturing practice (GMP) requirements [16, 17].

The test formulation is manufactured, packaged and labelled by [redacted] and imported and QP-released by [redacted]. The reference formulation is manufactured by [redacted] and packed, labelled, and QP-released [redacted]

The IMP will be shipped to the study pharmacy at [redacted]

10.3 Conditions for storage

The IMP will be stored at room temperature (15-25° C) in an access-controlled area at [redacted]

Temperature logs will be kept for the area where the IMP is stored. The temperature will be noted on a daily basis (working days only unless automatic temperature readings are available).

10.4 Preparation and accountability

IMP preparation will be done by trained personnel, *i.e.*, a site pharmacist or a registered nurse, in a dedicated room at [redacted]. There will be 2 persons working together, 1 person will handle the IMP and perform the preparation according to the randomization list and the other person will supervise the process.

[redacted] and the Investigator will maintain a storage and accountability log as well as a drug dispensing log detailing the dates and quantities of study medication received, prepared for, and used by each subject and study medication returned or destroyed at the end of the study. Any discrepancies between prepared and returned IMP must be explained and documented.

Products deliberately and/or accidentally destroyed by the site or the subject must be accounted for.

10.5 Treatment administration

10.5.1 Fasting conditions

Following an overnight fast of at least 10 hours, subjects will be administered the IMP together with 240 mL of tap water. Subjects will be instructed not to chew or crush the tablets. Water, but no other drinks, will be allowed *ad libitum*, except from 1 hour before dosing to 30 minutes after dosing. No food will be allowed for at least 4 hours post-dose.

10.5.2 Fed conditions

Following an overnight fast of at least 10 hours, subjects will start a high-fat, high-calorie breakfast meal 30 minutes prior to dosing. Subjects should eat this meal in 30 minutes or less, however, the IMP must be administered 30 minutes after start of the meal together with 240 mL of tap water. Subjects will be instructed not to chew or crush the tablets. Water, but no other drinks, will be allowed *ad libitum*, except from 1 hour before dosing to 30 minutes after dosing. No food will be allowed for at least 4 hours post-dose.

The high-fat, high-calorie breakfast will consist of the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces (113 g) of hash brown potatoes, and 8 ounces (236 mL) of whole milk. This test meal derives approximately 150 kcal from protein, 250 kcal from carbohydrates, and 500-600 kcal from fat. Substitutions will not be allowed; hence subjects must be willing and able to consume this meal to be eligible for participation in the study (inclusion criterion 6).

10.6 Continuation of treatment with investigational medicinal product

This is a Phase I study in healthy volunteers who will receive no medical benefit from the treatment and thus there will be no treatment with linaprazan glurate after the end of study participation.

10.7 Treatment compliance

All IMP will be administered at the study clinic under medical supervision to ensure compliance.

10.8 Return and destruction of investigational medicinal product

Any unused study medication and all empty containers will be returned to the Sponsor or destroyed at the site upon confirmation from the Sponsor. The Monitor will perform final IMP accountability reconciliation at the study end to verify that all unused IMP is adequately destroyed/returned and documented.

11 STUDY ASSESSMENTS

Study assessments are described in the sections below. The timing of assessments are detailed in the schedule of events (Table 8.1-1 and Table 8.1-2 in Section 8.1).

11.1 Recording of data

The PI will provide the Sponsor with all data produced during the study from the scheduled study assessments. They will ensure the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor in the eCRF and in all required reports.

It is important that PK blood sampling occurs as close as possible to scheduled time. In order to achieve this, the timing priority order at a particular time point is:

1. PK blood sampling
2. Safety laboratory blood sampling
3. 12-lead safety ECG
4. Vital signs

Time points for PK blood sampling, safety laboratory samples, safety 12-lead ECG and vital signs are outlined in Table 8.1-2 in Section 8.1. Actual times for PK blood sampling must not deviate more than ±10% from the planned times.

11.2 Demographics and other baseline characteristics

11.2.1 Informed consent

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 14.3.

11.2.2 Eligibility criteria

Eligibility criteria should be checked during screening and verified before randomization. The criteria are specified in Sections 9.4 and 9.5.

11.2.3 Demographic information

The following demographic data will be recorded: gender, age, ethnicity, and race.

11.2.4 Weight and height

Weight and height will be measured without shoes. BMI will be calculated from the height and weight recorded and calculated with 1 decimal.

11.2.5 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.

11.2.6 Prior and concomitant medication

Prior medications taken within 2 weeks will be obtained by subject interview in order to verify that the eligibility criteria are met (see also Section 9.6.2).

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. To distinguish between prior and concomitant medications on Day 1 (*i.e.*, the first dosing day), the start time of any newly introduced medication or the stop time of any previously ongoing medication must be recorded in the eCRF.

Any use of concomitant medication from screening until the end-of-study visit must be documented appropriately in the subject's eCRF. Relevant information (*i.e.*, name of medication, dose, unit, frequency, dose form, route, start and stop dates, reason for use) must be recorded. All changes in medication should be noted in the eCRF.

11.2.7 HIV and Hepatitis B/C

Subjects will be tested for hepatitis B surface antigen (HbsAg), hepatitis C antibody and HIV prior to inclusion into the study. Any positive result not explained by hepatitis B vaccination in the subject's medical history will exclude the subject from participation in the study.

11.2.8 Pregnancy test

All female subjects of child-bearing potential will do a urine pregnancy at screening and at subsequent visit specified in Table 8.1-1 and Table 8.1-2 in Section 8.1.

11.2.9 Urine drug screen

Urine will be screened for drugs of abuse at time points outlined in the schedule of events, refer to Table 8.1-1 and Table 8.1-2 in Section 8.1. The Drug-Screen Multi-15 Dip Test from nal von minden GmbH (Moers, Germany) or equivalent will be employed. Additional random tests can be performed during the study period at the discretion of the Investigator.

11.2.10 Alcohol test

An alcohol test will be performed at time points outlined in the schedule of events, refer to Table 8.1-1 and Table 8.1-2 in Section 8.1. Additional random tests can be performed during the study period at the discretion of the Investigator.

11.2.11 Baseline symptoms

A baseline symptom is defined as an event that occurs between the subject's signing of the ICF until the first administration of IMP (*i.e.*, an event that occurs during the screening period). Such events are not AEs and will be recorded as baseline symptoms in the Medical History Log in the eCRF.

11.3 Pharmacokinetic assessment

11.3.1 Pharmacokinetic sampling and analysis

Venous blood samples (approximately 3 mL) for the PK characterization of linaprazan glurate and linaprazan will be collected through an indwelling venous catheter at the pre-specified time-points detailed in Table 8.1-1 and Table 8.1-2 of Section 8.1. PK blood sampling must not deviate more than ±10% from the planned time points (refer to Section 11.1). The date and time of collection of each sample will be recorded in the eCRF.

The blood samples will be collected in pre-labelled tubes. BD Collection tubes with anticoagulant (Lithium Heparine) shall be used. Tubes shall be gently inverted 8-10 times after addition of blood. After collection tubes shall be placed on ice/water bath. All the collected blood samples will be centrifuged to separate plasma. Centrifugation will be performed at 1300 g for up to 10 minutes at room temperature. Samples shall be centrifuged within 30 minutes from collection. Approximately 1 mL of separated plasma from each blood sample will be divided into 2 aliquots in pre-labelled cryotubes (1 A sample and 1 B [backup] sample, approximately 500 µL in each tube) for PK analyses and frozen at -70 °C within 2 hours from centrifugation. Further details will be described in a separate laboratory manual.

Plasma samples for determination of plasma concentrations and PK characterization of linaprazan glurate and linaprazan will be [redacted]

The details of the analytical method(s) used will be described in a separate bioanalytical report.

11.4 Safety assessments

11.4.1 Adverse event reporting

The PI is responsible for ensuring that all medical staff involved in the study is familiar with the content of this section and the content of the [redacted] standard operating procedures (SOPs) regarding emergencies and Phase I studies.

11.4.1.1 Definition of adverse event (AE)

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.

11.4.1.2 Definition of serious adverse event (SAE)

An SAE is any AE which:

- results in death,

- is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might had led to death if the event was more severe),
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is an important medical event (IME, this refers to an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent any of the other outcomes defined above).

Examples of IMEs include intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalization, development of drug dependency, and drug abuse.

Planned hospitalizations or surgical interventions for a condition that existed before the subject signed the ICF, and that did not change in intensity, are not SAEs.

If there is any doubt as to whether an AE meets the definition of an SAE, a conservative viewpoint will be taken, and the AE will be reported as an SAE.

11.4.1.3 Definition of adverse reaction (AR)

The term adverse reaction (AR) will be used for all untoward and unintended responses to the IMP assessed as related to any administered dose.

11.4.1.4 Definition of serious adverse reaction (SAR)

The term serious adverse reaction (SAR) will be used whenever either the Investigator or Sponsor or designee assesses an SAE as related to the IMP.

11.4.1.5 Definition of suspected unexpected serious adverse reaction (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is any SAE that has a suspected causal relationship with the IMP (assessed as related by the Sponsor or Investigator), but the nature of which is not consistent with the applicable reference safety information (RSI) in the linaprazan glurate IB and is therefore assessed as unexpected.

11.4.1.6 Time period and frequency for collecting adverse events

All AEs (including SAEs) will be collected from the start of IMP administration (dosing) until the end-of-study visit.

Any AE with start date on the day of dosing must be recorded with start time.

At the end-of-study visit, information on new AEs or SAEs, if any, and stop dates for ongoing during events must be recorded as applicable.

Investigators will not be obliged to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

11.4.1.7 Assessment of intensity

The Investigator must assess the intensity of each AE and record it in the AE log of the eCRF using the intensity grades below:

Mild	The event is usually transient and requires minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living (ADL).
Moderate	The event is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADLs, causing discomfort but poses no significant or permanent risk or harm to the subject.
Severe	The event interrupts usual ADLs, or significantly affects clinical status, or may require intensive therapeutic intervention.

11.4.1.8 Assessment of causal relationship

The Investigator must assess the causal relationship between an AE and the IMP and record it the AE log of the eCRF using the definitions below:

Probable	The event has a strong temporal relationship to the IMP or recurs on re-challenge, and another etiology is unlikely or significantly less likely.
Possible	The event has a suggestive temporal relationship to the IMP, and an alternative etiology is equally or less likely.
Unlikely	The event has no temporal relationship to the IMP or is due to underlying or concurrent illness or effect of another drug (*i.e.*, there is no causal relationship between the IMP and the event).

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

11.4.1.9 Assessment of outcome

The Investigator must assess the outcome of an AE and record it on the AE log of the eCRF using the definitions below:

Recovered/resolved	The subject has recovered completely, and no symptoms remain.
Recovering/resolving	The subject's condition is improving, but symptoms still remain.
Recovered/resolved with sequelae	The subject has recovered, but some symptoms remain (*e.g.*, the subject had a stroke and is functioning normally, but has some motor impairment).
Not recovered/not resolved	The subject's condition has not improved, and the symptoms are unchanged (*e.g.*, an atrial fibrillation has become chronic).
Fatal	
Unknown	

11.4.1.10 Reporting of action taken with study treatment

The Investigator must report the action taken with study treatment and record it on the AE Log of the eCRF using the definitions below:

Dose increased

Dose not changed

Dose reduced

Drug interrupted

Drug withdrawn

Not applicable

Unknown

11.4.1.11 Collecting adverse events

AEs identified using any of the following methods will be recorded:

AEs spontaneously reported by the subject.

- AEs observed by the Investigator or medical personnel.
- AEs elicited based on non-leading questions from the Investigator or medical personnel.

11.4.1.12 Recording adverse events

AEs must be recorded in the AE Log of the eCRF. The Investigator must provide information on the AE, preferably with a diagnosis or at least with signs and symptoms, start and stop dates, start and stop times, intensity, causal relationship to IMP, action taken, and outcome.

If the AE is serious, this must be indicated in the eCRF.

AEs, including out-of-range clinically significant (CS) clinical safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

11.4.1.13 Reporting of serious adverse events

SAE reporting must be performed by the Investigator within 24 hours of awareness via the. eCRF. All available information regarding the SAE must be entered in the AE log for the specific subject.

By saving the event as "serious" in the eCRF, and once the Investigator has signed-off of the event, an e-mail alert will be sent to predefined recipients to highlight that an SAE has been registered. The same information will be sent to [redacted] SAE inbox at [redacted] (with a copy to the Sponsor).

The SAE report will be reviewed by a designated person at [redacted] pharmacovigilance department to ensure that the report is valid and correct. For SAEs where important or relevant information is missing, follow-up is undertaken and queries to the site are raised promptly to keep the regulatory timelines. Investigators or other site personnel must inform [redacted] pharmacovigilance department of any follow-up information on a previously reported SAE no later than the end of the next business day of when they become aware of it. This includes rationale for changes, *e.g.*, changes in causality, assessment, and intensity, that should be described in the SAE narrative.

If the SAE report in the eCRF is updated, a new e-mail alert will be sent to the predefined recipients.

If any additional documentation is required (*e.g.*, autopsy report), [redacted] pharmacovigilance department will request this information from the study site.

In case the eCRF cannot be accessed, the SAE must be reported by manually completing the paper SAE form provided in the investigator site file (ISF). The completed, signed, and dated paper SAE form must, within 24 hours, be scanned and delivered via encrypted e-mail or secure file transfer to [redacted] SAE inbox at [redacted]

The study site must notify the site Monitor via phone or e-mail about the submission of the SAE report. As soon as the site personnel have access to the eCRF, the SAE must be reported electronically as well.

The Sponsor or delegate will assume responsibility for reporting SAEs to the competent authority (CA) and IEC in accordance with local regulations.

11.4.1.14 Reporting of suspected unexpected serious adverse reactions to EudraVigilance, local competent authority and independent ethics committee

The term SAR will be used whenever either the Investigator or Sponsor or designee assesses an SAE as related to the IMP, as per Section 11.4.1.4. If a SAR is assessed as unexpected based on the applicable product information (*i.e.*, the IB), it is a potential SUSAR as per Section 11.4.1.5. If the event is assessed as a SUSAR it will be reported to the local CA via the EudraVigilance database, and to the IEC in accordance with local regulations and [redacted] SOPs within the following timelines:

- 7 calendar days if fatal or life-threatening.
- 15 calendar days if non-fatal and non-life-threatening.

The clock for expedited initial reporting (Day 0) starts as soon as the Sponsor has received the information containing the minimum reporting criteria. The date must be documented on an acknowledgement receipt.

The Medical Monitor is responsible for medical review of the SAE narrative in the Council for International Organizations of Medical Sciences (CIOMS) form (or equivalent) prior to expedited reporting.

The Sponsor or delegate is responsible for informing the Investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

The Sponsor or delegate is responsible for once a year throughout the clinical study (or on request), submit a safety report to the CA and the IEC taking into account all new available safety information received during the reporting period.

11.4.1.15 Treatment and follow-up of adverse events

Subjects with AEs that occur during the study must be treated according to daily clinical practice at the discretion of the Investigator.

AEs must be followed up until resolution or to the end-of-study visit, whichever comes first. At the end-of-study visit, information on new AEs, if any, and stop dates for previously reported AEs must be recorded (if known). AEs assessed as stable by the Investigator at the end-of-study visit will not have to be followed up until resolution.

It is the responsibility of the Investigator to follow up on all SAEs until the subject has recovered, stabilized, or recovered with sequelae, and to report to the Sponsor all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultation.

11.4.1.16 Procedures in case of pregnancy

In case of pregnancy or suspicion of possible pregnancy, the study treatment must be stopped immediately, and the subject discontinued from participation in the study. Pregnancy itself will not be regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of the contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even after the subject was discontinued from the study.

All events of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages must also be reported and handled as AEs. All outcomes of pregnancy must be reported to the Sponsor and the PI on the pregnancy outcomes report form.

11.4.1.17 Treatment of overdose

An overdose is a dose in excess of the doses specified in this CSP.

All IMP will be administered by site personnel under medical surveillance. In cases of accidental overdose, subjects will be monitored appropriately, and standard supportive measures and symptomatic treatments will be adopted as required.

Overdoses must be documented in the eCRF. An overdose with associated AE will be recorded as the AE diagnosis/symptoms in the AE log of the eCRF. An overdose without associated symptoms will only be reported in the subject's medical records and documented in the PD log.

The IMP is a glutaric acid prodrug of linaprazan, a P-CAB that has been extensively studied by AstraZeneca in more than 2000 patients and 400 healthy subjects. Based on published data, linaprazan was safe and well tolerated [3]. There are no known antidotes.

Management of IMP overdose:

- Symptomatic therapy should be started for relief of symptoms.
- If justified, gastric emptying with charcoal.
- Controlled breathing if necessary.
- Volume substitution and possibly the addition of inotropic agents (*e.g.*, dopamine) in case of fall in blood pressure.

11.4.2 Safety 12-lead electrocardiograms

Single 12-lead ECGs will be recorded at the time-points specified in Table 8.1-1 and Table 8.1-2 with the subject in a supine position after 10 minutes of rest. The time window for the 4h post dose ECG is within 30 minutes, *i.e.* between 4 hours and 4 hours 30 minutes after dosing and must occur after the PK and safety blood samples have been drawn.

The resting heart rate (HR) and PQ/PR, QRS, QT and QTcF intervals will be recorded. Safety ECGs will be reviewed and interpreted on-site by the Investigator.

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

11.4.3 Safety laboratory assessments

Blood samples for the analysis of clinical chemistry, hematology and coagulation parameters will be collected through venipuncture or an indwelling venous catheter and sent to the certified clinical chemistry laboratory at [redacted] (refer to Section 5) and analyzed by routine analytical methods.

Urinalysis will be performed at the study clinic using standard dip sticks used in routine medical care.

Safety laboratory parameters are defined in Table 11.4-1 and will be assessed at visits and time-points specified in Table 8.1-1 and Table 8.1-2 in Section 8.1.

Safety laboratory values will be specified and documented as normal, abnormal NCS, or abnormal CS in the eCRF. Abnormal values assessed by the Investigator as CS will be reported as AEs. If an abnormal value is associated with corresponding clinical signs or symptoms, the sign/symptom must be reported as the AE.

Table 11.4-1 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

Category	Parameter
	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.

11.4.4 Vital signs

Systolic and diastolic blood pressure and pulse will be measured at the time-points specified in Table 8.1-1 and Table 8.1-2 with the subject in a supine position after 10 minutes of rest. Body temperature will be measured using a digital thermometer.

Any vital signs outside of normal ranges will be specified and documented as CS or NCS in the eCRF. Abnormal post-dose findings assessed by the Investigator as CS will be reported as AEs.

11.4.5 Physical examinations

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 not clinically significant (NCS) in the eCRF. Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

11.5 Appropriateness of measurements

All methods used for safety assessments are commonly used in standard medical care and in Phase I clinical studies. Non-compartmental analysis of PK parameters is standard for Phase I clinical studies.

12 PROCEDURES FOR BIOLOGICAL SAMPLES

12.1 Sample collection

The sample collection procedure for PK analysis is described in Section 11.3.1.

Safety laboratory samples will be collected according to standard procedures.

12.2 Volume of blood

The anticipated total volume of blood collected from each subject is approximately 335 mL (Table 12.2-1). For reference, a regular blood donation consists of between 350 mL to 450 mL (±10%) for persons weighing at least 45-50 kg [18].

Additional PK and safety lab blood samples may be collected, if considered appropriate by the Investigator and/or Sponsor, which may affect the total volume of blood. The additional blood volume collected from each subject is not expected to exceed 50% of the anticipated total volume (Table 12.2-1).

Table 12.2-1 Estimated maximum blood volumes

Assessment	Estimated number of sampling occasions	Estimated volume per occasion (mL)	Total (mL)
PK blood sampling	52	3 mL	156 mL
Screening for HIV and hepatitis B/C	1	7 mL	7 mL
Clinical chemistry, hematology, coagulation	7	25 mL	175 mL
		Total:	**338 mL**

12.3 Handling, storage, and destruction of laboratory samples

All biological samples will be registered in a biobank at [redacted]

Any remains from the safety laboratory samples will be disposed of after analyses.

The samples for analyses of PK parameters will be stored at ≤70 °C until analyzed. The samples will be disposed of after the clinical study report [redacted] has been finalized.

All plasma samples transferred to the Sponsor's biobank will, if not used, be disposed of after 10 years.

12.4 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their lifecycle.

[redacted] will keep full traceability of collected biological samples from the study subjects while in storage at the study clinic and until shipment. [redacted] will keep documentation of receipt of arrival. The sample receiver (the analytical laboratory) will keep full traceability of the samples while in their custody until the samples are used up or disposed of. The Sponsor will keep oversight of the entire life cycle of the samples through internal procedures, monitoring of study sites and auditing of external laboratory providers.

12.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of the donated biological samples, the samples will be disposed of/destroyed, if not already analyzed and documented.

The PI will ensure that:

The subject's withdrawal of consent is notified immediately to the Sponsor.

Biological samples from the subject, if stored at the study clinic, are immediately identified, disposed of/destroyed and the action is documented.

The Sponsor must ensure that the laboratory(-ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed or returned to the study clinic and the action is documented.

13 QUALITY MANAGEMENT, QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Quality management: critical process, system, and data identification

During CSP development, the Sponsor will identify those processes, systems (facilities, computerized systems) and data that are critical to ensure human subject protection and the reliability of trial results according to applicable SOPs and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R2) guideline [20].

Identified risks will be categorized separately from the CSP.

13.2 Quality assurance and quality control

The Sponsor has delegated the responsibilities outlined below to [redacted] whilst maintaining overall study oversight:

- Implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs with regard to management of identified risks, CSP compliance, good clinical practice (GCP) compliance and applicable regulatory requirements.
- Securing agreements with involved subcontractors and to perform regular subcontractor oversight to ensure CSP compliance, GCP compliance and compliance with applicable regulatory requirements.
- Implementing a risk-based validated EDC system and maintain SOPs for the whole life cycle of the system.
- QC application to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [19] and are consistent with the ICH E6 (R2) guideline for GCP [20], the European Union (EU) Clinical Trials Directive 2001/20/EC [21], and applicable local regulatory requirements.

14.2 Ethics and regulatory review

The PI is responsible for submission of the CSP, the subject information and ICF, any other written information to be provided to the subjects and any advertisements used for recruitment of subjects to applicable IEC for approval.

The Sponsor has delegated to [redacted] the responsibility for submission of study documents to the applicable CA according to local regulatory requirements.

Approval must be obtained in writing from both IEC and CA before the first subject can be recruited.

The Sponsor will provide the CA, IEC, and PI with safety updates/reports according to local requirements. Progress reports and notifications of SUSARs will be provided to the IEC according to local regulations and guidelines.

14.3 Subject information and consent

It is the responsibility of the Investigator or an authorized associate to give each potential study subject adequate verbal and written information before any study specific assessments are performed.

The information will include the objectives and the procedures of the study as well as any risks or inconvenience involved. It will be emphasized that participation in the study is voluntary and that the subject may withdraw from participation at any time and for any reason, without any prejudice. All subjects will be given the opportunity to ask questions about the study and will be given sufficient time to consider participation before signing the ICF.

The ICF includes information that data will be recorded, collected and processed, and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the EU general data protection regulation (GDPR) 2016/679 [22], the data will not identify any persons taking part in the study.

The potential study subject must be informed that by signing the ICF they approve that authorized representatives from the Sponsor and [redacted] as well as the concerned IEC and CA, have direct access to their medical records for verification of clinical study procedures.

Before performing any study-related procedures the ICF must be signed and personally dated by the subject and by the Investigator. A copy of the subject information including the signed ICF will be provided to the subject.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the eCRF. The subject information card and the signed ICF must be filed by the Investigator for possible future audits and/or inspections.

The final approved version of the subject information and ICF must not be changed without approval from the Sponsor and the applicable IEC.

14.4 Subject information card

The subject will be provided with a subject information card including the following information:

- That they are participating in a clinical study.
- Subject study ID .
- That they are treated with the IMP.
- The name and phone number of the Investigator.
- The name and address of the Sponsor.

14.5 Data protection

For this study, the Sponsor Cinclus Pharma is the data controller of all data processed during the study (*e.g.*, TMF, study reports) and [redacted] is the data processor. Any subcontractors used in the study are also data processors.

For data that are processed at the study clinic (*e.g.*, medical records and ISF), [redacted] is the data controller.

14.5.1 Ensuring confidentiality of personal data and medical records,

Involved personell who process and use personal data in their work are trained and are familiarised with the Personal Data Protection Act, with the General Data Protection Regulation (REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND COUNCIL - GDPR), dated 27. in April 2016 and with regional legislation - Personal Data Protection Act (Official Gazette of the Republic of Slovenia, No. 94/2007) and its supplements that regulates each area of their work.

The protection of personal data and medical records includes legal, organizational and, accordingly, logistical and technical procedures and measures, which:

- protect premises, equipment and system software, that is protected by application software that processes personal data,
- ensures security of transmission and transfer of personal data,
- prevents unauthorized persons from accessing devices on which personal data is processed and their collections,
- enables subsequent determination of when individual data was entered and used in the database for the period for which individual data is stored.

During processing, sensitive personal data are secured in such a way that unauthorized persons are denied access to them.

The subject has the right to request access to his/her personal data and the right to request rectification of any data that is not correct and/or complete in accordance with EU regulation 2016/679 [22] and the request will be raised to the PI.

14.5.2 Organizational and technical arrangements to avoid unauthorized access

The privacy of subjects will be protected in accordance with ICH-GCP and local legal requirements. The confidentiality of participating volunteers or patients will be ensured by the use of subject identification code numbers (subject number). The collected data will thereby be pseudonymized. Only the research center team will be able to link a subject number to a person . The "Subject Identification Code List" is used to document the connection between the subject number and the subject's first and last name. No personal information (name, initials, address) will be collected by the Sponsor, nor leave the research site . Disclosure of personal information to third parties is limited to special cases such as inspections, audits, IRB / IEC members. Premises in which personal data carriers, hardware and software are located (secured premises) are protected by organizational and physical and/or technical measures that prevent unauthorized persons from accessing the data.

14.5.3 Measures in case of data security breach,

All involved personnel are obliged to immediately notify an authorized person of activities related to the discovery or unauthorized destruction of confidential data, malicious or unauthorized use, appropriation, modification or damage, and they themselves try to prevent such activity. Appropriate actions to stop an ongoing security breach will be taken immediately. The breach will be reported to the local data protection authorities in accordance with reporting timelines, and actions to prevent continuation and reoccurance of the data breach will be taken as appropriate.

14.6 Changes to the approved clinical study protocol

Any proposed change to the approved final CSP, including appendices, will be documented in a written and numbered clinical protocol amendment. All substantial amendments to the protocol must be approved by the appropriate IEC and/or CA before implementation according to applicable regulations.

14.7 Audits and inspections

Authorized representatives of the Sponsor, CA, or IEC may perform audits or inspections at the study clinic, including source data verification (SDV). The purpose of an audit or inspection is to examine all study-related activities and documents systematically and independently, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH-GCP guidelines and any applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by the CA about an inspection at the study site.

14.8 Insurance

Subjects will be covered under Cinclus Pharma Holdings AB's liability insurance policy through the [redacted] request. The participating subjects are also protected in accordance with national regulations, as applicable. [redacted] has a company insurance covering services performed by [redacted]

15 STUDY MANAGEMENT

15.1 Training of study site personnel

Before inclusion of the first study subject, a Sponsor representative or delegate will perform a study initiation visit at the study clinic. The requirements of the CSP and related documents will be reviewed and discussed, and the investigational staff will be trained in any study specific procedures and system(s) that are required.

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this study must be forwarded to the staff involved in a timely manner.

The Investigator will keep a list of all personnel involved in the study together with their function and study related duties delegated. A Curriculum Vitae will be available for all staff delegated study-specific duties.

15.2 Clinical monitoring

The Sponsor is responsible for securing agreement from all involved parties to ensure direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities.

As defined in the risk-based monitoring (RBM) plan, approved by the Sponsor and provided separately, the responsible Monitor will periodically visit the study site at times agreed upon by the Investigator and the Monitor. At the time of each monitoring visit, the role of the Monitor will be (but will not be limited to) the following:

- To provide information and support to the investigational team.
- To confirm that facilities and resources remain acceptable.
- To confirm that the investigational team is adhering to the CSP, applicable SOPs, guidelines, manuals, and regulatory requirements.
- To verify that data are being accurately and timely recorded in the eCRFs and that IMP accountability checks are being performed.
- To verify that data in the eCRF are consistent with the clinical records (SDV) in accordance with the RBM plan.
- To verify that the correct informed consent procedure has been adhered to for participating subjects.
- To ensure that withdrawal of informed consent to the use of the subject's biological samples will be reported and biological samples are identified and disposed of/destructed accordingly, and that this action is documented and reported to the subject.
- To verify that AEs are recorded and reported in a timely manner and according to the CSP.
- To raise and escalate any serious quality issues, serious GCP breach and any data privacy breach to the Sponsor.

Centralized monitoring will also be performed continuously by study team members at [redacted] in accordance with the RBM plan. When the study has been completed and all queries have been resolved and the database has been locked, the Monitor will perform a close-out visit.

15.3 Source data documents

A separate origin of source data list will be generated for the study site before the start of enrolment, specifying the location of the source of derived information appearing in the eCRF. This document must be signed by the PI and the Monitor to confirm agreement before start of recruitment.

Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, and that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, *et c*. The eCRF may constitute source data if clearly defined in the origin of source data list.

The Investigator must guarantee access to source documents to the Monitor, CAs and the IECs, if required.

15.4 Study agreements

The PI must comply with all the terms, conditions, and obligations of the clinical study agreement for this study.

Agreements between the Sponsor, Cinclus Pharma, and [redacted] must be in place before any study-related procedures can take place, or subjects be randomized.

15.5 Study timetable and end of study

The study is expected to be started during Q3 2022 and completed during Q4 2022.

A subject is considered to have completed the study if they have completed all visits to which they have been allocated, including the end-of-study visit.

The end of the study is defined as the date of the last visit of the last subject participating in the study.

15.6 Termination of the study

The Investigator or the Sponsor may terminate this study prematurely for any reasonable cause. The IEC and CA must be informed promptly. Conditions that may warrant study termination include, but are not limited to the following:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects included in the study or potential study subjects.
- A decision by the Sponsor to suspend or discontinue the development of the IMP.

If the CA obtains information that raises doubts about the safety or scientific validity of the study, the CA may also suspend or prohibit the study. Before the CA reaches its decision, it shall, except where there is imminent risk, ask the Sponsor and/or the Investigator for their opinion, to be delivered within 1 week (Directive 2001/20/EC, Article 12, Section 1) [21].

If the study is prematurely terminated or suspended for any reason, the Investigator/institution must promptly inform the study subjects and must assure appropriate follow-up for the subjects.

15.7 Reporting and publication

15.7.1 Clinical study report

A summarizing report will be submitted to a publicly available database (*e.g.*, EudraCT) within 12 months after completion of the study, in accordance with applicable regulations.

After completion of the study, an ICH E3 [23] guideline-compliant [redacted] describing the conduct of the study, any statistical analyses performed, and the results obtained will be prepared by the Sponsor or their designee. The [redacted] will be reviewed and approved by, as a minimum, the PI and the Sponsor. The study results will be reported in the EudraCT database per applicable regulations within 12 months after completion of the study.

15.7.2 Annual safety report

If the study duration exceeds 1 year, the Sponsor must submit development safety update report (DSUR) to the CA and to the IEC. The report must summarize all pertinent safety information collected during the reporting period and contain an update of the risk-benefit evaluation if there has been any change since the approval of the clinical study.

15.7.3 Confidentiality and ownership of study data

Any confidential information relating to the IMP or the study, including any data and results from the study, will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the study are responsible for protecting the confidentiality of this proprietary information belonging to the Sponsor.

15.7.4 Publication

The results from this study may be submitted for publication at the discretion of the Sponsor.

15.8 Archiving

The PI is responsible for maintaining essential documents, (as defined in ICH E6(R2), Section 8 [20]) for 10 years after finalization of the [redacted] This includes any original source documents related to the study, the subject identification list (providing the sole link between named subject source records and pseudonymous eCRF data), the original signed ICFs and detailed records of IMP disposition.

It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The Sponsor will archive the TMF in accordance with the ICH E6(2) guideline, Section 8 [20], and applicable regulatory requirements [21].

The data from the eCRFs will be sent to the Sponsor and a copy will be sent to the clinic and filed in the Investigator Site File for archiving for 10 years after finalization of the [redacted]

The completed original eCRFs are the sole property of the Sponsor and must not be made available in any form to third parties, except for authorized representatives of appropriate health/regulatory authorities, without written permission from the Sponsor.

15.9 Database lock

When all data have been entered and discrepancies solved, clean file will be declared, the database will be locked and the data will be analyzed.

16 DATA MANAGEMENT

The data management routines include procedures for handling of the eCRF, database set-up and management, data entry and verification, data validation, QC of the database, and documentation of the performed activities including information of discrepancies in the process. The database, data entry screens, and program will be designed in accordance with the CSP.

Data validation/data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of computerized online edit checks identifying *e.g.*, data values that are outside the allowed range and SAS-programmed offline checks on data exports. All study-specific and standard data validation programming will be tested prior to being used on final data.

Detailed information on data management will be described in a study-specific Data Management Plan (DMP).

16.1 The web-based eCRF

Clinical data will be entered into a 21 CFR Part 11-compliant eCRF [redacted] provided by [redacted] The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents or at bedside (if the eCRF data constitutes source data). Source data are to be defined at the site before inclusion of the first subject (Section 15.3).

Authorized site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorized trial site personnel prior to the trial being initiated and any data being entered into the system for any study subject.

16.2 The entering of data into the eCRF

All entries, corrections, and alterations are to be made by the Investigator or designee. Neither the Monitor nor any other study team member besides site staff can enter data in the eCRF. All data will be entered in English. The eCRFs will be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort will be made to ensure that preferably same individual who made the initial baseline determinations completes all corresponding follow-up evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable, or unknown, the Investigator or assigned clinical staff will record such information in the eCRF. The Investigator will be required to electronically sign off on the clinical data. This will be performed by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature.

16.3 The query process

The Monitor will review the eCRFs and evaluate them for completeness and consistency. Data in the eCRF will be compared with the respective source documents to ensure that there are no discrepancies for critical data as described in the risk-based monitoring plan. All entries, corrections, and alterations are to be made by the Investigator or designee. Neither the Monitor nor any other study team member besides site staff can enter data in the eCRF.

If corrections are needed, queries will be raised within the eCRF. An appropriate member of the site staff will answer the queries in the eCRF either by correcting the data or by entering a response to the query.

16.4 Audit trail

All entries in the eCRF will be fully recorded in a protected audit trail. Once clinical data have been saved, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged.

16.5 External data

External data consists of data that are not recorded in the eCRF. Data may be received in electronic format or as a paper printout. Key variables are defined in order to uniquely identify each sample record. File and data formats are agreed with the external data provider.

16.6 Medical coding

Medical coding will be performed by trained personnel at [redacted] AEs and medical/surgical history verbatim terms are coded using the medical dictionary of regulatory activities (MedDRA, latest version available at eCRF setup). Prior and concomitant medications will be coded according to the World Health Organization (WHO) drug dictionary classification system WHODrug. All coding will be approved by the Sponsor prior to database lock.

16.7 Database lock

When all data have been entered and discrepancies solved, clean file will be declared, the database will be locked and the data will be analyzed.

17 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The principal features of the statistical analysis to be performed are described in this section. A more technical and detailed elaboration of the principal features will be presented in a separate statistical analysis plan (SAP), which will be signed and approved prior to database lock.

Analyses of the primary and secondary endpoints will be performed by [redacted]

17.1 General

Continuous data will be presented in terms of evaluable observations, arithmetic mean, standard deviation (SD), as well as median, minimum and maximum values.

Categorical data will be presented as counts and percentages.

When applicable, summary data will be presented by treatment and by assessment time. Individual subject data will be listed by subject number, treatment sequence and, where applicable, by treatment and assessment time.

All descriptive summaries and statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC).

Baseline will be defined as the latest measurement prior to the first exposure to the IMP.

No imputation of missing data will be performed.

17.2 Determination of sample size

The sample size used in this relative bioavailability study has been obtained using the principles used to determine sample sizes in bioequivalence studies. This is for guidance only. The goal is to estimate the relative bioavailability with reasonable precision (the 90% confidence interval for the ratio of geometric means).

[redacted]

17.3 Analysis data sets

17.3.1 Full analysis set

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.

17.3.2 Pharmacokinetic analysis set

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 the SAP. 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).

17.4 Description of study population

17.4.1 Demographics and baseline characteristics

Descriptive statistics for demographics, weight, height, and BMI will be presented by treatment sequence.

17.4.2 Medical/surgical history and prior/concomitant medication

Medical/surgical history will be presented by system-organ-class (SOC) and preferred term (PT). Prior/concomitant medications will be presented by WHODrug preferred names.

All data will be listed by treatment sequence and subject.

17.4.3 Treatment compliance

The subjects in each treatment sequence and their individual doses will be listed.

17.5 Analysis of pharmacokinetic endpoints

17.5.1 Primary analysis of pharmacokinetics

The PK analysis will be based on the PKAS. The PK parameters will be calculated by non-compartmental analysis (NCA) using the software Phoenix WinNonlin® version 8.3 or later (Certara Inc, Princeton NJ, United States).

The following primary non-compartmental PK parameters will be assessed for linaprazan glurate and linaprazan if sufficient data is available:

- AUC_{inf}.
- AUC_{last}.
- C_{max}.

For AUC_{inf}, the area under the plasma concentration *vs.* time curve will be calculated to the time point of the last quantifiable plasma concentration and then extrapolated to infinity using the concentration in the last quantifiable sample and the estimated terminal elimination rate constant ($Lambda_z$).

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_{last}, and C_{max}, the geometric mean and geometric coefficient of variation (CV%) will also be presented.

All data will be listed by treatment and subject.

17.5.2 Estimation of relative bioavailability

The analyses performed on the PK parameters will also include estimation of relative bioavailability between the test formulation (Treatment B) and the reference formulation (Treatment A) in fasting conditions, as well as between the test formulation in fasting conditions (the reference condition, Treatment B) and in fed conditions (the test condition, Treatment C).

Relative bioavailability will be estimated using a linear model with the natural logs of AUC_{inf}, AUC_{last}, and C_{max} as the dependent variables and treatment, period, sequence and subject within sequence as the independent variables. The estimated LSMeans difference between Treatment B and Treatment A, as well as between Treatment B and Treatment C, will be back-transformed into the original scale to present the ratio of geometric LSMeans as well as the corresponding 90 % Confidence Interval. . .

17.5.3 Secondary analysis of pharmacokinetics

In addition to the PK analysis related to primary objectives (Section 17.5.1), the following secondary non-parametric PK parameters will be assessed for linaprazan glurate and linaprazan, if sufficient data is available:

- T_{max}.
- T_{lag}.
- $T_{1/2}$.
- $AUC_{extrapol\%}$.
- CL/F.
- V_z/F.

Additional PK parameters may be determined if deemed appropriate.

Secondary PK data will be presented by treatment using summary statistics with number of measurements, arithmetic mean, standard deviation (SD), as well as median, minimum and maximum values. 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.

17.6 Analysis of safety endpoints

17.6.1 Adverse events

An overview of all AEs, including SAEs, intensity, relationship to IMP, and deaths will be presented. The incidence of AEs and SAEs will be summarized by SOC and PT by treatment and overall. An overview of any treatment-related AEs will be summarized by SOC and PT if considered appropriate.

All AE data will be listed by treatment and subject and include the verbatim term entered by the Investigator as well as PT.

17.6.2 Safety 12-lead ECG

All ECGs will be categorized as "normal", "abnormal, NCS," or "abnormal, CS" (as judged by the Investigator). ECG measurements and interpretations will be summarized by treatment

sequence using frequency tables. Changes over time may be presented using shift tables, if appropriate.

All ECG data will be listed by treatment sequence and subject.

17.6.3 Safety laboratory analyses

Safety laboratory measurements will be summarized by treatment sequence with absolute and relative (%) change from baseline at each assessment time point. Safety laboratory interpretations ("normal", "abnormal, NCS," or "abnormal, CS") may be summarized separately, if warranted.

All safety laboratory data will be listed by treatment sequence and subject.

17.6.4 Vital signs

Vital signs (systolic/diastolic blood pressure, pulse rate and body temperature) measurements will be summarized by treatment sequence with absolute and relative (%) change from baseline at each assessment time point. Vital signs interpretations ("normal", "abnormal, NCS," or "abnormal, CS") may be summarized separately, if warranted.

All vital signs data will be listed by treatment sequence and subject.

17.6.5 Physical examinations

The interpretations ("normal", "abnormal, NCS," or "abnormal, CS") of physical examination findings will be summarized by treatment sequence for each assessment time point.

All physical examination data will be listed by treatment sequence and subject.

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19 SIGNATURES

19.1 Principal Investigator statement

I, the undersigned, have read and understood this CSP and agree to conduct the study accordingly and to comply with the Investigator obligations stated in this CSP, GCP and applicable regulatory requirements.

Principal Investigator

[redacted]

[redacted] MD

[redacted]

23/12/2022

19.2 Approval of the clinical study protocol

I, the undersigned, approve this CSP.

Sponsor signatory

[redacted]

12 October 2022

[redacted], PhD, CMO
Cinclus Pharma Holding AB