Statistical Analysis Plan for Part I and Part II

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

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Statistical Analysis Plan for Part I and Part II	
EudraCT no.	2022-001403-41
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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

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1 SIGNATURES

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
ADaM	Analysis Data Model
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration *vs.* time curve
AUC_{0-t}	AUC from time 0 to time t
$AUC_{extr\%}$	AUC percent extrapolation
AUC_{inf}	AUC from 0 to infinity
AUC_{tau}	AUC to end of dosing period
BID	*Bis in die*, twice daily
CDISC	Clinical Data Interchange Standards Consortium
CF	Clean File
CI	Confidence interval
CL	Apparent total body clearance following *i.v.* administration
CL/F	Apparent total body clearance following extravascular administration
C_{last}	Last observed plasma concentration
C_{max}	Maximum observed concentration
CS	Clinically significant
CSP	Clinical study protocol
CSR	Clinical study report
CT	Controlled terminology
CTC	Clinical Trial Consultants AB
CV	Coefficient of variation
DDI	Drug-drug interaction
DDP	Data display plan
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
FDA	United States Food and Drug Administration
Geo	Geometric
IG	Implementation guideline
IMP	Investigational medicinal product
lin	Linear

Abbreviation	Explanation
LLOQ	Lower limit of quantification
LS	Least square
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
Min	Minimum
NA	Not applicable/not available
NC	Not calculated
NCA	Non-compartmental analysis
NCS	Not clinically significant
PgP	P-glycoprotein
PK	Pharmacokinetic(s)
PKAS	PK analysis set
PT	Preferred term
R_{acc}	Accumulation ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study data tabulation model
SOC	System organ class
T_{last}	Time of occurrence of C_{last}
T_{max}	Time of occurrence of C_{max}
$T_{1/2}$	Terminal elimination half-life
V/F	Volume of distribution following extravascular administration

4 INTRODUCTION

4.1 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).

For more details on the study design, please refer to the CSP.

4.2 Study objectives and endpoints Part I

Objectives	Endpoints	Assessments	Analyses	Data display plan (DDP)
Primary objective, Part I	**Primary endpoint, Part I**	**Assessments, Part I**	**Analyse, Part I**	**DDP, Part I**
To investigate the effect of repeated administration of clarithromycin on linaprazan glurate and linaprazan PK after single dose of linaprazan glurate.	Linaprazan glurate and linaprazan PK parameters with and without co-administration of clarithromycin:	Pharmacokinetic sampling and analysis	Summary statistics for PK parameters. See Section 9. Linear mixed-effects analysis of variance model, see Section 9.2.2	Table PP 1, Table PC 1 and Figure PC 1
	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 objective, Part I	**Secondary endpoint, Part I**	**Assessments, Part I**	**Analyse, Part I**	**DDP, Part I**
To assess the safety and tolerability after single dose of linaprazan glurate with and without co-administration of clarithromycin.	Frequency, seriousness, and intensity of AEs.	Adverse events	Descriptive statistics, Section 9.3.1	Table AE 1, Table AE 3
	Clinically significant changes in physical examinations, vital signs (blood pressure and pulse), electrocardiograms (ECG), and laboratory variables (haematology, clinical chemistry, and urinalysis).	Physical examinations, Vital signs, 12-lead electrocardiograms, Safety laboratory assessments	Descriptive statistics, Section 9.3.2 to 9.3.5	Table PE 1, Table VS 1, Table EG 1, Table EG 3, Table LB 1, Table LB 3 and Table LB 5
To evaluate additional PK characteristics	Additional PK parameters for linaprazan glurate and	Pharmacokinetic sampling and analysis	Summary statistics for PK parameters. See Section 9.3.6	Table PP 5

Objectives	Endpoints	Assessments	Analyses	Data display plan (DDP)
of linaprazan glurate and linaprazan.	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 ($AUC_{extr\%}$)			
To investigate the effect of linaprazan glurate on clarithromycin PK.	Clarithromycin PK parameters with and without co-administration of linaprazan glurate:	Pharmacokinetic sampling and analysis	Summary statistics for PK parameters. See Section 9.3.7	
	AUC to the end of the dosing period (AUC_{tau})			
	C_{max}			
	Additional PK parameters for clarithromycin, not limited to:	Pharmacokinetic sampling and analysis		
	T_{max}			
	$T_{1/2}$			
Exploratory objective, Part I	**Exploratory endpoint, Part I**	**Assessments, Part I**	**Analyse, Part I**	**DDP, Part I**
To explore the metabolites of linaprazan glurate in plasma with and without co-administration of clarithromycin.	Plasma collected for future exploratory analyses of linaprazan glurate metabolites.	Not covered in the SAP	NA	NA

4.3 Study objectives and endpoints Part II

Objectives	Endpoints	Assessments	Analyses	Data display plan (DDP)
Primary objective, Part II	**Primary endpoint, Part II**	**Assessments, Part II**	**Analyse, Part II**	**DDP, Part II**
To investigate the effects after single and repeated	Midazolam PK parameters in the presence and absence of	Pharmacokinetic sampling and analysis	Summary statistics for PK parameters. See Section 9.	

Objectives	Endpoints	Assessments	Analyses	Data display plan (DDP)
administration of linaprazan glurate on the PK properties of midazolam.	linaprazan glurate administration:		Linear mixed-effects analysis of variance model, see Section 9.2.3	Table PP 2,
	AUC_{inf}			
	AUC_{0-t}			
	Cmax			Table PC 2 and
				Figure PC 3
Secondary objective, Part II	**Secondary endpoint, Part II**	**Assessments, Part II**	**Analyse, Part II**	**DDP, Part II**
To assess the safety and tolerability after repeated doses of linaprazan glurate with and without co-administration of midazolam.	Frequency, seriousness, and intensity of AEs.	Adverse events	Descriptive statistics, Section 9.3.1	Table AE 2, Table AE 4
	Clinically significant changes in physical examinations, vital signs (blood pressure and pulse), ECG, and laboratory variables (haematology, clinical chemistry, and urinalysis).	Physical examinations, Vital signs, 12-lead electrocardiograms, Safety laboratory assessments	Descriptive statistics, Section 9.3.2 to 9.3.5	Table PE 2, Table VS 2, Table EG 2, Table EG 4, Table LB 2, Table LB 4, Table LB 6
To evaluate PK data on linaprazan glurate and linaprazan after single and repeated oral doses of linaprazan glurate.	Linaprazan glurate and linaprazan PK parameters after repeated administration of linaprazan glurate twice daily (BID) for 13 days (if feasible):	Pharmacokinetic sampling and analysis	Summary statistics for PK parameters. See Section 9.3.9	*4.3.1.1* *Additional PK parameters Part II*
	AUC_{inf}			Table PP 7
	AUC_{0-t}			
	C_{max}			
	T_{max}			
	$T_{1/2}$			
	$AUC_{extr\%}$			
	CL/F			
	V/F			
	Accumulation ratio (R_{acc}).			
To evaluate additional PK characteristics of midazolam in the presence and absence of linaprazan	Midazolam PK parameters in the presence and absence of linaprazan glurate administration (if feasible):	Pharmacokinetic sampling and analysis	Summary statistics for PK parameters. See Section 9.3.8	

Objectives	Endpoints	Assessments	Analyses	Data display plan (DDP)
glurate administration.	T_{max}			
	$T_{1/2}$			
	$AUC_{extr\%}$			
	CL/F			
	V/F			
Exploratory objective, Part II	**Exploratory endpoint, Part II**	**Assessments, Part II**	**Analyse, Part II**	**DDP, Part II**
To explore the metabolites of linaprazan glurate in plasma and urine after single and repeated doses of linaprazan glurate.	Plasma and urine collected for future exploratory analyses of linaprazan glurate metabolites.	Not covered in the SAP	NA	NA

Cinclus Pharma AB is responsible for analysing the exploratory objectives/endpoints. Results related to exploratory objectives/endpoints in Part I and II will not be reported in the clinical study report (CSR). Therefore, these will not be covered in this SAP.

4.4 Randomisation and number of subjects

This is a non-randomized study.

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.

4.5 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.

4.6 Blinding

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

5 STATISTICAL AND ANALYTICAL PLANS

5.1 Statistical hypotheses

The statistical hypothesis to be tested in Part I is that coadministration of linaprazan glurate + clarithromycin as opposed to linaprazan glurate alone has no effect on CYP3A.

The statistical hypothesis to be tested in Part II is that coadministration of midazolam + linaprazan glurate as opposed to midazolam alone has no effect on CYP3A.

5.2 Sample size calculation

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.

5.3 Definition of analysis sets

The analysis sets defined for the study are outlined in Table 1.

Table 1 Analysis sets

Analysis set	Definition	Use of analysis set
Full analysis set (FAS)	The full analysis set (FAS) will consist of all subjects who have received at least 1 dose of IMP and who provided at least 1 post-baseline data point. There will be 1 FAS per part.	All objectives/endpoints except PK objectives/endpoints.
Pharmacokinetic analysis set (PKAS)	The PK analysis set (PKAS) will consist of all subjects who received at least 1 dose of IMP 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. Subjects with a calculated compliance of less than 82% during the home administration period will be excluded from the PKAS for the corresponding study part. 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.	All PK objectives/endpoints.

5.4 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.

Percent compliance will be calculated, per study part, for the home administration period as

100 * (number of tablets delivered – number of tablets returned) / expected number of tablets taken

If the electronic diary indicates the morning dose being taken later than 12.00 or the evening dose being taken before 17.00, the corresponding tablet will be judged as "returned" in the formula above. Calculated percent compliance will have an impact on inclusion to the PKAS, as described in Table 1 Analysis sets.

5.5 Definition of baseline

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).

5.6 Rounding principles

Generally, no rounding of data will be done prior to calculating statistics. However, if reported data contains more than 8 significant digits it will be rounded to 8 significant digits in the database.

In statistical output and descriptive summaries, the following principles will be followed:

- Data will be presented as reported in input data in listings.
- 2 significant digits will be used for percentages (for example relative change from baseline).
- p-values and similar statistical output will be presented using 4 decimal points.
- 3 significant digits will be used for PK parameters and similar when presenting min and max values in tables.
- Descriptive summaries of PK parameters and similar (e.g. mean, SD, median etc.) will be presented with 4 significant digits.
- Descriptive summaries of all other numerical data (e.g. mean, SD, median etc.) will be presented with one extra decimal compared to reported input data.

5.7 Significance level

All statistical hypotheses in this study will be answered using two-sided 90% confidence intervals. This is not a confirmatory study. Hence, point estimates and CIs will be used exploratorily.

5.8 Multiple comparisons/multiplicity

No adjustment for multiple comparison/multiplicity will be performed. All significant findings will be reviewed for medical relevance.

5.9 Handling of dropouts, missing data and outliers

Outliers will be included in summary tables and listings and will not be handled separately in any analyses. Generally, no imputation of data will be performed. However, when calculating statistics for PK plasma concentrations, concentrations under LLOQ will be replaced with LLOQ/2 if more than 50% of the values for a given time point is above LLOQ. Otherwise, no

statistics will be calculated for that time point. For imputation of PK plasma concentration below LLOQ with the purpose of calculating PK parameters, see Section 9 below.

In case of missing start and stop times of AEs that cannot be investigated further, missing data will be imputed according to a worst-case scenario. This means that start time will be imputed as the closest time point post first intake of IMP and end time as 23:59, resulting in the longest possible treatment emergent duration of the AE.

6 CHANGES FROM THE CLINICAL STUDY PROTOCOL

NA

7 CLINICAL DATABASE PROCESSING

7.1 General information

The clinical database is processed and generated according to The Clinical Data Interchange Standards Consortium (CDISC). CDISC is a Standard Developing Organization which develops and publishes standards to normalise the structure of clinical study data and thereby simplify submissions to and reviews by authorities such as the Food and Drug Administration (FDA).

The CDISC standards for clinical studies are the Study Data Tabulation Model (SDTM) and the Analysis Data Model (ADaM). The study data will be structured into a database model reflecting the SDTM and be compliant to SDTM Implementation Guide (SDTM-IG) version 3.2. The data used for statistical analysis will be structured to reflect the Analysis Data Model (ADaM) and be compliant to ADaM Implementation Guide (ADaM-IG) version 1.1.

Data values are collected according to, or mapped into, Controlled Terminology (CT) codelists defined by CDISC, whenever possible. The codelists are updated quarterly at CTC and the latest version available at study start will be used. As per default, CT codelists will be used in all tables, listings, and figures. Custom codelists for test or parameter names will be used if applicable upon Sponsor's request, to align with protocol texts, or to adhere to other standard naming conventions (e.g. PK parameter name "Tmax" will be used instead of the CDISC term "Time of CMAX"). These custom codelists will be mapped in the "Parameter Name" field in the ADaM structure, while the CT will be kept in the SDTM predecessor fields to provide traceability back to CDISC codelists.

7.1.1 CDISC Compliance

The study database will be CDISC compliant which means that the clinical database will be processed and generated according to CDISC standard. The database will be validated against SDTM and ADaM Validation rules using Pinnacle 21.

The following CDISC documentation will be generated:

- SDTM Data Definition Specification (also referred to as a Define -XML)
  - Define-XML transmits metadata that describes any tabular dataset structure and supports the interchange of dataset metadata for clinical research applications in a machine-readable format.
- ADaM Data Definition Specification (also referred to as a Define -XML)
  - Define-XML transmits metadata that describes any tabular dataset structure and supports the interchange of dataset metadata for clinical research applications in a machine-readable format.
- Annotated eCRF
  - Links the data collection fields used to capture study data to the corresponding variables in the study database. It enables the user to understand how the study data were collected and to trace back from study analysis results to the origin where it was collected.
- SDTM Reviewers' Guide
  - Intended to provide additional context and act as a single point of orientation for the SDTM datasets.
- ADaM Reviewers' Guide
  - Provides regulatory agency reviewers an orientation to the submitted analysis data in a consistent way and usable format.

7.2 Database modeling of study design

The study design is mapped to a SDTM study design model containing the following structural components:

EPOCH: An interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g., screening, randomization, treatment, follow-up), and applies across all arms of the study. Study epochs follow a controlled terminology to represent the different study parts (e.g. SCREENING, TREATMENT [X], FOLLOW-UP)

ELEMENT: Building blocks used to build up the entire study length for all subjects. Information on ELEMENTs is extracted from the study design and schedule of events in the protocol. ELEMENTs are defined to span the entire study without gaps. One EPOCH may contain one or several ELEMENTs. All ELEMENTs must have transition rules in accordance with the protocol to determine start and end.

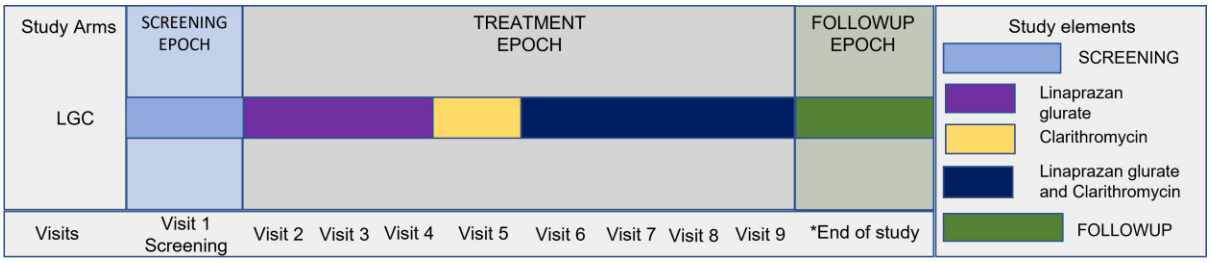
ARM: Subjects are allocated to study arms depending on the study design, either by randomization or other allocation processes defined in the study protocol. ARMs are defined as the total number of planned ways a subject can go through the study (unique combination of study ELEMENTs). All ARMs must contain a unique sequence of ELEMENTs.

VISIT: Study visits are defined as planned timepoints during the study where study data is collected. A visit can be performed in clinic, by off-site contact with study personnel (phone call, video conference or similar), or by subject initiated recordings of data. The visit schedule is extracted from protocol and eCRF design.

A schematic representation of the SDTM study design is presented in Figure 1.

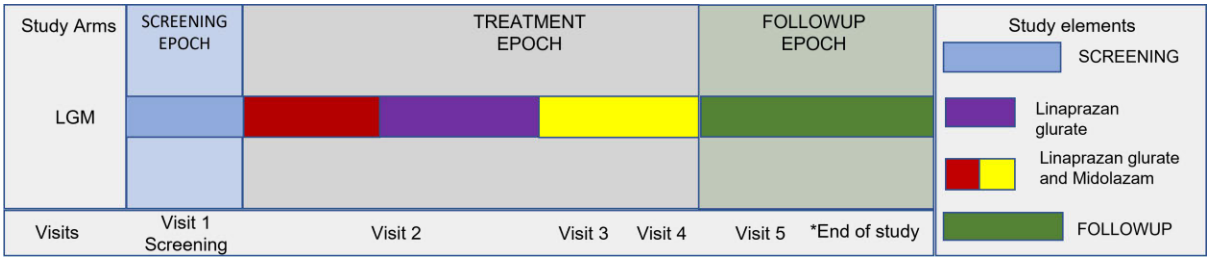
Figure 1 Schematic representation of the SDTM study design

Part I:



*End of study is modeled as a unique visit, but it is performed together with the last participation in the study.

Part II:



*End of study is modeled as a unique visit, but it is performed together with the last participation in the study.

8 STATISTICAL DELIVERABLES

The following items will be delivered:

- Statistical analyses, summary tables, listings and figures as described under Section 10.
- Clinical study database delivered as a SAS-export file.
- Define -XML for SDTM
- Define -XML for ADaM
- Annotated eCRF
- SDTM Reviewer´s Guide
- ADaM Reviewer´s Guide

9 STATISTICAL METHODOLOGY

There will be two clean files (CF) in this study, corresponding to the two study parts. Therefore, output in this study (tables, figures and listings) will be done in two different sets, one per study part. However, there will only be one CSR including both study parts.

All collected data will be listed by treatment and subject.

Details on statistical analyses and descriptive summaries are specified below.

All statistical analysis and descriptive summaries will be performed using SAS version 9.4 (SAS institute, Cary, NC).

9.1 Pharmacokinetic calculations

PK parameters will be calculated by Non-Compartmental Analysis (NCA) using the software Phoenix WinNonlin® version 8.3 (Certara, U.S.A).

The following NCA PK parameters will be calculated for linaprazan glurate and linaprazan, for secondary endpoints the parameters will only be calculated when feasible:

- C_{max} – The maximum observed plasma concentration
- $AUC_{0\text{-}t}$ – The area under the plasma concentration versus time curve (AUC) from timepoint 0 to t, where t represents the timepoint of the last detectable plasma concentration per dosing occasion.
- Partial AUCs– AUC from time t_1 to time t_2. Partial AUCs will be calculated between 0-24 h, 24-48 h Day 2 and 0-24 h Day 14 (only in Part II)
- $AUC_{0\text{-}inf}$ – AUC from timepoint 0 extrapolated to infinity (not calculated for steady state/repeated dose data)
- AUC_{tau} – AUC per dosing interval (calculated at steady state and for the first dose)
- T_{max} – Time to reach C_{max}
- CL/F – Total body clearance for extravascular administration (only for linaprazan glurate as there is no dose data for linaprazan)
- V_z/F – Apparent volume of distribution associated with terminal slope (only for linaprazan glurate as there is no dose data for linaprazan)
- $T_{1/2}$ – The terminal plasma elimination half-life
- $AUC_{extr\%}$ – Percentage of $AUC_{0\text{-}inf}$ due to extrapolation from T_{last} to infinity
- R_{acc} C_{max} – Accumulation ratio for C_{max} (only in Part II)
- R_{acc} AUC – Accumulation ratio for AUC (only in Part II)

The following NCA PK parameters will be calculated for clarithromycin:

- AUC_{tau} – The AUC during dosing interval at steady state
- C_{max}
- T_{max}
- $T_{1/2}$

The following NCA PK parameters will be calculated for midazolam:

- $AUC_{0\text{-}t}$
- $AUC_{0\text{-}inf}$
- $AUC_{extr\%}$

- C_{max}
- T_{max}
- $T_{1/2}$
- CL/F
- V_z/F

Additional PK parameters that will be calculated (and only presented in listing if not specified above) for linaprazan glurate, linaprazan, clarithromycin and midazolam:

- $Lambda_z$ – The eliminate rate constant associated with the terminal phase of the curve
- Rsq adj – Coefficient of determination adjusted for the independent variable time
- No points $lambda_z$ – Number of points used in computing $lambda_z$
- $Lambda_z$ lower – Lower limit on time included in the calculation of $lambda_z$
- $Lambda_z$ upper – Upper limit on time included in the calculation of $lambda_z$
- Span – The ratio between the interval used for determination of $lambda_z$ and the terminal $T_{1/2}$
- $AUC_{extr\%}$

Non-compartmental analysis will be based on the actual sampling times recorded during the study. For the purpose of calculating PK parameters, concentrations below lower limit of quantification (LLOQ) occurring before C_{max} will be treated as zero. Concentrations below LLOQ occurring after C_{max} will be omitted from the analysis.

T_{max} and C_{max} will be based on the observed plasma concentration data.

All AUCs will be assessed by integration of the plasma concentration vs time curve using linear interpolation for increasing plasma levels and logarithmic interpolation for decreasing plasma levels (Linear Up-Log Down method using uniform weighting).

$AUC_{0\text{-}t}$ will be calculated from time 0 to the time t of the last detectable plasma concentration. For $AUC_{0\text{-}inf}$ the area will be calculated to the last timepoint showing a measurable plasma concentration and then extrapolated to infinity using the concentration in the last quantifiable sample and $lambda_z$.

$$AUC_{0-inf} = AUC_{0-t} + \frac{C_{last}}{lambda_z}$$

Partial AUC (possible relevant for AUC_{tau} calculations) will be derived according to specified time windows, if the end time of the interval does not occur at an actual timepoint either linear interpolation or extrapolation will be used for derivation of the partial AUC. Extrapolation, using $lambda_z$, will only be used if the end time of specified interval occur after last detectable plasma concentration.

Formulas for calculation of AUC

- Linear trapezoidal rule:

$$AUC|_{t1}^{t2} = \delta t \times \frac{C_1 + C_2}{2}$$

- Logarithmic trapezoidal rule:

$$AUC|_{t1}^{t2} = \delta t \times \frac{C_2 - C_1}{ln(\frac{C_2}{C_1})}$$

where t = time, c = concentration, $\delta t = t_2 - t_1$.

Formulas for interpolation (to find C* at time t* for t1 < t* < t2)

- Linear interpolation rule:

$$C^* = C_1 + |\frac{t^* - t_1}{t_2 - t_1}| (C_2 - C_1)$$

- Logarithmic interpolation rule:

$$C^* = exp(ln(C_1) + |\frac{t^* - t_1}{t_2 - t_1}| * (ln(C_2) - ln(C_1)))$$

where t = time, c = concentration

$Lambda_z$, the first order rate constant associated with the terminal portion of the curve, will be determined by lin-logarithmic regression of the terminal elimination phase of individual plasma concentration vs time curves. Determination of $lambda_z$ requires identification of a sufficiently linear terminal phase (as determined by visual inspection of the lin-log plasma concentration vs time plot with the regression line) consisting of at least 3 terminal concentration values (not including C_{max}). If this is not achieved, $lambda_z$ and its dependent PK parameters will not be reported for that profile.

In the following cases, $lambda_z$ dependent PK parameters will be flagged in listings as potentially unreliable:

- $Lambda_z$ estimation is based on a period of less than 1.5 times the resulting $T_{½}$.
- The adjusted R_2 value of the regression line is < 0.85.
- The estimated % extrapolated AUC is > 20% (($AUC_{0\text{-inf}}$ -$AUC_{0\text{-last}}$ / $AUC_{0\text{-inf}}$)*100).
    - In case the extrapolated AUC is > 30% $lambda_z$ dependent parameter will excluded from analysis and descriptive statistics.

$T_{½}$ will be calculated by ln2 / $lambda_z$, and Span will be calculated by ($lambda_z$_upper – $lambda_z$-lower) / $T_{1/2}$.

CL/F for single doses will be calculated by Dose / $AUC_{0\text{-inf}}$ and CL/F at steady state will be calculated by Dose / AUC_{tau}.

V_z/F for single doses will be calculated by Dose / ($lambda_z$ x $AUC_{0\text{-inf}}$), and V_z/F at steady state will be calculated by Dose / ($lambda_z$ x AUC_{tau}).

The accumulation ratio for C_{max} will be calculated by C_{max} at steady state / C_{max} first dose, and the accumulation ratio for AUC will be calculated by AUC_{tau} at steady state / AUC_{tau} first dose.

If there is a confirmed dosing error during the study, the pharmacokinetic data for that period will only be included in the listings but excluded from descriptive and statistical analyses. In case of missed blood samples, potential impact on PK parameters will be assessed for each individual case. PK parameters with a high degree of uncertainty due to missing samples (e.g. multiple samples missing around C_{max}) will be flagged as unreliable in the report and may in rare cases be excluded from summary tables, descriptive statistics, and statistical analysis.

Relevant 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.

9.2 Analysis of the primary endpoint

9.2.1 Analysis of PK parameters

Part I:

The following PK parameters will be assessed for linaprazan glurate and linaprazan, in the presence (Day 10) and absence (Day 1) of clarithromycin administration:

- $AUC_{0\text{-}inf}$
- $AUC_{0\text{-}t}$
- C_{max}

Part II:

The following PK parameters will be assessed for midazolam, in the presence (Day2 and 14 respectively) and absence (Day 1) of linaprazan glurate administration:

- $AUC_{0\text{-}inf}$
- $AUC_{0\text{-}t}$
- C_{max}

9.2.2 Mixed model for PK parameters Part I

The PK parameters AUC_{inf}, $AUC_{0\text{-}t}$ 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. Kenward-Rogers approximation for degrees of freedom will be used. Model results will be back-transformed to the original scale to present, 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 same analysis will also be done for linaprazan + clarithromycin vs. linaprazan alone. The SAS proc mixed code to be used will be:

```
ods output lsmeans=lsmeans
              diffs=diffs
              solutionr=randeffects;
proc mixed data=indata;
      by paramn param ppcat;
      class USUBJID Treatment;
      model ln_PK_var = Treatment / ddfm=kenwardroger outp=residuals
outpm=randeffects2 RESIDUAL;
      lsmeans Treatment / alpha=0.1 diff cl adjust=tukey ADJDFE=ROW;
      random USUBJID / solution;
run;
```

9.2.3 Mixed model for PK parameters Part II

Midazolam PK parameters AUC_{inf}, AUC_{0-t} and C_{max} for the comparisons midazolam + linaprazan glurate Day 14 / midazolam Day 1, midazolam + linaprazan glurate Day 14 / midazolam + linaprazan glurate Day 2 and midazolam + linaprazan glurate Day 2 / midazolam Day 1 will be estimated using the same model as described under section 9.2.2 above.

9.3 Analysis of secondary endpoints

9.3.1 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.

9.3.2 Physical examinations

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

9.3.3 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.

9.3.4 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.

9.3.5 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.

9.3.6 Additional PK parameters Part I for linaprazan glurate and linaprazan, not limited to:

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
- $AUC_{extr\%}$

9.3.7 Clarithromycin PK parameters Part I with and without co-administration of linaprazan glurate:

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}
- $T_{1/2}$

9.3.8 Additional Midazolam PK parameters Part II in the presence and absence of linaprazan glurate administration (if feasible):

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

9.3.9 Linaprazan glurate and linaprazan PK parameters Part II (if feasible):

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

- AUC_{tau}
- AUC_{0-t}
- C_{max}
- $AUC_{extr\%}$
- CL/F (only for linaprazan glurate)
- V/F (only for linaprazan glurate)
- R_{acc}
- T_{max}
- $T_{1/2}$

Additional PK parameters may be determined if deemed appropriate.

9.4 Description of study population

Other study population/demographics data will be presented in listings and summarized descriptively as described in section 10 below.

10 DATA DISPLAY PLAN

10.1 Table of contents DDP

List of tables

List of figures

10.2 Study tables

10.2.1 Demographic data

Table DM 1 Baseline characteristics and demographics for Part I (Full analysis set)

Assessment (unit)		Total (N=XX)
Age (years)	n	x
	Mean (SD)	xx.x (xx.x)
	Median (Min, Max)	xx.x (xx, xx)
Height (cm)	n	x
	Mean (SD)	xxx.x (xx.x)
	Median (Min, Max)	xxx.x (xxx, xxx)
Weight (kg)	n	x
	Mean (SD)	xx.xx (xx.xx)
	Median (Min, Max)	xx.xx (xx.x, xx.x)
Body Mass Index (kg/m2)	n	X
	Mean (SD)	xx.xx (xx.xx)
	Median (Min, Max)	xx.xx (xx.x, xx.x)
Sex	Female	xx (xx%)
	Male	xx (xx%)
Ethnicity	Hispanic or latino	xx (xx%)
	Not hispanic or latino	xx (xx%)
	Not reported	xx (xx%)
	Unknown	xx (xx%)
Race	American Indian or Alaska Native	xx (xx%)
	Asian	xx (xx%)
	Black or African American	xx (xx%)
	Native Hawaiian or Other Pacific Islander	xx (xx%)

Assessment (unit)	Total (N=XX)
White	xx (xx%)

Data based on [ANALYSIS SET]. N: number of subjects in treatment group. Mean values and percentages are based on n. n: Number of observations.
SD: Standard deviation. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table DM 2 Baseline characteristics and demographics for Part II (Full analysis set)

Use the same format as for Table DM 1.

Table DS 1 Subject disposition for Part I (All subjects)

	Total (N=XXX)
Screened subjects	xxx
Withdrawn prior to dose	xxx
Reason for withdrawal prior to dose	
--- Reason 1	xxx
--- Reason 2	xxx
--- …	xxx
Subjects included in study	xxx
Withdrawn subjects	
--- Reason 1	xxx
--- Reason 2	xxx
--- …	xxx
Subjects completing all study visits	xxx
Included in Full analysis set	xxx
Included in Pharmacokinetic analysis set	xxx
Subjects at each visit	
--- Visit 1	xxx
--- Visit 2	xxx
--- Visit 3	xxx
--- Visit 4	xxx
--- Visit 5	xxx
--- Visit 6	xxx
--- Visit 7	xxx
--- Visit 8	xxx
--- Visit 9	xxx
--- Visit 10	xxx

Data based on All subjects. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table DS 2 Subject disposition for Part II (All subjects)

Use the same format as for Table DS 1.

Table MH 1 Medical history events by system organ class and preferred term part I (Full analysis set)

	Total (N=XX)	
System organ class Preferred term	n (%)	m
Total	**xx (xx%)**	**xx**
[SOC 1]	**xx (xx%)**	**xx**
[SOC 1 PT 1]	xx (xx%)	xx
[SOC 1 PT 2]	xx (xx%)	xx
[SOC 1 PT …]	xx (xx%)	xx
[SOC 2]	**xx (xx%)**	**xx**
[SOC 2 PT 1]	xx (xx%)	xx
[SOC 2 PT 2]	xx (xx%)	xx
[SOC 2 PT …]	xx (xx%)	xx
[SOC …]	**xx (xx%)**	**xx**
[SOC … PT 1]	xx (xx%)	xx
[SOC … PT 2]	xx (xx%)	xx
[SOC … PT …]	xx (xx%)	xx

Data based on [ANALYSIS SET]. n, number of subjects. m, number of events. Percentages are based on the number of subjects in the treatment period. The following events are coded with multiple terms and are represented as separate events in tables and listings: '[MH TERM 1], [MH TERM 2]'. See listings for detailed information. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table MH 2 Medical history events by system organ class and preferred term part II (Full analysis set)

Use the same format as for Table MH 1.

Table CM 1 Prior medications by ATC levels 4 and 5 for Part I (Full analysis set)

ATC classification Active ingredients	Total (N=XX) n (%)	m
Total	**xx (xx%)**	**xx**
[L4 1]	**xx (xx%)**	**xx**
[L4 1 L5 1]	xx (xx%)	xx
[L4 1 L5 2]	xx (xx%)	xx
[L4 1 L5 …]	xx (xx%)	xx
[L4 2]	**xx (xx%)**	**xx**
[L4 2 L5 1]	xx (xx%)	xx
[L4 2 L5 2]	xx (xx%)	xx
[L4 2 L5 …]	xx (xx%)	xx
[L4 …]	**xx (xx%)**	**xx**
[L4 … L5 1]	xx (xx%)	xx
[L4 … L5 2]	xx (xx%)	xx
[L4 … L5 …]	xx (xx%)	xx

Data based on [ANALYSIS SET]. n, number of subjects. m, number of events. Percentages are based on the number of subjects in the treatment period. The following records are coded with multiple terms and are represented as separate events in tables and listings: '[CM TERM 1], [CM TERM 2]'. See listings for detailed information. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table CM 2 Prior medications by ATC levels 4 and 5 for Part II (Full analysis set)

Use the same format as for Table CM 1.

Table CM 3 Concomitant medications by ATC levels 4 and 5 for Part I (Full analysis set)

Use the same format as for Table CM 1.

Table CM 4 Concomitant medications by ATC levels 4 and 5 for Part II (Full analysis set)

Use the same format as for Table CM 1.

10.2.2 Primary endpoints

10.2.2.1 Analysis of pharmacokinetics

Table PP 1 PK parameters for linaprazan glurate and linaprazan for Part I (Pharmacokinetic analysis set)

Assessment (unit)		Linaprazan glurate alone (N=XX)	Linaprazan glurate co-administred with clarithromycin (N=XX)	Linaprazan alone (N=XX)	Linaprazan co-administred with clarithromycin (N=XX)
AUC_{inf} (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)
AUC_{0-t} (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)
C_{max} (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)

Data based on [population]. n: Number of observations. SD: Standard deviation. CV%: Coefficient of variation described as percentage. Geo CV%: Geometric coefficient of variation described as percentage calculated using log-transformed standard deviation. NC: Not calculated - number of evaluable observations less than 3. NA: Not available - no evaluable observations. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table PP 2 PK parameters for midazolam for Part II (Pharmacokinetic analysis set)

Assessment (unit)		Midazolam alone, Day 1 (N=XX)	Midazolam co-administred with linaprazan glurate, Day 2 (N=XX)	Midazolam co-administred with linaprazan glurate, Day 14 (N=XX)
AUC_{inf} (unit)	n	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)
AUC_{0-t} (unit)	n	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)
C_{max} (unit)	n	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)

Data based on [population]. n: Number of observations. SD: Standard deviation. CV%: Coefficient of variation described as percentage. Geo CV%: Geometric coefficient of variation described as percentage calculated using log-transformed standard deviation. NC: Not calculated - number of evaluable observations less than 3. NA: Not available - no evaluable observations. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table PP 3 Mixed model results for PK parameters for Part I (Pharmacokinetic analysis set)

Parameter	Test treatment	Reference treatment	90% CI lower bound	Ratio of geometric least square means	90% CI upper bound
AUC_{inf} (unit)	Linaprazan glurate co-administred with clarithromycin	Linaprazan glurate alone	x.xxx	x.xxxx	x.xxx
	Linaprazan co-administred with clarithromycin	Linaprazan glurate alone	x.xxx	x.xxxx	x.xxx
AUC_{0-t} (unit)	Linaprazan glurate co-administred with clarithromycin	Linaprazan glurate alone	x.xxx	x.xxxx	x.xxx
	Linaprazan co-administred with clarithromycin	Linaprazan glurate alone	x.xxx	x.xxxx	x.xxx
C_{max} (unit)	Linaprazan glurate co-administred with clarithromycin	Linaprazan glurate alone	x.xxx	x.xxxx	x.xxx
	Linaprazan co-administred with clarithromycin	Linaprazan glurate alone	x.xxx	x.xxxx	x.xxx

Pairwise treatment comparisons are based on a mixed effects model with treatment as a fixed effect and subject as a random effect. Kenward-Rogers approximation for degrees of freedom has been used.
Data based on PK analysis set.
[STUDYID], SAS program: [PROGRAM NAME]. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]. Data extracted at: [TIMESTAMP]

Table PP 4 Mixed model results for PK parameters for Part II (Pharmacokinetic analysis set)

Parameter	Test treatment	Reference treatment	90% CI lower bound	Ratio of geometric least square means	90% CI upper bound
AUC_{inf} (unit)	Midazolam co-administred with linaprazan glurate, Day 14	Midazolam alone, Day 1	x.xxx	x.xxxx	x.xxx
	Midazolam co-administred with linaprazan glurate, Day 2	Midazolam alone, Day 1	x.xxx	x.xxxx	x.xxx
	Midazolam co-administred with linaprazan glurate, Day 14	Midazolam co-administred with linaprazan glurate, Day 2	x.xxx	x.xxxx	x.xxx
AUC_{0-t} (unit)	Midazolam co-administred with linaprazan glurate, Day 14	Midazolam alone, Day 1	x.xxx	x.xxxx	x.xxx
	Midazolam co-administred with linaprazan glurate, Day 2	Midazolam alone, Day 1	x.xxx	x.xxxx	x.xxx
	Midazolam co-administred with linaprazan glurate, Day 14	Midazolam co-administred with linaprazan glurate, Day 2	x.xxx	x.xxxx	x.xxx
C_{max} (unit)	Midazolam co-administred with linaprazan glurate, Day 14	Midazolam alone, Day 1	x.xxx	x.xxxx	x.xxx
	Midazolam co-administred with linaprazan glurate, Day 2	Midazolam alone, Day 1	x.xxx	x.xxxx	x.xxx
	Midazolam co-administred with linaprazan glurate, Day 14	Midazolam co-administred with linaprazan glurate, Day 2	x.xxx	x.xxxx	x.xxx

Pairwise treatment comparisons are based on a mixed effects model with treatment as a fixed effect and subject as a random effect. Kenward-Rogers approximation for degrees of freedom has been used.
Data based on PK analysis set.
[STUDYID], SAS program: [PROGRAM NAME]. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]. Data extracted at: [TIMESTAMP]

Table PC 1 Plasma concentrations for part I (Pharmacokinetic analysis set)

Assessment (unit)	Assessment timepoint		Total (N=XX)
[PARAMETER 1] (unit)	[Assessment timepoint 1]	n	xx
		Mean (SD)	x.xx (x.xx)
		Median (Min, Max)	x.xx (x.x, x.x)
	[Assessment timepoint 2]	n	xx
		Mean (SD)	x.xx (x.xx)
		Median (Min, Max)	x.xx (x.x, x.x)
		…	…

Data based on [population]. *Dynamic footnote based on table content:* n: Number of observations. SD: Standard deviation. NC: Not calculated - number of evaluable observations less than 3. NA: Not available - no evaluable observations. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table PC 2 Plasma concentrations for part II (Pharmacokinetic analysis set)

Use the same format as for

Table PC 1.

10.2.3 Secondary endpoints

10.2.3.1 Additional PK parameters Part I

Table PP 5 Additional PK parameters for linaprazan glurate and linaprazan for Part I (Pharmacokinetic analysis set)

Assessment (unit)		Linaprazan glurate alone (N=XX)	Linaprazan glurate co-administred with clarithromycin (N=XX)	Linaprazan alone (N=XX)	Linaprazan co-administred with clarithromycin (N=XX)
[T_{max}] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
[$T_{1/2}$] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
[CL/F] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
[V/F] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
[$AUC_{extr\%}$] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)

Data based on [population]. n: Number of observations. SD: Standard deviation. CV%: Coefficient of variation described as percentage. Geo CV%: Geometric coefficient of variation described as percentage calculated using log-transformed standard deviation. NC: Not calculated - number of evaluable observations less than 3. NA: Not available - no evaluable observations. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table PP 6 PK parameters for clarithromycin for Part I (Pharmacokinetic analysis set)

Assessment (unit)		Clarithromycin alone (N=XX)	clarithromycin co-administred with linaprazan glurate (N=XX)
[AUC_{tau}] (unit)	n	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)
[C_{max}] (unit)	n	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)
[T_{max}] (unit)	n	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
[$T_{1/2}$] (unit)	n	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)

Data based on [population]. n: Number of observations. SD: Standard deviation. CV%: Coefficient of variation described as percentage. Geo CV%: Geometric coefficient of variation described as percentage calculated using log-transformed standard deviation. NC: Not calculated - number of evaluable observations less than 3. NA: Not available - no evaluable observations. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

10.2.3.2 Additional PK parameters Part II

Table PP 7 Additional PK parameters for midazolam for Part II (Pharmacokinetic analysis set)

Assessment (unit)		Midazolam alone, Day 1 (N=XX)	Midazolam co-administred with linaprazan glurate, Day 2 (N=XX)	Midazolam co-administred with linaprazan glurate, Day 14 (N=XX)
[T_{max}] (unit)	n	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
[$T_{1/2}$] (unit)	n	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
[CL/F] (unit)	n	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
[V/F] (unit)	n	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
[$AUC_{extr\%}$] (unit)	n	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)

Data based on [population]. n: Number of observations. SD: Standard deviation. CV%: Coefficient of variation described as percentage. Geo CV%: Geometric coefficient of variation described as percentage calculated using log-transformed standard deviation. NC: Not calculated - number of evaluable observations less than 3. NA: Not available - no evaluable observations. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table PP 8 Additional PK parameters for linaprazan glurate and linaprazan for Part II (Pharmacokinetic analysis set)

Assessment (unit)		Linaprazan glurate, Day 2 (N=XX)	linaprazan glurate, Day 14 (N=XX)	Linaprazan, Day 2 (N=XX)	linaprazan, Day 14 (N=XX)
[AUC_{inf}] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)
[AUC_{0-t}] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)
[C_{max}] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)
[$AUC_{extr\%}$] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
	Geometric Mean (geo CV%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)	x.xxx (x.x%)
[CL/F] (unit)	n	xx	xx	NC	NC
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	NC	NC
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	NC	NC
[V/F] (unit)	n	xx	xx	NC	NC
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	NC	NC
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	NC	NC
[R_{acc}] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)

Assessment (unit)		Linaprazan glurate, Day 2 (N=XX)	linaprazan glurate, Day 14 (N=XX)	Linaprazan, Day 2 (N=XX)	linaprazan, Day 14 (N=XX)
[T_{max}] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
[$T_{1/2}$] (unit)	n	xx	xx	xx	xx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)

Data based on [population]. n: Number of observations. SD: Standard deviation. CV%: Coefficient of variation described as percentage. Geo CV%: Geometric coefficient of variation described as percentage calculated using log-transformed standard deviation. NC: Not calculated - number of evaluable observations less than 3. NA: Not available - no evaluable observations. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

10.2.3.3 Adverse events

Table AE 1 Overview of adverse events for Part I (Full analysis set)

	Total (N=XX)		linaprazan glurate (Visit 2 to 4) (N=XX)		clarithromycin (Visit 5) (N=XX)		linaprazan glurate and clarithromycin (Visit 6 to 9) (N=XX)		Follow-up (N=XX)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Any AE	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
Any SAE	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
Any AE leading to withdrawal from study	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
Any AE leading to death	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
Causality	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[Unlikely related]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[Possibly related]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[Probably related]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
Severity	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
Grade 1 - Mild	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
Grade 2 - Moderate	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
Grade 3 - Severe	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
Grade 4 - Life-Threatening	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
Grade 5 - Death	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx

AEs are allocated to respective columns, if the AE starts during the time window indicated by the column headings. Data based on [ANALYSIS SET].
N: number of subjects in treatment group. Percentages are based on N. n, number of subjects. m, number of events. The following AEs are coded with multiple MedDRA terms and are represented as separate AEs in tables and listings: '[AE TERM 1]', '[AE TERM 2]', '[AE TERM 3]. See listings for detailed information. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table AE 2 Overview of adverse events for Part II (Full analysis set)

Use the same format as for Table AE 1. Change the column headings to the relevant victim and perpetrator drugs.

Table AE 3 Adverse events by system organ class and preferred term for Part I (Full analysis set)

	Total (N=XX)		linaprazan glurate (Visit 2 to 4) (N=XX)		clarithromycin (Visit 5) (N=XX)		linaprazan glurate and clarithromycin (Visit 6 to 9) (N=XX)		Follow-up (N=XX)	
System organ class Preferred term	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Total	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**
[SOC 1]	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**
[SOC 1 PT 1]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[SOC 1 PT 2]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[SOC 1 PT …]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[SOC 2]	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**
[SOC 2 PT 1]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[SOC 2 PT 2]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[SOC 2 PT …]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[SOC …]	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**	**xx (xx%)**	**xx**
[SOC … PT 1]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[SOC … PT 2]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx
[SOC … PT …]	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx	xx (xx%)	xx

AEs are allocated to respective columns, if the AE starts during the time window indicated by the column headings. Data based on [ANALYSIS SET]. N, number of subjects. M, number of events. Percentages are based on the number of subjects in the treatment period. The following events are coded with multiple terms and are represented as separate events in tables and listings: '[AE TERM 1], [AE TERM 2]'. See listings for detailed information. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table AE 4 Adverse events by system organ class and preferred term for Part II (Full analysis set)

Use the same format as for Table AE 3. Change the column headings to the relevant victim and perpetrator drugs.

10.2.3.4 Physical examinations

Table PE 1 Physical examinations for Part I (Full analysis set)

Assessment	Assessment timepoint		Total (N=XX)
[PARAMETER 1]	Screening	Normal	x (xx%)
		Abnormal NCS	x (xx%)
		Abnormal CS	x (xx%)
		Not assessed	x (xx%)
	Visit 2	Normal	x (xx%)
		Abnormal NCS	x (xx%)
		Abnormal CS	x (xx%)
		Not assessed	x (xx%)
	End of study	Normal	x (xx%)
		Abnormal NCS	x (xx%)
		Abnormal CS	x (xx%)
		Not assessed	x (xx%)

Data based on [population]. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table PE 2 Physical examinations for Part II (Full analysis set)

Use the same format as for Table PE 1.

10.2.3.5 Vital signs

Table VS 1 Vital signs measurements for Part I (Full analysis set)

Assessment (unit)	Result category	Assessment timepoint		Total (N=XX)
[PARAMETER 1] (unit)	Measured value	[Assessment timepoint 1]	n	xx
			Mean (SD)	x.xx (x.xx)
			Median (Min, Max)	x.xx (x.x, x.x)
		[Assessment timepoint 2]	n	xx
			Mean (SD)	x.xx (x.xx)
			Median (Min, Max)	x.xx (x.x, x.x)
	Absolute change from baseline	[Assessment timepoint 2]	n	xx
			Mean (SD)	x.xx (x.xx)
			Median (Min, Max)	x.xx (x.x, x.x)
	Relative change from baseline (%)	[Assessment timepoint 2]	n	xx
			Mean (SD)	x.xx (x.xx)
			Median (Min, Max)	x.xx (x.x, x.x)

Data based on [population]. *Dynamic footnote based on table content:* n: Number of observations. SD: Standard deviation. NC: Not calculated - number of evaluable observations less than 3. NA: Not available - no evaluable observations. SAS program: [PROGRAM NAME].sas. Run by: [USERNAME] YYYY-MM-DDTHH:MM:SS. Data extracted at: YYYY-MM-DDTHH:MM:SS

Table VS 2 Vital signs measurements for Part II (Full analysis set)

Use the same format as for Table VS 1.

10.2.3.6 12-lead safety ECG

Table EG 1 ECG measurements for Part I (Full analysis set)

Use the same format as for Table VS 1.

Table EG 2 ECG measurements for Part II (Full analysis set)

Use the same format as for Table VS 1.

Table EG 3 ECG interpretations for Part I (Full analysis set)

Use the same format as for Table PE 1.

Table EG 4 ECG interpretations for Part II (Full analysis set)

Use the same format as for Table PE 1.

10.2.3.7 Safety laboratory analyses

Table LB 1 Safety laboratory measurements - clinical chemistry for part I (Full analysis set)

Use the same format as for Table VS 1.

Table LB 2 Safety laboratory measurements - clinical chemistry for part II (Full analysis set)

Use the same format as for Table VS 1.

Table LB 3 Safety laboratory measurements - haematology for part I (Full analysis set)

Use the same format as for Table VS 1.

Table LB 4 Safety laboratory measurements - haematology for part II (Full analysis set)

Use the same format as for Table VS 1.

Table LB 5 Safety laboratory interpretations – urinalysis for part I (Full analysis set)

Use the same format as for Table VS 1.

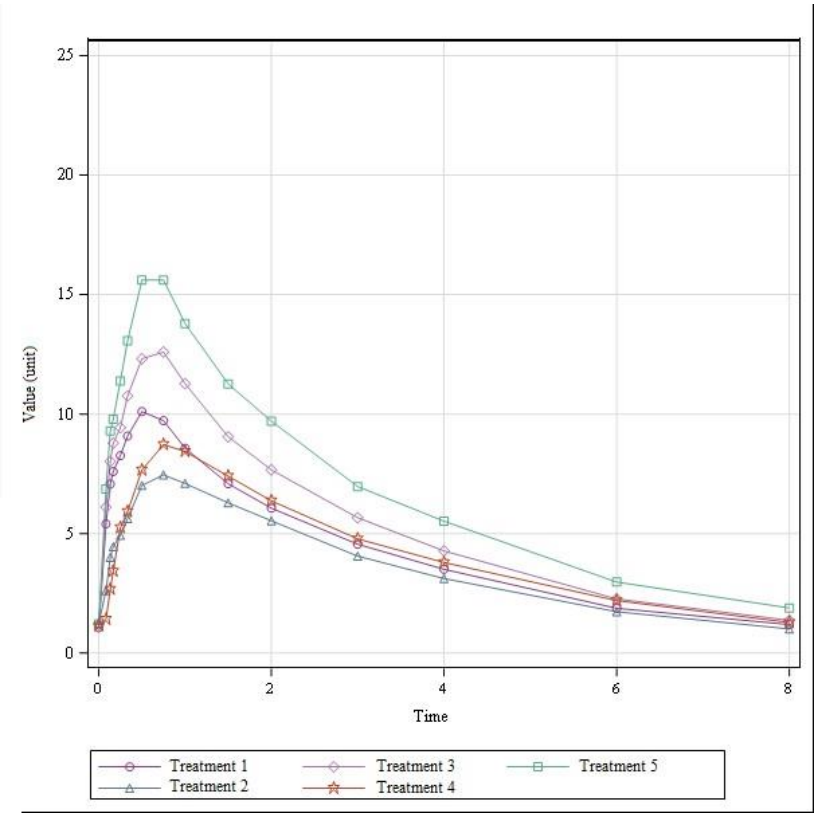
Table LB 6 Safety laboratory interpretations – urinalysis for part II (Full analysis set)

Use the same format as for Table VS 1.

10.3 Study figures

10.3.1 Primary endpoint(s)

Figure PC 1 Geometric mean plasma concentrations over time (lin-log) for Part I (Pharmacokinetic analysis set)



Data based on [ANALYSIS SET].
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: [PROGRAM NAME]. Run by: [USERNAME], [TIMESTAMP]

Plot all PK profiles in the same graph – Victim drug, perpetrator drug and victim drug + perpetrator drug -> 3 series in the same graph, with a legend outlining which data series corresponds to what (combination of) drugs.

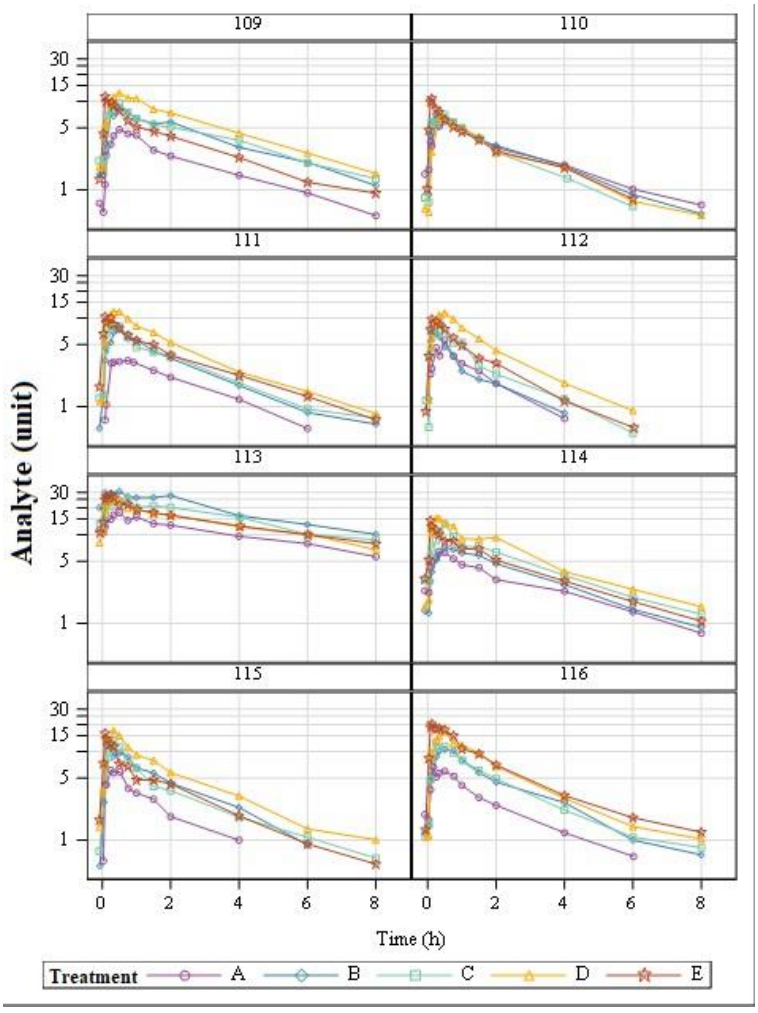
Figure PC 2 Geometric mean plasma concentrations over time (lin-log) for Part II (Pharmacokinetic analysis set)

Use the same format as for Figure PC 1.

Figure PC 3 Geometric mean plasma concentrations over time (lin-lin) for Part I (Pharmacokinetic analysis set)
Use the same format as for Figure PC 1, but plot on linear Y-axis scale.

Figure PC 4 Geometric mean plasma concentrations over time (lin-lin) for Part II (Pharmacokinetic analysis set)
Use the same format as for Figure PC 1, but plot on linear Y-axis scale.

Figure PC 5 Individual plasma concentrations over time (lin-log) for Part I (Full analysis set)



Data based on [ANALYSIS SET].

[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: [PROGRAM NAME]. Run by: [USERNAME], [TIMESTAMP]

Plot all PK profiles in the same graph – Victim drug, perpetrator drug and victim drug + perpetrator drug -> 3 series in the same graph, with a legend outlining which data series corresponds to what (combination of) drugs.

Figure PC 6 Individual plasma concentrations over time (lin-log) for Part II (Full analysis set)

Use the same format as for Figure PC 5.

Figure PC 7 Individual plasma concentrations over time (lin-lin) for Part I (Full analysis set)

Use the same format as for Figure PC 5, but plot on linear Y-axis scale.

Figure PC 8 Individual plasma concentrations over time (lin-lin) for Part II (Full analysis set)

Use the same format as for Figure PC 5, but plot on linear Y-axis scale.

10.4 Study listings

Produce separate listings for Part I and Part II respectively. Update listings titles to reflect which Part is intended.

16.2.1 Discontinued subjects

- **Listing 16.2.1- 1 Discontinued subjects (All subjects)**
- **Listing 16.2.1- 2 Non-eligible subjects (All subjects)**
- **Listing 16.2.1- 3 Disposition (All subjects)**
- **Listing 16.2.1- 4 Subject visits (All subjects)**
- **Listing 16.2.1- 5 Subject elements (All subjects)**

16.2.2 Protocol deviations

- **Listing 16.2.2- 1 Protocol deviations (All subjects)**
- **16.2.3 Subjects excluded from the efficacy analysis**
- **Listing 16.2.3- 1 Subjects excluded from Full analysis set (All subjects)**
- **Listing 16.2.3- 2 Subjects excluded from Pharmacokinetic analysis set (All subjects)**
- **Listing 16.2.3- 3 Population definitions (All subjects)**

16.2.4 Demographic data

- **Listing 16.2.4- 1 Demography (Full analysis set)**
- **Listing 16.2.4- 2 Medical History (Full analysis set)**
- **Listing 16.2.4- 3 Prior and concomitant medications (Full analysis set)**

16.2.5 Compliance and/or Drug Concentration Data

- **Listing 16.2.5- 1 Plasma concentration data (Full analysis set)**
- **Listing 16.2.5- 2 Pharmacokinetic parameters (Full analysis set)**
- **Listing 16.2.5- 3 Treatment compliance (Full analysis set)**

16.2.6 Individual Efficacy Response Data

- **Listing 16.2.6- 1 IMP administration (Full analysis set)**

16.2.7 Adverse event listings (each subject)

- **Listing 16.2.7- 1 Adverse events (Full analysis set)**
- **Listing 16.2.7- 2 Serious adverse events (Full analysis set)**

16.2.8 Listings of individual laboratory measurements by subject

- **Listing 16.2.8- 1 Safety laboratory measurements (Full analysis set)**

Abnormal values and assessment of clinical significance must be included.

- **Listing 16.2.8- 2 Other laboratory measurements (Full analysis set)**

Urine drug screen, alcohol test, pregnancy test

16.2.9 Listings of vital signs, ECG, physical examination data by subject

- **Listing 16.2.9- 1 Vital signs (Full analysis set)**
- **Listing 16.2.9- 2 ECG (Full analysis set)**
- **Listing 16.2.9- 3 Physical examinations (Full analysis set)**