NOVARTIS

Clinical Development

LOU064/Generic name/Trade name®

LOU064A2201

A multicenter, randomized, double-blind, placebo-controlled Phase 2b dose-finding study to investigate the efficacy, safety and tolerability of LOU064 in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines

Statistical Analysis Plan (SAP)

Author:	Trial Statistician, [redacted]

Document type:	SAP Documentation
Document status:	Amendment v3.0
Release date:	17-May-2021
Number of pages:	39

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
27-May-2019	Prior to FPFV	Creation of final version	First version	NA
24-Jul-2020	[redacted]	Protocol amendment v2.0; Address the comments from dry-run review; Update the analysis visit window for eDairy assessment; [redacted]	SAP amendment Final v2.0	Section 2.1.1.3 Update the assessment window for eDiary assessment (i.e. UAS7, AAS); [redacted] Define rule for derive the AAS7= 0 response; Section 2.7.1.1 drop table to define adverse event of special interest; Section 2.7.3 update the CTCAE grade to v5.0; include local lab due to covid-19; Section 2.7.4.1 include local ECG due to covid-19; [redacted]
17-May-2021	Prior to final DBL	Update the offset in negative binomial analysis of number of weeks with AAS7=0 response Update the treatment emergent adverse	SAP amendment final v3.0	[redacted] Section 2.7.1 update the treatment emergent adverse event definition as "Treatment-emergent events are defined as any events started on or after the first dose of study treatment day or any events

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		events definition		presented prior to the first dose of study treatment day but increased in severity based on preferred term and before end of the study."
		Update the censor rule for time to event analysis		Section 5.4.2 is [redacted]
		Update the PD code in rule of exclusion critieria of analysis set		Section 5.5 Table 5-1 is updated with latest protocol deviation code for inform consent not signed or missing as "P-INCL01B-ICF not signed".

Table of contents

List of abbreviations

AAS	Angioedema Activity Score
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC_{last}	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUC_{tau}	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
b.i.d.	bis in diem/twice a day
BP	Blood Pressure
C_{max}	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
CSR	Clinical Study report
CSU	Chronic Spontaneous Urticaria
CV	Coefficient of Variation
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRS	Electronic Case Retrieval Strategy
ED_{50}	Dose at which 50% of Emax is achieved
E_{max}	Maximum Change in Effect over Placebo
EOT	End of treatment period
EOS	End of study period
E_0	Expected Placebo Effect
FAS	Full Analysis Set
GCP	Good Clinical Practice
HSS7	Weekly Hives Severity Score
Ig	Immunoglobulin
INR	International Normalized Ratio
IRT	Interactive Response Technology
ISS7	Weekly Itch Severity Score
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MAR	Missing at Random
[redacted]	[redacted]
MedDRA	Medical Dictionary for Drug Regulatory Affairs
[redacted]	[redacted]
PD	Pharmacodynamics
PK	Pharmacokinetics

q.d.	Qua'que di'e / once a day
QTcF	QT interval corrected by Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBL	Total bilirubin
T_{max}	The time to reach the maximum concentration after drug administration [time]
ULN	Upper Limit of Normal
ULOQ	Upper Limit Of Quantification
UPDD	Urticaria Patient Daily Diary

1 Introduction

Data will be analyzed by Novartis according to the data analysis section 12 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

This document covers statistical and analytical plans for the [redacted] analysis of all data collected up to end of the study for CLOU064A2201 study with reference to the study protocol.

[redacted]

1.1 Study design

This is a global Phase 2b multicenter, randomized, double-blind, parallel-group, placebo-controlled study investigating the efficacy, safety and tolerability of six dosing groups of oral LOU064 in subjects with inadequately controlled CSU despite treatment with (second generation) H1-antihistamine treatment.

Throughout the study (i. e. Day -14 until Day 113), subjects must be on a stable treatment regimen with a second generation H1-antihistamine at a locally approved posology ("background medication").

The study will consist of three periods: screening (up to 2 weeks), treatment period (12 weeks), and follow-up period (4 weeks).

Approximately 308 patients will be randomized in a 1:1:1:1:1:1:1 ratio stratified by prior exposure to anti-IgE biologics (including omalizumab and ligelizumab) and by geographical region at randomization visit to the following treatment arms:

- **LOU064 10mg q.d.:** 10 mg LOU064 once daily
- **LOU064 35mg q.d.:** 35 mg LOU064 once daily
- **LOU064 100mg q.d.:**100 mg LOU064 once daily
- **LOU064 10mg b.i.d.:** 10 mg LOU064 twice a day
- **LOU064 25mg b.i.d.:** 25 mg LOU064 twice a day
- **LOU064 100mg b.i.d.:** 100 mg LOU064 twice a day
- **Placebo**

The following study periods will be considered for analysis:

- **Screening period** (Screening to Randomization)
- **Treatment period** (Randomization to scheduled Week 12 visit including follow-up visits for patients prematurely discontinued)
- **Entire study period** (Randomization to scheduled Week 16 visit including follow-up visits for all patients)

Randomization will be stratified by prior exposure to anti-IgE biologics (including omalizumab and ligelizumab) and by geographical region (Japan, US, LaCan, and RE).). [redacted]

1.2 Study objectives and endpoints

The purpose of this study is to evaluate the efficacy and safety of LOU064 in subjects suffering from CSU inadequately controlled by H1-antihistamines and to select a LOU064 dosing regimen for the subsequent Phase 3 program.

Key efficacy evaluation criteria are the reduction of signs (hives) and symptoms (itch) of CSU measured with the 7-day version of the Urticaria Activity Score (UAS7) and the improvement of health-related quality of life as measured by the Dermatology Life Quality Index (DLQI).

Table 1-1 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To characterize the dose-response relationship of LOU064 administered once or twice daily in subjects with CSU with respect to change from baseline in UAS7 at Week 4	• Change from baseline in UAS7 at Week 4
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline in UAS7 at Week 12	• Change from baseline in UAS7 at Week 12
• To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline in UAS7 over time	• Change from baseline in UAS7 over time
• To evaluate the efficacy of LOU064 compared to placebo with respect to achievement of complete clinical response (UAS7= 0) over time	• Complete absence of hives and itch, assessed as UAS7= 0 response over time
• To evaluate the efficacy of LOU064 compared to placebo with respect to achievement of disease control (UAS7≤ 6) over time	• UAS7≤ 6 response over time
• To evaluate the effect of LOU064 on angioedema (AAS7) with respect to the number of weeks with an AAS7= 0	• Cumulative number of weeks with an AAS7= 0 response between baseline and Week 12

response from baseline through Week 12 • To evaluate the effect of LOU064 on disease-related quality of life with respect to achievement of a DLQI score of 0 or 1 at Week 4 and Week 12	• DLQI score of 0 or 1 at Week 4 and 12
• To evaluate the effect of LOU064 on CSU-related quality of life with respect to change from baseline in DLQI at Week 4 and Week 12	• Change from baseline in DLQI score at Week 4 and 12
• To evaluate the pharmacokinetics of LOU064 resulting from oral dosing at Week 4 and Week 12	• Concentrations of LOU064 in blood and calculation of respective PK parameters
• To evaluate safety and tolerability of LOU064 in subjects with CSU	• Safety endpoints will include but not be limited to: o Occurrence of treatment emergent adverse events during the study o Occurrence of treatment emergent serious adverse events during the study

[redacted]

2 Statistical methods

Novartis will be performing [redacted] the final analysis. Statistical software R version 3.3.3 and SAS version 9.4 or later will be used.

2.1 Data analysis general information

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum.

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

The p-values will be presented as one-sided with level of significance 5%. 90% confidence intervals will be displayed but not be used for decision making; they will only be used for estimation and will therefore always be two-sided.

2.1.1 General definitions

2.1.1.1 Study treatment

The following treatment groups will be presented:

- LOU064 10 mg q.d.
- LOU064 35 mg q.d.
- LOU064 100 mg q.d.
- LOU064 10 mg b.i.d.
- LOU064 25 mg b.i.d.
- LOU064 100 mg b.i.d.
- Any LOU064
- Placebo

2.1.1.2 Study Day 1 and Study Day

For safety analysis, the day of first dose of study treatment is defined as *Study Day 1* or *Day 1*.

For efficacy analysis, the day of randomization is defined as *Study Day 1* or *Day 1*.

All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date is calculated as [Date of event] – [Date of first dose/Randomization] + 1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For the dates before Day 1, study day for an event date is calculated as [Date of event] – [Date of first dose/Randomization], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1). The descriptor "Day 0" will not be used.

2.1.1.3 Assessment window

2.1.1.3.1 Assessment window for eDiary data

For completers, the study weeks for assessment completed on eDiary are defined based on the study days starting with Day 1 (Randomization Day). The study day for the eDiary date will be calculated as [Date of Diary] – [Date of Randomization] + 1 for post-baseline assessment and [Date of Diary] – [Date of Randomization] for baseline assessment. The analysis Week 1 through Week 11 of the treatment period will be derived based on scheduled visit day as defined in Table 2-1. The analysis Week 12 score will be derived as Day -7 to Day -1 of actual Week 12 study visit day.

During the follow-up period, the study weeks for assessment completed on eDiary are defined based on the study days starting with Day 1 of follow-up period (actual Week 12 visit day). The study day for the eDiary date will be calculated as [Date of Diary] – [Date of Week 12 visit day] + 1. The analysis follow-up Week 1 to Week 4 will be derived based on the actual Week 12 study visit day as defined in Table 2-1.

Table 2-1 Assessment window for eDiary (for completers)

Analysis visit	Scheduled Visit Day	eDiary Assessment Window
Baseline	1	Day -7 to Day -1
Week 1	-	Day 1 to Day 7
Week 2	15	Day 8 to Day 14
Week 3	-	Day 15 to Day 21
Week 4	29	Day 22 to Day 28
Week 5	-	Day 29 to Day 35
Week 6	-	Day 36 to Day 42
Week 7	-	Day 43 to Day 49
Week 8	57	Day 50 to Day 56

Week 9	-	Day 57 to Day 63
Week 10	-	Day 64 to Day 70
Week 11	-	Day 71 to Day 77
Week 12	85	Day -7 to Day -1 of Week 12 study visit
Follow-up Week 1	-	Day 1 to Day 7 of follow-up period
Follow-up Week 2	-	Day 8 to Day 14 of follow-up period
Follow-up Week 3	-	Day 15 to Day 21 of follow-up period
Follow-up Week 4	113	Day 22 to Day 28 of follow-up period

The baseline week is comprised of the 7 days prior to Day 1 (Day -7 to Day -1).

For early discontinued patients, it is suggested to collect the eDiary data even after the patient discontinued from treatment per "Treatment policy strategy" (this part of data is named as "retrieved drop-out data". The retrieved drop-out data will be included in the weekly score derivation.

The study weeks for assessment completed on eDiary are defined based on the study days starting with Day 1 (Randomization Day). The study day for the eDiary date will be calculated as [Date of Diary] – [Date of Randomization] + 1 for post-baseline assessment and [Date of Diary] – [Date of Randomization] for baseline assessment.

Table 2-2 Assessment window for eDiary (for early discontinued patients)

Analysis visit	**Scheduled Visit Day**	**eDiary Assessment Window**
Baseline	1	Day -7 to Day -1
Treatment Week 1	-	Day 1 to Day 7
Treatment Week 2	15	Day 8 to Day 14
Treatment Week 3	-	Day 15 to Day 21
Treatment Week 4	29	Day 22 to Day 28
Treatment Week 5	-	Day 29 to Day 35
Treatment Week 6	-	Day 36 to Day 42
Treatment Week 7	-	Day 43 to Day 49
Treatment Week 8	57	Day 50 to Day 56
Treatment Week 9	-	Day 57 to Day 63
Treatment Week 10	-	Day 64 to Day 70
Treatment Week 11	-	Day 71 to Day 77
Treatment Week 12	85	Day 78 to Day 84

2.1.1.4 Baseline

Baseline for safety is the last assessment (including unscheduled visits) obtained on or before the day of the first dose of study treatment. All assessments obtained after the first dose of study treatment are considered as post-baseline unless otherwise specified.

Baseline for efficacy is comprised of the 7 days prior to Day 1 (Randomization Day) for UAS7 and other assessment on or prior randomization day.

2.1.1.5 On-treatment

All safety events happened after first dose of study treatment will be considered on-treatment no matter if during treatment period or follow-up period.

2.2 Analysis sets

The following analysis sets will be used for the data analysis, details refer to section 5.5.

The **Randomized Set** will consist of all randomized subjects, regardless of whether or not they actually received study medication. Subjects will be analyzed according to the treatment assigned to at randomization.

The **Full Analysis Set (FAS)** will consist of all randomized subjects. Following the intent-to-treat principle, subjects will be analyzed according to the treatment and strata assigned to at randomization. Mis-randomized subjects (mis-randomized in IRT) will be excluded.

Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject.

The **Safety Set** will consist of all subjects who received at least one dose of study medication whether or not being randomized. Subjects will be analyzed according to treatment received.

If a subject has received the wrong treatment during more than 50% of the time of the entire treatment period, the treatment received will be set to this wrong treatment; otherwise it will be set to the original assigned treatment. Except for patients assigned to placebo arm, they will be summarized under LOU064 in case they took LOU064 during the treatment period independent of the time on LOU064.

2.2.1 Subgroup of interest

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of screened and screen failure subjects will be shown for all subjects (total). The reason for screen failure will be summarized.

The number of subjects in each analysis set will be presented for each treatment group and all subjects (total). The reason for excludedexcluding from any analysis set will be listed.

The number and percentage of complete Week 4 visits, Week 12 (EOT) visits, Week 16 (EOS) visits or early discontinued from treatment/study will be presented by treatment groups and all patients (total) based on Randomized Set.

The number and percentage of patients who have experienced protocol deviations (PD) will be tabulated by deviation category, treatment groups and all patients (total). The summary of overall important PDs (including COVID-19 related PDs), important PDs excluding COVID-19 related PDs, and COVID-19 related PDs will be provided.

2.3.2 Demographic and baseline characteristics

Demographics and baseline characteristics will be summarized using the randomized set. including disease characteristics, prior and background medications to treat urticaria, and relevant medical histories.

Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment group and all patients (total).

Continuous variables:

- Age (years)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2
- Baseline UAS7 score
- Baseline AAS7 score
- Baseline DLQI score
- Time since diagnosis of urticaria = (inform consent date – diagnosis date + 1)/365.25

The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all patients (total).

Categorical variables:

- Age categories (< 65, >= 65-<85years , >=85 years)
- Gender

- Race
- Ethnicity
- BMI groups (< 25, 25 -<30, >= 30 kg/$m^2$$m^2$)
- Baseline UAS7 (Mild disease: UAS7 6-<16; Moderate disease: UAS7 16-<28; Severe disease UAS7 28-42)
- Baseline AAS7 = 0 response (Yes, No)
- Previous exposure to anti-IgE therapy (Yes, No)
- Geographic region (Japan, US, LaCAN, RE)
- Previous experience of Angioedema (Yes, No)
- Baseline CU-index (Positive, Negative)
- Baseline total IgE level (High, Low) (the median value of all patients at each analysis will be used as threshold)

2.3.3 Medical history

Any significant prior or current medical condition at the time of signing informed consent will be coded using the MedDRA dictionary.

Non-urticaria related medical conditions will be summarized by primary system organ class and preferred term.

The urticaria related medical history will be summarized separately.

Cardiovascular history and family malignancy history will be listed if needed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The analysis of study treatment data will be based on the safety set.

2.4.1 Study treatment / compliance

The duration of exposure to study treatment and duration of study will be summarized by treatment group. In addition, the number of subjects with exposure of at least certain thresholds (eg, any exposure, ≥1 week, ≥2 weeks, ≥4 weeks, ≥8 weeks, etc.) will be displayed.

Duration of exposure is defined as last dose of study treatment – first dose of study treatment + 1.

Duration of study is defined as last study visit – first dose of study treatment + 1.

The start date and end date of study treatment will be collected on eCRF and will be used to calculate the duration of exposure. In addition, the study treatment taken on each day (morning/evening) will be also be entered in the eDiary and will be listed.

2.4.2 Prior, concomitant and post therapies

Prior urticaria related medication will be summarized by type of therapy and preferred term.

Prior non-urticaria related medication will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term for each treatment group.

Background medications will be summarized by Anatomical Therapeutic Chemical (ATC) code, preferred term and dose per administrationfor each treatment group.

Rescue medications will be summarized by Anatomical Therapeutic Chemical (ATC) code, preferred term and dose per administration for each treatment group.

Concomitant medications other than background or rescue medications will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term for each treatment group.

Prior and concomitant significant surgeries and medical procedures will be summarized by primary system organ class and MedDRA preferred term for each treatment group.

Prior medications are defined as treatment taken and stopped prior to first dose of study treatment; Concomitant medications are defined as any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit.

Medications will be identified using the Novartis Drug and Therapy Dictionary (NovDTD) including the Anatomical Therapeutic Chemical (ATC) code. Medications will be presented in alphabetical order, by ATC code.

2.5 Analysis of the primary objective

All analyses for efficacy data will be based on the FAS.

The primary objective of this study is to determine a dose response signal and characterize the dose-response relationship in either LOU064 q.d. and b.i.d. doses (10 mg, 35 mg, 100 mg q.d. and 10 mg, 25 mg, 100 mg b.i.d.) compared to placebo with respect to the change from baseline in UAS7 at Week 4, and to select an appropriate dose(s) to use in Phase 3 studies.

[redacted]

2.5.1 Primary endpoint

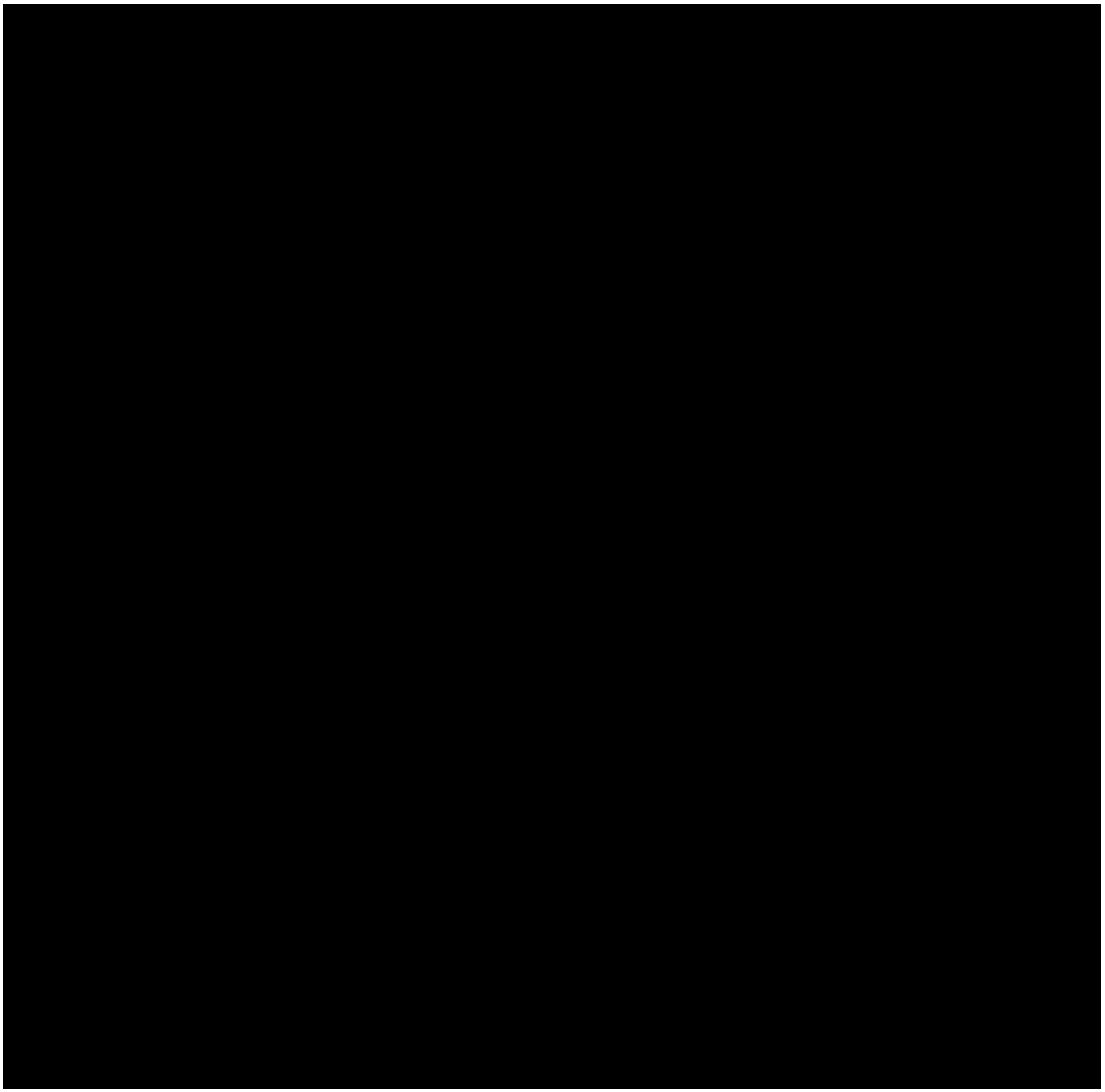
The primary variable for the study is the change from baseline in UAS7 at Week 4. The UAS7 is the sum of the average daily UAS over 7 days (range from 0 to 42). Note that the weekly score is derived according to the analysis week defined in Table 2-1 and Table 2-2.

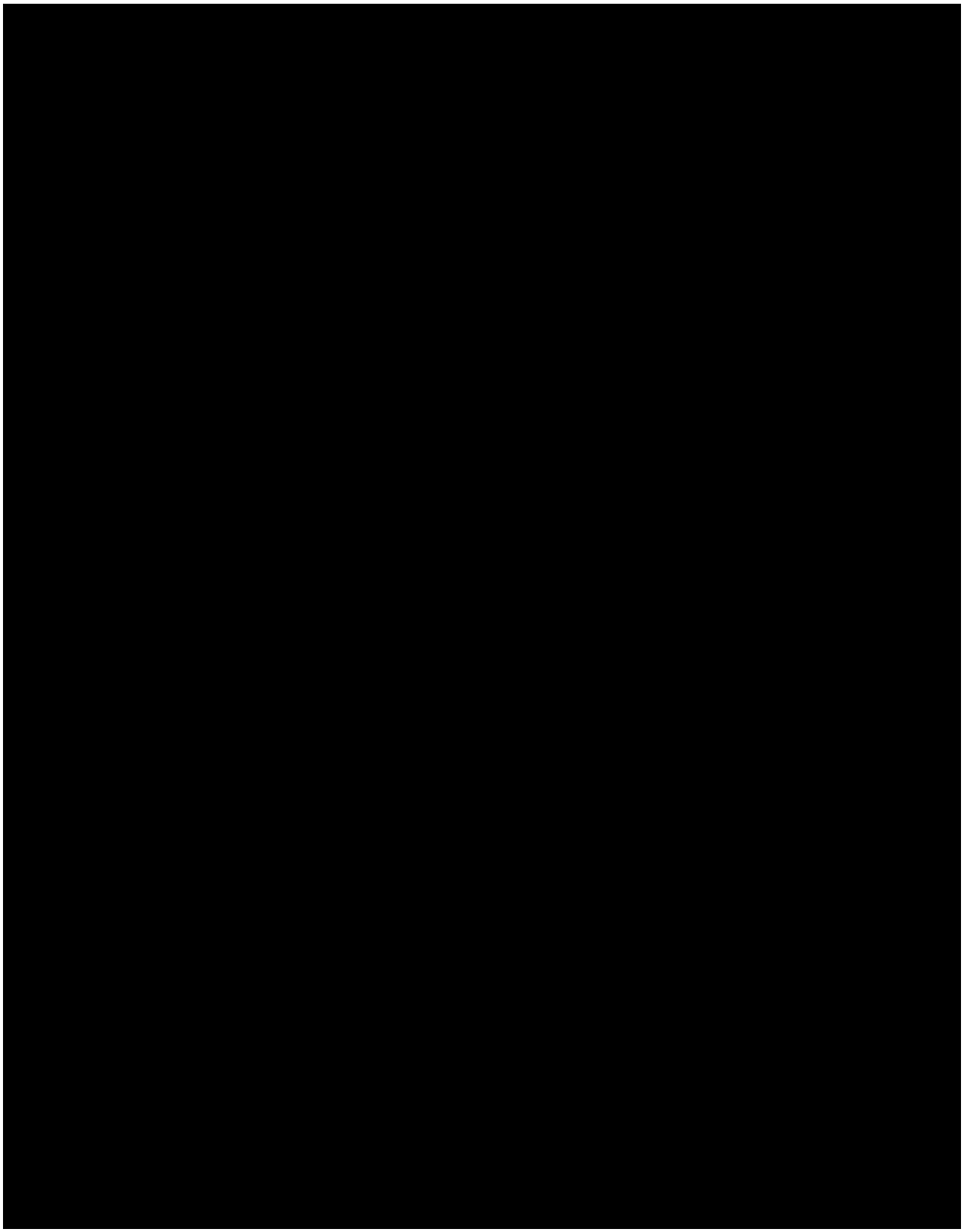
If one of the morning or evening score for HSS and ISS is missing, then the non-missing score for that day (morning or evening) will be used as the daily score. If one or more of the daily scores are missing, then the following principles will be applied to handle the missing data:

- The weekly Urticaria Activity Score is the sum of both the HSS7 score and the ISS7 score and will be missing if at least one of them is missing.

- If a patient has at least 4 non-missing daily scores within the 7 days, then the weekly score for HSS or ISS will be calculated as the sum of the available eDiary scores of that week, divided by the number of non-missing days multiplied by 7.
- If there are less than 4 non-missing daily scores within the 7 days, then the weekly score for HSS or ISS will be missing for that week. Accordingly, no UAS7 can be calculated.

2.5.2 Statistical hypothesis, model, and method of analysis





2.5.3 Handling of missing values/censoring/discontinuations

Subjects who discontinue from study treatment early will be encouraged to stay in the study and complete all the scheduled measurements. All the available data collected will be used for the primary analysis no matter if they took rescue medication or prohibited medication (Treatment policy).

[redacted]

2.5.4 Supportive analyses

Considering the primary efficacy endpoint is UAS7 score at week 4, the missing data rate is expected to be approximately 5%. So no supportive analyses is planned for the primary efficacy analysis.

2.6 Analysis of the Secondary objective

All analyses for secondary efficacy data will be based on the FAS.

Summary tables will be presented by treatment group and visit (as applicable) using descriptive statistics, which include absolute and relative frequencies for categorical variables and arithmetic mean, standard deviation, minimum, maximum, median and first and third quartile for continuous variables.

2.6.1 Secondary endpoint

UAS7 over time

Mean estimation and standard error for absolute value, change, and percent change from baseline in UAS7 score will be presented by treatment group and visit for entire study period [redacted]

Summary statistics of the absolute value, change, and percent change from baseline in UAS7 will be presented by treatment group and visit for entire study period.

[redacted]

Summary statistics of the absolute value, change, and percent change from baseline in HSS7 will be presented by treatment group and visit for entire study period.

Summary statistics of the absolute value, change, and percent change from baseline in ISS7 will be presented by treatment group and visit for entire study period.

Complete clinical response (UAS7 = 0)

The complete clinical response, i.e. absence of hives and itch, is defined as subjects achieving UAS7= 0.

The number of subjects with UAS7= 0 will be summarized by treatment group and visit for entire study period.

[redacted]

Controlled disease (UAS7≤ 6)

The number of subjects with UAS7≤ 6 will be summarized by treatment group and visit for entire study period.

[redacted]

Absence of angioedema (AAS7= 0)

The cumulative number of weeks with an AAS7= 0 response between baseline and Week 12 will be summarized by treatment group.

[redacted]

Summary statistics on AAS7 weekly score will be presented by visit and treatment group.

DLQI

Seven scores will be derived from the DLQI: the score of each of the six dimensions as well as the total score of the DLQI will be calculated based on the developers' rules.

For the DLQI subscale and total score derivation, if there is only one missing score per visit, then it will be imputed to 0 and then the subscale including this item and the total score will be calculated accordingly. If there are two or more missing scores per visit, then the score will be missing.

Summary statistics will be calculated for the absolute values as well as for the change and percentage change for DLQI total score broken down by visit and treatment group.

Summary tables of the number of subjects with DLQI score of 0 or 1 will be presented by treatment group and visit for entire study period.

2.6.2 Statistical hypothesis, model, and method of analysis

For the secondary analysis of UAS7, complete clinical response, controlled disease and AAS7= 0, pairwise comparisons of each LOU064 doses to Placebo will be performed. No adjustment for multiple comparisons will be done due to the exploratory nature of this study.

2.6.3 Handling of missing values/censoring/discontinuations

Missing values for binary response like UAS7 = 0 response, UAS7 <=6 response and DLQI 0/1 of secondary analyses will be imputed by non-responder imputation method regardless of the reason for missingness.

[redacted]

2.7 Safety analyses

All safety endpoints (i.e. AEs, laboratory data, vital signs, and ECG as well as potential risks defined in the safety profiling plan) will be summarized by actual treatment group using the safety set.

All data will be included in the analysis regardless of rescue medication use.

2.7.1 Adverse events (AEs)

All information obtained on adverse events will be displayed by treatment group and any LOU064 dose.

Treatment-emergent events are defined as any events started on or after the first dose of study treatment day or any events presented prior to the first dose of study treatment day but increased in severity based on preferred term and before end of the study.

The number (and percentage) of subjects with treatment- emergent AEs will be summarized in the following ways:

- by primary system organ class and preferred term
- by primary system organ class, preferred term and maximum severity
- by Standardized MedDRA Query (SMQ) and preferred term

Summaries will also be presented for AEs by severity and for study treatment related AEs.

Separate summaries will be provided for deaths, SAEs, and other significant AEs such as AEs leading to discontinuation and AEs leading to treatment interruption.

If a subject reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a subject reported more than one AE within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

All AEs and SAEs including the non-treatment emergent AEs will be listed.

2.7.1.1 Adverse events of special interest / grouping of AEs

Crude incidence rate for adverse events of special interest will be provided. The latest project eCRS will be used for reporting.

2.7.2 Deaths

All deaths will be listed and reason for death will be summarized by SOC and PT.

2.7.3 Laboratory data

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry).

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group and any LOU064 dose. Change from baseline will only be summarized for subjects with both baseline and post baseline values.

For each parameter, the maximum change from baseline (maximum decrease and maximum increase) will be analyzed analogously.

Laboratory data will be listed and values outside the normal ranges will be flagged by treatment group, subject, and visit/time for patients who have experienced any abnormalities.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the most extreme laboratory test value within a treatment period. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value is normal, low, or high (including category "high and low"). These summaries will be presented by laboratory test and treatment group.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Event (CTCAE) grades (version 5.0), given in Table 2-3: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP).

CTCAE grades based on lab results alone will be applied programmatically, Clinical assessments (in *italic* below) will not be considered. In case of missing baseline laboratory assessment, it will be assumed as normal.

The number and percentage of subjects with CTCAE grade newly occurring or worsening after baseline will be presented. Shift tables will be provided on CTCAE grades. These summaries will be split into hematology and chemistry.

Table 2-2 CTCAE grades for laboratory parameters to be analyzed

CTCAE term	Laboratory assessment	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin (Hgb)	<LLN-10.0 g/dL;	<10.0- 8.0 g/dL;	<8.0 g/dL;	Life-threatening consequences;
Platelet count decreased	Platelet	<LLN-75,000/mm;	<75,000-50,000/mm3;	<50,000-25,000/mm3;	<25,000/mm3;
White blood cell decreased	White blood cell	<LLN-3000/mm3;	<3000-2000/mm3;	<2000-1000/mm3;	<1000/mm3;
Neutrophil count decreased	Neutrophils	<LLN-1500/mm3;	<1500-1000/mm3;	<1000-500/mm3;	<500/mm3;
Lymphocyte count decreased	lymphocytes	<LLN-800/mm3;	<800-500/mm3;	<500-200/mm3;	<200/mm3;
INR increased	INR	>1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation ; monitoring only indicated*	>1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation ; dose adjustment indicated*	>2.5; *>2.5 x baseline if on anticoagulation ; bleeding*	-
Creatinine increased	Serum creatinine	>1-1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Blood urea Nitrogen (BUN) increased	Urea	>1- 1.5xULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0xULN
Blood bilirubin increased	Total bilirubin (TBL)	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
GGT increased	Gamma-glutamyl transferase (GGT)	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if	>20.0 x ULN if baseline was normal; >20.0 x baseline if

			baseline was abnormal	baseline was abnormal	baseline was abnormal
Alanine aminotransferase increased	Alanine aminotransferase (ALT)	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase increased	Aspartate aminotransferase (AST)	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	Alkaline phosphatase (ALP)	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

ULN: Upper limit of normal range; LLN: Lower limit of normal range.

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively.

Local lab result due to covid-19 situation will only be listed but not include in the summary table.

[redacted]

Abnormalities in urinalysis result will be summarized by visit separately and listed.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

Summary statistics will be provided for ECG parameters by treatment group and any LOU064 dose, and visit/timepoint (pre-dose or 1 hr post-dose). Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized.

Triplicates measurements on ECG are scheduled for some visits. For numeric measurements, the mean of the scheduled measurements will be used. For ECG overall interpretation, most common interpretation (normal/abnormal) of the three assessments taken will be used.

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each subject during the study. Frequency tables will be produced for the number and percentage of subjects with notable QT and QTcF intervals and with noteworthy PR, QRS and Heart Rate interval or changes from baseline.

For ECGs, a notable QT and QTcF interval value is defined as:

- QT > 500 msec;
- QTc (Fridericia's) interval > 450 msec (males), QTc (Fridericia's) interval > 460 msec (females);
- QTc (Fridericia's) interval change from baseline > 30 msec, >60 msec;
- PR > 250 msec.

All ECG data will be listed by treatment group, subject and visit/time for patients experienced and ECG abnormalities.

Local ECG data will be included in the summary in case central reading was applied.

[redacted]

[redacted]

2.7.4.2 Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign, treatment group and visit/time. Change from baseline will only be summarized for subjects with both baseline and post-baseline values. Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized.

Clinical notable vital sign values:

- Sitting pulse rate
  - < 50 bpm and 25% decrease from baseline
  - > 100 bpm and 25% increase from baseline
- systolic blood pressure
  - < 90
  - ≥ 140 mmHg
- diastolic blood pressure
  - < 60
  - ≥ 90 mmHg

All vital signs data will be listed by treatment group, subject, and visit/time for patients who ever experience any vital sign abnormalities.

2.7.4.3 Liver events

To evaluate potential drug-induced liver injury, newly occurring liver enzyme abnormalities will also be summarized based on the event criteria given below. For potential Hy's Law case, all the elevations must occur at the same post-baseline timepoint. A case will be considered as newly occurring if a criterion is not met or missing at baseline but is met thereafter.

Table 2-3 Liver enzyme abnormalities

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
(ALT or AST) & TBL	>3xULN & (TBL>1.5xULN; >2xULN)
(ALT or AST) & INR	>3xULN & INR>1.5
TBL	>1xULN; >1.5xULN; >2xULN;
ALP	>1.5xULN; >2xULN; >5xULN
ALP & TBL	>3xULN; >5xULN & TBL>2xULN
(ALT or AST) & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law**)

2.8 Pharmacokinetic endpoints

Summary statistics for PK analysis will include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV) (arithmetic and geometric), median, minimum and maximum.

Concentrations below LLOQ will be treated as zero in summary statistics for PK concentration and for PK parameter calculations.

Descriptive summary statistics will be provided for PK concentration by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ.

LOU064 blood concentration data will be listed by treatment, subject, and visit/sampling time point.

Descriptive summary statistics will be provided for PK parameters listed in Table 2-3 by treatment. An exception to this is T_{max} where median, minimum and maximum will be presented.

PK parameters will be listed by treatment and subject.

Table 2-4 pharmacokinetic parameters

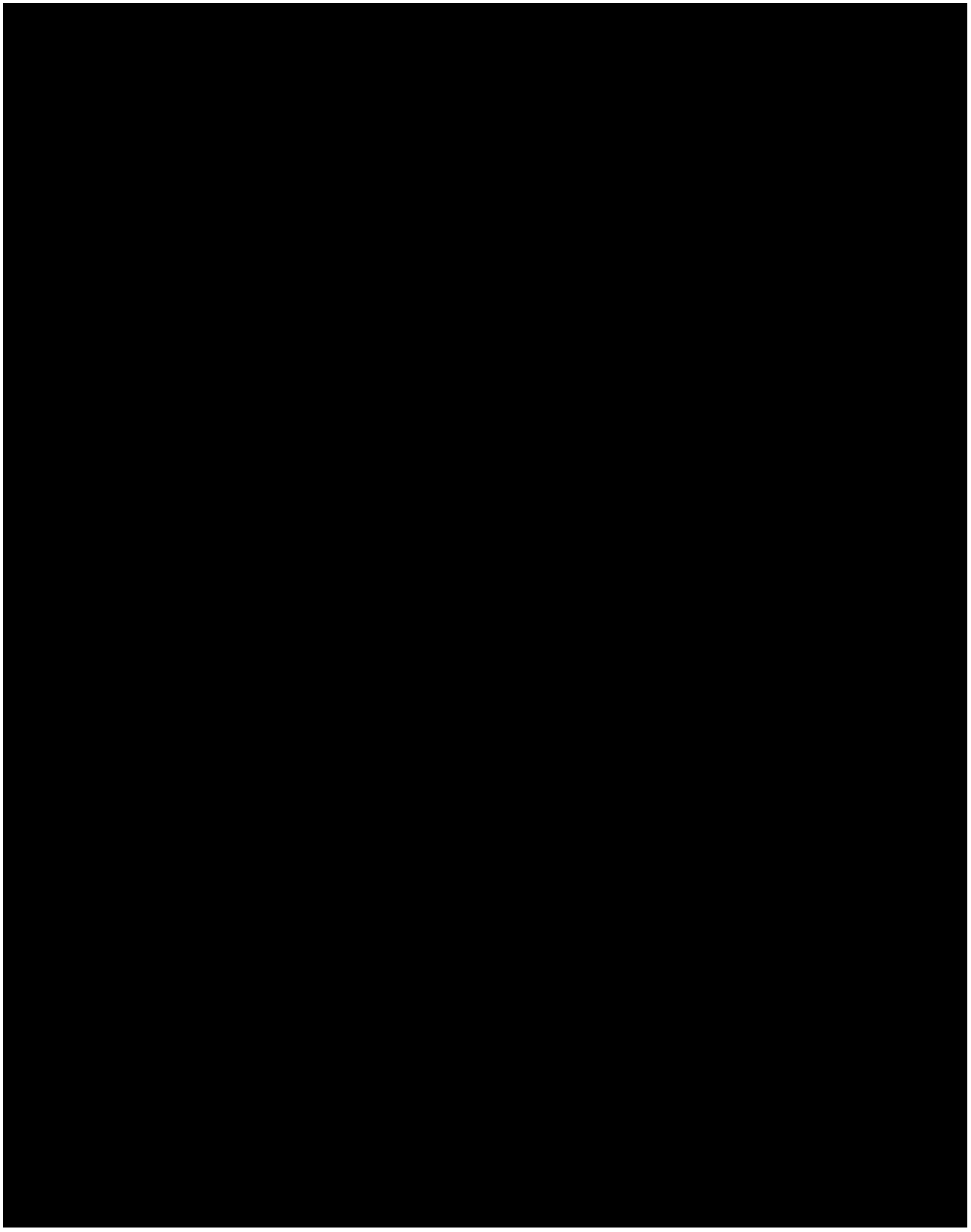
AUC_{last}	The AUC from time zero to the last measurable concentration sampling time (t_{last}) (ng x h/mL)
AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady-state (ng x h/mL)
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (ng/mL)
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (h)

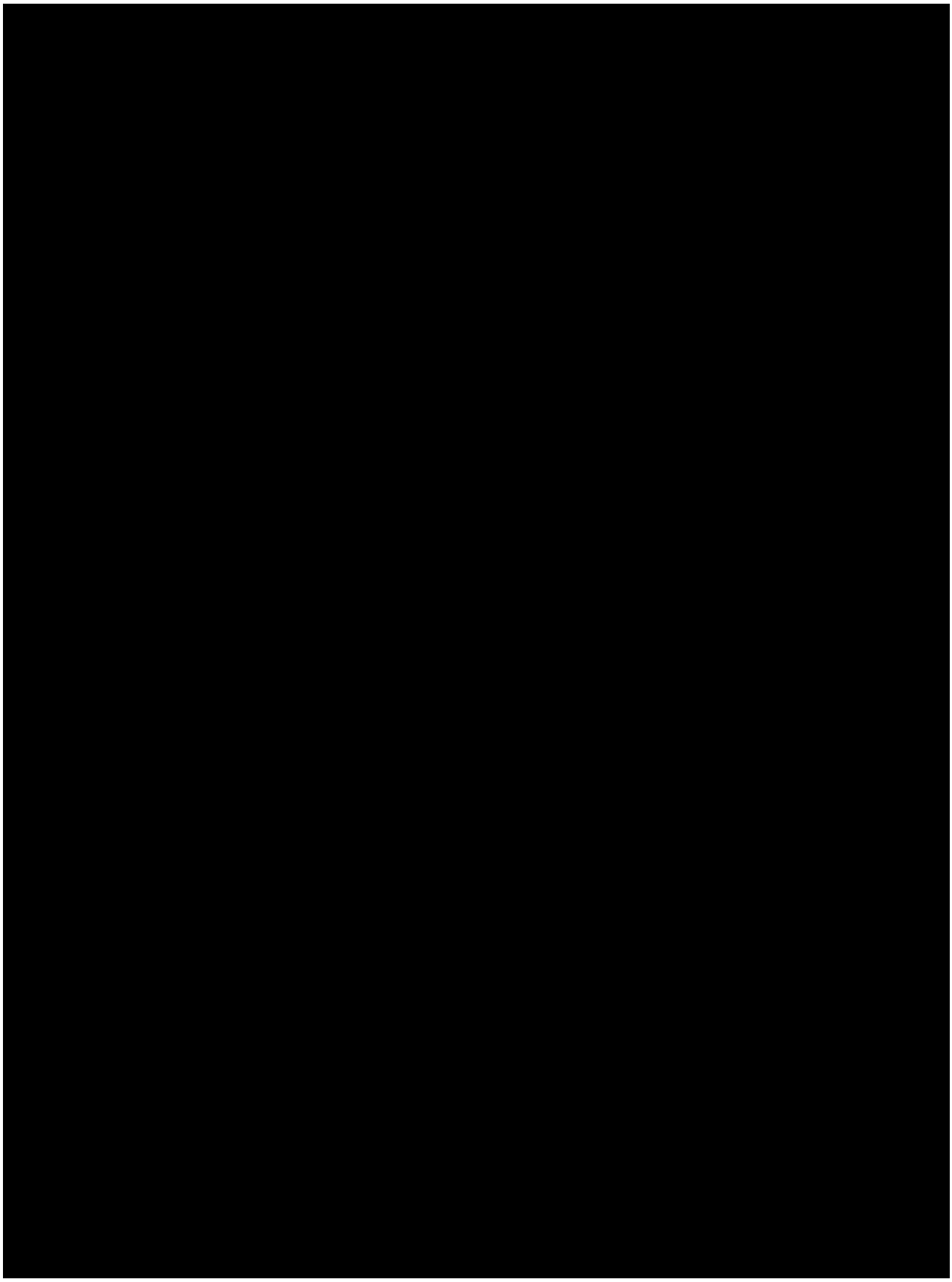
Other PK parameters will be provided if feasible.

[redacted]

2.10 Patient-reported outcomes

Please refer to section 2.6.1 for DLQI analysis.





[redacted]

3 Sample size calculation

The sample size calculation is based on the primary endpoint.

The primary objective of this study is to characterize the dose-response relationship among LOU064 q.d. and b.i.d doses (10 mg, 35 mg 100 mg q.d and 10 mg, 25 mg and 100 mg b.i.d) and placebo with respect to change from baseline in UAS7 at Week 4. The sample size was determined with the software R, version 3.0.3.

[redacted]

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Partial dose date is not allowed in data collection.

5.1.2 AE date imputation

Impute AE end date:

1. If the AE end date 'month' is missing, the imputed end date should be set to the earliest of the (last visit date, 31DECYYYY, date of death).

2. If the AE end date 'day' is missing, the imputed end date should be set to the earliest of the (last visit date, last day of the month, date of death).

3. If AE 'year' is missing or AE is ongoing, the end date will not be imputed.

Impute AE start date:

Before imputing AE start date, find the AE start reference date as below

- If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).

- Else AE start reference date = treatment start date

1. If the AE start date 'year' value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.

2. If the AE start date 'year' value is less than the treatment start date year value, the AE started before treatment. Therefore:

a. If AE 'month' is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

b. Else if AE 'month' is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:

a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:

a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.

b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

Impute concomitant medication (CM) end date:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.

2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).

3. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

Impute CM start date:

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.

2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:

    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).

    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).

3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:

    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).

    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

4. If the CM start date year value is equal to the treatment start date year value:

    a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.

    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).

    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.3.1 Prior therapies date imputation

See Section 5.1.3.

5.1.3.2 Other imputations

First diagnosis date imputation

1. If the first diagnosis day/ month are missing and the year is non-missing:

    a. If the year part of the first diagnosis date is equal to the year part of the inform consent date, then the imputed first diagnosis date is set to the year start point (01JanYYYY).

    b. Otherwise the imputed first diagnosis date is set to the mid-year point (01JulYYYY).

2. If the first diagnosis day is missing and the month/year are non-missing:

    a. If the month and year part of the first diagnosis date is equal to the month and year part of the inform consent date, then the imputed first diagnosis date is set to the month start point (01MONYYYY).

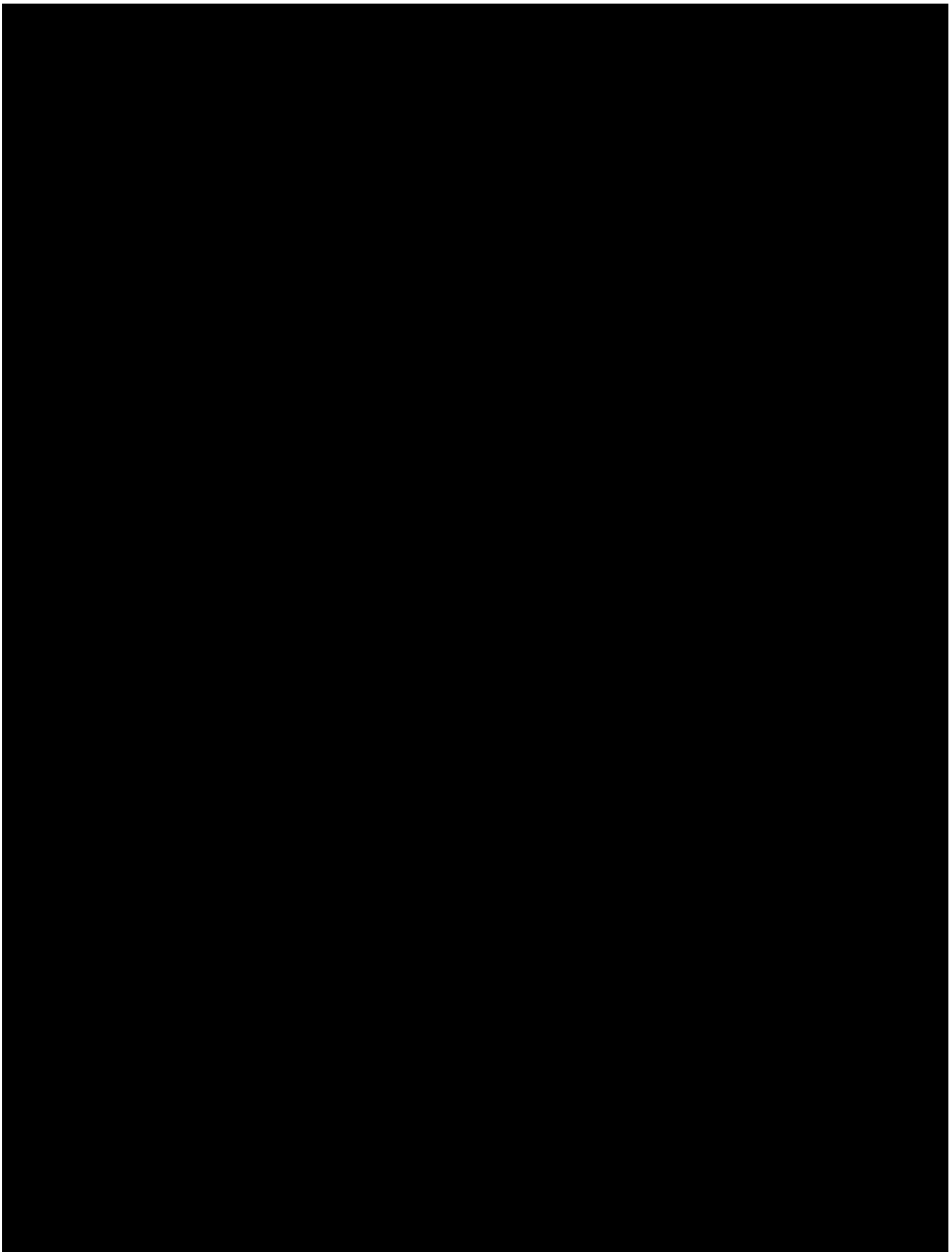
    b. Otherwise the imputed first diagnosis date is set to the mid-month point (15MONYYYY).

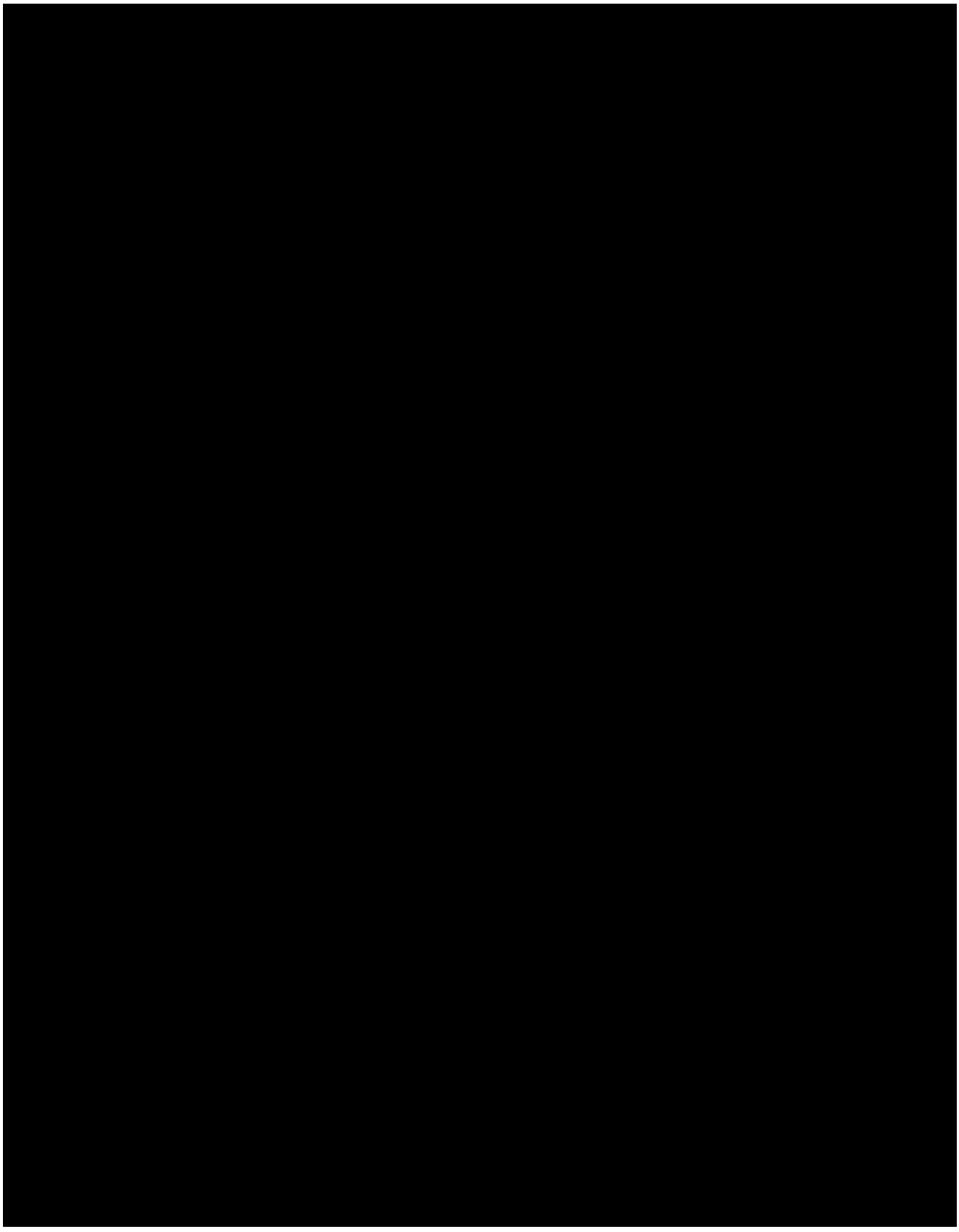
5.2 AEs coding/grading

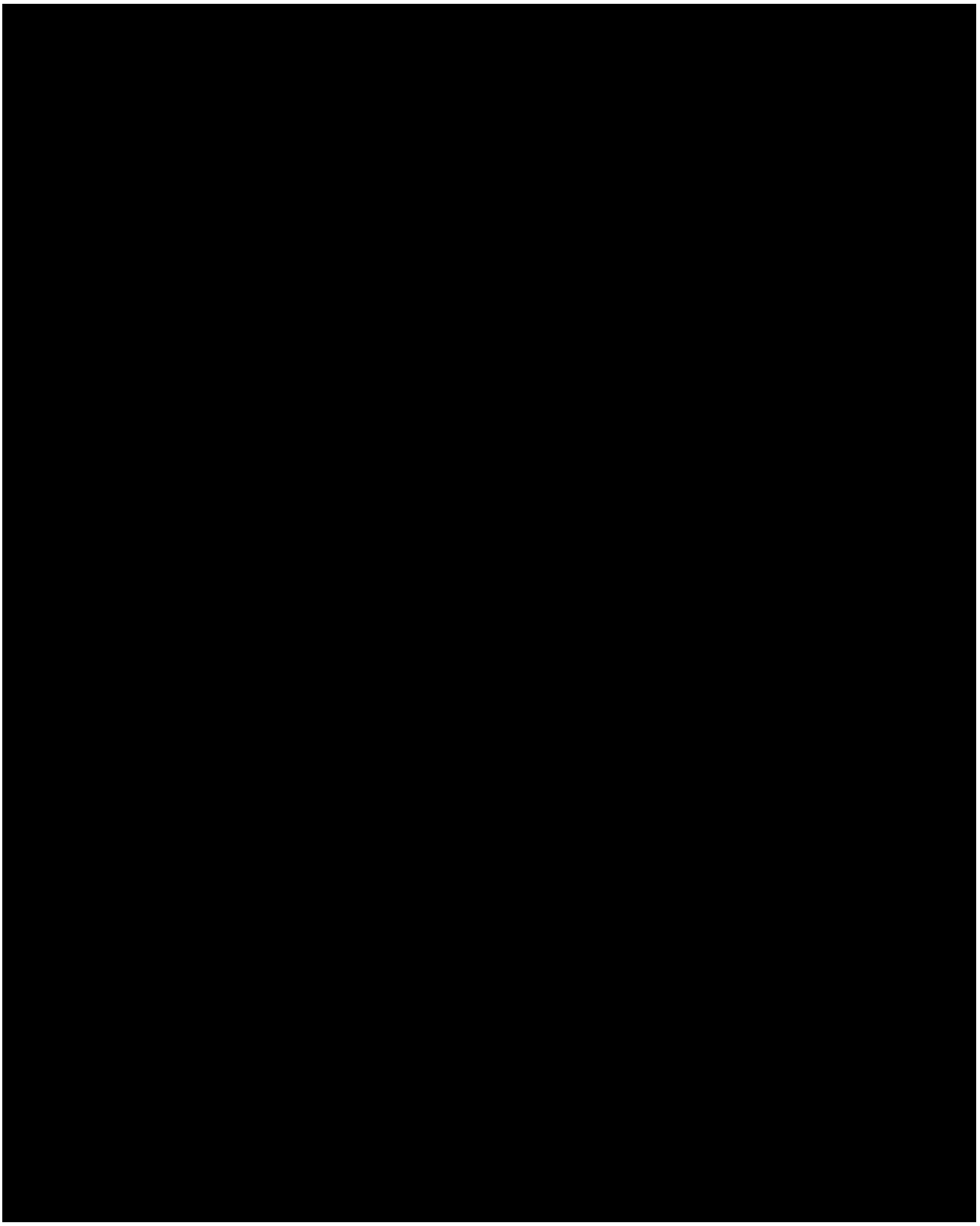
Not applicable.

5.3 Laboratory parameters derivations

Not applicable.







5.5 Rule of exclusion criteria of analysis sets

Table 5-1 Subject classification rule

Analysis Set	PD categories codes that cause subject to be excluded	Non-PD criteria that cause subjects to be excluded
Randomized set (RAN)	*DVSPID: P-INCL01B-ICF not signed;*	*Not randomized;*
Full analysis set (FAS)	*DVSPID: P-INCL01B-ICF not signed; OTH11-ICH-GCP*	*Not in RAN; Mis randomized*
Safety analysis set (SAF)	*DVSPID: P-INCL01B-ICF not signed; OTH11-ICH-GCP; M-TRT04*	*NA.*

P-INCL01B-ICF not signed: ICF missing or not obtained.
OTH11-ICH-GCP: Severe ICH-GCP non-compliance of study site
TRT04: Subject randomized but no study treatment was taken.

6 Reference

Bretz F, Pinheiro JC, Branson M (2005) Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics, 61(3): 738-48.

[redacted]

Newcombe, R. G. (1998). "Two-sided confidence intervals for the single proportion: comparison of seven methods". Statistics in Medicine. 17 (8): 857–872.

Pinheiro J, Bornkamp B, Glimm E, et al (2014) Model-based dose finding under model uncertainty using general parametric models. Stat Med; 33(10): 1646-61.