Clinical Study Protocol

EudraCT no.	2022-002725-10
Investigational medicinal product	Linaprazan glurate
Study code	CX842A2107
Protocol version and date	Final V.4.0; 10 MAR2023

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

Phase	I
Indication	Gastroesophageal reflux disease (GERD)
Test product and dose	Linaprazan glurate (formerly X842) 25, 50 and 75 mg
International non-proprietary name (INN)	Linaprazan glurate
Unique ingredient identifier (UNII)	3VG4D399DT
Sponsor signatory	[redacted] MD, PhD, CMO Cinclus Pharma Holding AB World Trade Center, Kungsbron 1 SE-111 22 Stockholm, Sweden
Principal Investigator	[redacted] MD, PhD [redacted]
Clinical study conduct and management	[redacted]

1 STUDY SYNOPSIS

Study title

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

Study code	**EudraCT no.**
CX842A2107	2022-002725-10
Planned study period	**Phase of development**
Q1 2023 to Q2 2023	I

Principal Investigator

[redacted] MD, PhD, [redacted]

Study design

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

Objectives

Primary objective

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

Secondary objectives

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

Exploratory objectives

[redacted]

Endpoints

Primary endpoints

- Linaprazan glurate and linaprazan PK parameters after single and repeated administration of linaprazan glurate (when applicable):
    - Area under the plasma concentration *vs.* time curve (AUC) at different timepoints: AUC_{0-24}, AUC_{0-12}, AUC_{12-24}, AUC_{24-48}, and AUC_{0-t}
    - The minimum, end-of-dosing interval, maximum and average plasma concentrations: C_{trough}, C_{max} and C_{aver},
    - Terminal elimination half-life ($t_{½}$,) and time of occurrence of C_{max} (t_{max}).

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

Secondary endpoints

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

Exploratory endpoints

[redacted]

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

Number of subjects planned

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

Diagnosis and eligibility criteria

Healthy male and female subject, 18-65 years of age, with a body mass index (BMI) of 18.5-30.0 kg/m^2 (inclusive), who are willing to comply with study procedures and who have given written informed consent are 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.

Methodology

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

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.

After all eligibility criteria from the screening visits have been confirmed, the subjects will be randomized and scheduled for the start of Visit 2.

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

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

Eligible subjects will be admitted to the CRU on Day -2 of Visit 2 and will remain at the study clinic until Day 2 (residential period) up until 24 hours after the first investigational medicinal product (IMP) dose. At 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.

A baseline intragastric pH measurement will be recorded for all subjects over the 24-hour period prior to the first IMP dose. The first IMP dose is given in the evening of Day 1 for Dose groups 1 to 3 and in the morning of Day 1 for Dose groups 4 to 6. It is important that the intake of food and snacks is standardized (see below) on the days of intragastric pH measurements including the baseline recording.

Following IMP administration on Day 1, measurement of intragastric pH for 24 hours post- dose will be performed. For Dose groups 4 to 6, the subjects must fast for ≥10 hours overnight before the anticipated dosing time on Day 1 until 30 minutes post-dose. During fasting, tap water, but no other drinks is allowed as desired, except for 1 hour before and 1 hour after dosing. For Dose group 1 to 3, the subjects are non-fasting and will follow a standardized food intake schedule.

PK blood samples will be collected for 24 hours after the first IMP dose on Day 1 to Day 2. The subjects will leave the clinic in the morning of Day 2 (Dose groups 4 to 6) or the evening of Day 2 (Dose groups 1 to 3) after PK sampling up until 24 hours post first dose.

The subjects will continue to take linaprazan glurate at home from Day 3 to Day 13. The subjects will be using a paper diary to record drug intake at home.

On Day 5 (Visit 3) and Day 10 (Visit 4) the subjects will return to the CRU for PK blood sampling (trough plasma concentration). Dose groups 1 to 3 will have their sample drawn prior to IMP intake in the evening and Dose groups 4 to 6 will have their sample drawn prior to the morning IMP dose.

The subjects will be admitted to the CRU on Day 14 (Visit 5) and will remain until Day 15 for PK blood sampling, measurement of intragastric pH and safety assessments. For Dose groups 4 to 6, the subjects must fast for ≥10 hours overnight before the anticipated dosing time on Day 14 until 30 minutes post-dose. During fasting, tap water, but no other drinks is allowed as desired, except for 1 hour before and 1 hour after dosing. PK blood samples will be collected for 24 hours post-dose on Day 14 to Day 15. The measurement of intragastric pH will start after the last dose of IMP on Day 14 and continue for 48 hours. The last IMP dose will be given in the evening of Day 14 (Dose groups 1 to 3) or in the morning of Day 14 (Dose group 4 to 6).

The subjects will return to the CRU in the morning of Day 16 (Visit 6) for PK blood sampling at 36- and 48-hours post-dose, and removal of the pH catheter 48 hours after the last IMP dose.

[redacted]

[redacted]A final remote follow-up visit (Visit 8) will be conducted via telephone 7 days (±2 days) after the final dose of IMP, or after early withdrawal, to follow-up on AEs and concomitant medications.

To oversee the safety of each subject, in addition to the regularly scheduled safety assessments at the site, there will be a bi-weekly internal safety review committee (iSRC) meeting, where all aggregate safety data will be reviewed. At the end of each meeting there will be a decision on if the study shall progress as planned or if additional safety measures should be added, including more visits for safety assessments and an adjusted length of the follow-up period.

Investigational Medicinal Product, dosage and mode of administration

The test product is linaprazan glurate, 25 mg oral tablet. Three (3) different dose levels will be investigated per dosing regimen (QD or BID). There will be 6 dose groups as follows:

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

[redacted]

The timing of food intake in relation to dose of linaprazan glurate is particularly important and will be standardized at days of intragastric pH measurement, *i.e.*, baseline before the first dose of linaprazan glurate and at Day 1 and Day 14. In dose groups 4 to 6 (BID dosing), the morning dose will be given at fasted state (overnight fast ≥10 hours) and breakfast will be served 30 min post-morning dose, further food will be served at 4, 6 (snack), 9 and 12 (snack) hours after dose. All meals should be completed within 30 minutes from the planned timepoint. Dose groups 1 to 3 will follow a standardized meal plan and the evening dose of IMP will be administered after the evening meal at the clinic.

During home administration with linaprazan glurate there are no fasting requirements. The subjects will be using a paper diary to record drug intake at home.

Duration of treatment

The participating subjects will receive 25, 50 or 75 mg doses of IMP, QD or BID for 14 days. After a [redacted]

Duration of each subject's involvement in the study

Each subject is expected to participate in the study for a maximum of 52-56 days, including an up to 28-day screening period.

Safety assessments

- AEs
- ECG recordings
- Vital signs (systolic/diastolic blood pressure [BP], pulse, body temperature)

- Physical examination
- Safety laboratory measurements

Pharmacokinetic assessments

Blood samples for analysis of PK parameters of linaprazan glurate and linaprazan will be collected for the QD posology; prior to IMP administration (pre-dose) and 0.25 0.5, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 14, 20 and 24 hours after dose Day 1, Day 2 and at Day 14; also 36 and 48 h after dose. For the BID dosing blood samples will be collected 0.25 0.5, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 12.25, 12.30, 13, 13.25, 13.5, 14, 15, 16, 18, 20 and 24 hours after dose hours after dose Day 1, Day 2 and at Day 14 also 36 and 48 h after last dose. In addition, trough plasma concentration will be sampled at 2 additional visits, at Day 5 and Day 10.

Pharmacodynamic assessments

Measurement of intragastric pH will be performed during 24 hours after dose of the IMP (*i.e.*, the dose on Day 1 and Day 14.

Statistical methods

No formal sample size calculation has been performed for this study. The proposed sample size is considered sufficient to provide adequate information for the study objectives.

The PK parameters will be calculated by non-compartmental analysis (NCA). Summary statistics for the PK parameters will be presented with number of measurements, arithmetic mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean, geometric CV%. Additional PK parameters may be determined if deemed appropriate.

All data will be listed by dose group and subject.

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

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

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by dose group and by assessment time. Individual subject data will be listed by subject number, dose group and, where applicable, by assessment time.

All AE data will be fully listed by Investigator terms and Medical Dictionary of Regulatory Activities (MedDRA) Preferred Term (PT). AE data will be summarized by System Organ Class (SOC) and PT.

Study reporting

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

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2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
AE	Adverse event
ADL	Activities of daily living
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin clotting time
AR	Adverse reaction
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration *vs.* time curve
AUC_{0-t}	AUC from time 0 to time t
$AUC_{0-24,\ 0-12,\ 12-24,\ 24-48}$	AUC from time 0-24, 0-12, 12-24, 24-48 hours, respectively
$AUC_{extrap\%}$	AUC percent extrapolation
AUC_{inf}	AUC from 0 to infinity
AUC	AUC from 0 to time of last measurable plasma concentration
BID	*Bis in die* (twice daily)
BMI	Body mass index
BP	Blood pressure
CA	Competent authority
C_{aver}	Average concentration
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent total body clearance following extravascular administration
CHL	Chinese hamster lung
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
C_{trough}	The plasma concentration observed at the start of a dosing interval.
CS	Clinically significant
[redacted]	
CSP	Clinical study protocol
CSR	Clinical study report

Abbreviation	Explanation
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DMP	Data management plan
DSUR	Development safety update report
ECG	Electrocardiogram
eCRF	Electronic Case report form
EDC	Electronic data capture
EEA	European Economic Area
eGERD	Erosive GERD
EU	European Union
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
HbsAg	hepatitis B virus surface antigen
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IME	Important medical event
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier

Abbreviation	Explanation
INN	International non-proprietary name
IR	Immediate release
ISF	Investigator site file
IUD	Intra-uterine device
IUS	Intra-uterine system
LLOQ	Lower limit of quantification
MAD	Multiple-ascending dose
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MTD	Maximum tolerated dose
MS	Mass spectrometry
NCA	Non-compartmental analysis
NCS	Not clinically significant
NOAEL	No observed adverse effect level
P-CABs	Potassium-competitive acid blockers
PD	Pharmacodynamics
PII	Personally identifiable information
PK	Pharmacokinetics
PK(INR)	Prothrombin complex international normalized ratio
PKAS	PK analysis set
PPI	Proton pump inhibitors
PT	Preferred term
QA	Quality assurance
QC	Quality control
QD	*Quaque die* (once daily)
QRS interval	(ECG) The time required for stimulus to spread through the heart's ventricles
QT interval	(ECG) The time from the beginning of the QRS complex to the end of the T wave

Abbreviation	Explanation
QTcF	(ECG) Corrected QT interval by Fredericia
R_{acc}	Accumulation ratio
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
TMF	Trial master file
T_{max}	Time of occurrence of C_{max}
$T_{1/2}$	Terminal elimination half-life
UNII	Unique ingredient identifier
V_z/F	Volume of distribution following extravascular administration
WHO	World Health Organization

3 IMPORTANT GUIDELINES TO BE FOLLOWED BY THE SPONSOR

The Sponsor hereby confirms that all relevant regulatory guidelines will be followed, including (but not limited to) the following guidelines:

- ICH E6 (R2) Good Clinical Practice
- ICH E8 General considerations for clinical studies
- ICH E9 Statistical Principles for Clinical Trials
- ICH M10 Bioanalytical method validation and study sample analysis

4 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

4.1 Medical emergencies contact

The Principal Investigator 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 responsible	[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] MD, PhD, CMO
Phone: [redacted]
E-mail: [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)	[redacted]
Investigational Medicinal Product (IMP) manufacturing, packaging and labelling	
IMP import and qualified person (QP) release	
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 observed 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. 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.

For Phase III, linaprazan glurate [redacted] has been developed in two strengths, 25 and 100 mg. The 25 mg tablet will be investigated 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 0-24 hours 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 investigational medicinal product (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. [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 levels of linaprazan glurate to be tested in this study is 25 mg, 50 mg and 75 mg (QD or BID dosing) for 14 days. [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]

This study aims to characterize the PK of linaprazan glurate and its active metabolite linaprazan following single- and 14-days repeated dosing of linaprazan glurate administered QD or BID at three dose levels. The PD (intragastric pH) will be determined in all treatment groups to generate exposure-response data to support the phase III dose selection. [redacted]

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.

Toxicology studies and previous clinical studies on linaprazan and linaprazan glurate have indicated low toxicity with no major concerns at the studied dose levels. 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). Only limited data are available at this stage on reproductive toxicology. 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 up to 150 mg BID 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 in healthy volunteers (public data). 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] 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).

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 and a pH-measuring electrode for measurement of intragastric pH), 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) [17], 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 the [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 [redacted] residential visits to the CRU, each comprising 2 to 3 days. 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

Linaprazan glurate has the potential to provide 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

7.1 Objectives and endpoints

The study objectives and endpoints are summarized in Table 7.1-1.

Table 7.1-1 Objectives and endpoints

Objectives	Endpoints	Assessments
Primary		
To characterize the PK and PD of linaprazan glurate and linaprazan after once (QD) or twice (BID) daily dosing after a single and repeated administration of linaprazan glurate.	Linaprazan glurate and linaprazan PK parameters (when applicable AUC_{0-24}, AUC_{0-12}, AUC_{12-24}, AUC_{24-48}, AUC_{0-t}, C_{trough}, C_{aver}, C_{max}, $t_{½}$, t_{max}) after single and repeated administration of linaprazan glurate.	Linaprazan glurate and linaprazan PK parameters (Section 11.3.1).
	Percentage of time gastric pH >4 at Day 1 and Day 14, over a 24-hour monitoring period following linaprazan glurate administration.	Intragastric pH at Day 1 and Day 14 (Section 11.3.2).
Secondary		
To assess the safety and tolerability after single and repeated doses of linaprazan glurate.	Additional PK parameters for linaprazan glurate and linaprazan PK parameters (e.g., but not limited to CL/F, V/F, R_{Acc}, C_{min}, AUC_{inf}, $AUC_{extrap\%}$).	Linaprazan glurate and linaprazan PK parameters (Section 11.3.1).
	Frequency, intensity and seriousness of adverse events (AEs).	AEs (Section 11.4.1).
	Clinically significant changes in: o Electrocardiogram (ECG) o Vital signs o Physical examinations o Safety laboratory parameters	ECG (Section 11.4.2).
		Vital signs (Section 11.4.3).
		Physical examinations (Section 11.4.4).
		Blood sampling for hematology, clinical chemistry and coagulation (Section 11.4.5).
Exploratory		
[redacted]		

Objectives	Endpoints	Assessments
[redacted]		

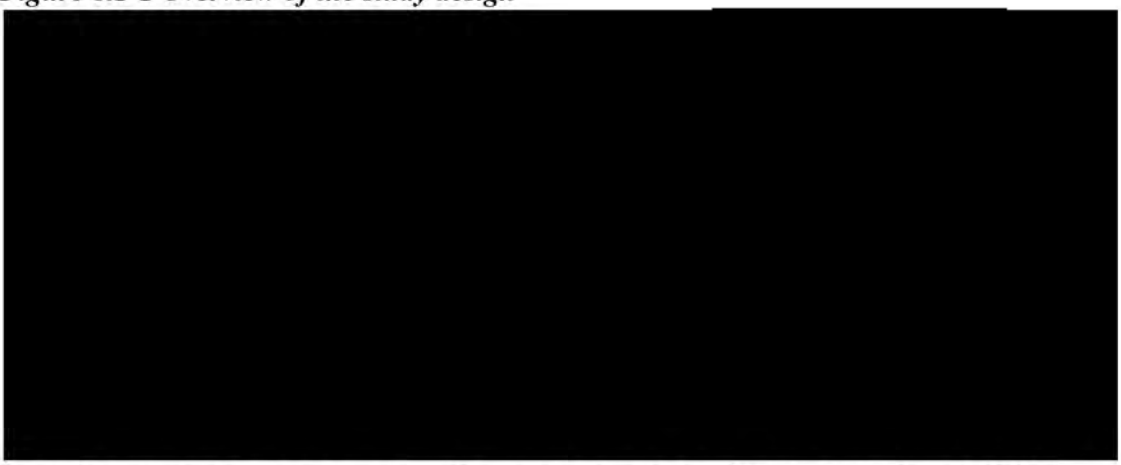
8 STUDY DESIGN

8.1 Overall study design and schedule of events

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

An overview of the study design is shown in Figure 8.1-1. The overall schedule of events is presented in Table 8.1-1 and the detailed schedule of events for Visit 2 is shown in Table 8.1-2 (QD dosing) and in Table 8.1-3 (BID dosing), for Visit 5-6 Table 8.1-4 (QD dosing) and in Table 8.1-4 (BID dosing) and for Visit 7 and Visit 8 in Table 8.1-6 (QD dosing) and in Table 8.1-7 D (BID dosing).

Figure 8.1-1 Overview of the study design



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

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.

After all eligibility criteria from the screening visits have been confirmed, the subjects will be randomized and scheduled for the start of Visit 2.

Subjects will be randomized into 1 of 6 dose groups (as detailed in Section 9.9). There will be 6 dose groups as follows:

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

Eligible subjects will be admitted to the CRU on Day -2 of Visit 2 and will remain at the study clinic until Day 2 (residential period) up until 24 hours after the first IMP dose. At 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.

A baseline intragastric pH measurement will be recorded for all subjects over the 24-hour period prior to the first IMP dose. The first IMP dose is given in the evening of Day 1 for Dose groups 1 to 3 and in the morning of Day 1 for Dose groups 4 to 6. It is important that the intake of food and snacks is standardized (see below) on the days of intragastric pH measurements including the baseline recording.

Following IMP administration on Day 1, measurement of intragastric pH for 24 hours post-dose will be performed. For Dose groups 4 to 6, the subjects must fast for ≥10 hours overnight before the anticipated dosing time on Day 1 until 30 minutes post-dose. During fasting, tap water, but no other drinks is allowed as desired, except for 1 hour before and 1 hour after dosing. For Dose group 1 to 3, the subjects are non-fasting and will follow a standardized food intake schedule.

PK blood samples will be collected for 24 hours after the first IMP dose on Day 1 to Day 2. The subjects will leave the clinic in the morning of Day 2 (Dose groups 4 to 6) or the evening of Day 2 (Dose groups 1 to 3) after PK sampling up until 24 hours post first dose.

The subjects will continue to take linaprazan glurate at home from Day 3 to Day 13. The subjects will be using a paper diary to record drug intake at home.

On Day 5 (Visit 3) and Day 10 (Visit 4) the subjects will return to the CRU for PK blood sampling (trough plasma concentration). Dose groups 1 to 3 will have their sample drawn prior to IMP intake in the evening and Dose groups 4 to 6 will have their sample drawn prior to the morning IMP dose.

The subjects will be admitted to the CRU on Day 14 (Visit 5) and will remain until Day 15 for PK blood sampling, measurement of intragastric pH and safety assessments. For Dose groups 4 to 6, the subjects must fast for ≥10 hours overnight before the anticipated dosing time on Day 14 until 30 minutes post-dose. During fasting, tap water, but no other drinks is allowed as desired, except for 1 hour before and 1 hour after dosing. PK blood samples will be collected for 24 hours post-dose on Day 14 to Day 15. The measurement of intragastric pH will start after the last dose of IMP on Day 14 and continue for 48 hours. The last IMP dose will be given in the evening of Day 14 (Dose groups 1 to 3) or in the morning of Day 14 (Dose group 4 to 6).

The subjects will return to the CRU in the morning of Day 16 (Visit 6) for PK blood sampling at 36- and 48-hours post-dose, and removal of the pH catheter 48 hours after the last IMP dose.

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

Each subject is expected to participate in the study for a maximum of 52-56 days, including an up to 28-day screening period.

The subjects will be carefully monitored by clinical staff during and after dosing. The subjects will be served standardized meals while they are in the CRU.

AEs and concomitant medications will be recorded from the first dose of linaprazan glurate and throughout the study.

Table 8.1-1 Overall schedule of events

Visit → Assessment↓	CSP Section	Visit 1 Screening	Visit 2 Residential	Visit 3 and Visit 4 Outpatient	Visit 5 Residential	Visit 6 Outpatient	[redacted]	Visit 8 Telephone follow-up
Day→		**Day -28 to Day -2**	**Day -2 to 2**	**Day 5 and Day 10**	**Day 14 to Day 15**	**Day 16**		**7 days (±2 days) post-last dose[1]**
Informed consent	11.2.1	X						
Eligibility criteria	9.4, 9.5	X	X[2]					
Demographics	11.2.3	X						
Weight/height (BMI)	11.2.4	X						
Medical/surgical history	11.2.5	X						
HIV, Hep B and C test	11.2.7	X						
FSH test[3]	11.2.8	X						
Pregnancy test		X	X					
Urine drug screen	11.2.9	X	X[4]					
Alcohol test	11.2.10	X	X[4]					
Screening for Helicobacter Pylori	11.2.11	X						
Safety laboratory profile	11.4.5	X	X	X	X	X		
Vital signs[5]	11.4.3	X	X		X			
Physical examination	11.4.4	X	X		X			
12-lead safety ECG	11.4.2	X	X		X			
Randomization	9.9	X[6]						
IMP administration[7]	10.5		X	X	X			
PK blood sampling[8]	11.3.1		X	X	X	X		
Intragastric pH measurement	11.3.2		X		X			
Standardized meals	9.6.1		X		X			
Hand-out of linaprazan glurate[9]	10.5		X					
Compliance check	10.7				X			
Overnight stay in clinic	N/A		X		X			
Baseline symptoms[10]	11.2.12	-------- X --------						
AEs[11]	11.4		---------- X ----------					

Visit → Assessment↓	CSP Section	Visit 1 Screening	Visit 2 Residential	Visit 3 and Visit 4 Outpatient	Visit 5 Residential	Visit 6 Outpatient	[redacted]	Visit 8 Telephone follow-up
Prior and concomitant medications	9.6.2	---------- X ----------						

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

1. A final remote follow-up visit (Visit 8) will be conducted via telephone 7 days (±2 days) after the final dose of IMP, or after early withdrawal, to follow-up on AEs and concomitant medications.
2. Confirmation of eligibility prior to start of baseline pH-measurement.
3. Confirmation of menopause. Only in questionable cases at the discretion of the Investigator.
4. Additional random alcohol and drug tests can be performed at subsequent visits at the discretion of the Investigator.
5. Resting systolic and diastolic blood pressure, pulse and body temperature. Blood pressure and pulse should be measured with the subject in a supine position, after 10 minutes of rest.
6. Randomization will take place after confirmation of all eligibility criteria evaluated at the screening visit and prior to the start of Visit 2.
7. Linaprazan glurate 25, 50 or 75 mg QD or BID for 14 days. First dose of IMP shall not be administered until after confirmation of day -2 evaluation of Eligibility criteria, Pregnancy test, Urine drug screen, Alcohol test, Safety laboratory profile, Vital signs, Physical examination and 12-lead safety ECG. [redacted]
8. The blood sampling for PK analysis are specified in Table 8.1-2 and Table 8.1-3 for Visit 2, in Table 8.1-4 and Table 8.1-5 for Visit 5 [redacted]
9. The subjects will administer linaprazan glurate at home from Day 3 to Day 13.
10. Baseline symptoms will be recorded from the signing of the informed consent form (ICF) up until first dose on Day 1.
11. AEs will be recorded from (first) dosing on Day 1 up until the follow-up visit (Visit 8), or early withdrawal.

Table 8.1-2 Detailed schedule of events Visit 2, QD dosing regimen

	Visit 2																	
	Day -2	Day -1	Day 1 &2															
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**
Eligibility criteria	X[1]																	
Pregnancy test	X																	
Urine drug screen	X																	
Alcohol test	X																	
Safety laboratory profile	X																	
Physical examination			X															
Vital signs		X[2]																X
12-lead safety ECG		X[2]																X
IMP administration[3]				X														X
Hand-out of linaprazan glurate																		X
PK blood sampling[4]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Baseline intragastric pH measurement		----------X----------																
Intragastric pH measurement					----------X----------													
Standardized meals[5]									X									
Baseline symptoms			X															
AEs												X						
Prior and concomitant medications									X									

1. Confirmation of eligibility.
2. Can be done on Day -2 to Day 1 prior to first dose administered.
3. The first dose of linaprazan glurate will be administered in the evening of Day 1.
4. 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. In general, actual times for PK blood sampling must not deviate more than 10% from the planned times. Refer to Section 11.3.1. For all PK sampling timepoints coinciding with an IMP administration timepoint, the PK sample should be drawn immediately *prior* to the IMP dose (within 5 minutes).
5. Standardized meals will be served. For timing of meals see Section 9.6.1.

Table 8.1-3 Detailed schedule of events Visit 2, BID dosing regimen

	Visit 2																												
	Day -2		Day -1	Day 1 & 2																									
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**	**12.15**	**12:30**	**13:00**	**13:15**	**13:30**	**14:00**	**15:00**	**16:00**	**18:00**	**20:00**	**24:00**
Eligibility criteria		X[1]																									
Pregnancy test	X																										
Urine drug screen	X																										
Alcohol test	X																										
Safety laboratory profile	X																										
Physical examination				X																							
Vital signs		X[2]																									X
12-lead safety ECG		X[2]																									X
IMP administration[3]					X											X											X
Hand-out of linaprazan glurate																											X
PK blood sampling[4]				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Baseline intragastric pH measurement			----------X---------																								
Intragastric pH measurement							----------	----------	----------	----------	----------	----------	----------	----------	----------	X	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	
Standardized meals[5]													X														
Baseline symptoms			X																								
AEs																X											
Prior and concomitant medications													X														

1. Confirmation of eligibility.
2. Can be done on Day -2 to Day 1 prior to first dose administered.
3. Linaprazan glurate will be administered in the morning and in the evening, there will be ≥10 hours overnight fasting prior to the first dose in the morning of Day 1.
4. 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. In general, actual times for PK blood sampling must not deviate more than 10% from the planned times. Refer to Section 11.3.1. For all PK sampling timepoints coinciding with an IMP administration timepoint, the PK sample should be drawn immediately *prior* to the IMP dose (within 5 minutes).
5. Subjects should fast for ≥10 hours prior to first dose on Day 1. Morning dose will be fasted and then breakfast 30 minutes post-morning dose, further for timing of meals see Section 9.6.1.

Table 8.1-4 Detailed schedule of events Visit 5 to Visit 6, QD dosing regimen

		Visit 5															Visit 6	
		Day 14 &15															Day 16	
Assessment↓/Time→	**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**
Safety laboratory profile	X																X	
Physical examination	X																	
Vital signs	X															X		
12-lead safety ECG	X															X		
IMP administration[1]		X																
PK blood sampling[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intragastric pH measurement			X								X							
Standardized meals[3]										X								
IMP compliance check	X																	
AEs											X							
Concomitant medications											X							

1. Linaprazan glurate will be administered in the evening of Day 14.
2. Pre-dose PK blood sampling should be done within 5 minutes of dosing on Day 14. 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. In general, actual times for PK blood sampling must not deviate more than 10% from the planned times. Refer to Section 11.3.1. For all PK sampling timepoints coinciding with an IMP administration timepoint, the PK sample should be drawn immediately *prior* to the IMP dose (within 5 minutes).
3. Standardized meals will be served. For timing of meals see Section 9.6.1.

Table 8.1-5 Detailed schedule of events Visit 5 to Visit 6, BID dosing regimen

		Visit 5																								Visit 6
		Day 14 &15																								Day 16
Assessment↓/Time→	**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**	**12.15**	**12:30**	**13:00**	**13:15**	**13:30**	**14:00**	**15:00**	**16:00**	**18:00**	**20:00**	**24:00**	**36:00**	**48:00**
Safety laboratory profile	X																								X
Physical examination	X																								
Vital signs	X																						X		
12-lead safety ECG	X																						X		
IMP administration[1]		X											X												
PK blood sampling[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																										
Intragastric pH measurement														X												
Standardized meals[4]													X													
IMP compliance check	X																									
AEs														X												
Concomitant medications														X												

1. Linaprazan glurate will be administered in the morning and in the evening on Day 14, there will be ≥10 hours overnight fasting prior to the dose in the morning of Day 14.
2. Pre-dose PK blood sampling should be done within 5 minutes of dosing in the morning of Day 14. 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. In general, actual times for PK blood sampling must not deviate more than 10% from the planned times. Refer to Section 11.3.1. For all PK sampling timepoints coinciding with an IMP administration timepoint, the PK sample should be drawn immediately *prior* to the IMP dose (within 5 minutes).

[redacted]

4. Subjects should fast for ≥10 hours prior to first dose on Day 14. Morning dose will be fasted and then breakfast 30 minutes post-morning dose, further for timing of meals see Section 9.6.1.

Table 8.1-6 [redacted]

[redacted]

Table 8.1-7

[redacted]

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 [14] was considered when designing this study.

The terminal elimination $t_{1/2}$ 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 sampling schedule around the predicted t_{max} of linaprazan glurate and linaprazan has been chosen to provide a reliable estimate of peak exposure.

[redacted]

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.

8.3 Justification of dose level

The planned dose levels to be used in this study are 25, 50 and 75 mg. The dose levels have been selected based on safety and tolerability in previous single and multiple dose clinical studies, nonclinical safety and toxicity data, and intragastric pH data from previous clinical studies.

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, doses up to 100 mg BID were administered for 4 weeks without safety concerns.

In a Phase 1 PK/PD study (intragastric pH was measured over 48 hours) with repeated BID dosing of 50, 100 and 150 mg linaprazan glurate during Day 1 and 2 and once daily on Day 3 showed a dose/exposure response relationship. The 50 mg BID dose provided acid control (intragastric pH >4 during the 24-48 h interval) 64% of the 24-hour interval, while the corresponding values for 100 and 150 mg dose was 79% and >90% of the 24-hour interval, respectively. There was no safety or tolerability concerns in this study. In the present study the selected doses 25, 50 and 75 mg have been chosen to characterize PK in a sufficient range [redacted] of linaprazan glurate and linaprazan and the intragastric pH (PD). The selected dose levels are covering the anticipated therapeutic dose.

[redacted]

[redacted]

For the dose decision will consist of an internal safety review meeting. Participants will be the principal investigator, a medical representative from the Sponsor and a project lead from the clinical CRO and any other expertise needed. The final decision on dosing schedule in study CX842A2107 will be based upon the prespecified criteria stated in table 8.3-1 and documented. If a dose adjustment is needed it will be valid immediately, the correct dosing table (according to Appendix A) will be used, and the protocol will be updated accordingly.

[redacted]

8.4 Internal safety review committee

An internal safety review committee (iSRC) will meet bi-weekly for review and assessment of aggregate study safety data, i.e. all relevant data collected for safety measures according to the protocol. The first meeting will occur 7-14 days after randomization of first subject. The voting members of the iSRC will consist of the PI, the Sponsor's Study Physician and the Sponsor's Safety Physician. The coordinating non-voting member will be the study clinical research manager (CRM). In addition other internal or external experts may be invited and consulted by the iSRC as appropriate. At each meeting, iSRC will decide if linaprazan glurate is considered safe and tolerable and if to proceed the study as planned and the recommendation of the iSRC will be provided to the Sponsor in writing. The recommendation to the Sponsor may be to continue dosing as planned or if any amendment is needed. The recommendations of the iSRC will be made in consensus between the iSRC members and documented as appropriate. In case of disagreement between the voting members the most conservative approach will be taken.

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 the [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, 116 healthy volunteers are planned to be screened to achieve 72 randomized subjects (assuming a screening failure rate of approximately 37 %). An estimated total of 12 subjects will be included per dose level. If less than 9 subjects are evaluable per dose level, addition of new a subject to replace a discontinued subject can be allowed.

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 subject aged 18 to 65 years, inclusive.
3. Body mass index ≥ 18.5 and ≤ 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.

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.

9.5 Exclusion criteria

Subjects must not enter the study if any of the following exclusion criteria are fulfilled:

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 IU/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 upper gastrointestinal surgery, nose, throat or scull base surgery, 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.
6. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the 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 during the course of the study.
10. Any positive result on screening for serum hepatitis B surface antigen, 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. Sensitive gag reflex believed to interfere with pH-catheter application through the nose, as judged by the Investigator at screening, or *e.g.,* excessive gagging, nose bleeds, pain or other conditions interfering with pH-catheter applications, as judged by the Investigator.
13. After 10 minutes supine rest at the time of screening, any vital signs outside the following ranges:
    - Systolic blood pressure (BP): <90 or ≥140 mmHg
    - Diastolic blood pressure <50 or ≥90 mmHg
    - Pulse <40 or >90 bpm
14. Prolonged QTcF (> 450 ms), cardiac arrhythmias or any clinically significant abnormalities in the resting ECG at the time of screening, as judged by the Investigator.
15. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to linaprazan glurate.
16. Use of prohibited medications as detailed in Section 9.6.2.
17. Regular use of any prescribed or non-prescribed medications, including antacids, analgesics, herbal remedies, vitamins and minerals, within 2 weeks prior to the first administration of IMP, except occasional intake of paracetamol (maximum 2000 mg/day and not exceeding 3000 mg/week), as well as nasal decongestants without cortisone, antihistamine or anticholinergics for a maximum of 10 days, at the discretion of the Investigator.
18. 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.

19. 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.
20. Positive screen for drugs of abuse or alcohol at screening or on admission to the study clinic prior to 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.
21. Positive result for *Helicobacter Pylori* at the time of the screening visit.
22. History of or current alcohol abuse or excessive intake of alcohol, as judged by the Investigator.
23. History of or current drug abuse and/or anabolic steroids, as judged by the Investigator.
24. 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.
25. Plasma donation within 1 month of screening or blood donation (or corresponding blood loss) during the last 3 months prior to screening.
26. 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 with the following restrictions during the full duration of the study, *i.e.*, from screening to the end-of-study visit.

9.6.1 General restrictions

1. 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 inclusion criterion 5 and exclusion criteria 1 and 2.
2. Fasting:
   Dose groups 4 to 6: During fasting conditions, subjects must fast for at least 10 hours overnight before the morning dose and until 30 minutes after the morning dose on Day 1 and 14. For details on IMP administration during fasting conditions, refer to Section 10.5.1.
3. Meals and dietary restrictions: Standardized meals 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.

   Breakfast will be served 30-60 minutes after dosing (if BID dosing) or approximately 2-3 hours before lunch (if QD dosing).

   Dose groups 1 to 3: Lunch, a mid-day snack, dinner, and an optional evening snack will be served at 16-16.5 hours, 18-18.5 hours, 21-21.5 hours, and 24-24.5 hours after dosing, respectively, or at corresponding times on non-dosing days.

   Dose groups 4 to 6: Lunch, a mid-day snack, dinner, and an optional evening snack will be served at 4-4.5 hours, 6-6.5 hours, 9-9.5 hours, and 12-12.5 hours after dosing, respectively, or at corresponding times 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 min after dosing.

4. Alcohol: The consumption of alcohol will not be allowed within 48 hours prior to admittance to the study clinic for Visits 2, 5 and 7 or during visits to the study clinic.
5. Xanthine/taurine containing beverages: The intake of energy drinks (*e.g.*, Red Bull, Monster Energy) or other xanthine/taurine-containing beverages will not be allowed within 48 hours prior to admittance to the study clinic for Visits 2, 5 and 7 or during visits to the study clinic, including the end-of-study visit.
6. Coffee: The consumption of up to 5 cups of coffee per day will be allowed during the study (*i.e.*, from screening visit to end-of-study visit).
7. Drugs of abuse: The use of drugs of abuse will not be allowed during the study (*i.e.*, from screening visit to end-of-study visit). In addition to the urine drug screens described in the schedule of events, additional random testing can be performed at any visit to the study clinic.
8. Nicotine: Smoking or the use of nicotine-containing products, including non-tobacco oral nicotine products, will not allowed during the study period (*i.e.*, from screening visit to end-of-study visit).
9. Grapefruit and grapefruit-containing products: The consumption of grapefruit and/or grapefruit-containing products such as jams, jellies, preserves and fruit juices will not be allowed during the study. This also includes Seville oranges, pomelo, exotic citrus fruits, and other grapefruit hybrids.
10. Exercise: The subjects must refrain from strenuous exercise, defined as greater than 70% of the maximal pulse rate for one hour or more, during the study period (*i.e.*, from screening visit to end-of-study visit).
11. Blood donation: The subjects must not donate blood or plasma during the study period and until 3 months after the final medical examination at the end-of-study visit.
12. Participation in other clinical studies: Study subjects will not be allowed to participate in any other interventional clinical study during the study period.
13. Leaving the study clinic: Subjects will not be allowed to leave the study clinic during study visits (Visit 2, 5 and Visit 7) unless authorized by the study personnel.

9.6.2 Prior and concomitant therapy

9.6.2.1 Prohibited medications

- 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 8).
- Any use of prescribed on non-prescribed antacid medication from 2 weeks prior to dosing and until the end-of-study visit (Visit 8).

9.6.2.2 Allowed medications

- Paracetamol in doses up to 2000 mg/day for a maximum of 3 consecutive days. If this amount of paracetamol is insufficient for the treatment of the subject, discontinuation from the study should be considered.
- Nasal decongestants without cortisone, antihistamine or anticholinergics for a maximum of 10 consecutive days.
- Contraceptives, as defined in inclusion criterion #5.

Other medications considered necessary for the subject's safety and wellbeing may be given at the discretion of the Investigator during the subject's stay at the study clinic. Following consultation with the Sponsor, the Investigator will determine whether or not the subject will be discontinued from the study or allowed to remain.

9.7 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical study but do not fulfil all eligibility criteria and 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) and reason(s) for screening failure.

Re-screening can be performed once 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 the allowed time windows.
- For subjects who are re-screened, a new screening number will be assigned and new signed ICF must be collected.

9.8 Subject withdrawal

9.8.1 General withdrawal criteria

Subjects are free to discontinue 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 must be documented.

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

Potential reasons for discontinuation include:

- Subject's own 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 as detailed in Section 12.5.
- Pregnancy.
- Death.
- Meeting of an exclusion criterion during the study, which, in the opinion of the Investigator, may pose a risk for the subject.
- The 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 they are willing to be assessed as soon as possible according to the procedures scheduled for the end-of-study visit. Any ongoing AEs will be followed-up 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. Subjects withdrawn after dosing may be replaced at the Sponsor's discretion after consultation with the Investigator.

9.9 Randomization

Randomization will be performed using a block-randomization of size 6 stratified by gender. After confirmation of eligibility criteria and prior to start of Visit 2, the subjects will be randomized to 1 of 6 dose groups, using the following nomenclature:

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

[redacted]

As this is an open label study, the dose group to which each subject is allocated will be recorded in the eCRF. A computer-generated randomization list will be created using SAS

Proc Plan, SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC). The randomization list will contain subject number (*e.g.,* 101-172), [redacted]

The randomization list will be generated by the [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

[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 [15,16].

The 25 mg tablets are manufactured, packaged and labelled by [redacted] and imported and QP-released by [redacted]

The IMP will be shipped to the local pharmacy in [redacted] (refer to Section 5), who will provide the IMP to the study clinic.

10.3 Conditions for storage

The IMP will be stored at room temperature (15-25° C) in an access-controlled area at the [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 the [redacted] There will be 2 persons working together, one person will handle the IMP and perform the preparation according to the randomization list and the other person will supervise the process.

The [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, as well as 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 study site or the subject must be accounted for.

10.5 Treatment administration

All subjects will be treated with linaprazan glurate 25 mg, 50 mg or 75 mg QD or BID for 14 days.

Dose group 1 to 3 (QD dosing): the first IMP dose will be administered at the clinic in the evening of Day 1. The subjects will take linaprazan QD as randomized at home on Days 4 to 13. The last dose in 14-days treatment period will be administered at the clinic in the evening of Day 14. [redacted]

Dose group 4 to 6 (BID dosing): the first IMP dose will be administered at the clinic in the morning of Day 1. The subjects will take linaprazan BID as randomized at home on Days 4 to 13. The last dose in 14-days treatment period will be administered at the clinic in the morning of Day 14. [redacted]

10.5.1 Fasting conditions

Dose groups 4 to 6 (BID dosing): At residential visits [redacted] following a fast of at least 10 hours overnight, subjects will be administered the morning dose of IMP together with 240 mL of tap water. The tablets should be swallowed whole, and the subjects will be instructed not to chew or crush the tablets. Breakfast will be served 30-60 minutes after dosing.

All dose groups: Water, but no other drinks, will be allowed *ad libitum*, except from 1 hour before dosing to 1 hour after dosing. No food will be allowed for at least 30 minutes post-dose. During home administration (Day 3 evening to Day 13) there are no fasting requirements.

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

During residential visits at the clinic, the IMP will be administered at the clinic under medical supervision. Doses administered at the clinic will be entered in the eCRF by study personnel. On other days, the subjects will self-administer IMP at home and register each intake of study drug in a paper diary. Text reminders to mobile phones will be sent to the subjects each day. At the Visit 5 (Day 14) to the clinic, subjects will be asked to return any unused study drugs and all empty containers. The number of remaining tablets as well as the date of the compliance check, as specified in Table 8.1-1, will be entered into the eCRF.

10.8 Return and destruction of investigational medicinal product

Any unused study medication will be returned to the Sponsor or the study pharmacy for destruction. Empty containers will be destroyed at the study site. The Monitor will perform final linaprazan glurate accountability reconciliation at the study end to verify that all unused study medication is adequately destroyed/returned and documented.

11 STUDY ASSESSMENTS

Study assessments are described in the sections below. The timing of assessments is detailed in the schedule of events (Table 8.1-1 to Table 8.1-7 D).

11.1 Recording of data

The Principal Investigator 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 timepoint is:

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

Timepoints for PK blood sampling, safety laboratory samples, safety 12-lead ECG and vital signs are outlined in Table 8.1-2 to Table 8.1-7 D in Section 8.1. In general, actual times for PK blood sampling must not deviate more than ±10% from the planned times (refer to Section 11.3.1).

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 must 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 Height, weight and body mass index

Weight and height will be measured without shoes. Body mass index (BMI) will be calculated, with one decimal, from the recorded height and weight.

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 prior to first IMP administration 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 last end-of-study visit must be documented appropriately in the subject's eCRF. Relevant information (*i.e.*, name of medication, dose, unit, frequency, start and stop dates, reason for use) must be recorded. All changes in medication must be noted in the eCRF.

11.2.7 HIV and hepatitis B/C

Subjects will be tested for HIV and hepatitis B virus surface antigen (HbsAg) as well as hepatitis C antibodies prior to inclusion into the study. Any positive results not explained by hepatitis B vaccination in the subject's medical history will exclude the subject from participating in the study.

11.2.8 Pregnancy test and FSH test

All female subjects of child-bearing potential will do a urine pregnancy test at screening and at subsequent visit specified in Table 8.1-1 in Section 8.1. Females of non-childbearing potential will, in questionable cases, do a blood sample to detect FSH levels for confirmation of menopause as specified in Table 8.1-1 in Section 8.1.

11.2.9 Urine drug screen

Urine will be screened for drugs of abuse at timepoints outlined in the schedule of events (Table 8.1-1) using the Drug-Screen Multi-15 Dip Test (nal von minden GmBH, Moers, Germany) or equivalent. 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 timepoints outlined in the schedule of events, refer to Table 8.1-1 in Section 8.1. Additional random tests can be performed during the study period.

11.2.11 Screening for Helicobacter Pylori

All subjects will be screened for presence of *Helicobacter pylori* at the screening visit. A positive screening result will exclude the subject from study participation.

11.2.12 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 Assessments related to primary endpoints

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 or by venipuncture at the pre-specified visits and time-points detailed in Table 8.1-1 to Table 8.1-7 D.

In general, actual time for blood PK sampling must not deviate more than ±10% from the planned timepoints. Samples taken at timepoints for IMP administration, should be taken within 5 minutes prior to dosing. 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, 1 B sample and 1 C [backup] sample approximately 500 µL in each tube) for PK and metabolite 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 analyzed by [redacted]

11.3.2 Intragastric pH following linaprazan glurate administration

Measurement of intragastric pH will be performed during 24 hours after dose of the IMP (*i.e.*, the dose on Day 1 and Day 14, refer to Table 8.1-2 to Table 8.1-5) by a means of a pH-measuring electrode in the stomach inserted by the nasogastric route. A baseline pH-measurement will be performed over 24 hours prior to the first IMP administration.

The date and time of collection of each measurement will be recorded in the eCRF. Further details will be described in a separate manual.

11.4 Assessments related to secondary endpoints

11.4.1 Adverse events

The Principal Investigator 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

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

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 are 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

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

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

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 reference safety information (RSI) in the 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 IMP administration 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 grading of the intensity of AEs will follow the common terminology criteria for adverse events (CTCAE) v5.0 [18]. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the intensity of an AE using the following definitions, and record it in the AE Log of the eCRF:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care ADL**.

Grade 4 Life-threatening consequences: urgent intervention indicated.

Grade 5 Death related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *et c.*

**Self- care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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 time; 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 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 [redacted] SAE inbox at [redacted] sent to predefined recipients to highlight that an SAE has been registered. The same information is automatically sent to the [redacted] SAE inbox at [redacted] (with a copy to the Sponsor).

The SAE report will be reviewed by a designated person at clinical [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 the [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), the [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 the clinical [redacted] SAE [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 and 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 Principal Investigator on the pregnancy outcomes report form.

11.4.1.17 Treatment of overdose

An overdose is a dose in excess of the dose specified for each dose group in this clinical study protocol (CSP).

In cases of accidental overdose, subjects will be monitored appropriately, and standard supportive measures 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 in supine position after 10 minutes of rest using an ECG machine. 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 abnormalities will be specified and documented as clinically significant (CS) or not clinically significant (NCS) in the eCRF. Abnormal post-IMP administration findings assessed by the Investigator as CS will be reported as AEs.

11.4.3 Vital signs

Systolic and diastolic BP and pulse will be measured in supine position after 10 minutes of rest. Body temperature will be measured orally 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-IMP administration findings assessed by the Investigator as CS will be reported as AEs.

11.4.4 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 NCS in the eCRF. Abnormal post-IMP administration findings assessed by the Investigator as clinically significant will be reported as AEs.

11.4.5 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 Adria Lab d.o.o. (refer to Section 5) and analyzed by routine analytical methods.

Urine analysis will be performed at the study clinic using dip sticks. The assessments will be performed at visits specified in Table 8.1-1.

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 to Table 8.1-7 D.

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

Category	Parameter
	Urea
Hematology	Erythrocyte count
	Leukocyte count with differential count
	Hematocrit (B-EVF)
	Hemoglobin (Hb)
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Platelet count
Coagulation	Activated Partial Thromboplastin Time (APTT)
	Prothrombin Complex International Normalized Ratio (PK[INR])
Urinalysis (dip stick)	Erythrocytes
	Glucose
	Ketones
	Leukocytes
	Nitrite
	pH
	Protein
	Specific gravity
	Urobilinogen
FSH-test (at screening, postmenopausal females only)	FSH
Pregnancy test (female subjects of childbearing potential only)	Urine pregnancy test

11.5 Assessments related to exploratory endpoints

Venous blood samples (approximately 3 mL) for the PK characterization of linaprazan glurate and linaprazan will be collected as specified in Section 11.3.1. [redacted]

11.6 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 (NCA) 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 volume of blood samples collected during the study from each subject will be approximately 393 to 465 mL (Table 12.2-2 and Table 12.2-2 for QD and BID dosing, respectively). For reference, a regular blood donation consists of between 350 mL to 450 mL (±10 %) for persons weighing at least 45-50 kg [19].

An additional 4 mL blood will be drawn from post-menopausal women (questionable cases).

Table 12.2-1 Estimated blood volumes, QD dosing

Assessment	Estimated number of sampling occasions	Estimated volume per occasion (mL)	Total (mL)
PK blood sampling	47	3 mL	141 mL
HIV, Hepatitis B/C	1	7 mL	7 mL
Clinical chemistry, hematology, microbiology	7	35 mL	1245 mL
		Total:	**393 mL**

Table 12.2-2 Estimated blood volumes, BID dosing

Assessment	Estimated number of sampling occasions	Estimated volume per occasion (mL)	Total (mL)
PK blood sampling	71	3 mL	213 mL
HIV, Hepatitis B/C	1	7 mL	7 mL
Clinical chemistry, hematology, microbiology	7	35 mL	245 mL
		Total:	**465 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 CSR 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 lifecycle 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 Principal Investigator 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/laboratories 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 Harmonization 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 the [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 [21] and are consistent with the ICH E6 (R2) guideline for GCP [20], the European Union (EU) Clinical Trials Directive 2001/20/EC [22], and applicable local regulatory requirements.

14.2 Ethics and regulatory review

The Principal Investigator 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 the [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 Principal Investigator 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 [23], 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 the [redacted] as well as the concerned IEC and CA, have direct access to their medical records for verification of clinical study procedures. For further details on the subject information and ICF process, refer to Section 14.3.

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 the [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), the [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 [23] and the request will be raised to the Principal Investigator.

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 [redacted] The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon 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 the [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 each 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 Principal Investigator 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 Principal Investigator 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 start in Q4 2022 and to be completed in Q1 2023.

A subject is considered to have completed the study if they have completed all visits in the study, 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 one week (Directive 2001/20/EC, Article 12, Section 1) [22].

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 must be submitted to the applicable CA and IEC within 12 months after completion of the study, in accordance with current guidelines.

After completion of the study, an ICH E3 [24] guideline-compliant CSR describing the conduct of the study, any statistical analyses performed, and the results obtained will be prepared by the Sponsor or their designee. The CSR will be reviewed and approved by, as a minimum, the Principal Investigator and the Sponsor. The study results will be reported in the EudraCT database per applicable regulations within 12 months after completion of the study.

All results obtained from any exploratory analyses may be reported separately.

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 Principal Investigator is responsible for maintaining essential documents, (as defined in ICH E6(R2), Section 8 [20]) for 10 years after finalization of the CSR. 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 [22].

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 CSR.

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.

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 Patient reported outcome

The subject's themselves will record data using paper patient reported and data will be entered to the eCRF. Text reminders can be sent to the subject through the mobile phone. All data entered to diary shall be stored together with other subject's documentation.

16.4 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.

16.5 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.

16.6 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.

16.7 Medical coding

Medical coding will be performed by trained personnel at the [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.

16.8 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.

The analyses of the primary, secondary and exploratory endpoints will be performed by the [redacted]

17.1 General

Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), 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, and, where applicable, by assessment time.

All descriptive summaries and statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC). The PK parameters will be calculated by NCA using the software Phoenix WinNonlin® version 8.3 or later (Certara, U.S.A.).

Baseline will be defined as the latest measurement prior to the first exposure to the IMP. All hypothesis testing will use a significance level of 5 %.

No imputation of missing data will be performed.

17.2 Determination of sample size

No formal sample size calculation has been performed for this study. The proposed sample size is considered sufficient to provide adequate information to meet the study objectives.

Approximately 116 subjects will be screened to achieve 72 randomized subjects (12 randomized and 9 evaluable subjects per dose group).

17.3 Analysis data sets

17.3.1 Full analysis set

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

This set 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.

17.4 Description of study population

17.4.1 Demographics and baseline characteristics

Descriptive statistics for demographics, weight and height will be presented by dose group.

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 WHO Drug preferred names.

All data will be listed by subject.

17.4.3 Treatment compliance

The subjects in each dose level and dose group 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 and performed by [redacted]. The PK parameters will be calculated by NCA using the software Phoenix WinNonlin® version 8.3 or later (Certara Inc, Princeton NJ, United States).

The following non-compartmental PK parameters will be assessed if sufficient data is available:

- AUC_{0-24}
- AUC_{0-12}
- AUC_{12-24}
- AUC_{24-48}
- AUC_{0-t}
- C_{trough}
- C_{aver}
- C_{max}
- $t_{1/2}$
- t_{max}

Additional parameters may be calculated if data permits.

17.5.2 Secondary analysis of pharmacokinetics

Additional PK parameters for linaprazan glurate and linaprazan PK parameters but not limited to:

- CL/F
- V/F
- R_{acc}
- C_{min}
- AUC_{inf}
- $AUC_{extrap\%}$

17.6 Analysis of pharmacodynamics

17.6.1 Primary analysis of pharmacodynamics

At Day 1 and Day 14, over a 24-hour monitoring period, the intragastric pH will be measured following linaprazan glurate administration. The following parameters for intragastric pH will be calculated:

- Percentage of time gastric pH >4

Listings for pH will be generated based on median values for 10 minutes interval (calculated with 10 min median interval).

17.7 Analysis of safety endpoints

17.7.1 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 dose group and overall. An overview of any treatment-related AEs will be summarized by SOC and PR if considered appropriate.

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

17.7.2 12-lead safety ECG

All ECGs will be categorized as "normal", "abnormal, NCS", or "abnormal, CS" (as judged by the Investigator) and summarized by dose group using frequency tables.

Changes over time will be presented using shift tables, if appropriate.

All data will be listed by subject.

17.7.3 Vital signs

Vital signs (systolic/diastolic BP, pulse rate and body temperature) will be summarized by dose group. Data will be presented with absolute and percent change from baseline.

All data will be listed by subject. If warranted, a separate listing may contain all values that were judged to be clinically significant.

17.7.4 Physical examinations

The interpretations ("normal", "abnormal, NCS," or "abnormal, CS") of physical examination findings will be summarized by dose group for each assessment timepoint. Changes over time will be presented using shift tables, if appropriate.

All data will be listed by subject.

17.7.5 Safety laboratory analyses

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

All safety laboratory data will be listed by subject.

17.8 Analysis of exploratory objectives

17.8.1 [redacted]

[redacted]

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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] 17 Mar 2017

[redacted], MD, Principal Investigator

19.2 Approval of the clinical study protocol

I, the undersigned, approve this CSP.

Sponsor signatory

27 March 2023

[redacted]

[redacted] MD, PhD
CMO Cinclus Pharma Holding AB

Appendix A [redacted]

[redacted]