Clinical Study Protocol

Title: A phase I, open-label, fixed-sequence, single-center study to determine the effect of repeated dosing with clarithromycin on the pharmacokinetics of linaprazan glurate/linaprazan and the effect of a single dose of linaprazan glurate on the pharmacokinetics of clarithromycin, and single and repeated dosing with linaprazan glurate on the pharmacokinetics of midazolam administrated to healthy subjects

NCT number: NCT05633147

Document date: Final v4.0; 20JAN2023

Clinical Study Protocol

EudraCT no.	2022-001403-41
Investigational medicinal product	Linaprazan glurate
Study code	CX842A2105
Protocol version and date	Final v4.0; 20JAN2023

A phase I, open-label, fixed-sequence, single-center study to determine the effect of repeated dosing with clarithromycin on the pharmacokinetics of linaprazan glurate/linaprazan and the effect of a single dose of linaprazan glurate on the pharmacokinetics of clarithromycin, and single and repeated dosing with linaprazan glurate on the pharmacokinetics of midazolam administrated to healthy subjects

Phase	I
Indication	Gastroesophageal reflux disease (GERD) and eradication of *Helicobacter pylori* infection
Test product and dose	Linaprazan glurate (formerly X842) (Part I: 100 mg victim drug and Part II: 75 mg)
Index inhibitor and dose	Clarithromycin, 500 mg oral tablets (Part I: perpetrator drug)
Substrate for CYP3A	Midazolam, 2.5 mg (Part II)
Sponsor signatory	[redacted] MD, PhD, CMO Cinclus Pharma Holding AB World Trade Center, Kungsbron 1 SE-111 22 Stockholm, Sweden
Principal Investigator	[redacted] MD CTC Clinical Trial Consultants AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden
Clinical study conduct and management	CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance 85, 2nd level SE-751 85 Uppsala, Sweden CTC Clinical Trial Consultants AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden CTC Clinical Trial Consultants AB Karolinska vägen 22 SE-171 64 Solna, Sweden

The following amendments have been made to the first regulatory approved version of this Clinical Study Protocol (version 2.0).

Type of change	Date	Summary of changes	Revised protocol version
Substantial amendment	20SEP2022	In Part I of the study clarithromycin 500 mg BID will be used as perpetrator drug instead of itraconazole. The study design has been adjusted accordingly.	Version 2.0
Non-substantial amendment	02NOV2022	Administrative changes: -correction of tables and figures (Section 7) -correction of table (Section 10) -corrected SUSAR definition in Section 11.4.1.5	Version 3.0
Substantial amendment	27JAN2023	In Part II of the study linaprazan glurate 75 mg BID will be administered instead of 100 mg BID. After finishing Part I and Part II respectively, the data will be analysed. After finishing Part II, the CSR will be prepared following the final DBL. Administrative changes: -the address to the Pharmacy has been updated (Section 5). -the risk assessment with regard to the Covid-19 pandemic has been removed according to the updated guidelines.	Version 3.1

1 STUDY SYNOPSIS

Study title

A phase I, open-label, fixed-sequence, single-center study to determine the effect of repeated dosing with clarithromycin on the pharmacokinetics of linaprazan glurate/linaprazan and the effect of a single dose of linaprazan glurate on the pharmacokinetics of clarithromycin, and single and repeated dosing with linaprazan glurate on the pharmacokinetics of midazolam administrated to healthy subjects.

Study code	**EudraCT no.**
CX842A2105	2022-001403-41
Planned study period	**Phase of development**
Q4 2022 -Q2 2023	I

Principal Investigator

[redacted] MD

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SE-752 37 Uppsala, Sweden

Study design

This is a phase I, open-label, fixed design, drug-drug-interaction (DDI) study divided in 2 parts. Part I is designed to evaluate whether concomitant treatment with linaprazan glurate and clarithromycin, a strong inhibitor of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein P (PgP), leads to an effect on the systemic exposure to linaprazan glurate and linaprazan and whether there is an effect on the pharmacokinetics of clarithromycin after a single dose of linaprazan glurate. Part II is designed to evaluate the effect of repeated doses of linaprazan glurate on the pharmacokinetics (PK) of a sensitive substrate of CYP3A (midazolam).

Objectives

Part I:

Primary objective:

- To investigate the effect of repeated administration of clarithromycin on linaprazan glurate and linaprazan PK after single dose of linaprazan glurate.

Secondary objectives:

- To assess the safety and tolerability after single dose of linaprazan glurate with and without co-administration of clarithromycin.
- To evaluate additional PK characteristics of linaprazan glurate and linaprazan.
- To investigate the effect of linaprazan glurate on clarithromycin PK.

Exploratory objective:

- To explore the metabolites of linaprazan glurate in plasma with and without co-administration of clarithromycin.

Part II:

Primary objective:

- To investigate the effects after single and repeated administration of linaprazan glurate on the PK properties of midazolam.

Secondary objective:

- To assess the safety and tolerability after repeated doses of linaprazan glurate with and without co-administration of midazolam.
- To evaluate PK data of linaprazan glurate and linaprazan after single and repeated oral doses of linaprazan glurate.
- To evaluate additional PK characteristics of midazolam in the presence and absence of linaprazan glurate administration

Exploratory objective (Part II):

- To explore the metabolites of linaprazan glurate in plasma and urine after single and repeated doses of linaprazan glurate.

Endpoints

Part I:

Primary endpoint:

- Linaprazan glurate and linaprazan PK parameters with and without co-administration of clarithromycin:
  - Area under the plasma concentration curve from 0 to infinity (AUC_{inf})
  - AUC from time 0 to time t (AUC_{0-t})
  - Maximum plasma concentration (C_{max})

Secondary endpoints:

- Frequency, seriousness, and intensity of adverse events (AEs).
- Clinically significant changes in physical examinations, vital signs (blood pressure and pulse), electrocardiograms (ECG), and laboratory variables (hematology, clinical chemistry, and urinalysis).
- Additional PK parameters for linaprazan glurate and linaprazan, not limited to:
  - Time of occurrence of C_{max} (T_{max})
  - Terminal elimination half-life ($T_{1/2}$)
  - Apparent clearance (CL/F)
  - Apparent volume of distribution (V/F)
  - Percent extrapolated AUC ($AUC_{extr\%}$)
- Clarithromycin PK parameters with and without co-administration of linaprazan glurate:
  - AUC to the end of the dosing period (AUC_{tau})
  - C_{max}
- Additional PK parameters for clarithromycin, not limited to:
  - T_{max}
  - $T_{1/2}$

Exploratory endpoint:

- Plasma collected for future exploratory analyses of linaprazan glurate metabolites.

Part II:

Primary endpoints:

- Midazolam PK parameters in the presence and absence of linaprazan glurate administration:
  - AUC_{inf}
  - AUC_{0-t}
  - C_{max}

Secondary endpoints:

- Frequency, seriousness and intensity of AEs.
- Clinically significant changes in physical examinations, vital signs (blood pressure and pulse), ECG, and laboratory variables (hematology, clinical chemistry, and urinalysis).
- Linaprazan glurate and linaprazan PK parameters after repeated administration of linaprazan glurate twice daily (BID) for 13 days (if feasible):
  - AUC_{inf}
  - AUC0-t
  - C_{max}
  - T_{max}
  - $T_{1/2}$
  - $AUC_{extr\%}$
  - CL/F
  - V/F
  - Accumulation ratio (R_{acc}).
- Midazolam PK parameters in the presence and absence of linaprazan glurate administration (if feasible):
  - T_{max}
  - $T_{1/2}$
  - $AUC_{extr\%}$
  - CL/F
  - V/F

Exploratory endpoint:

- Plasma and urine collected for future exploratory analyses of linaprazan glurate metabolites.

Number of subjects planned

In Part I, 18 healthy subjects are planned to be included in the study to ensure 12 evaluable subjects.

In Part II, 18 healthy subjects are planned to be included in the study to ensure 12 evaluable subjects.

In total, approximately 54 subjects will be screened in the study (27 subjects for each part).

Diagnosis and eligibility criteria

Healthy male subjects and healthy female subjects of non-childbearing potential, 18-60 years of age (inclusive), with a body mass index (BMI) of 18-30 kg/m^2, 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. Use of CYP3A4 inhibitors, antacids, proton pump inhibitors (PPIs) or any medication that changes gastric pH or use of any prescribed or non-prescribed CYP3A4-inducing medication (*e.g.*, efavirenz, nevirapine, rifampicin, rifabutin, modafinil, phenytoin, carbamazepine, glitazones, oral glucocorticoids) or other metabolic enzyme inducers, including herbal remedies such as St John's wort, within 14 days prior to administration of first dose of linaprazan glurate is prohibited.

Methodology

Part I:

The subjects will come for 10 visits to the clinical research unit (CRU).

Screening (Visit 1) will take place at any time point between Day -28 and Day -1 and will include an eligibility check and collection of demographic and medical history data as well as a review of health status, including a physical examination and collection of vital signs and safety laboratory blood samples.

At Visit 2, eligible subjects will be admitted to the CRU on Day -1 and stay until the morning on Day 2. The subjects will be dosed in the morning of Day 1, with a single dose of linaprazan glurate (100 mg: 4x25 mg oral tablets). The subjects must fast for at least 8 hours before the anticipated dosing time on Day 1. During fasting, water, but no other drinks, is allowed as desired. No drinks are allowed for 1 hour before and 30 minutes after dosing. Blood will be sampled for PK analysis up to 24 hours after dose (24-hour sample on Day 2) and safety will be assessed. The subjects will leave the CRU in the morning of Day 2 (after the 24-hour sample) and return in the evening of Day 2 (Visit 3) for the 36-hour PK-blood sample. The subjects will thereafter return to the CRU for blood sampling at 48 hours on Day 3 (Visit 4) and at 72 hours on Day 4 (Visit 5). At Visit 5, the subjects will start clarithromycin dosing, (500 mg BID) and continue dosing until Day 12.

On Day 9 (Visit 6), the subjects will be admitted to the CRU and stay until Day 11. In the morning on Day 9 clarithromycin (500 mg BID) will be administered. The subjects must fast for at least 8 hours before the anticipated dosing time on Day 9 and Day 10. During fasting, water, but no other drinks, is allowed as desired. No drinks are allowed for 1 hour before and 30 minutes after dosing. Thereafter, blood samples for PK analysis of clarithromycin will be collected up to 12 h after dose. In the morning on Day 10, linaprazan glurate (100 mg: 4x25 mg tablets) and clarithromycin (500 mg, BID) will be co-administered and blood samples for PK analysis of linaprazan glurate and linaprazan will be collected up to 24 hours after dose (24-hour sample on Day 11) and the subjects will leave the CRU in the morning on Day 11 (after the 24-hour PK sample).

In the evening on Day 11 (Visit 7), the subjects will return to the CRU for the 36-hour PK sample. The subjects will thereafter return to the CRU for blood sampling on 48 hours on Day 12 (Visit 8) and at 72 hours on Day 13 (Visit 9).

A final end-of-study visit (Visit 10) will take place on Day 14 (±2) or after early withdrawal.

Blood samples for analysis of PK parameters for linaprazan glurate and linaprazan will be collected prior to linaprazan glurate administration (pre-dose) and 15, 30, 45 min, 1.15, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48 and 72 hours after dosing (on dosing Days 1 and 10).

Blood samples for analysis of PK parameters for clarithromycin will be collected prior to clarithromycin administration (pre-dose) and 30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours after dosing (on dosing Day 9 when dosed alone and on Day 10 when dosed with linaprazan glurate).

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

Part II:

The subjects will come for 5 visits to the CRU. Screening (Visit 1) will take place at any time point between Day -28 and Day -1 and will include an eligibility check and review of health status.

Screening (Visit 1) will take place at any time point between Day -28 and Day -1, 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 vital signs and safety laboratory blood samples.

At Visit 2, eligible subjects will be admitted to the CRU on Day -1. In the morning of Day 1, the subjects will be administered a single dose of midazolam (2.5 mg), followed by PK blood sampling

up to and including 24 hours after dosing. Starting on Day 2, after the 24-hour PK blood sample, the subjects will be co-administered linaprazan glurate (75 mg:3x25 mg oral tablets, BID) and midazolam (2.5 mg QD) in the morning. The subjects must fast for at least 8 hours before the anticipated dosing time on Day 1 and Day 2 until 2 hours post-dose. During fasting, water, but no other drinks, is allowed as desired except for 1 hour before and 30 minutes after dosing.

From Day 2 to Day 4, blood sampling for linaprazan glurate and linaprazan PK will take place at pre-determined time points until 24 hours after the morning doses. The subjects will be discharged from the CRU on Day 4 and will be home-based until Day 13 when they will be re-admitted for Visit 3. The subjects will self-administer linaprazan glurate (75 mg:3x25 mg oral tablets, BID) at home. An electronic diary will be handed out for the subjects to record the intake of linaprazan glurate at home between Visit 2 and Visit 3.

On Day 13, the subjects will be admitted to the CRU (Visit 3). In the morning of Day 14, the subjects will be co-administering a second dose of midazolam (2.5 mg) together with the morning dose of linaprazan glurate (75 mg:3x25 mg oral tablets), followed by blood sampling for midazolam PK in the presence of linaprazan glurate at pre-determined time points up to and including 24 hours after co-administration as well as blood sampling for linaprazan glurate PK until 36 hours. The subjects must fast for at least 8 hours before the anticipated dosing time on Day 14. During fasting, water, but no other drinks, is allowed as desired except for 1 hour before and 30 minutes after dosing. The subjects will be discharged from the CRU on Day 15 (after the 36-hour sample) and return in the morning of Day 16 (Visit 4) for the 48-hour PK sample.

A final end-of-study visit will take place as a telephone call on Day 22 (±2 days) (Visit 5) or after early withdrawal.

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 will be recorded continually from the first dose of midazolam during visits to the CRU. Upon re-admission to the CRU on Day 13 subjects will be asked to report any AEs that arose between discharge on Day 4 and re-admission on Day 13.

Investigational Medicinal Product (IMP) dosage and mode of administration

Linaprazan glurate will be provided as tablets for oral administration.

Part I:

- Linaprazan glurate in base form, 100 mg once daily (4x25 mg oral tablets) will be administered under fasting conditions (8 hours after meal until 2 hours post-dose).

Part II:

- Linaprazan glurate hydrochloride (HCl), 75 mg twice a day (3x25 mg oral tablet, BID) for 13 days. The morning dose will be administered under fasting conditions on Day 2 and Day 14 (8 hours after meal until 2 hours post-dose). During home-administration there are no fasting requirements.

Index inhibitor (perpetrator drug) (Part I)

Clarithromycin 500 mg will be provided as tablets for oral administration.

Clarithromycin 500 mg twice daily (500 mg in the morning and 500 mg in the evening, approximately 12 hours apart). Clarithromycin may be administered with food except when co-administered with linaprazan glurate *i.e.*, on the linaprazan glurate co-administration and clarithromycin PK sampling days. The fasting requirements for linaprazan glurate apply for the morning dose.

Substrate for CYP3A (Part II)

Midazolam (substrate for CYP3A): midazolam APL will be provided as an oral solution, 1 mg/mL.

Midazolam 2.5 mg once daily (2.5 mL oral solution). Midazolam will be administered under fasting conditions (8 hours after meal until 2 hours post-dose).

Duration of treatment

Part I: Subjects will be administered 2 oral doses of linaprazan glurate (100 mg) and 18 doses of clarithromycin 500 mg.

Part II: Subjects will be administered oral 75 mg doses of linaprazan glurate BID for 13 consecutive days. In total, 26 doses will be given. Subjects will also be administered 3 doses of midazolam (2.5 mg).

Duration of each subject's involvement in the study

Part I: Each subject is expected to participate in the study for approximately 42 (±2) days, including an up to 28-day screening period.

Part II: Each subject is expected to participate in the study for approximately 49 (±2) days, including an up to 28-day screening period.

The Screening visits will be performed within 28 days prior to dosing (Day 28 to Day -1) for Part I and Part II.

Safety assessments

Safety assessments will include AEs, physical examination, vital signs, ECG, and clinical laboratory assessments.

AEs will be recorded from the first dose of linaprazan glurate in Part I and midazolam in Part II and throughout the study. Prior medications will be recorded from 14 days before screening (Visit 1) and concomitant medications will be recorded from Day 1, until the last visit in the study.

Pharmacokinetic (PK) assessments

Blood sampling for bioanalysis and subsequent calculation of PK parameters.

Statistical methods

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 non-compartmental analysis (NCA) using the software Phoenix WinNonlin® version 8.3 or later (Certara, U.S.A.).

Baseline will be defined as the visit with last data collection point prior to the first administration of linaprazan glurate (Part I) and midazolam (Part II).

In Part I, the PK parameters AUC, $AUC_{(0-t)}$ and C_{max} will be analyzed using a mixed model following a natural logarithmic transformation, with fixed effect for treatment and random effect for subject. Ratios of geometric means together with 2-sided 90% CI of test treatment (linaprazan glurate + clarithromycin) and reference treatment (linaprazan glurate alone) will be estimated and presented.

The corresponding statistical analysis will be performed and presented for clarithromycin.

In Part II, for AUC_{inf}, the AUC will be calculated to the time point of the last quantifiable plasma concentration and then extrapolated to infinity using the concentration in the last quantifiable sample and the estimated terminal elimination rate constant ($Lambda_z$). Midazolam PK parameters will be presented and statistically analyzed using the same mixed-effects model as in Part I. The ratios of geometric least squares mean (midazolam in the presence and absence of linaprazan glurate) with the corresponding 90% confidence interval (CI) will be presented. If the CI for AUC_{inf} is between 0.8 and 1.25, and the CI for C_{max} is between 0.7 and 1.43, it can be concluded that linaprazan glurate has no effect on CYP3A.

No imputation of missing data will be performed.

Study reporting

For Part I and Part II respectively, 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. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 guideline-(ICH-E3) compliant clinical study report (CSR) will be prepared following the final DBL.

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
AE	Adverse event
ADL	Activities of daily living
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Adverse reaction
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration *vs.* time curve
AUC_{0-t}	AUC from time 0 to time t
AUC_{extr}	Extrapolated AUC
$AUC_{extr\%}$	AUC percent extrapolation
AUC_{inf}	AUC from 0 to infinity
BMI	Body mass index
BID	Bis in die, twice daily
CA	Competent authority
C_{avg}	Average concentration
CHL	Chinese hamster lung
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent total body clearance following extravascular administration
C_{max}	Maximum observed concentration
CK	Creatinine kinase
CL/F	Apparent total body clearance following extravascular administration
CNS	Central nervous system
CRU	Clinical research unit
CS	Clinically significant
CSP	Clinical study protocol
CSR	Clinical study report
CTC	Clinical Trial Consultants AB
CTCAE	Common terminology criteria for adverse events
CV%	Coefficient of variation
CYP	Cytochrome P450

Abbreviation	Explanation
DDI	Drug-drug interaction
DMP	Data management plan
DMSO	Dimethyl sulfoxide
DSUR	Development safety update report
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
eGERD	Erosive GERD
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ePRO	Electronic patient reported outcomes
EU	European Union
FAS	Full analysis set
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GDPR	General data protection regulation
GERD	Gastroesophageal reflux disease
GMP	Good manufacturing practice
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCL	Hydrochloride
HCVAb	Hepatitis C antibodies
HIV	Human immunodeficiency virus
H. pylori	*Helicobacter pylori*
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
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier

Abbreviation	Explanation
IR	Immediate release
ISF	Investigator site file
IUD	Intra-uterine device
IUS	Intra-uterine system
$Lambda_z$	Terminal elimination rate constant,
LLOQ	Lower limit of quantification
MAD	Multiple-ascending dose
MDMA	Methylenedioxy-methamphetamine
MedDRA	Medical dictionary for regulatory activities
MPA	Medical products agency
MTD	Maximum tolerated dose
NCA	Non-compartmental analysis
NCS	Not clinically significant
NOAEL	No observed adverse effect level
P-CABs	Potassium-competitive acid blockers
PD	Pharmacodynamic
PgP	P-glycoprotein
PII	Personally identifiable information
PK	Pharmacokinetics
PKAS	PK analysis set
PPI	Proton pump inhibitors
PT	Preferred term
QA	Quality assurance
QC	Quality control
QP	Qualified person
R_{acc}	Accumulation ratio
RBM	Risk based monitoring
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD	Standard deviation
SDV	Source data verification
SMP	Safety management plan

Abbreviation	Explanation
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
THC	Tetrahydro-cannabinoids
TMF	Trial master file
$T_{1/2}$	Terminal elimination half-life
T_{max}	Time of occurrence of C_{max}
V/F	Volume of distribution following extravascular administration
WHO	World Health Organization

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 (Table 4.1-1).

Table 4.1-1 Medical emergencies contact

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

5 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor

Cinclus Pharma Holding AB

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

Sponsor's medical representative

[redacted] MD, PhD, CMO
Phone: [redacted]
E-mail: [redacted]

Sponsor's project manager

[redacted] (*until December 2022*)
Phone: [redacted]
E-mail: [redacted]

[redacted] MSc (*from 22DEC2022*)
Phone: [redacted]
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Clinical conduct

Clinical Trial Consultants (CTC) AB

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Principal Investigator

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Study management

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Pharmacokineticist

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E-mail: [redacted]

Medical writer

[redacted] PhD
Phone: [redacted]
E-mail: [redacted]

Medical monitor

[redacted] MD
Phone: [redacted]
E-mail: [redacted]

Laboratories (safety)	Clinical Microbiology Uppsala University Hospital Dag Hammarskjölds väg 38 SE-752 37 Uppsala, Sweden Clinical Chemistry and Pharmacology Uppsala University Hospital Entrance 61, 2nd level SE-751 85 Uppsala, Sweden
Laboratory (bioanalysis)	Lablytica Life Science AB Virdings Allé 16 SE-754 50 Uppsala, Sweden Phone: +46 76 614 87 39
Investigational Medicinal Product (IMP) manufacturing (Part I)	Recipharm Pharmaceutical Development AB Gårdsvägen 10A SE-169 70 Solna, Sweden
IMP packaging, labelling and qualified person (QP) release (Part I)	Clinigen Clinical Supplies Management SA Watson & Crick Hill, Rue Granbonpré 11 1435 Mont-Saint-Guibert, Belgium
IMP manufacturing, packaging, and labelling (Part II)	Xcelience, a Lonza company 4910 Savarese Circle Tampa FL 33636, United States
IMP import and QP release (Part II)	Nextpharma Ploërmel ZI de Camagnon Ploërmel 56804, France
Pharmacy	Apoteket AB Nationella Enheten Uppsala Clinical Trial Unit Södra Depågatan 2 SE-754 54 Uppsala, Sweden
Electronic data capture (EDC) system provider	Viedoc Technologies AB Stationsgatan 23 SE-753 40 Uppsala, Sweden

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].

The Taipei Global Consensus emphasized the role of *Helicobacter pylori* (*H. pylori*) eradication in accomplishing the goal of reducing or eliminating deaths from gastric cancer. A number of different therapies have been introduced, including triple therapies consisting of a proton pump inhibitor (PPI), amoxicillin and clarithromycin and also PPI and amoxicillin dual therapy. The recent introduction of potassium-competing acid blockers has rekindled interest in these therapies based on the observation that the marked acid suppression obtained resulted in an increase in efficacy with amoxicillin-containing regimens [3].

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 [4,5]. After oral administration, linaprazan glurate shows a slower uptake compared to 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 should 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 [6].

The investigational medicinal product (IMP) in the first-in-human (FIH) study of linaprazan glurate (single ascending dose [SAD], and multiple ascending dose [MAD]), study CX842A2101 (EudraCT no. 2016 002506-39) [7], was a liquid formulation to allow dosing per kg.

An immediate release (IR) tablet formulation was developed for use in a Phase II study. The pharmacokinetic (PK) and pharmacodynamic (PD) properties of this tablet formulation have been evaluated in 2 Phase I studies: a 2-period crossover relative bioavailability study, CX842A2102 [8] and an exploratory PK/PD parallel-group study CX842A2103 [9]. Both studies were designed to support the dose selection for future Phase II studies of linaprazan glurate.

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 [7]. 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 CX842A2102 (EudraCT no. 2019-001231-31) [8], the anticipated target 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) [9], 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 the previous studies (CX842A2101, CX842A2102 and CX842A2103), 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 previous clinical studies. The number of subjects experiencing AEs assessed as related to the IMP did not 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

Plasma concentrations of linaprazan glurate were mostly low and close to the lower limit of quantification (LLOQ) in the SAD/MAD study with the oral suspension [7]. Thus, PK parameters and dose linearity could not be calculated for linaprazan glurate in this study. 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 to 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 exposure 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 expected 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 with a tablet formulation [8], linaprazan glurate was detectable but plasma concentrations were low and variable. There was an approximate linear increase in linaprazan glurate plasma exposure between 50 mg and 150 mg on Day 1. The 50 mg dose resulted in comparable mean C_{max} and AUC on Day 1 and Day 2. For the 150 mg dose, mean exposure (C_{max} and AUC) was lower on Day 2 compared to Day 1. There was a less than dose proportional increase in both C_{max} and AUC when the dose was increased from 50 mg to 150 mg on Day 1. On Day 2 there was no further increase in exposure with the 150 mg dose compared to the 50 mg dose.

In the explorative PK/PD study, with 50 mg, 100 mg and 150 mg doses [9], a non-dose proportional increase of linaprazan plasma concentrations was observed with increasing doses of linaprazan glurate for each dosing interval. The highest average concentration (C_{avg}) for any of the dose intervals was seen after administration of the first linaprazan glurate dose for all 3 treatment arms. The mean C_{avg} indicated a non-dose proportional increase of exposure with increasing dose of linaprazan glurate.

The terminal elimination half-life ($T_{1/2}$) of linaprazan is 12-21 hours, according to the results from the FIH SAD/MAD study and the bioavailability study.

6.1.3 Indication

Linaprazan glurate is under development for the treatment of GERD and for eradication of *H. pylori* infection.

6.1.4 Dosage

The dose levels of linaprazan glurate to be tested in this study are 100 mg (Part I, 2 single doses) and 75 mg (Part II, BID for 13 days). For rationale for selection of doses, refer to Section 8.3.1.

6.1.5 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 [4,5].

The intention with the prodrug linaprazan glurate was to attain a lower acute C_{max} than linaprazan compared to after the administration of linaprazan, and to increase the plasma residence time of the compound, hence increasing the number of hours of full intragastric acid control. Linaprazan glurate was found to inhibit the H+, K+-ATPase activity in isolated membrane vesicles in a concentration-dependent manner. Furthermore, linaprazan glurate was found to inhibit acid formation in rabbit gastric glands *in vitro*, a more complex model than isolated membrane vesicles. Linaprazan glurate was also tested in 2 *in vivo* models, in chronic gastric fistula rats and in Heidenhain pouch dogs. In both models, linaprazan glurate was shown to be a potent inhibitor of gastric acid secretion.

6.1.6 Drug description

The drug substance is linaprazan glurate. It is a prodrug for the active substance linaprazan, (8-[(2,6-dimethylbenzyl) amino]-N-[2-hydroxyethyl]-2,3-dimethylimidazo[1,2-a] pyridine-6-carboxamide).

In its base form, (5-(2-(8-((2,6-dimethylbenzyl) amino)-2,3-dimethylimidazo[1,2-a] pyridine-6-carboxamido) ethoxy)-5-oxopentanoic acid), it has been used in previous studies and will be used in Part I of the study. As a hydrochloride (HCl) salt, 5-{2-[({8-[(2,6-Dimethylbenzyl) amino]-2,3-dimethylimidazo[1,2-a] pyridin-6-yl} carbonyl) amino] ethoxy}-5-oxopentanoic acid HCl (1:1), it will be used in Part II of the study. Linaprazan glurate lacks a chiral center.

Linaprazan glurate as base is soluble in dimethyl sulfoxide (DMSO), slightly soluble in methanol and nearly insoluble in dichloromethane and water. For linaprazan glurate HCl the solubility in water is 0.03 mg/mL. It is unstable in 0.1 M HCl and degrades to the active structure linaprazan. The solubility of both linaprazan and linaprazan glurate is pH-dependent and increases exponentially at pH values below the pKa (6.1 for linaprazan and 5.5 for linaprazan glurate).

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

This is a Phase I, single-center, drug-drug interaction (DDI) study divided in 2 parts designed to evaluate whether concomitant treatment with linaprazan glurate and a strong inhibitor of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein P (PgP) leads to an effect on the systemic exposure to linaprazan glurate and linaprazan and if single and/or repeated doses of linaprazan glurate have effect on the PK of a sensitive CYP3A substrate.

Based on *in vitro* data the elimination of both linaprazan glurate and its active metabolite linaprazan is metabolized by CYP3A4. Furthermore, linaprazan glurate and linaprazan have both showed a potential of CYP3A induction *in vitro* and linaprazan glurate has shown a potential to inhibit CYP3A4 at the intestinal level *in vitro.*

Part I of the study will investigate whether concomitant treatment with linaprazan glurate and a strong inhibitor of CYP3A4/PgP (clarithromycin) leads to an increase of systemic exposure to linaprazan glurate and linaprazan. Clarithromycin is also part of the standard of care regimen in the treatment of *H. pylori*, an indication of clinical interest for combination therapy with linaprazan glurate.

Part II of the study will investigate the potential for clinically relevant inhibition and/or induction caused by linaprazan glurate of a sensitive CYP3A substrate (midazolam).

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. No treatment related changes were observed in studies on embryo-fetal development in rats and rabbits or in fertility mating behavior and early embryonic development in rats. Nevertheless, there is a clear need for attention to risk mitigation.

Only limited data is available at this stage on reproductive toxicology. Contraception requirements will be applied to prevent pregnancy and only females of non-childbearing potential will be included in the study.

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. Linaprazan glurate 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 [4].

In Part I of the study, 2 single doses of 100 mg linaprazan glurate in its base form will be administered to healthy males and females of non-childbearing potential. The second dose will be co-administered with clarithromycin. The predicted systemic exposure to linaprazan glurate is not expected to exceed what was achieved in the FIH single ascending dose study with a maximum dose level of 4 mg/kg linaprazan glurate. The highest SAD dose level is approximately 3-fold compared to the dose level in Part I. The major metabolic pathway for linaprazan glurate in liver microsomes was via ester hydrolysis to the active metabolite linaprazan. Furthermore, linaprazan was formed by several CYPs, among them CYP3A4, when investigated *in vitro* with recombinant cytochrome P450s, therefor a large increase in linaprazan glurate exposure is not expected when co-administered with a CYP3A4 inhibitor. Severe adverse reactions (ARs) associated with linaprazan glurate are hence not expected.

Overdosing of linaprazan glurate is not likely to occur in Part I since all linaprazan glurate will be administered by clinic personnel under medical supervision. In Part II, the subjects will take some of the doses of linaprazan glurate at home. In cases of accidental overdose of linaprazan glurate, subjects will be urged to contact the clinical research unit (CRU) and standard supportive measures should be adopted as required. For further information regarding overdosing, refer to Section 11.4.1.17.

Aside from the risks related to the administration of linaprazan glurate as detailed above, there may also be risks related to the administration of clarithromycin in Part I and midazolam in Part II of the study. The most common adverse effects associated with clarithromycin include central nervous system (CNS) events such as dizziness, headache and dysgeusia, psychological disturbances such as insomnia and anxiety, gastrointestinal evens such as abdominal pain, diarrhea, vomiting, nausea and dyspepsia, skin and subcutaneous tissue disorders such as rash, administration site conditions as well as general disorders such as pyrexia. Clarithromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia; however, clarithromycin is a commonly used index inhibitor of CYP3A4 and is part of standard of care regimen for the treatment of *H. pylori*, making it important to study together with acid controlling agents.

Each volunteer will be provided with a subject information card with information about the subject's participation in a study including known and expected benefits and risks, see Section 14.4.

The Principal Investigator at the CRU will ensure that adequate facilities and procedures are available to handle emergency situations should they occur during the study.

Besides the risks related to linaprazan glurate, clarithromycin and midazolam, as detailed above, there may also be risks related to the medical devices used in the study (*e.g.*, indwelling venous catheters). However, these devices are used in routine medical care and the risk associated with their use is considered low and ethically justifiable.

Study-specific evaluations and sampling procedures, such as blood-pressure measurements using a blood pressure cuff and frequent blood-sampling, may cause transient discomfort but the risk is deemed to be low and ethically justifiable.

More detailed information about the known and expected benefits and risks and reasonably expected ARs is found in the current version of the IB (version 3.3, dated 11JUL2022). More information about risks associated with clarithromycin and midazolam can be found in the summary of product characteristics (SmPC) for each product.

6.3.2 Risk/benefit conclusion

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

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 Study objectives and endpoints Part I

7.1.1 Primary objective

- To investigate the effect of repeated administration of clarithromycin on linaprazan glurate and linaprazan PK after single dose of linaprazan glurate.

7.1.2 Primary endpoint

- Linaprazan glurate and linaprazan PK parameters with and without co-administration of clarithromycin:
  - Area under the plasma concentration curve from 0 to infinity (AUC_{inf})
  - AUC from time 0 to time t (AUC_{0-t})
  - Maximum plasma concentration (C_{max})

7.1.3 Secondary objectives

- To assess the safety and tolerability after single dose of linaprazan glurate with and without co-administration of clarithromycin.
- To evaluate additional PK characteristics of linaprazan glurate and linaprazan.
- To investigate the effect of linaprazan glurate on clarithromycin PK.

7.1.4 Secondary endpoints

- Frequency, seriousness, and intensity of AEs.
- Clinically significant changes in physical examinations, vital signs (blood pressure and pulse), electrocardiograms (ECG), and laboratory variables (hematology, clinical chemistry, and urinalysis).
- Additional PK parameters for linaprazan glurate and linaprazan, not limited to:
  - Time of occurrence of C_{max} (T_{max})
  - Terminal elimination half-life ($T_{1/2}$)
  - Apparent clearance (CL/F)
  - Apparent volume of distribution (V/F)
  - Percent extrapolated AUC ($AUC_{extr\%}$)
- Clarithromycin PK parameters with and without co-administration of linaprazan glurate:
  - AUC to the end of the dosing period (AUC_{tau})
  - C_{max}
- Additional PK parameters for clarithromycin, not limited to:
  - T_{max}
  - $T_{1/2}$

7.1.5 Exploratory objective

- To explore the metabolites of linaprazan glurate in plasma with and without co-administration of clarithromycin.

7.1.6 Exploratory endpoint

- Plasma collected for future exploratory analyses of linaprazan glurate metabolites.

7.2 Study objectives and endpoints Part II

7.2.1 Primary objective

- To investigate the effects after single and repeated administration of linaprazan glurate on the PK properties of midazolam.

7.2.2 Primary endpoint

- Midazolam PK parameters in the presence and absence of linaprazan glurate administration:
  - AUC_{inf}
  - AUC_{0-t}
  - C_{max}

7.2.3 Secondary objectives

- To assess the safety and tolerability after repeated doses of linaprazan glurate with and without co-administration of midazolam.
- To evaluate PK data on linaprazan glurate and linaprazan after single and repeated oral doses of linaprazan glurate.
- To evaluate additional PK characteristics of midazolam in the presence and absence of linaprazan glurate administration

7.2.4 Secondary endpoints

- Frequency, seriousness, and intensity of AEs.
- Clinically significant changes in physical examinations, vital signs (blood pressure and pulse), ECG, and laboratory variables (hematology, clinical chemistry, and urinalysis).
- Linaprazan glurate and linaprazan PK parameters after repeated administration of linaprazan glurate twice daily (BID) for 13 days (if feasible):
  - AUC_{inf}
  - AUC_{0-t}
  - C_{max}
  - T_{max}
  - $T_{1/2}$
  - $AUC_{extr\%}$
  - CL/F
  - V/F
  - Accumulation ratio (R_{acc}).
- Midazolam PK parameters in the presence and absence of linaprazan glurate administration (if feasible):
  - T_{max}
  - $T_{1/2}$
  - $AUC_{extr\%}$
  - CL/F
  - V/F

7.2.5 Exploratory objectives

- To explore the metabolites of linaprazan glurate in plasma and urine after single and repeated doses of linaprazan glurate.

7.2.6 Exploratory endpoints

- Plasma and urine collected for future exploratory analyses of linaprazan glurate metabolites.

Results related to exploratory analyses may not be reported in the clinical study report (CSR).

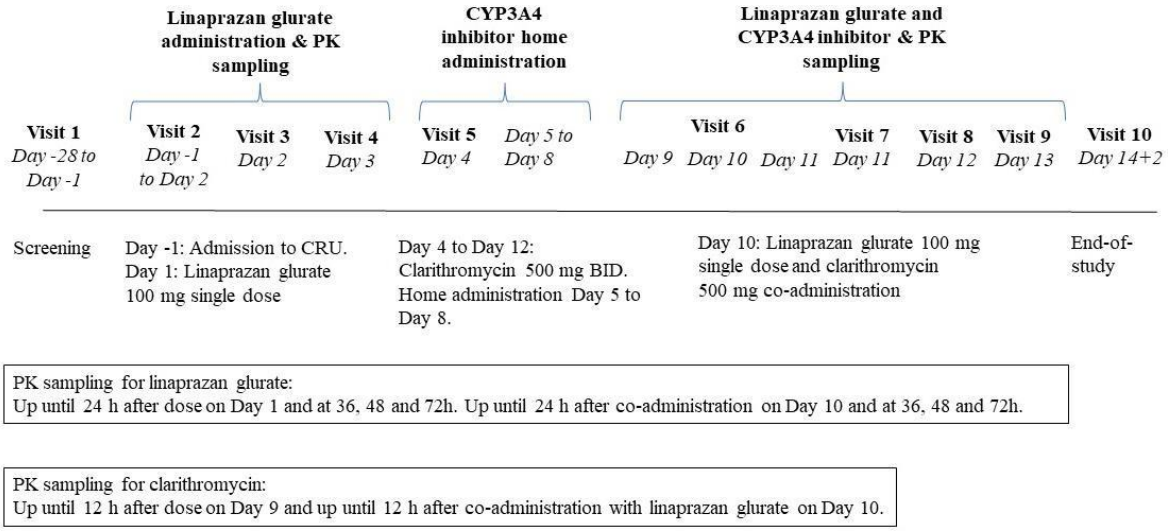
8 STUDY DESIGN

8.1 Overall study design and schedule of events, Part I

Part I of the study is an open-label, fixed sequence, DDI study designed to evaluate whether concomitant treatment with linaprazan glurate and clarithromycin, a strong inhibitor of CYP3A4/PgP, leads to an effect of systemic exposure to linaprazan glurate and linaprazan. First, all subjects will be administered a single dose of linaprazan glurate (100 mg: 4x25 mg oral tablets) alone. Next, the CYP3A4/PgP inhibitor clarithromycin will be given from Day 4 to Day 12 and on Day 10 linaprazan glurate (100 mg: 4x25 mg oral tablets) and clarithromycin will be co-administrated.

An overview of the study design is shown in Figure 8.1-1. The schedule of events for Part I is presented in Table 8.1-1 and is detailed for Visit 2 in Table 8.1-2 and for Visit 6 in Table 8.1-3 and Table 8.1-4. Study assessments are described in Section 11.

Figure 8.1-1 Overview of the study design, Part I



A total of 18 healthy male and female subjects of non-childbearing potential are planned to be included in Part I of the study to ensure 12 evaluable subjects.

The subjects will come for 10 visits to the clinical research unit (CRU).

Screening (Visit 1) will take place at any time point between Day -28 and Day -1 and will include an eligibility check and collection of demographic and medical history data as well as a review of health status, including a physical examination and collection of vital signs and safety laboratory blood samples.

At Visit 2, eligible subjects will be admitted to the CRU on Day -1 and stay until the morning on Day 2. The subjects will be dosed in the morning of Day 1, with a single dose of linaprazan glurate (100 mg: 4x25 mg oral tablets). The subjects must fast for at least 8 hours before the anticipated dosing time on Day 1. During fasting, water, but no other drinks, is allowed as desired. No drinks are allowed for 1 hour before and 30 minutes after dosing. Blood will be sampled for PK analysis up to 24 hours after dose (24-hour sample on Day 2) and safety will be assessed. The subjects will leave the CRU in the morning of Day 2 (after the 24-hour sample) and return in the evening of Day 2 (Visit 3) for the 36-hour PK-blood sample. The subjects will thereafter return to the CRU for blood sampling at 48 hours on

Day 3 (Visit 4) and at 72 hours on Day 4 (Visit 5). At Visit 5, the subjects will start clarithromycin dosing, (500 mg BID) and continue dosing until Day 12.

On Day 9 (Visit 6), the subjects will be admitted to the CRU and stay until Day 11. In the morning of Day 9 clarithromycin (500 mg BID) will be administered. Thereafter, blood samples for PK analysis of clarithromycin will be collected up to 12 h after dose. The subjects must fast for at least 8 hours before the anticipated dosing time on Day 9 and Day 10. During fasting, water, but no other drinks, is allowed as desired. No drinks are allowed for 1 hour before and 30 minutes after dosing. In the morning on Day 10, linaprazan glurate (100 mg: 4x25 mg tablets) and clarithromycin (500 mg, BID) will be co-administered and blood samples for PK analysis of linaprazan glurate and linaprazan will be collected up to 24 hours after dose (24-hour sample on Day 11) and the subjects will leave the CRU in the morning on Day 11 (after the 24-hour PK sample).

In the evening on Day 11 (Visit 7), the subjects will return to the CRU for the 36-hour PK sample. The subjects will thereafter return to the CRU for blood sampling on 48 hours on Day 12 (Visit 8) and at 72 hours on Day 13 (Visit 9).

A final end-of-study visit (Visit 10) will take place on Day 14 (±2) or after early withdrawal.

Blood samples for analysis of PK parameters for linaprazan glurate and linaprazan will be collected prior to linaprazan glurate administration (pre-dose) and 15, 30, 45 min, 1.15, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48 and 72 hours after dosing (on dosing Days 1 and 10).

Blood samples for analysis of PK parameters for clarithromycin will be collected prior to clarithromycin administration (pre-dose) and 30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours after dosing (on dosing Day 9 when dosed alone and on Day 10 when dosed with linaprazan glurate).

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, as detailed in Table 8.1-1.

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

Table 8.1-1 Overall schedule of events, Part I

Visit→		**Screen-ing**	**In-clinic treatment visit**			**Outpatient visits**			**Home admin**	**In-clinic treatment visit**			**Outpatient visits**			**End-of-study**
			Visit 2[1]			Visit 3	Visit 4	Visit 5		Visit 6[2]			Visit 7	Visit 8	Visit 9	Visit 10
Assessment↓/Day→	CSP Section	Day -28 to Day -1	Day -1	Day 1	Day 2	Day 2	Day 3	Day 4	Day 5–8	Day 9	Day 10	Day 11	Day 11	Day 12	Day 13	Day 14 (+2 days)[3]
Informed consent	11.2.1	X														
Eligibility criteria	11.2.2	X	X[4]													
Demographics	11.2.3	X														
Weight/height (BMI)	11.2.4	X														
Medical/surgical history	11.2.5	X														
HIV, hepatitis B and C	11.2.7	X														
Physical examination	11.4.2	X	X													X
Urine drug screen[6]	11.2.8	X	X							X						
Alcohol test	11.2.9	X	X							X						
Safety laboratory profile[7]	11.4.5	X	X		X					X		X				X
12-lead safety ECG	11.4.4	X	X[5]		X					X		X				X
Vital signs[8]	11.4.3	X	X[5]		X					X		X				X
Linaprazan glurate administration	10.5			X							X					
Clarithromycin administration[9]	10.5.1							X	X	X	X	X	X	X		
Hand out of electronic diary	16.3							X								
Electronic diary to be filled in by subject	16.3							X	X				X	X		

Visit→		Screen-ing	In-clinic treatment visit			Outpatient visits			Home admin	In-clinic treatment visit			Outpatient visits			End-of-study
				Visit 2[1]		Visit 3	Visit 4	Visit 5		Visit 6[2]			Visit 7	Visit 8	Visit 9	Visit 10
Assessment↓/Day→	CSP Section	Day -28 to Day -1	Day -1	Day 1	Day 2	Day 2	Day 3	Day 4	Day 5–8	Day 9	Day 10	Day 11	Day 11	Day 12	Day 13	Day 14 (+2 days)[3]
Hand out of clarithromycin	10.5.1							X								
Compliance check	10.7									X					X	
PK blood sampling for linaprazan glurate and linaprazan[10]	11.3.1			X	X	X	X	X			X	X	X	X	X	
PK blood sampling for clarithromycin[11]										X	X					
Blood sampling for metabolites	11.5.1			X	X	X	X	X			X	X	X	X	X	
Standardized meals[12]	9.6.1			X	X					X	X	X				
Baseline symptoms[13]	11.2.10	X														
Adverse events[14]	11.3.1			----------X----------												
Prior and concomitant medications[15]	11.2.6	----------X----------														

BMI=body mass index, ECG=electrocardiogram, HIV=human immunodeficiency virus

1. Detailed schedule for Visit 2 is shown in Table 8.1-2.
2. Detailed schedule for Visit 6 is shown in Table 8.1-3 (Day 9) and in Table 8.1-4 (Day 10 and 11).
3. Or after early withdrawal.
4. Confirmation of eligibility criteria. Can be done on Day -1 or Day 1 prior to linaprazan glurate administration.
5. Pre-dose assessments can be done on Day -1 or Day 1 prior to linaprazan glurate administration.
6. Drug screens may also be performed at additional random occasions, at the discretion of the Investigator.
7. Clinical chemistry, hematology, and urinalysis (dipstick).
8. Systolic and diastolic blood pressure, pulse, and body temperature. On Day -1 or Day 1 pre-dose: blood pressure and pulse.
9. Clarithromycin administration 500 mg BID Day 4 to Day 12.

10. Day 1 and Day 10: Pre-dose and for 24 hours post-dose. Day 2 and Day 11 at 36 hours post-dose, Day 3 and Day 12 at 48 hours post-dose and Day 4 and Day 13 at 72 hours post-dose. Actual time for PK blood sampling must not deviate more than ±10% from the planned time. The pre-dose sample may be taken within 60 minutes prior to IMP administration. For timing of PK blood sampling. refer to Table 8.1-2.
11. Day 9 and Day 10: Pre-dose and for 12 hours post-dose (morning dose). Actual time for PK blood sampling must not deviate more than ±10% from the planned time. The pre-dose sample may be taken within 60 minutes prior to IMP administration. For timing of PK blood sampling on Day 9 refer to Table 8.1-3 and on Day 10, refer to Table 8.1-4.
12. Subjects must fast for 8 hours before linaprazan glurate administration until 2 hours post-dose on Day 1, Day 9 and Day 10 (Visit 2 and Visit 6). Meals Day 1, Day 9 and Day 10: breakfast (2 hours post-dose), lunch, snack, dinner, and optional evening snack. Lunch will be served at least 4 hours post-linaprazan glurate (Day 1 and Day 10) or clarithromycin administration (Day 9). Snack, dinner and evening snack will be served approximately 6-, 9- and 12-hours post-linaprazan glurate administration (Day 1 and Day 10) or clarithromycin administration (Day 9), respectively. Day 2 and Day 11: optional breakfast after PK sampling.
13. Baseline symptoms will be recorded up until the first administration of linaprazan glurate on Day 1.
14. AEs will be recorded from first administration of linaprazan glurate.
15. For definition of prior and concomitant medications, see Section 11.2.6. For prohibited and allowed medications, see Section 9.6.2.

Table 8.1-2 Detailed schedule of events for Visit 2, Part I

Visit→	**Visit 2**																
Day	**Day -1**	**Day 1**														**Day 2**	
Assessment↓/Time→	**Admission**	**Pre-dose**	**00:00**	**00:15**	**00:30**	**00:45**	**01.15**	**01:30**	**02:00**	**03:00**	**04:00**	**06:00**	**08:00**	**10:00**	**12:00**	**18:00**	**24:00**
Eligibility criteria	X[1]																
Physical examination	X[2]																
Alcohol test	X																
Urine drug screen	X																
Safety laboratory profile	X																
Vital signs	X[2]																X
12-lead safety ECG	X[2]										X						X
Linaprazan glurate administration			X														
PK blood sampling		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for metabolites		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standardized meals[3]										X							
Baseline symptoms	X																
Adverse events			----------X----------														
Prior and concomitant medications	----------X----------																

1. Confirmation of eligibility criteria. Can be done on Day -1 or Day 1 prior to linaprazan glurate administration.
2. Can be done on Day -1 or Day 1 prior to linaprazan glurate administration. Symptom driven physical examination.
3. Subjects must fast for 8 hours before linaprazan glurate administration on Day 1. Meals Day 1: breakfast, lunch, snack, dinner and optional evening snack. Meals Day 2: optional breakfast. Lunch will be served at least 4 hours post-linaprazan glurate administration. Snack, dinner and evening snack will be served approximately 6-, 9- and 12-hours post-linaprazan glurate administration, respectively

Table 8.1-3 Detailed schedule of events for Visit 6 (Day 9, PK blood sampling for clarithromycin), Part I

Visit→	**Visit 6**															
Day	**Day 9**															
Assessment↓/Time→	**Admission**	**Pre-dose**	**00:00**	**00:30**	**01:00**	**01:30**	**02:00**	**02:30**	**03:00**	**03:30**	**04:00**	**05:00**	**06:00**	**08:00**	**10:00**	**12:00**
Clarithromycin administration			X													X
PK blood sampling for clarithromycin		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Standardized meals[1]		X														
Adverse events	----------X----------															
Prior and concomitant medications	----------X----------															

1. Subjects must fast for 8 hours before clarithromycin administration on Day 9. Meals Day 9: breakfast, lunch, snack, dinner and optional evening snack. Lunch will be served at least 4 hours post-clarithromycin administration. Snack, dinner and evening snack will be served approximately 6-, 9- and 12-hours post-clarithromycin administration, respectively.

Table 8.1-4 Detailed schedule of events for Visit 6 (Day 10 to Day 11), Part I

Visit→	**Visit 6**																			
Day	**Day 10**																		**Day 11**	
Assessment↓/Time→	**Pre-dose**	**00:00**	**00:15**	**00:30**	**00:45**	**01.00**	**01:15**	**01:30**	**02:00**	**02:30**	**03:00**	**03:30**	**04:00**	**05:00**	**06:00**	**08:00**	**10:00**	**12:00**	**18:00**	**24:00**
12-lead safety ECG													X							
Linaprazan glurate administration		X																		
Clarithromycin administration		X																X		X
PK blood sampling for linaprazan glurate and linaprazan	X		X	X	X		X	X	X		X		X		X	X	X	X	X	X
PK blood sampling for clarithromycin	X			X		X		X	X	X	X	X	X	X	X	X	X	X		
Standardized meals[1]		X									X									
Adverse events	——————————————————————————————X——————————————————————————————																			
Prior and concomitant medications	——————————————————————————————X——————————————————————————————																			

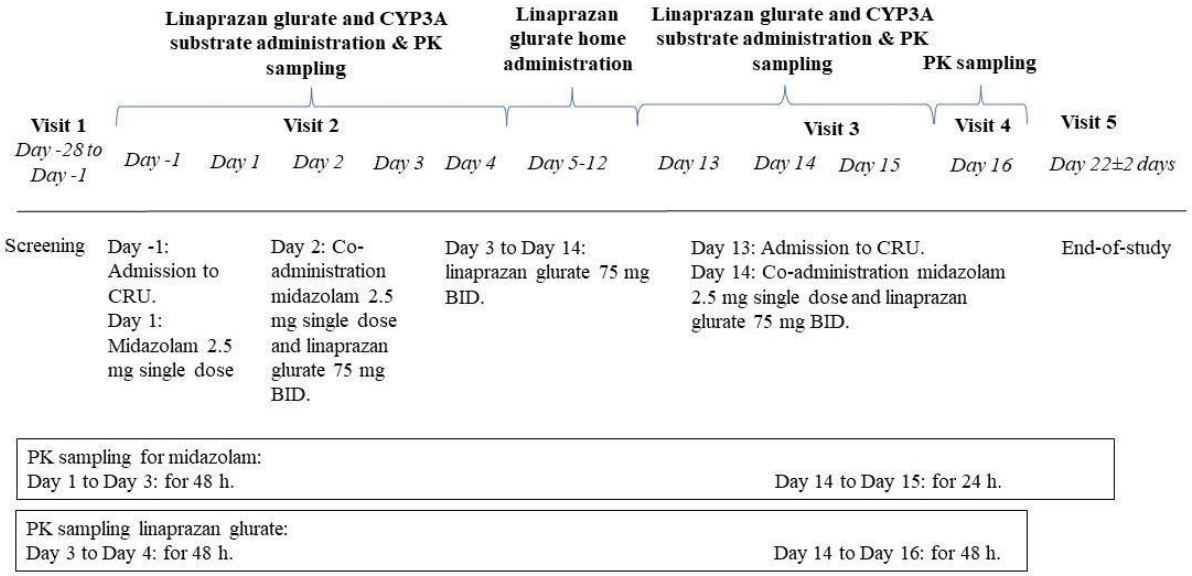
1. Subjects must fast for 8 hours before co-administration (clarithromycin and linaprazan glurate) on Day 10: breakfast, lunch, snack, dinner and optional evening snack. Lunch will be served at least 4 hours post co-administration. Snack, dinner and evening snack will be served approximately 6-, 9- and 12-hours post co-administration, respectively. Meals on Day 11: optional breakfast.

8.2 Overall study design and schedule of events, Part II

Part II of the study is an open-label, fixed sequence, drug-drug-interaction (DDI) study designed to evaluate whether concomitant treatment with linaprazan glurate and a sensitive substrate of CYP3A (midazolam) leads to clinically relevant increase of systemic exposure to linaprazan glurate and linaprazan. The study will further evaluate if single and/or repeated doses of linaprazan glurate have effect on the PK of midazolam. In Part II, the PK of midazolam (2.5 mg) will be investigated in the presence and absence of linaprazan glurate. In addition, Part II of the study will explore the PK of linaprazan glurate and linaprazan, as well as safety and tolerability, after repeated administration of 75 mg of linaprazan glurate twice a day (BID) for 14 consecutive days.

An overview of the study design of Part II is shown in Figure 8.2-1 . The overall schedule of events for Part II is presented in Table 8.2-1. The detailed schedule of PK blood sampling is presented in Table 8.2-2 (Day -1 to Day1, Table 8.2-3 (Day 2 to Day 4) and Table 8.2-4 (Day 14 to Day 16). Study assessments are described in Section 11.

Figure 8.2-1 Overview of the study design, Part II



A total of 18 healthy male and female subjects of non-childbearing potential are planned to be included in Part II of the study to ensure 12 evaluable subjects.

Screening (Visit 1) will take place at any time point between Day -28 and Day -1, 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 vital signs and safety laboratory blood samples.

At Visit 2, eligible subjects will be admitted to the CRU on Day -1. In the morning of Day 1, the subjects will be administered a single dose of midazolam (2.5 mg), followed by PK blood sampling up to and including 24 hours after dosing (see Table 8.2-2). Starting on Day 2, after the 24-hour PK blood sample, the subjects will be co-administered linaprazan glurate (75 mg: 3x25 mg oral tablets, BID) and midazolam (2.5 mg) in the morning. The subjects must fast for at least 8 hours before the anticipated dosing time on Day 1 and Day 2 until 2 hours post-dose. During fasting, water, but no other drinks, is allowed as desired except for 1 hour before and 30 minutes after dosing.

From Day 2 to Day 4, blood sampling for linaprazan glurate and linaprazan PK will take place at pre-determined time points until 24 hours after the morning doses, as detailed in (Table 8.2-3). The subjects will be discharged from the CRU on Day 4 and will be home-based until Day 13 when they will be re-admitted for Visit 3. The subjects will self-administer linaprazan glurate (75 mg:3x25 mg oral tablets, BID) at home. An electronic diary will be handed out for the subjects to record the intake of linaprazan glurate at home between Visit 2 and Visit 3.

On Day 13, the subjects will be admitted to the CRU (Visit 3). In the morning of Day 14, the subjects will be co-administered a second dose of midazolam (2.5 mg) together with the morning dose of linaprazan glurate (75 mg:3x25 mg oral tablets), followed by blood sampling for midazolam PK in the presence of linaprazan glurate at pre-determined time points up to and including 24 hours after co-administration as well as blood sampling for linaprazan glurate PK until 36 hours (Table 8.2-4). The subjects must fast for at least 8 hours before the anticipated dosing time on Day 14. During fasting, water, but no other drinks, is allowed as desired except for 1 hour before and 30 minutes after dosing. The subjects will be discharged from the CRU on Day 15 (after the 36-hour sample) and return in the morning of Day 16 (Visit 4) for the 48-hour PK sample.

A final end-of-study visit will take place as a telephone call on Day 22 (±2 days) (Visit 5) or after early withdrawal.

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, as detailed in Table 8.2-1.

AEs will be recorded continually from the first dose of midazolam during visits to the CRU. Upon re-admission to the CRU on Day 13 subjects will be asked to report any AEs that arose between discharge on Day 4 and re-admission on Day 13.

Table 8.2-1 Overall schedule of events, Part II

Visit →		**Visit 1 Screening**	**Visit 2 In-clinic visit**					**Home admin.**	**Visit 3 In-clinic visit**			**Visit 4 Outpatient visit**	**Visit 5 Telephone follow-up[2]**
Assessment↓/Day→	CSP section	Day -28 to -1	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5 to Day 12	Day 13	Day 14	Day 15	Day 16	Day 22 (±2 days)
Informed consent	11.2.1	X											
Eligibility criteria	11.2.2	X	X[3]										
Demographics	11.2.3	X											
Weight/height (BMI)	11.2.4	X											
Medical/surgical history	11.2.5	X											
HIV, hepatitis B and C	11.2.7	X											
Urine drug screen	11.2.8	X	X						X				
Alcohol test	11.2.9	X	X						X				
Safety laboratory profile	11.4.5	X	X		X				X		X		
Physical examination	11.4.2	X		X							X		
12-lead safety ECG	11.4.4	X	X[4]		X	X	X[5]			X	X		
Vital signs[6]	11.4.3	X	X[4]		X	X	X[5]			X	X		
MDZ administration	10.5.2			X	X					X			
Linaprazan glurate administration[7]	10.5.2				X	X	X	X[8]	X[8]	X			
Hand-out of linaprazan glurate	10.5.2						X						
Hand-out of electronic diary	16.3						X						
Compliance check	10.7								X				
PK blood sampling	11.3.1			X	X	X	X			X	X	X	
Blood sampling for metabolites	11.5.1				X	X	X			X	X	X	
Collection of urine[9]	11.5.1				X					X			

Standardized meals[10]	9.6.1			X	X	X				X	X		
Baseline symptoms[11]	11.2.10	X											
Adverse events (AEs)[12]	11.4.1			---------- X ----------									
Prior and concomitant medications	11.2.6	X											

BMI= body mass index, ECG= electrocardiogram, HIV=human immunodeficiency virus, MDZ=midazolam.

1. Detailed schedule for Visit 2 and Visit 3 are shown in Table 8.2-2, Table 8.2-3 and Table 8.2-4.
2. Or after early withdrawal.
3. Confirmation of eligibility. Can be done on Day -1 or Day 1 prior to dosing.
4. Pre-dose assessments can be done on Day -1 or Day 1 prior to midazolam administration.
5. In association with discharge from the CRU.
6. Resting systolic and diastolic blood pressure, pulse, blood oxygen saturation and body temperature.
7. Administration of linaprazan glurate BID (75 mg:3x25 mg oral tablets, BID).
8. At-home administration of linaprazan glurate (75 mg:3x25 mg oral tablets, BID). On Day 13, the morning dose will be taken at home and the evening dose will be taken at the CRU.
9. For exploratory analysis of linaprazan glurate metabolites. Urine to be collected: 0-6 hours and 6-12 hours.
10. Subjects must fast for at least 8 hours before each midazolam/linaprazan glurate administration until 2 hours-post dose. Meals Day 1 to Day3 and Day 14 and 15: breakfast, lunch, snack, dinner and optional evening snack. Meals Day 4: optional breakfast. Breakfast will be served approximately 2 hours after midazolam/linaprazan glurate administration. Lunch, a mid-day snack, dinner, and optional evening snack will be served approximately 4 hours, 6 hours, 9 hours, and 12 hours after midazolam/linaprazan glurate administration.
11. Baseline symptoms will be recorded from the signing of the ICF up until the first administration of midazolam on Day 1.
12. AEs will be recorded from the administration of midazolam on Day 1 up until the follow-up visit (Visit 5), or until early withdrawal.

Table 8.2-2 Detailed schedule of events, Part II – Visit 2, Day -1 to Day 2

Day →	**Day -1**	**Day 1**										**Day 2**
Assessment↓/Time→	Admission	Pre-dose <-01:00	00:00	00:15	00:30	01:00	02:00	04:00	08:00	12:00	14:00	20:00
Eligibility criteria	X[1]											
Urine drug screen	X											
Alcohol test	X											
Safety laboratory profile	X											
Physical examination		X[2]										
12-lead safety ECG	X[2]							X				
Vital signs	X[2]											
MDZ administration			X									
MDZ PK blood sampling		X		X	X	X	X	X	X	X	X	X
Standardized meals							X					
Baseline symptoms	---------- X ----------											
Adverse events			X									
Prior and concomitant medications	X											

1. Confirmation of eligibility. Can be done on Day -1 or Day 1 prior to dosing.
2. Prior to midazolam administration. Symptom driven physical examination.

Table 8.2-3 Detailed schedule of events, Part II – Visit 2, Day 2 to Day 4

Day →	**Day 2**														**Day 3**																**Day 4**		
Assessment↓/Time →	24:00	Pre-dose <-01:00	00:00	00:15	00:30	01:00	02:00	04:00	08:00	12:00	12:15	12:30	13:00	14:00	16:00	20:00	24:00	00:00	00:15	00:30	01:00	02:00	04:00	08:00	12:00	12:15	12:30	13:00	14:00	16:00	20:00	24:00
12-lead safety ECG		X[1]						X										X[2]							X							X
Vital signs		X[1]																X[2]														X
Safety laboratory profile								X																								
MDZ PK blood sampling[5]		X[3]		X	X	X	X	X	X	X				X		X	X															
MDZ administration			X																													
Linaprazan glurate administration[4]			X							X								X							X							X
Linaprazan glurate PK blood sampling[5]		X		X	X	X	X	X	X	X[2]	X[6]	X	X	X	X	X	X[7]		X	X	X	X	X	X	X[2]	X[6]	X	X	X	X	X	X[2]
Blood sampling for metabolites[8]		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	X	X	X	X
Standardized meals																			X[9]													
Collection of urine						X[10]																										
Adverse events	——— X ———																															
Prior and concomitant medications	X																															

1. 24:00 hh:mm post-MDZ administration assessments also serve as pre-dose assessments.
2. Prior to linaprazan glurate administration. At 12:00, prior to the second linaprazan glurate administration.
3. Midazolam PK 24:00 hh:mm blood sample must be taken prior to linaprazan glurate administration on Day 2.
4. Administration of linaprazan glurate BID (morning and evening every 12th hour).
5. PK blood samples for midazolam and linaprazan glurate: when blood samples should be taken at the same time point only 1 blood sample will be taken.
6. The PK blood sample should be taken 15 minutes after the linaprazan glurate administration given at 12:00.
7. The PK blood sample 24:00 hh:mm after the dose of linaprazan glurate on Day 2 also serves as the pre-dose PK sample for the dose of linaprazan glurate on Day 3.
8. Aliquoted from linaprazan glurate PK blood samples.

9. Subjects must fast for at least 8 hours before each midazolam/linaprazan glurate administration until 2 hours-post dose.
10. Pre-dose urine sample (5 mL) will be collected from the first morning void. Urine will be collected 0-6 hours and 6-12 hours after co-administration of midazolam and Day 2.

Table 8.2-4 Detailed schedule of events, Part II – Visit 3

Day →	**Day 13**	**Day 14**													**Day 15**				**Day 16**
Assessment↓/Time→	Admiss-ion	Pre-dose <-01:00	00:00	00:15	00:30	01:00	02:00	04:00	08:00	12:00	12:15	12:30	13:00	14:00	16:00	20:00	24:00	36:00	48:00
Urine drug screen	X																		
Alcohol test	X																		
Safety laboratory profile	X																X		
Physical examination																	X		
12-lead safety ECG		X						X									X		
Vital signs		X															X		
Compliance check	X																		
MDZ administration			X																
Linaprazan glurate administration[1]	X		X							X									
MDZ PK blood sampling[2]		X		X	X	X	X	X	X	X				X		X	X		
Linaprazan glurate PK blood sampling[2]		X		X	X	X	X	X	X	X[3]	X[4]	X	X	X	X	X	X	X	X
Blood sampling for metabolites[5]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collection of urine							X[6]												
Standardized meals													X[7]						
Adverse events											X								
Prior and concomitant medications											X								

1. Administration of linaprazan glurate BID (morning and evening every 12th hour).
2. PK blood samples for midazolam and linaprazan glurate: when blood samples should be taken at the same time point only 1 blood sample will be taken.
3. Before the second linaprazan glurate administration.

4. The PK blood sample should be taken 15 minutes after the second linaprazan glurate administration.
5. Aliquoted from linaprazan glurate PK blood samples.
6. Pre-dose urine sample (5 mL) will be collected from the first morning void. Urine will be collected 0-6 hours and 6-12 hours.
7. Subjects must fast for at least 8 hours before each midazolam/linaprazan glurate administration until 2 hours-post dose.

8.3 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 [12] was considered when designing this study.

The terminal $T_{1/2}$ of linaprazan is approximately 12-21 hours and the C_{max} of linaprazan is estimated to be reached after 2-3 hours, based on results from previous studies (refer to Section 6.1.1). In Part I, a prolongation of linaprazan $T_{1/2}$ can be expected when co-administered with a CYP3A4/PgP inhibitor, therefore blood sampling for PK purpose up to 72 hours is considered appropriate for the study objectives. In Part II, the 48-hour PK blood sampling interval, in order to capture the elimination phase, is considered appropriate for the study objectives.

Based on *in vitro* data, the elimination of both linaprazan glurate and its active metabolite linaprazan is metabolized by CYP3A4. Furthermore, linaprazan glurate and linaprazan have both showed a potential of CYP3A induction *in vitro* and linaprazan glurate has shown a potential to inhibit CYP3A4 at the intestinal level. The design of the study is therefore based on the aim to study whether concomitant treatment with a strong inhibitor of CYP3A4/PgP leads to clinically relevant increase of systemic exposure to linaprazan glurate and linaprazan in a limited number of healthy volunteers. Clarithromycin is chosen as a strong inhibitor of CYP3A4/PgP as it is commonly used index inhibitor of CYP3A4 and used as standard of care in the treatment of *H. pylori*, an indication of clinical interest for combination therapy with linaprazan glurate. In Part I, when the effect of a strong CYP3A4/PgP inhibitor on the exposure of linaprazan glurate/linaprazan will be investigated, the formulation of linaprazan glurate will be in its base form. This formulation and dose levels has been used previously in Phase I and in an ongoing Phase II study and thus the exposure and safety are established.

Part II of the study will further evaluate if single and/or repeated doses of linaprazan glurate have effect on the PK of a sensitive CYP3A substrate. This will be investigated at the first occasion when linaprazan glurate and midazolam is co-administrated. Furthermore, since linaprazan glurate is a potential inducer of CYP3A metabolism, *i.e.*, the plasma exposure of midazolam may be reduced rather than increased after repeated dosing of linaprazan glurate. This will be investigated at the second occasion when linaprazan glurate and midazolam is co-administered. In Part II, when the effect of linaprazan glurate/linaprazan on the exposure of a CYP3A4 index drug is investigated, a new HCl salt IR tablet formulation will be used. The salt formulation is the intended Phase III formulation.

The fixed-sequence design of the study was chosen to yield an efficient comparison of treatments. There are only few subjects required since each subject will serve as his or her own control. To avoid carryover effects, a washout period of 4 days has been incorporated between the first linaprazan dose and start of clarithromycin treatment in Part I.

8.3.1 Selection of doses

The dose level of linaprazan glurate to be used in this study is 100 mg single dose in Part I and 75 mg BID repeated dosing in Part II.

In the FIH (SAD and MAD) study of linaprazan glurate, 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. Previous studies (refer to Section 6.1.1) including a Phase I PK/PD study (EudraCT no. 2019-003963-24) where repeated doses of 50 mg, 100 mg and 150 mg, linaprazan glurate were administered without any safety concerns. The selected doses of linaprazan glurate will lie in the projected upper therapeutic dose rage and, hence, is judged to be clinically relevant with regard to drug interactions.

The dose of clarithromycin, 500 mg BID, is chosen since this is the normal dosage for eradication of *H. pylori*. The selected dosing regimen of midazolam, 2.5 mg QD, in Part II is within the standard recommended range in the label for the product.

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

The subjects will be recruited from CTC's 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 etc.) may be used to reach the target audience. The advertisement texts approved by the independent ethics committee (IEC) will be used to create all the digital, radio and print material for recruitment.

9.2 Screening and enrolment log

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

A screening number generated automatically in the electronic case report form (eCRF) will be allocated to each subject in connection to the informed consent process at the screening visit (Visit 1). 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 the first dose administration) the subject must be rescreened before being allowed to proceed in the study. For details on re-screening, see Section 9.7

9.3 Number of subjects

In total, approximately 54 subjects will be screened in the study (27 subjects for each part).

In Part I, a total of 18 healthy subjects are planned to be included for an estimated total of 12 evaluable subjects.

In Part II, a total of 18 healthy subjects are planned to be included for an estimated total of 12 evaluable subjects.

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 and female subjects of non-childbearing potential aged 18 to 60 years, inclusive.
3. Body mass index $\geq$ 18.0 and $\leq$ 30.0 kg/m^2.
4. Medically healthy subjects without abnormal clinically significant medical history, physical findings, vital signs, ECG, or laboratory values at the time of screening, as judged by the Investigator.

5. Females of non-childbearing potential are defined as pre-menopausal females who are sterilized (tubal ligation or permanent bilateral occlusion of fallopian tubes) or post-menopausal defined as at least 12 months of amenorrhea (in questionable cases a blood sample with simultaneous detection of Follicle Stimulating Hormone [FSH] ≥ 25 IU/L is confirmatory).

   Male subjects must be willing to use condom or be vasectomized or practice sexual abstinence to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the date of dosing until 3 months after (last) dosing with linaprazan glurate. Their female partner of child-bearing potential must use highly effective contraceptive methods with a failure rate of < 1% to prevent pregnancy (combined [estrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device [IUD]or intrauterine hormone-releasing system [IUS]) from the first dose in the study until 3 months after the last dose of linaprazan glurate.

9.5 Exclusion criteria

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

1. Have known allergies to any components of the linaprazan glurate formulation, or to clarithromycin or to any drugs of a similar class (*e.g.*, macrolides, in Part I) or to midazolam or to any drugs of a similar class (*e.g.*, benzodiazepines, in Part II), including excipients associated with any of the drugs.
2. Use of CYP3A4 inhibitors, antacids, PPIs or any medication that changes gastric pH within 14 days prior to the first administration of linaprazan glurate in Part I and midazolam in Part II.
3. Use of any prescribed or non-prescribed CYP3A4-inducing medication (*e.g.*, efavirenz, nevirapine, rifampicin, rifabutin, modafinil, phenytoin, carbamazepine, glitazones, oral glucocorticoids) or other metabolic enzyme inducers, including herbal remedies such as St John's wort, within 14 days prior to administration of first dose of linaprazan glurate in Part I and midazolam in Part II.
4. Use of any other prescribed or non-prescribed medication within 14 days prior to the first administration of linaprazan glurate except occasional intake of paracetamol (maximum 2000 mg/day; and not exceeding 3000 mg/week) and nasal decongestants without cortisone, antihistamine, or anticholinergics for a maximum of 10 days, at the discretion of the Investigator.
5. 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.
6. History of liver disease or elevated transaminases.
7. Subject has consumed grapefruit or grapefruit juice within 7 days of the first administration of linaprazan glurate.
8. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the administration of linaprazan glurate in Part I and midazolam in Part II.
9. Malignancy within the past 5 years, with the exception of *in situ* removal of basal cell carcinoma.

10. Any planned major surgery within the duration of the study.
11. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C antibodies (HCVAb) and/or human immunodeficiency virus (HIV).
12. After 10 minutes supine rest at the time of screening, any vital signs outside the following ranges:
    - Systolic blood pressure: <90 or >140 mmHg, or
    - Diastolic blood pressure <50 or >90 mmHg, or
    - Pulse <40 or >90 bpm
13. 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.
14. Planned treatment or treatment with another investigational drug within 3 months prior to Day -1 of each part. Subjects consented and screened but not dosed in previous Phase I studies will not be excluded.
15. Subject has swallowing difficulties, which may affect the subject's capability to swallow the IMP.
16. 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.
17. Positive screen for drugs of abuse or alcohol at screening or on admission to the study clinic prior to administration of linaprazan glurate.
18. History of or current alcohol abuse or excessive intake of alcohol, as judged by the Investigator.
19. History of or current drug abuse, as judged by the Investigator.
20. History of or current use of anabolic steroids, as judged by the Investigator.
21. Excessive caffeine consumption defined by a daily intake of > 5 cups (1 cup = approximately 240 mL) of caffeine-containing beverages, as judged by the Investigator.
22. Plasma donation within 1 month of screening or blood donation (or corresponding blood loss) during the last 3 months prior to screening.
23. The Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements.

9.6 Restrictions during the study

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

9.6.1 General restrictions

1. Contraception requirements: The male volunteers are expected to use condom in combination with use of contraceptive methods with a failure rate of <1% (see Inclusion Criterion No 5) to prevent pregnancy and drug exposure of a female partner and refrain from donating sperm from the date of first dose until 3 months after the last dose of the linaprazan glurate.
2. Fasting: Subjects must fast overnight (at least 8 hours) prior to the anticipated dosing times with linaprazan glurate (Day 1 and Day 10) and with clarithromycin (Day 9) in

Part I and prior to dosing with midazolam or co-administration with midazolam and linaprazan glurate (Day1, Day 2 and Day 14) in Part II, and until 2 hours post-dose. During fasting, water, but no other drinks, is allowed as desired except for 1 hour before and 30 minutes after dosing. Linaprazan glurate will be taken in the morning together with a glass of water (approximately 240 mL) in Part I and in the morning and in the evening together with a glass of water (approximately 240 mL) in Part II.

In Part I, clarithromycin will be taken in the morning and evening. When co-administered with linaprazan glurate and on the clarithromycin PK sampling day (Day 9), clarithromycin will be administered in the fasted state as defined for linaprazan glurate. Otherwise, clarithromycin may be administered with a meal.

In Part II, midazolam will be taken in the morning. Subjects must fast overnight (at least 8 hours) prior to the anticipated dosing with midazolam until 2 hours post-dose. During fasting, water, but no other drinks, is allowed as desired except for 1 hour before and 30 minutes after dosing.

3. Meals and dietary restrictions: Standardized meals will be served while the subjects are in the CRU. The meal selection is standardized in the sense that the nutritional content of the meals is similar at each time point of each treatment day at the study clinic. Breakfast is served approximately 2 hours post-dose and lunch is served approximately 4 hours post-dose. A mid-day snack, dinner, and an optional evening snack is served approximately 6 -, 9 -, and 12- hours post-dose, respectively.
4. Alcohol: The consumption of alcohol will not be allowed within 48 hours prior to the study visits.
5. Xanthine/taurine containing beverages: The intake of energy drinks (*e.g.*, Red Bull, Monster Energy) or other xanthine/taurine-containing beverages are not allowed within 48 hours prior to administration of linaprazan glurate or clarithromycin and during treatment periods.
6. Coffee: The consumption of up to 5 cups of coffee per day will be allowed during the study.
7. Drugs of abuse: The use of drugs of abuse will not be allowed during the study. In addition to the urine drug screens described in the schedule of events in Table 8.1-1 and Table 8.2-1, additional random testing can be performed at any visit to the CRU.
8. Nicotine: Smoking or the use of nicotine-containing products, including non-tobacco oral nicotine products, will not be allowed during the study.
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 within 7 days of the first administration of linaprazan glurate and 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.
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 CRU: Subjects will not be allowed to leave the CRU during study visits unless authorized by the study personnel.

9.6.2 Prior and concomitant therapy

9.6.2.1 Prohibited prior medications

Use of CYP3A4 inhibitors, antacids, PPIs or any medication that changes gastric pH within 14 days prior to the first administration of linaprazan glurate.

Use of prescribed or non-prescribed CYP3A4-inducing medication (*e.g.*, efavirenz, nevirapine, rifampicin, rifabutin, modafinil, phenytoin, carbamazepine, glitazones, oral glucocorticoids) or other metabolic enzyme inducers, including herbal remedies such as St John's wort, within 14 days prior to administration of first dose of linaprazan glurate.

Any use of other prescribed or non-prescribed medication within 14 days prior to the first administration of linaprazan glurate except occasional intake of paracetamol (maximum 2000 mg/day; and not exceeding 3000 mg/week) and nasal decongestants without cortisone, antihistamine or anticholinergics for a maximum of 10 days, at the discretion of the Investigator.

9.6.2.2 Prohibited concomitant medication.

Any use of prescribed or non-prescribed medication including CYP3A4 inhibitors and inducers, antacids, analgesics, herbal remedies, vitamin supplements and minerals from the first administration of linaprazan glurate until the last visit in the study except as detailed below.

9.6.2.3 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.
- Hormone replacement therapy.

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 included 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

The 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.

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

Potential reasons for discontinuation can include:

- Subject's own decision.
- Withdrawal of consent.
- Severe non-compliance to study protocol procedures, as judged by the Investigator and/or Sponsor.
- The 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.
- 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. If the reason for discontinuation was one or several AEs, the AEs must be specified in the end-of-study form of the eCRF.

9.8.3 Subject replacement

Subjects who are prematurely withdrawn from the study for any reason except the occurrence of AEs assessed as possibly or probably related to study treatment may be replaced during the course of the study.

9.9 Randomization

This is a non-randomized study.

9.10 Blinding

This is an open-label study, *i.e.*, the Investigator, study staff and study subjects will know the type of treatment received.

10 STUDY TREATMENTS

10.1 Identity of investigational medicinal products

10.1.1 Investigational medicinal product

The IMP (linaprazan glurate) will be provided in tablets.

- **Part I**: Linaprazan glurate in base form, 25 mg oral tablets
- **Part II:** Linaprazan glurate HCl, 25 mg oral tablets

Part I: the 25 mg oral tablets will be packed in blister strips containing 4 tablets with a carton as secondary packaging.
Part II: the 25 mg oral tablets will be packed in screw-capped bottles containing 30 tablets per bottle.
The composition of the tablets is provided in the investigational medicinal product dossier (IMPD) for each formulation.
Part I: the 25 mg tablet is an IR oral tablet containing the base form of linaprazan glurate. It contains excipients commonly used in pharmaceutical preparations for oral administration.
Part II: the 25 mg tablet is an IR oral tablet containing linaprazan glurate HCl. It also contains common excipients used in preparations for oral administration, however different ones from the base formulation.

10.1.2 Index inhibitor (perpetrator drug), Part I

Clarithromycin 500 mg, oral tablets.

10.1.3 Substrate of CYP3A, Part II

Midazolam APL, oral solution 1mg/mL.

10.2 Manufacturing, packaging, labelling and release

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

Part I: Linaprazan glurate 25 mg oral tablets are manufactured by Recipharm Pharmaceutical Development AB (Solna, Sweden) and packed, labelled, and QP-released by Clinigen Clinical Supplies Management SA (Mont Saint-Guibert, Belgium).

Part II: Linaprazan glurate 25 mg oral tablets are manufactured, packaged and labelled by Xcelience, A Lonza company (Tampa FL, United States) and imported and QP-released by Nextpharma Ploërmel (Ploërmel, France).

For both study parts, linaprazan glurate oral tablets will be shipped to the pharmacy in Uppsala, Sweden (refer to Section 5), who will provide linaprazan glurate to the study clinic (CTC, Uppsala, Sweden).

Clarithromycin and midazolam APL will be purchased from the local pharmacy.

10.3 Conditions for storage

Linaprazan glurate tablets, clarithromycin and midazolam will be stored in room temperature (15 to 25°C) in an access-controlled area at CTC.

Temperature logs will be kept for the area where the drugs are stored. The temperature will be noted on a daily basis.

10.4 Preparation and accountability

Part I:

Linaprazan glurate will always be administered by site personnel. Two nurses/site staff will be present, one who provides the linaprazan glurate (and clarithromycin when taken at the clinic) to the subject and one who checks the procedure.

Clarithromycin will be handed out to the subjects on Day 4 (Visit 5) for home-based self-administration by the subjects. For details on clarithromycin administration and on clarithromycin and linaprazan glurate co-administration, refer to Section 10.5.

Part II:

Linaprazan glurate will be handed out to the subjects on Day 4 (Visit 2) for home-based self-administration by the subjects.

Midazolam will always be administered by site personnel. Two nurses/site staff will be present, one who provides the midazolam (and linaprazan glurate when taken at the clinic) to the subject and one who checks the procedure.

CTC 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

10.5.1 Treatment with linaprazan glurate and clarithromycin, Part I

Following an overnight fast for at least 8 hours, the subjects will be administered 100 mg linaprazan glurate (4 tablets containing 25 mg linaprazan glurate) together with a glass of water (approximately 240 mL). The tablets should be swallowed whole. Water, but no other drinks, is allowed as desired except for 1 hour before and 30 minutes after linaprazan glurate administration. No food is allowed for at least 2 hours post-administration. Water, but no other drinks, is allowed as desired except for one hour before and 30 minutes after linaprazan glurate administration.

There are no fasting restrictions in relation to clarithromycin administration, which may be taken in association with or without a meal (except on the clarithromycin PK sampling day (Day 9) and when co-administered with linaprazan glurate on Day 10), see Table 10.5-1. On each dosing occasion, 500 mg clarithromycin will be administered. After swallowing the clarithromycin tablet, subjects should drink a glass of water (approximately 240 mL).

Details on linaprazan glurate and clarithromycin administration per day are provided in Table 10.5-1.

Table 10.5-1 Administration of linaprazan glurate and clarithromycin, Part I

Study day	**Treatment**	**At clinic or at home**	**Fasting requirement**	**Other instructions**
Day 1	Linaprazan glurate 100 mg (in the morning)	Clinic	Yes	Linaprazan glurate (4x25 mg tablets) should be taken with a glass of water (approximately 240 mL).
Day 2	-	-	-	-
Day 3	-	-	-	-
Day 4	Clarithromycin 500 mg BID (approximately 12 hours apart)	Clinic (morning dose) Home (evening dose)	No	After swallowing each tablet, subjects should drink a glass of water (approximately 240 mL).
Day 5	Clarithromycin 500 mg BID (approximately 12 hours apart)	Home	No	After swallowing each tablet, subjects should drink a glass of water (approximately 240 mL).
Day 6	Clarithromycin 500 mg BID (approximately 12 hours apart)	Home	No	After swallowing each tablet, subjects should drink a glass of water (approximately 240 mL).
Day 7	Clarithromycin 500 mg BID (approximately 12 hours apart)	Home	No	After swallowing each tablet, subjects should drink a glass of water (approximately 240 mL).
Dag 8	Clarithromycin 500 mg BID (approximately 12 hours apart)	Home	No	After swallowing each tablet, subjects should drink a glass of water (approximately 240 mL).
Dag 9	Clarithromycin 500 mg BID (approximately 12 hours apart)	Clinic	Yes – morning dose only	After swallowing each tablet, subjects should drink a glass of water (approximately 240 mL).
Day 10	Clarithromycin 500 mg BID (approximately 12 hours apart). Linaprazan glurate 100 mg (in the morning)	Clinic	Yes (morning dose only)	After swallowing the tablet/tablets, subjects should drink a glass of water (approximately 240 mL).
Day 11	Clarithromycin 500 mg BID (approximately 12 hours apart)	Clinic (morning dose) Home (evening dose)	No	After swallowing each tablet, subjects should drink a glass of water (approximately 240 mL).

Day 12	Clarithromycin 500 mg BID (approximately 12 hours apart)	Home	No	After swallowing each tablet, subjects should drink a glass of water (approximately 240 mL).

10.5.2 Treatment with linaprazan glurate and midazolam, Part II

During co-administration with midazolam, the morning dose of linaprazan glurate will be administered after an overnight fast for at least 8 hours. The subjects will be administered 75 mg linaprazan glurate (3 tablets containing 25 mg linaprazan glurate) together with a glass of water (approximately 240 mL). The tablets should be swallowed whole. No food is allowed for at least 2 hours post-administration. Water, but no other drinks, is allowed as desired except for one hour before and 30 minutes after linaprazan glurate administration. Water, but no other drinks, is allowed as desired except for 1 hour before and 30 minutes after linaprazan glurate administration. In the evening, subjects will be administered linaprazan with 240 mL of water. There are no fasting requirements during home administration with linaprazan glurate.

Midazolam will be administered in the fasted state. Following an overnight fast for at least 8 hours, the subjects will be administered 2.5 mg midazolam (2.5 mL oral solution, 1 mg/mL). After swallowing the midazolam solution, subjects should drink a glass of water (approximately 240 mL).

Midazolam will be administered once daily (Day 1, Day 2 and Day 14).

Details on midazolam administration in relation to linaprazan glurate administration are provided in

Table 10.5-2.

Table 10.5-2 Administration of linaprazan glurate and midazolam, Part II

Study day	**Treatment**	**At clinic or at home**	**Fasting requirement**	**Other instructions**
Day 1	Midazolam 2.5 mg.	Clinic	Yes	After swallowing the dose (2.5 mL), subjects should drink a glass of water (approximately 240 mL).
Day 2	Midazolam 2.5 mg Linaprazan glurate 75 mg BID	Clinic	Yes	Midazolam (2.5 mL) will be swallowed and after swallowing, linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 3	Linaprazan glurate 75 mg BID	Clinic	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 4	Linaprazan glurate 75 mg BID	Clinic (morning dose). Home (evening dose)	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).

Day 5	Linaprazan glurate 75 mg BID	Home	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 6	Linaprazan glurate 75 mg BID	Home	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 7	Linaprazan glurate 75 mg BID	Home	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 8	Linaprazan glurate 75 mg BID	Home	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 9	Linaprazan glurate 75 mg BID	Home	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 10	Linaprazan glurate 75 mg BID	Home	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 11	Linaprazan glurate 75 mg BID	Home	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 12	Linaprazan glurate 75 mg BID	Home	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 13	Linaprazan glurate 75 mg BID	Home (morning dose). Clinic (evening dose).	No	Linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).
Day 14	Midazolam 2.5 mg Linaprazan glurate 75 mg BID	Clinic	Yes:	Midazolam (2.5 mL) will be swallowed and after swallowing linaprazan glurate (3x25 mg tablets, BID) should be taken with a glass of water (approximately 240 mL).

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, clarithromycin or midazolam after the end of study participation.

10.7 Treatment compliance

During visits at the clinic, the study drugs 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, subjects will self-administer clarithromycin (Part I) or linaprazan glurate (Part II) at home and register each intake of study drug in an electronic diary. Text reminders will be sent to the subjects each day. At the compliance visit to the clinic, subjects will be asked to return any unused study drugs and all empty containers.

In Part I, the number of remaining tablets as well as the date of compliance visit to the clinic as specified in Table 8.1-1. The weight at the compliance visit will be entered in the eCRF.

In Part II, the number of remaining tablets as well as the date of the compliance check as specified in Table 8.2-1 will be entered into the eCRF.

10.8 Return and destruction of investigational medical 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, clarithromycin and midazolam 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, refer to Section 8.1 (Part I) and Section 8.2 (Part II).

11.1 Recording of data

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

Time points for PK blood sampling, safety laboratory samples, 12-lead safety ECG and vital signs are outlined in Table 8.1-1 to Table 8.1-4 for Part I and in Table 8.2-1 to Table 8.2-4 for Part II. Allowed time windows for PK sampling are outlined in 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 administration of the first dose of linaprazan glurate on Day 1 in Part I and before administration of the first dose of midazolam on Day 1 in Part II. 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 should 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 14 days prior to first linaprazan glurate administration (Part I) or midazolam (Part II) 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 of linaprazan glurate in Part I and midazolam in Part II) 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 as well as hepatitis C antibodies prior to inclusion into the study. Any positive results will exclude the subject from participating in the study.

11.2.8 Urine drug screen

Urine will be screened for drugs of abuse using the Drug-Screen Multi-15 Dip Test (Nal von Minden [GmBH] or equivalent). Additional random tests can be performed during the study period. The test screens for 4 methylpentedrone, 7 aminoclonazepam, amphetamine, benzodiazepines, buprenorphine, fentanyl, tetrahydro-cannabinoids (THC), cocaine, methadone, methamphetamine, methylenedioxy-methamphetamine (MDMA, ecstasy), morphine, oxycodone, pregabalin and tramadol, along with pH and creatinine.

11.2.9 Alcohol test

An alcohol test will be performed at pre-specified visits. Additional random tests can be performed during the study period.

11.2.10 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 linaprazan glurate (Part I) or midazolam (Part II) (*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 pharmacokinetic endpoints

11.3.1 Pharmacokinetic sampling and analysis

Venous blood samples for the determination of plasma concentrations and PK characterization of linaprazan glurate and linaprazan, clarithromycin (Part I) and midazolam (Part II) after administration will be collected through an indwelling venous catheter or by venipuncture at the pre-specified visits (Table 8.1-1 to Table 8.1-4 for Part I and Table 8.2-1 to Table 8.2-4 for Part II). In Part II, some of the PK blood samples for linaprazan glurate and midazolam will be taken at the same time points, hence only 1 blood sample will be taken and the plasma will be aliquoted as described below (refer to Table 8.2-3 and Table 8.2-4). Actual time for blood PK sampling must not deviate more than ±10% from the planned time, except as detailed below. The date and time of collection of each sample will be recorded in the eCRF.

In Part I, pre-dose PK sampling before the first dose and at Visit 6 may be performed within 60 minutes prior to dosing. In Part II, pre-dose PK sampling will be done as close to dose with midazolam and linaprazan glurate as possible at the occasions when co-administered.

The blood samples will be collected in pre-labelled tubes. All the collected blood samples will be centrifuged to separate plasma, which will be divided into aliquots after centrifugation for PK analysis. The separated plasma from each blood sample will be divided into 3 aliquots in pre-labelled cryotubes (1 A sample, 1 B sample and 1 C [backup] sample approximately 500 µL in each tube) and frozen at -70°C. Further details will be described in a separate laboratory manual.

Remaining plasma will be added to a pre-labelled cryotube and frozen at -70 °C for future exploratory analyses of potential linaprazan glurate metabolites (see Section 11.5.1)

Plasma samples for determination of plasma concentrations of linaprazan glurate, linaprazan and for midazolam (Part II) will be analyzed by Lablytica Life Science AB, Uppsala, Sweden, by means of a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The details of the analytical method used will be described in a separate bioanalytical report.

11.4 Safety assessments

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 CTC 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 (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 such events 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 (AR)

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

11.4.1.4 Definition of serious adverse reaction (SAR)

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

11.4.1.5 Definition of suspected unexpected serious adverse reaction (SUSAR)

An SAE will be classified as a SUSAR when either the Investigator or Sponsor or designee assesses that there is a reasonable possibility of a causal relationship between the SAE and the IMP, and the Sponsor or designee assesses the event as unexpected based on the applicable reference safety information (*i.e.*, the IB for linaprazan glurate or the SmPC for clarithromycin and midazolam).

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 until the end-of-study visit of each part.

Any AE with start date on the day 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 linaprazan glurate and clarithromycin or midazolam, respectively, 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 (linaprazan glurate, clarithromycin or midazolam) 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, *i.e.*, term, intensity, causality, outcome, SAE criteria, action taken, narrative including rationale for causality assessment. By saving the event as "serious" in the eCRF, and once the Investigator has signed-off of the event, an e-mail alert is automatically sent to predefined recipients to highlight that an SAE has been registered. The same information is automatically sent to CTC's SAE inbox at sae@ctc-ab.se.

The SAE report will be reviewed by a designated person at CTC's 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 CTC's 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), CTC's 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 CTC's SAE inbox at sae@ctc-ab.se.

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 is used whenever either the Investigator or Medical Monitor deems an SAE as possibly or probably related to any of the IMPs. If an SAR is assessed as unexpected by the Medical Monitor, it is a SUSAR and will be reported to the CA and to the IEC in accordance with local regulations and the SOPs applicable for the Pharmacovigilance department 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. Detailed information on SUSAR processing and reporting will be specified in the safety management plan (SMP).

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

The 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 (female partner to male participant), 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/cohort in this clinical study protocol (CSP).

During in-clinic study visits, all linaprazan glurate, clarithromycin (Part I) and midazolam (Part II) will be administered by site personnel under medical surveillance. In cases of accidental overdose, subjects will be monitored appropriately, and standard supportive measures and symptomatic treatments will be adopted as required.

An overdose should be documented as follows:

- An overdose with associated AE is recorded as the AE diagnosis/symptoms in the AE Log of the eCRF.
- An overdose without associated symptoms is only reported in the subject's medical records.

No known antidote to linaprazan glurate is available. Any ARs should be treated symptomatically.

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.

Symptoms of clarithromycin overdose and midazolam overdose are generally similar to the common adverse effects given in Section 6.3.1 or to the less frequent adverse effects given in the SmPC for clarithromycin and midazolam. Any ARs should be treated symptomatically. No known antidote to clarithromycin is available. Flumazenil can be used as an antidote to midazolam. Clarithromycin cannot be removed by hemodialysis. Midazolam will only be administered by site personnel under medical surveillance; hence overdosing is unlikely to occur.

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

11.4.3 Vital signs

Systolic and diastolic blood pressure and pulse will be measured in supine position after 10 minutes of rest. Blood oxygen saturation will be measured by pulse oximetry. 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-dose administration findings assessed by the Investigator as CS will be reported as AEs.

11.4.4 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 CS or not NCS in the eCRF. Abnormal post-dose administration findings assessed by the Investigator as CS will be reported as AEs.

11.4.5 Safety laboratory assessments

Blood samples for the analysis of clinical chemistry and hematology will be collected through venipuncture or an indwelling venous catheter and sent to the certified clinical chemistry laboratory at Uppsala University Hospital (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 (Part I) and Table 8.2-1 (Part II).

Safety laboratory parameters are defined in Table 11.4-1 and will be assessed at visits and time-points specified in Table 8.1-1 and Table 8.1-2 for Part I and in Table 8.2-1 to Table 8.2-4 for Part II.

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)
	Calcium
	Creatinine (estimated glomerular filtration rate [eGFR] included)
	Creatine kinase (CK)
	Glucose
	Potassium
	Sodium
Hematology	Leukocyte count with differential count
	Hemoglobin (Hb)
	Thrombocyte count
Urinalysis (dip stick)	Glucose
	Urobilinogen
	Protein
FSH-test	FSH (at screening, postmenopausal females, in questionable cases only)

11.5 Assessments related to exploratory endpoints (Part I and Part II)

11.5.1 Collection of plasma (Part I and Part II) and urine (Part II) for future exploratory analyses of linaprazan glurate metabolites

One (1) aliquot of separated plasma will be taken from PK blood samples at all days in Part I and in Part II (refer to Section 11.3.1) collected at the time-points specified in Table 8.1-1 and Table 8.2-1 and stored frozen pending exploratory analyses of potential linaprazan glurate metabolites.

In Part II, pre-dose urine sample (5 mL) will be collected from the first morning void. Thereafter, urine will be collected on Day 2 and Day 14. Urine will be collected and pooled for each subject at 0-6 hours and 6-12 hours and aliquoted in pre-labelled polypropylene cryotubes and frozen at -70°C within 1 hour after collection. The date and time of collection of each sample will be recorded in the eCRF.

The sampling procedures will be described in further detail in a separate sampling instruction. Samples will be analyzed by a validated bioanalytical method at a certified laboratory. Metabolite data will not be reported in the CSR.

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 and urine 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 325 mL in Part I (Table 12.2-1) and 368 mL in Part II (Table 12.2-2). For reference, a regular blood donation consists of between 350 mL to 450 mL (±10 %) for persons weighing at least 45-50 kg [17].

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

Table 12.2-1 Estimated blood volumes, Part I

Assessment	Estimated number of sampling occasions	Estimated volume per occasion (mL)	Total (mL)
PK blood sampling	54	5	270
HIV, Hepatitis B/C	1	4	4
Clinical chemistry, hematology, microbiology	3	14	42
Glucose	3	3	9
		Total:	**325**

Table 12.2-2 Estimated blood volumes, Part II

Assessment	Estimated number of sampling occasions	Estimated volume per occasion (mL)	Total (mL)
PK blood sampling	57	5	285
HIV, Hepatitis B/C	1	4	4
Clinical chemistry, hematology, microbiology	5	14	70
Glucose	3	3	9
		Total:	**368 mL**

12.3 Handling, storage and destruction of laboratory samples

All biological samples will be registered in a biobank at CTC (Swedish Health and Social Care Inspectorate biobank registry number 893).

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 and urine 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.

CTC will keep full traceability of collected biological samples from the study subjects while in storage at the study clinic and until shipment. CTC will keep documentation of receipt of arrival. The sample receiver (the analytical laboratory) will keep full traceability of the samples while in their custody until the samples are used up or disposed of.

The Sponsor will keep oversight of the entire life cycle of the samples through internal procedures, monitoring of study sites and auditing of external laboratory providers.

12.5 Withdrawal of informed consent for donated biological samples

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

The 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 [19].

Identified risks will be categorized separately from the CSP. See also Section 6.3.1.

13.2 Quality assurance and quality control

The Sponsor has delegated the responsibilities outlined below to CTC whilst maintaining overall study oversight:

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

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

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

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 linaprazan glurate.
- The name and phone number of the Investigator.
- The name and address of the Sponsor.

14.5 Subject data protection

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 European Union (EU) general data protection regulation (GDPR) 2016/679 [13], 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 CTC, 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.

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 [13] and the request will be raised to the Principal Investigator.

The Investigator must file a subject identification list which includes sufficient information to link records, *i.e.*, the eCRF and clinical records. This list must be preserved for possible future inspections/audits but must not be made available to the Sponsor except for monitoring or auditing purposes.

Personal data that are collected in the study such as health information and ethnicity are considered as sensitive personal data. This data will be pseudonymized, *i.e.*, personally identifiable information (PII) will be removed and replaced by a unique subject ID and will be processed by the Sponsor and other involved parties during the study. After the study end, only pseudonymized data can be used.

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

For data that are processed at the clinic (s) (*e.g.*, medical records and ISF), CTC AB is the data controller.

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

The subjects will be covered under Cinclus Pharma ’s liability insurance policy through the Swedish Pharmaceutical Insurance (Läkemedelsförsäkringen). The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request. The participating patients are also protected in accordance with national regulations, as applicable. CTC has a company insurance covering services performed by CTC.

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 CTC 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, and CTC must be in place before any study-related procedures can take place, or subjects can be enrolled.

15.5 Study timetable and end of study

The study is expected to start in Q4 2022 and to be completed by Q2 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) [21].

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

15.7 Reporting and publication

15.7.1 Clinical study report

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

After completing Part I, unblinded data will be prepared from the cleaned database for that part. An ICH E3 [14] guideline-compliant clinical study report (CSR) will be written based on data from Part I and Part II. The 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, the Statistician 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 will be reported separately.

15.7.2 Annual safety report

If the study duration exceeds one 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 [21].

The data from the eCRFs will be sent to the Sponsor and a copy will be sent to the clinic and filed in the Investigator Study 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 (Viedoc™) provided by Viedoc Technologies AB. 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 Electronic patient reported outcome

Subject reported intake of clarithromycin (Part I) and linaprazan glurate (Part II) will be recorded using an electronic patient reported outcome (ePRO) system (ViedocMe™) linked to the eCRF during home-administration. The ePRO system includes password protection and internal quality checks. Text reminders will be sent to the subject through the ePRO. All data registered in the ePRO are stored together with the eCRF data.

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 CTC. 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

For Part I and Part II respectively, 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. A complete CSR including both parts of the study will be written following the final DBL.

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 and secondary endpoints will be performed by CTC.

17.1 General

Continuous data will be presented in terms of evaluable, 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 non-compartmental analysis (NCA) using the software Phoenix WinNonlin® version 8.3 or later (Certara, U.S.A.).

Baseline will be defined as the last non-missing data collection point prior to administration of IMP (*i.e.*, linaprazan glurate in Part I) and midazolam (Part II).

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.

17.3 Analysis data sets

17.3.1 Full analysis set

The full analysis set (FAS) will consist of all subjects who have received at least 1 dose of linaprazan glurate and who provided at least 1 post-baseline data point. There will be 1 FAS per part.

The FAS will also be used for all safety analyses.

17.3.2 Pharmacokinetic analysis set

The PK analysis set (PKAS) will consist of all subjects who received at least 1 dose of linaprazan glurate and provided an evaluable plasma concentration profile, and who have no AEs or protocol deviations judged to affect the PK analysis. There will be 1 PKAS per part. The compliance criteria for self-administration of clarithromycin in Part I and linaprazan glurate in Part II will be specified in the SAP. Individual PK values may be excluded from the analysis as specified in the SAP.

All protocol violations will be judged as major or minor prior to database lock.

17.4 Description of study population

17.4.1 Demographics and baseline characteristics

Descriptive statistics for demographics, weight and height will be presented for all enrolled subjects.

All data will be listed by subject.

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 anatomical therapeutic chemical (ATC) level as applicable.

All data will be listed by subject.

17.4.3 Exposure

The number of subjects treated in each study part and their individual doses will be listed.

17.5 Analysis of pharmacokinetic endpoints

17.5.1 Analysis of pharmacokinetics

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

Part I:

The following primary NCA PK parameters will be assessed for linaprazan glurate and linaprazan:

- AUC_{inf}
- AUC_{0-t}
- C_{max}

The following secondary NCA PK parameters will be assessed for linaprazan glurate and linaprazan, but are not limited to:

- T_{max}
- $T_{1/2}$
- CL/F
- V/F
- $AUC_{extr\%}$

The PK parameters AUC, $AUC_{(0-t)}$ and C_{max} will be analyzed using a mixed model following a natural logarithmic transformation, with fixed effect for treatment and random effect for subject. Ratios of geometric means together with 2-sided 90% CI of test treatment (linaprazan glurate + clarithromycin) and reference treatment (linaprazan glurate alone) will be estimated and presented.

The following secondary NCA PK parameters will be assessed for clarithromycin with and without co-administration of linaprazan glurate, not limited to:

- AUC to the end of the dosing period (AUC_{tau})
- C_{max}
- T_{max}
- $T_{1/2}$

Part II:

The following primary NCA PK parameters will be assessed for midazolam, in the presence and absence of linaprazan glurate administration:

- AUC_{inf}
- AUC_{0-t}
- C_{max}

The following secondary NCA PK parameters will be assessed for midazolam, in the presence and absence of linaprazan glurate administration (if feasible):

- T_{max}
- $T_{1/2}$
- $AUC_{extr\%}$
- CL/F
- V/F

Midazolam PK parameters will be presented and statistically analyzed using the same mixed-effects model as in Part I. The ratios of geometric least squares mean (midazolam in the presence and absence of linaprazan glurate) with the corresponding 90% confidence interval (CI) will be presented. If the CI for AUC_{inf} is between 0.8 and 1.25, and the CI for C_{max} is between 0.7 and 1.43, it can be concluded that linaprazan glurate has no effect on CYP3A.

The following secondary NCA PK parameters will be assessed for linaprazan glurate and linaprazan (if feasible):

- AUC_{inf}
- AUC_{0-t}
- C_{max}
- $AUC_{extr\%}$
- CL/F
- V/F
- R_{acc}
- T_{max}
- $T_{1/2}$

Additional PK parameters may be determined if deemed appropriate.

For AUC_{inf}, AUC will be calculated to the time point of the last quantifiable plasma concentration and then extrapolated to infinity using the concentration in the last quantifiable sample and the estimated terminal elimination rate constant ($Lambda_z$). PK data will be presented by using summary statistics with number of measurements, arithmetic mean, SD, as

well as median, minimum and maximum values. In addition, for the parameters AUC and C_{max} the geometric mean and coefficient of variation (CV%) will be presented.

All data will be listed by subject.

17.6 Analysis of safety endpoints

17.6.1 Adverse events

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

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

17.6.2 Physical examinations

Clinically significant and non-clinically significant abnormal findings will be specified and presented by subject and summarized by treatment.

All data will be listed by subject.

17.6.3 Vital signs

Vital signs (systolic/diastolic BP, pulse rate, and body temperature) will be summarized by treatment and overall. 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.

17.6.4 12-lead safety ECG

All ECGs will be categorized as ”normal”, ”abnormal, not clinically significant”, or ”abnormal, clinically significant” (as judged by the Investigator) and summarized by treatment using frequency tables.

All data will be listed by subject.

17.6.5 Safety laboratory analyses

Safety laboratory data will be summarized by treatment, with absolute and percent change from baseline at each visit.

Abnormal, clinically significant values will be summarized separately if considered appropriate.

All data will be listed by subject.

17.7 Analysis of exploratory endpoints

Data related to exploratory analyses in Part I and Part II of the study will not be included in the study database, and analyses related to exploratory analyses will not be covered by the SAP.

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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

DocuSigned by:

[redacted]

[redacted], *MD*

Clinical Trial Consultants AB

19.2 Approval of the clinical study protocol

I, the undersigned, approve this CSP.

Sponsor signatory

DocuSigned by:

[redacted]

[redacted], *MD, PhD*

CMO Cinclus Pharma Holding AB