NOVARTIS

Clinical Development

LOU064/Remibrutinib

CLOU064A2305 / NCT05795153

A multicenter, open-label Phase 3 study: ambulatory blood pressure monitoring in adult patients with chronic spontaneous urticaria inadequately controlled by H1-antihistamines treated with remibrutinib up to 12 weeks.

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
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15-Mar-2024	*Prior to DB lock*	*Addresses the findings and comments from dry run and TFL shells review*	*SAP Amendment 1*	
			Updated the Edit Check Plan version	*Section 1*
			Corrected the reference endpoint	*Section 1.2.2*
			Added R as possible software	*Section 2.1*
			We do not show p-values (non-inferiority study)	
			Specified Week 4 for ABPM	
			Replaced 'Geographic region' with 'Country'	*Section 2.3.2*
			Background medication based on Enrolled Set	*Section 2.4.2*
			Changed the PD used according to the new Edit Check Plan	*Sections 2.5.3; 2.5.6*
			Added a clarification on the intercurrent events for the sensitivity analysis	*Section 2.5.5*
			*Updated the "*Derivation of the ABPM based averages" section with more details	*Section 2.5.4*
			Updated Table 2-15 and the urinalysis paragraph	*Section 2.7.3*
			Changed Pulse into Heart rate in Table 2-18 to align with the protocol	*Section 2.7.4.2*
			[redacted]	
			Completed the SAS pseudo-code according to the description	*Section 5.4.1*
			Adapted the text to be consistent also with more than 48h of data	*Section 5.4.1.1*
			Updated Table 5-2	*Section 5.5*
			Minor corrections (typos, removed 'by treatment' as it is only one arm, etc.)	*Entire document*
7-May-2024	*Prior to DB lock*	*Addresses the findings from the CDC dry run*	*Updated the definition of "on-treatment" to avoid inflating the exposure time and ensure alignment with the pivotal studies. Added also its use cases.*	*Section 2.1.1*
			Specified the source for background and rescue medications	*Section 2.4.2*
			Made the handling of an intercurrent event more precise. The intercurrent event and the estimand did not change	*Section 2.5.3*
12-Sep-2024	*After DB lock*	*Minor edits for documentation*	*SAP Addendum 1*	
			Added ETD remapping information	*Section 2.1.1*
			*Updated text: "*For the combination criteria of parameters, except potential Hy's Law case, all the elevations must occur at the same post-baseline timepoint."	*Section 2.7.3*
			Updated to match used criteria	*Section 2.7.4.1*
			Updated imputation rule to match the programs	*Section 5.1.3*

Table of contents

List of tables

List of figures

List of abbreviations

AAS7	Weekly Angioedema Activity Score
ABPM	Ambulatory Blood Pressure Monitoring
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
b.i.d.	bis in diem/twice a day
BMI	Body Mass Index
CINDU	Chronic Inducible Urticaria
CM	Concomitant Medication
CRF	Case Report Form
CSR	Clinical Study Report
CSU	Chronic Spontaneous Urticaria
CTCAE	Common Terminology Criteria for Adverse Event
CU	Chronic Urticaria
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
[redacted]	[redacted]
DMS	Document Management System
FAS	Full Analysis Set
GGT	Gamma-Glutamyl Transferase
H1-AH	H1-antihistamine
HR	Heart Rate
HSS7	Weekly Hives Severity Score
IA	Interim Analyses
IE	Intercurrent Event
Ig	Immunoglobulin
ISS7	Weekly Itch Severity Score
LLN	Lower Limit of Normal range
LLOQ	Lower Limit Of Quantification
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PD	Protocol deviation
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
PT	Preferred Term
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class

TBL	Total Bilirubin
TEAE	Treatment Emergent AE
TFLs	Tables, Figures, Listings
[redacted]	[redacted]
ULN	Upper Limit of Normal range
ULOQ	Upper Limit Of Quantification
WHO	World Health Organization

1 Introduction

Data will be analyzed by Novartis according to the data analysis Section 12 of the CLOU064A2305 study protocol which will be made available in Appendix 16.1.1 of the Clinical Study Report (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 primary analysis (at Week 4), if conducted, and the final analysis of CLOU064A2305 study with reference to

- the study protocol version 1.0
- The Edit Check Plan version 8.0

1.1 Study design

This is a global, open-label Phase 3 study assessing the safety of remibrutinib 25 mg b.i.d., in adult participants with CSU inadequately controlled by second generation H1-AH in regards to change from baseline in 24-hour weighted average SBP at Week 4 measured by ABPM at baseline and Week 4 and overall efficacy, safety and tolerability over 12 weeks.

This study consists of a screening period of up to 4 weeks, a 12-week treatment period and a treatment-free follow-up period of 4 weeks, with a total study duration of up to 20 weeks.

A primary analysis may be conducted once all participants have completed their Week 4 visit or discontinued early.

A final analysis will be conducted once all participants have completed the study or discontinued early.

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To rule out an increase of >3mmHg in 24-hour average SBP at steady state (Week 4) compared to baseline, measured by ABPM.	• The change in the ABPM-measured 24-hour weighted average SBP at Week 4 compared to baseline
Secondary	
• To evaluate changes in 24-hour average SBP at steady state (Week 4) compared to baseline	• The change in the ABPM-measured 24-hour weighted average SBP at Week 4 compared to baseline
• To evaluate changes in 24-hour average DBP at steady state (Week 4) compared to baseline	• The change in the measured ABPM 24-hour weighted average DBP at Week 4 compared to baseline
• To evaluate changes in daytime and nighttime SBP at 4 weeks	• The change in the measured ABPM daytime and nighttime weighted average SBP at Week 4
• To evaluate changes in daytime and nighttime average DBP at 4 weeks.	• The change in the measured ABPM daytime and nighttime weighted average DBP at Week 4

• To evaluate the safety and tolerability of remibrutinib 25 mg b.i.d.	• Occurrence of treatment emergent adverse events and serious adverse events (SAEs) during the study, evaluation of laboratory and vital signs data
[redacted]	

1.2.1 Primary estimand(s)

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The primary clinical question of interest is: Does remibrutinib treatment increase on average the 24-hour weighted average SBP at a steady state (Week 4) compared to baseline, by more than 3 mmHg, in adult participants without ongoing or past history of hypertension and with 90 < SBP <140mmHg, 60 < DBP< 90 mmHg at screening, with CSU who are inadequately controlled by H1-AH and receiving a stable local label-approved standard dose of a second generation H1-AH, excluding participants who discontinue from study treatment for any reason

before Week 4 and considering intake of prohibited antihypertensive treatment as an unfavorable outcome?

The primary estimand is described by the following attributes:

1. **Population**: participants without ongoing or past history of hypertension and with 90< SBP <140mmHg, 60< DBP<90 mmHg at screening, with inadequately controlled CSU despite treatment with second generation H1-AH who have CSU duration ≥ 6 months, a UAS7 score ≥ 16, ISS7 ≥ 6 and HSS7 score ≥ 6 in the last 7 days prior to Baseline (Day 1).
2. **Endpoint:** change from baseline in 24-hour weighted average SBP at Week 4 measured by ABPM.
3. **Treatment of interest:** the study treatment (remibrutinib 25 mg b.i.d.).
4. **Summary Measurement**: the mean change from baseline.
5. **Handling of intercurrent events**:
   - Discontinuation of study treatment due to any reason prior to Week 4: participants will be excluded from the analysis
   - Intake of prohibited antihypertensive treatment prior to Week 4: Composite strategy (irrespective of potential occurrence of other intercurrent events). Measurements after this event will be excluded from the analysis and will be imputed using an increase of 3mmHg in 24-hour average SBP from baseline at Week 4.

1.2.2 Secondary estimand(s)

The secondary clinical question of interest is: What is the effect of remibrutinib treatment on the change from baseline in 24-hour weighted average SBP at steady state (Week 4) compared to baseline in adult participants without ongoing or past history of hypertension and with 90< SBP <140mmHg, 60< DBP<90 mmHg at screening, with CSU who are inadequately controlled by H1-AH and receiving a stable local label-approved standard dose of a second generation H1-AH, excluding participants who discontinue from study treatment for any reason before Week 4 and considering intake of prohibited antihypertensive treatment as an unfavorable outcome?

The secondary estimand attributes are identical to the ones described in Section 1.2.1.

Secondary estimand on the secondary endpoints

A similar estimand approach will be implemented for Change from baseline in 24-hour weighted average DBP at Week 4 measured by ABPM as for Change from baseline in 24-hour weighted average SBP at Week 4 measured by ABPM.

A similar estimand approach will be implemented for Change from baseline in daytime weighted average SBP at Week 4 measured by ABPM as for Change from baseline in 24-hour weighted average SBP at Week 4 measured by ABPM.

A similar estimand approach will be implemented for Change from baseline in nighttime weighted average SBP at Week 4 measured by ABPM as for Change from baseline in 24-hour weighted average SBP at Week 4 measured by ABPM.

A similar estimand approach will be implemented for Change from baseline in daytime weighted average DBP at Week 4 measured by ABPM as for Change from baseline in 24-hour weighted average SBP at Week 4 measured by ABPM.

A similar estimand approach will be implemented for Change from baseline in nighttime weighted average DBP at Week 4 measured by ABPM as for Change from baseline in 24-hour weighted average SBP at Week 4 measured by ABPM.

2 Statistical methods

2.1 Data analysis general information

The statistical analysis will be performed by Novartis personnel, using R version 4.1 or above and/or SAS version 9.4 or above.

Statistical Analysis Plan for the DMC analyses will be prepared separately.

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

Summary statistics for categorical variables will be presented in contingency tables and will include frequencies and percentages.

95% confidence intervals will be displayed and will be two-sided if not specified otherwise.

2.1.1 General definitions

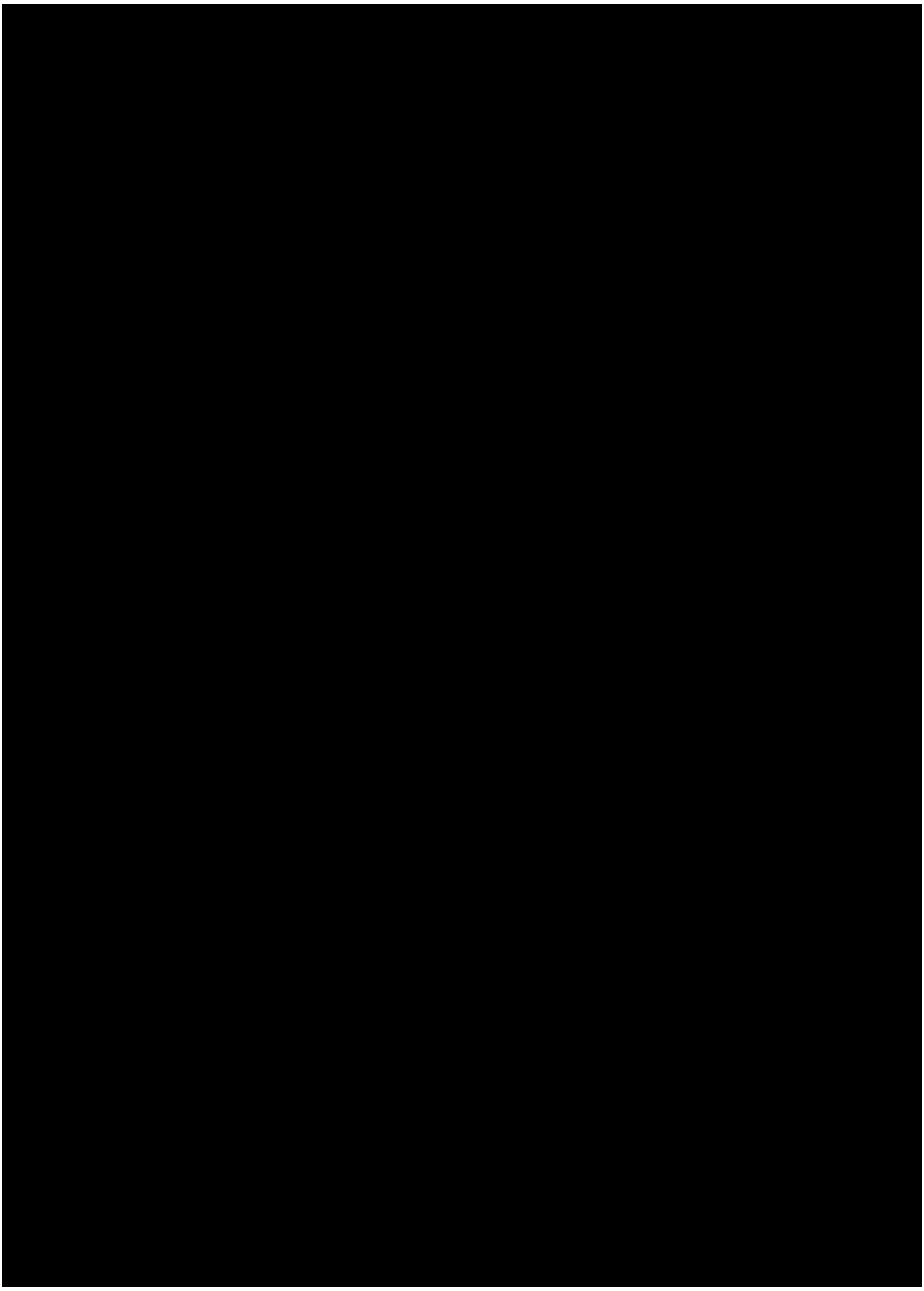
All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date is calculated as [Date of event] – [Date of first dose intake] + 1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For the dates before Day 1, study day for an event date is calculated as [Date of event] – [Date of first dose intake], 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.

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.

[redacted] For other assessments, baseline is the assessment on or before Day 1. For the ABPM based assessments baseline is the last assessment on or before the day of the first dose of study treatment.

For the ABPM based assessments Week 4 is the last assessment on or after Week 4 - 1 day.

The On-treatment period is defined as the minimum between the period from the first date of dose intake of treatment to either (i) the last date of dose intake + 28 days or (ii) and the end of study. This is the reference for safety analyses of adverse events, laboratory, vital signs, etc., as well as exposure-adjusted incidence rates.



[redacted]

Assessment window for the assessments performed at study until Week 12

When the assessments are summarized by visit, they are based on the visit numbers as recorded in eDiary or eCRF except for end of treatment (ETD) visit. **ETD visit,** will be remapped to the scheduled visit. Safety follow-up visit or unscheduled visits will NOT be remapped (except for the unscheduled visit to be considered as baseline).

Table 2-3 shows the assessment windows for the assessments collected at every visit (i.e., Vital signs, Clinical Chemistry, Hematology, Urinalysis).

If more than one assessment falls into the interval,

- Then if there is the scheduled visit recorded in eDiary or eCRF, this visit will be chosen.
- If not, the earliest visit day will be chosen.

Table 2-3 Assessment windows by assessment

Assessment Visit	Week 4	Week 8	Week 12
Scheduled visit day	29	57	85
Vital Signs	2-29	30-57	58-85
Weight	-	-	2-85
ECG [redacted] Clinical Chemistry Hematology Urinalysis [redacted]	2-29	-	30-85

2.2 Analysis sets

The following analysis sets will be used in this study.

Enrolled Analysis Set: The Enrolled Analysis Set consists of all participants who have been enrolled, regardless of whether or not they receive a dose of study drug. This set substitutes the Randomized Analysis Set as this study is open label. Hence, screen failures are not part of the Enrolled Analysis Set.

Safety Set (SAF): The Safety Set includes all participants who received at least one dose of study treatment. The safety set will be used in the analysis of all safety variables.

Full Analysis Set (FAS): The FAS comprises all participants to whom study treatment has been assigned and received at least one dose of the treatment. The FAS will be used for all efficacy variables, unless otherwise stated.

Mis-enrolled participants will be excluded from the FAS.

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

Note that the SAF and the FAS are the same except that the Safety Set allows inclusion of participants to whom study treatment has not been assigned but received study drug in error.

2.2.1 Subgroup of interest

Not applicable

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of participants screened will be presented. The number and percentage of participants who completed screening phase, and who discontinued screening phase will be presented for all screened participants. The reasons for screen failure will also be summarized if available. For participants screened more than once, the data from the last screening visit will be used in the summaries.

The number and percentage of participants in the Enrolled analysis set who completed the study treatment period, who discontinued the study treatment and the reason for treatment discontinuation will be presented.

The number and percentage of participants in the Enrolled analysis set who completed the study (including FU period), who discontinued the study and the reason for discontinuation will be presented as well.

The number of participants in each analysis set (Enrolled analysis set, FAS and SAF) will be presented. The reason for exclusion from any analysis set will be listed.

The number and percentage of participants who have experienced protocol deviations (PD) will be tabulated by deviation category. The summary of overall important PDs (including COVID-19 related PDs), important COVID-19 related PDs will be provided for the Enrolled analysis set.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for the Enrolled analysis set.

The following common background, demographic and disease characteristics variables will be analyzed:

Continuous variables:

- Screening Age (years)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) calculated as (body weight in kilograms) / (height in meters)^2
- [redacted]
- Duration of CSU defined as Time since diagnosis of urticaria (years) = (informed consent date – diagnosis date + 1)/365.25
- Baseline SBP and DBP (vital signs, not measured by ABPM)

Categorical variables:

- Age categories (≥18 - <65, ≥ 65 - <85years , ≥85 years)
- Gender
- Race
- Ethnicity
- BMI groups (< 25, 25 - <30, ≥ 30 kg/m^2)
- [redacted]
- Previous exposure to anti-IgE therapy (Yes, No)
- Country
- Previous experience of Angioedema (Yes, No)
- Baseline CU-index category (Positive:>=10, Negative: <10)
- Baseline total IgE level (Normal/High: >43 IU/mL, Low: ≤ 43 IU/mL)

Relevant medical histories and current medical conditions at baseline will be summarized combined by system organ class and preferred term, for the Enrolled analysis set.

- CSU related history (CSU, Urticaria related history)
- Non-CSU related history (general medical history)

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

2.4.1 Study treatment / compliance

The analysis of study treatment data and the analysis of duration of study will be based on the Safety set.

The first (last) dose of study treatment is defined as the date of the first (last) dose intake. The last study visit is defined as the maximum among Week 12, the date of study discontinuation, the date of study completion, the date of the last safety follow-up.

Duration of exposure (days) will be defined as last dose of study treatment – first dose of study treatment + 1.

Duration of study (days) will be defined as last study visit – first dose of study treatment + 1.

The duration of exposure/study in weeks will be derived as follows,

- Duration of exposure (weeks) = duration of exposure (days) / 7
- Duration of study (weeks) = duration of study (days) / 7
- Duration of exposure (years) = duration of exposure (days) / 365.25
- Duration of study (years) = duration of study (days) / 365.25

The duration of exposure and duration of study in weeks of LOU064 25mg b.i.d. will be summarized.

The number of participants with the duration of exposure/study of at least certain thresholds (e.g., any exposure, >0 - <2 weeks, ≥2 weeks - <4 weeks, ≥4 weeks - < 8 weeks, ≥8 weeks - <12 weeks, ≥12 weeks) will be displayed.

2.4.2 Prior, concomitant and post therapies

Medications will be identified using the WHODrug including Anatomical Therapeutic Chemical (ATC) code. In the summary tables, medications (including background or rescue medications) will be presented in alphabetical order, by ATC codes and preferred term. Tables will show the overall number and percentage of participants receiving at least one drug of a particular ATC code and at least one drug in a particular preferred term.

Prior medications are defined as drugs taken and stopped prior to first dose of study medication. Any medication given at least once between the day of first dose of study treatment and the last day of study visit will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period. Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taking.

Prior urticaria medications and prior non-urticaria medications will be summarized separately by ATC code and preferred term in the Enrolled analysis set.

Concomitant urticaria medications (excluding background or rescue medications) and concomitant non-urticaria medications will be summarized separately by ATC code, preferred term in the Safety set.

Background medications will be summarized by ATC code, preferred term, and dose per administration in the Enrolled set.

Rescue medication: H1-antihistamines will be summarized by ATC code, preferred term, and dose per tablet in the Safety set.

Rescue medication: oral corticosteroids will be summarized by ATC code, preferred term, and dose per tablet in the Safety set.

In addition, non-drug therapies/procedures will be summarized separately by primary system organ class and preferred term of MedDRA dictionary. Prior non-drug therapies/procedures will be summarized in the Enrolled analysis set. Concomitant non-drug therapies/procedures will be summarized in the Safety set.

Background and rescue medications will be filtered from the concomitant medications.

2.5 Analysis supporting primary objective(s)

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

A primary analysis may be conducted when all participants have completed their Week 4 visit or discontinued early.

2.5.1 Primary endpoint(s)

The primary clinical question of interest is: does remibrutinib treatment increase on average the 24-hour weighted SBP pressure between baseline and Week 4 by more than 3 mmHg, in adult participants without ongoing or past history of hypertension and with 90<SBP <140mmHg, 60< DBP<90 mmHg at screening, with CSU who are inadequately controlled by H1-AH and receiving a stable local label-approved standard dose of a second generation H1-AH, excluding participants who discontinue from study treatment for any reason before Week 4 and considering intake of prohibited antihypertensive treatment as an unfavorable outcome?

The primary endpoint of the study is the change in the ABPM-measured 24-hour weighted average SBP at Week 4 compared to baseline.

2.5.2 Statistical hypothesis, model, and method of analysis

A linear regression model will be used with baseline SBP as a covariate to analyze the primary efficacy endpoint. The change in SBP from baseline to Week 4 will be predicted at the median baseline level, and the predicted value, standard error and 95% confidence interval will be listed. The upper limit of 95% CI will be compared with 3 mmHg.

Change from baseline of 24-hour weighted average SBP measured by ABPM will be calculated using the time weighted average of area under the curve (AUC divided by time duration) of SBP obtained over 24-hours. That is, the time weighted average of AUC of 24-hour SBP obtained at baseline will be subtracted from corresponding time weighted average of AUC of SBP at Week 4.

Median weighted average of SBP at baseline is the sample median of the weighted average of AUC of SBP at baseline.

The statistical hypothesis test for the primary endpoint being tested is that the change from baseline of 24-hour weighted average SBP at Week 4 measured by ABPM is greater or equal than 3mmHg i.e.

H_{01}: $\mu_{remibrutinib} \geq 3mmHg$ versus H_{A1}: $\mu_{remibrutinib} < 3mmHg$

where μ is the change from baseline of 24-hour weighted average SBP at Week 4 measured by ABPM.

2.5.3 Handling of intercurrent events

The analysis will account for different intercurrent events as explained in the following

- Discontinuation of study treatment due to any reason prior to Week 4: participants will be excluded from the analysis.
- Intake of prohibited antihypertensive treatment prior to Week 4 (PD M-COMD05): Composite strategy (irrespective of potential occurrence of other intercurrent events). Measurements after this event will be excluded from the analysis and will be imputed using an increase by 3mmHg in 24-hour SBP from baseline at Week 4.

For the first intercurrent event Week 4 is defined as the date of the first dose intake + 28 days.

2.5.4 Handling of missing values not related to intercurrent event

If a participant's data are missing at the start or the end, the values will be considered missing for the computation of averages, the actual times for analyzing the average will be taken based on the data available.

If a participant's data are missing in the middle of the data collection window, the values will be considered as missing for the given timepoints and the average will be computed based on the area under the curve for the remaining timepoints.

For a participant if there are data missing at Baseline and / or at Week 4 for a complete hour, for the purpose of computing the average values, the corresponding times from both the Baseline and Week 4 will be considered missing. For example, at baseline if a participant's data are missing from 2 to 3 PM in the afternoon, however corresponding exit values are available, for assessing change from baseline, the average calculation will not consider the 2 to 3 PM data even at Week 4.

This approach is true only if an entire hour of data are missing. If there are partial data within an hour missing, then all of the available data will be used in computation of averages.

Participants with a missing 24-hour SBP baseline value will be excluded from the analysis. For missing 24-hour SBP values at Week 4 for participants who did not discontinue study treatment, the missing at random (MAR) assumption will be applied. Participants with a missing 24-hour SBP change from baseline at Week 4 will be excluded from the analysis. This can happen if the intersection of the time intervals for which we have data at Baseline and Week 4 is empty. See Section 5.4.1.1 for more details on the derivation of the change from baseline.

2.5.5 Sensitivity analyses

A sensitivity analysis will be performed on the missing 24-hour SBP values at Week 4 for participants who did not discontinue study treatment and handled under the MAR assumption in the primary analysis. For the primary endpoint, the sensitivity analysis will exclude participants who did not discontinue treatment and have a missing 24-hour SBP value at Week 4. All other intercurrent events will remain the same.

2.5.6 Supplementary analyses

In addition to the intercurrent events (IEs) described in Section 1.2.1, the following IE will be considered in the analysis of the primary endpoint:

- Intake of prohibited BP-modifying treatment prior to Week 4 (PD M-COMD02, M-COMD03, M-COMD05 & M-COMD06): Composite strategy (irrespective of potential occurrence of other IEs). Measurements after this event will be excluded from the analysis and will be imputed using an increase by 3mmHg in 24-hour SBP from baseline at Week 4.

2.6 Analysis supporting secondary objectives

For all secondary endpoints analyses, the FAS will be used.

2.6.1 Secondary endpoint(s)

The secondary clinical question of interest is: What is the effect of remibrutinib treatment on the change from baseline in 24-hour average SBP after 4 weeks treatment in adult participants without past or ongoing history of hypertension and with 90< SBP <140mmHg, 60< DBP<90 mmHg at screening, with CSU who are inadequately controlled by H1-AH and receiving a stable local label-approved standard dose of a second generation H1-AH, excluding participants who discontinue from study treatment for any reason before Week 4 and considering intake of prohibited antihypertensive treatment as an unfavorable outcome?

Other secondary endpoints are listed below:

- the change in the ABPM-measured 24-hour weighted average SBP at Week 4 compared to baseline

The change in 24-hour weighted average SBP will be analyzed using linear regression model with baseline SBP as a covariate.

- the change in the ABPM-measured 24-hour weighted average DBP at Week 4 compared to baseline

The change in 24-hour weighted average DBP will be analyzed using linear regression model with baseline DBP as a covariate.

- the change in the measured ABPM daytime and nighttime weighted average SBP at Week 4 compared to baseline

The change in daytime (respectively nighttime) weighted average SBP will be analyzed using linear regression model with baseline weighted average daytime SBP (respectively nighttime) as a covariate.

- the change in the measured ABPM daytime and nighttime weighted average DBP at Week 4 compared to baseline

The change in weighted average daytime (respectively nighttime) DBP will be analyzed using linear regression model with baseline daytime weighted average DBP (respectively nighttime) as a covariate.

2.6.2 Statistical hypothesis, model, and method of analysis

The same analysis described for the primary endpoint in Section 2.5.2 will be performed.

2.6.3 Handling of intercurrent events

The same intercurrent events defined for the primary estimand will be used for the secondary estimands and will be handled in the same way.

2.6.4 Handling of missing values not related to intercurrent event

For missing data not related to intercurrent events, the same strategy described for the primary endpoint will be followed.

2.6.5 Sensitivity analyses

Not applicable.

2.6.6 Supplementary analyses

Not applicable.

2.7 Safety analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by visit.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries).

For details of the on-treatment period, please see Section 2.1.1.

2.7.1 Adverse events (AEs)

All information obtained on adverse events will be listed by participant.

The number (and percentage) of participants with treatment emergent adverse events (the events which occurred during the on-treatment period, TEAE) will be summarized in the following ways:

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

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The most common adverse events reported (≥ 3 % in any group for each preferred term in the SOC-PT table or ≥ 3 % in any group for each SMQ table) will be presented in descending frequency according to its incidence in LOU064A 25mg b.i.d. starting from the most common event. The cut-off of 3% can be re-evaluated based on the number of participants and events.

In these summary tables, a participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

In the summary of AEs by severity, if a participant reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level.

In addition, for adverse events and serious adverse events, exposure-adjusted incidence rates will be estimated. The rate estimates will be reported with exact Poisson 95% CIs (Garwood 1936, Sahai and Khurshid 1993).

Table 2-13 presents overview of analyses on TEAEs.

Table 2-13 Overview of safety analyses on TEAEs

Analysis	Study period	Treatment groups	AEs, SAEs, AESI	AEs by severity, AEs by SMQ, Study med. related AEs, Death, AEs leading to discontinuation,
Primary / Final analysis	Entire study	• LOU064 25mg b.i.d.	Crude incidence EAIR	Crude incidence

EAIR: Exposure-Adjusted Incidence Rate, AESI: Adverse Events of Special Interest

2.7.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) for remibrutinib (such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis) will be defined based on the latest Case Retrieval Strategy (eCRS). The comprehensive search of AESI will be performed for all TEAEs.

The number (and percentage) of participants with AESI will be summarized by safety topic of interest (i.e. risk name) and PT. Exposure-adjusted incidence rate will also be provided for the entire study period.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent AEs: non-serious AEs with an incidence greater than 5% , and deaths and serious AEs (SAEs) including the events suspected to be related to study treatment, will be provided by SOC and PT on the Safety Set. The cut-off of 5% can be re-evaluated based on the number of participants.

If for a same participant, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

These tables will be provided at the final analysis after completion of the study.

2.7.2 Deaths

A separate summary for death including on treatment and post treatment deaths will be provided. If there are few deaths, only listing will be provided.

2.7.3 Laboratory data

All laboratory data will be listed by participant, and visit and if normal ranges are available abnormalities will be flagged.

For Hematology and Serum chemistry, central laboratory data will be included in the summary tables. Local laboratory data will only be listed but not be included in the summary tables.

For Urinalysis, local laboratory data will be included in the summary tables. For participants who have only central laboratory data, central data will be used in the summary tables. Local and central data will be listed.

For by-visit summary tables, scheduled visits (including remapped visits following the assessment window in Section 2.1.1) will be considered in the analysis. Unscheduled visits will not be included.

For notable summary tables, all post-baseline visits including unscheduled visits will be considered in the analysis

Table 2-14 presents overview of safety analysis on laboratory data.

Table 2-14 Overview of safety analyses on laboratory data

Analysis	Period	Treatment groups	Summary by visit	Notables
Primary / Final analysis	Entire study	• LOU064 25mg b.i.d.	X	X

X: to be provided

The summary of laboratory evaluations will be presented for three groups of laboratory tests (Hematology, Serum chemistry and Urinalysis).

For continuous variables, descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test.

Change from baseline will only be summarized for participants with both baseline and post baseline values and will be calculated as:

- change from baseline = post baseline value – baseline value

For categorical variables, descriptive statistics will be presented in contingency tables including the number and percentage of participants for each category.

For Hematology and Serum chemistry, the maximum change from baseline (maximum decrease and maximum increase) will be summarized.

In addition, for laboratory parameters where normal ranges are available, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the worst on-treatment value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test.

The laboratory parameters given in Table 2-15 will be analyzed with respect to numerical Common Terminology Criteria for Adverse Event (CTCAE) grades (version 5.0).

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 participants with CTCAE grade newly occurring or worsening after baseline will be presented. A case is considered as newly occurring abnormality if the value is not notable or missing at baseline but is notable thereafter. A case is considered as worsening abnormality if the value is notable at baseline and at least one post-baseline value is worse than baseline.

Shift tables will be provided on CTCAE grades to compare baseline relative to the worst grade. These summaries will be split into hematology and chemistry.

Table 2-15 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;
Serum amylase increased	Amylase	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Triglyceride increased	Triglyceride	>=1.71 - 3.42 mmol/L	>3.42 - 5.7 mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L
Platelet count decreased	Platelet	<LLN-75,000/mm;	<75,000-50,000/mm3;	<50,000-25,000/mm3;	<25,000/mm3;
Total cholesterol increased	Total Cholesterol	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Creatine phosphokinase (CPK)	Creatine phosphokinase	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5x ULN - 10 x ULN	>10 x ULN
White blood cell decreased	White blood cell	<LLN-3000/mm3;	<3000-2000/mm3;	<2000-1000/mm3;	<1000/mm3;

CTCAE term	Laboratory assessment	Grade 1	Grade 2	Grade 3	Grade 4
Lipase increased	Lipase	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN;	>2.0 - 5.0 x ULN	>5.0 x ULN
Hemoglobin increased	Hemoglobin	>0 - 2 g/dL	>2 - 4 g/dL	>4 g/dL	-
Neutrophil count decreased	Neutrophils	<2000-1500/mm3;	<1500-1000/mm3;	<1000-500/mm3;	<500/mm3;
Lymphocyte count decreased	lymphocytes	<1500-800/mm3;	<800-500/mm3;	<500-200/mm3;	<200/mm3;
Lymphocyte count increased	lymphocytes	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-
INR increased	INR	>1.2 - 1.5	>1.5 - 2.5	>2.5	-
Creatinine increased	Serum creatinine	>1-1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Blood bilirubin increased	Total bilirubin (TBL)	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	Gamma-glutamyl transferase (GGT)	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alanine aminotransferase increased	Alanine aminotransferase (ALT)	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	Aspartate aminotransferase (AST)	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase increased	Alkaline phosphatase (ALP)	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ULN: Upper limit of normal range; LLN: Lower limit of normal range.					

To evaluate potential drug-induced liver injury, newly occurring liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-16. For the combination criteria of parameters, e.g. except 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. A case is considered as worsening abnormality if the value is notable at baseline and at least one post-baseline value is worse than baseline.

Similarly, participants meeting specific renal alert criteria at any post-baseline will be summarized according to Table 2-17.

Table 2-16 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

Parameter	Criterion
ALP & TBL	>3xULN; >5xULN & TBL>2xULN
(ALT or AST) & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law**)

Table 2-17 Specific renal alert criteria

Parameter	Notable criterion
Serum creatinine	increase 25% – <50% (%change from baseline), increase ≥ 50%
Dipstick proteinuria	≥ 3+ (Newly occurring)
Dipstick hematuria (occult blood)	≥ 3+ (Newly occurring)

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted centrally.

All ECG data will be listed by participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by visit.

In case multiple measurements on ECG are done 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. At visits with pre- and post-dose assessments, they will be presented separately.

The number and percentage of participants with the following criteria will be summarized:

- QT Interval > 500 msec;
- Absolute QTc (Fridericia's) interval > 450 msec (males), absolute QTc (Fridericia's) interval > 460 msec (females);
- QTc (Fridericia's) interval change from baseline > 30 msec to <60 msec, >= 60 msec;
- PR Interval > 250 msec.
- PR Interval > 250 msec and PR Interval increase from baseline > 25%
- QRS Duration >110 msec, >120 msec
- QRS Duration > 120 msec and QRS Duration increase from baseline > 25%

2.7.4.2 Vital signs

All vital signs data will be listed by participant, and visit/time and if ranges are available, abnormalities (and relevant changes) will be flagged. Summary statistics will be provided by visit.

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed. Change from baseline will only be summarized for participants with both baseline and post-baseline values and will be calculated as:

- change from baseline = post-baseline value – baseline value

The number and percentage of participants with clinically notable vital signs changes from baseline will be presented. Clinically notable vital sign results are provided in Table 2-18 below.

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]:

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

2.12 Other Exploratory analyses

Not applicable.

2.13 Interim analysis

A primary analysis may be conducted when all participants have completed their Week 4 visit or discontinued early. It will focus on ABPM, safety [redacted]. The results of the primary analysis will further inform decision making for the remibrutinib development program.

[redacted]

4 Change to protocol specified analyses

Demographics and baseline characteristics will be reported using the Enrolled analysis set instead of the SAF.

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

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Concomitant therapies

Please see Section 5.1.3.

5.1.3.4 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

AEs are coded using the MedDRA terminology with the latest version at the analysis.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

Summary statistics for continuous variables (including N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum) will be provided for continuous data by visit. If applicable and not otherwise stated, means +/- SE will be plotted. If appropriate, summary statistics will also be derived for absolute and percentage changes from baseline.

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. If applicable, confidence intervals will be derived as well based on the score method including continuity correction (Newcombe 1998):

With z as (1-α/2)-quantile of the standard normal distribution, and p as estimated crude incidence (number of subjects with event / n) it is $q = 1 - p$

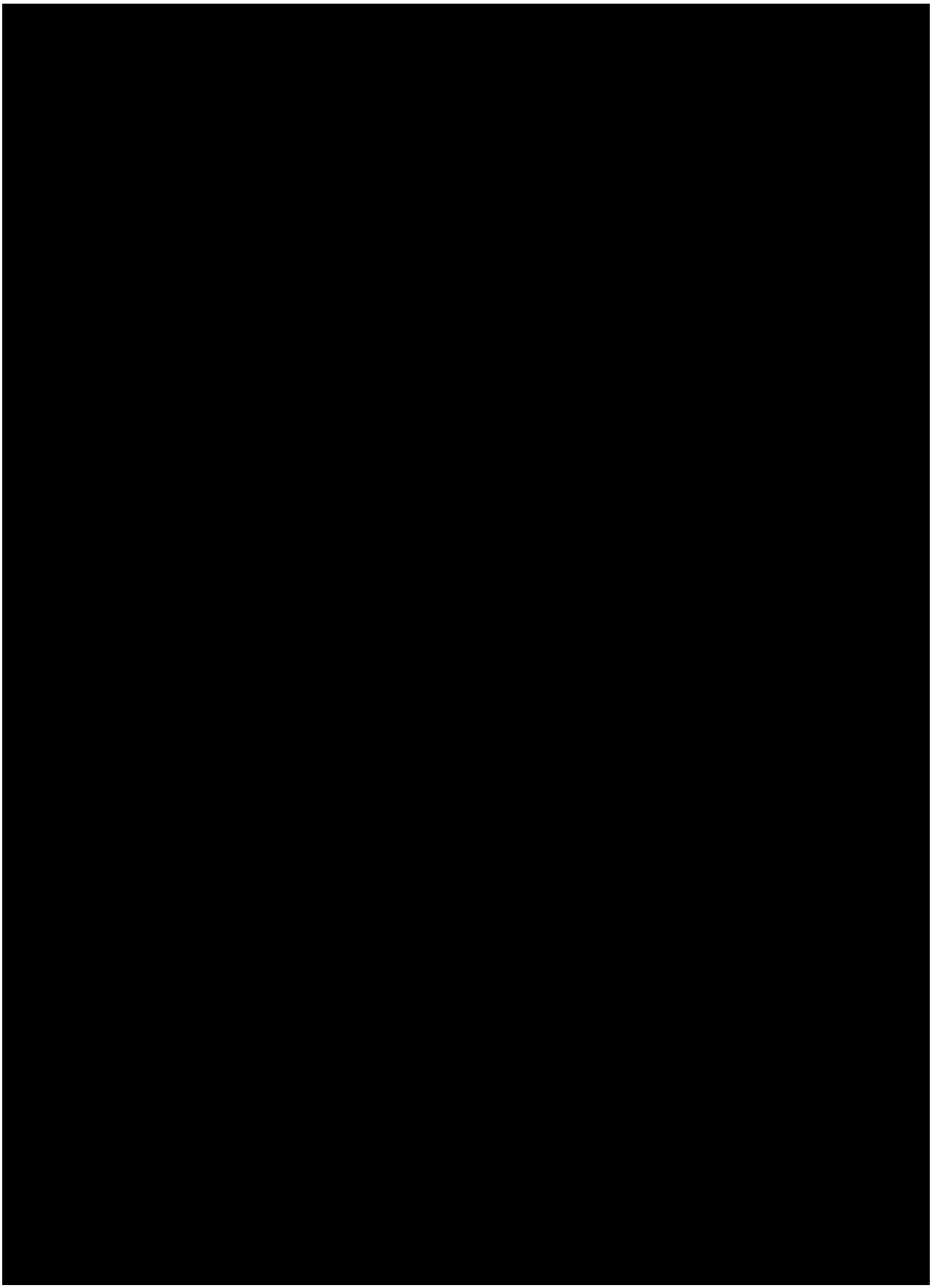
Then the lower limit is for $p > 0, (L = 0 \text{ for } p = 0),$

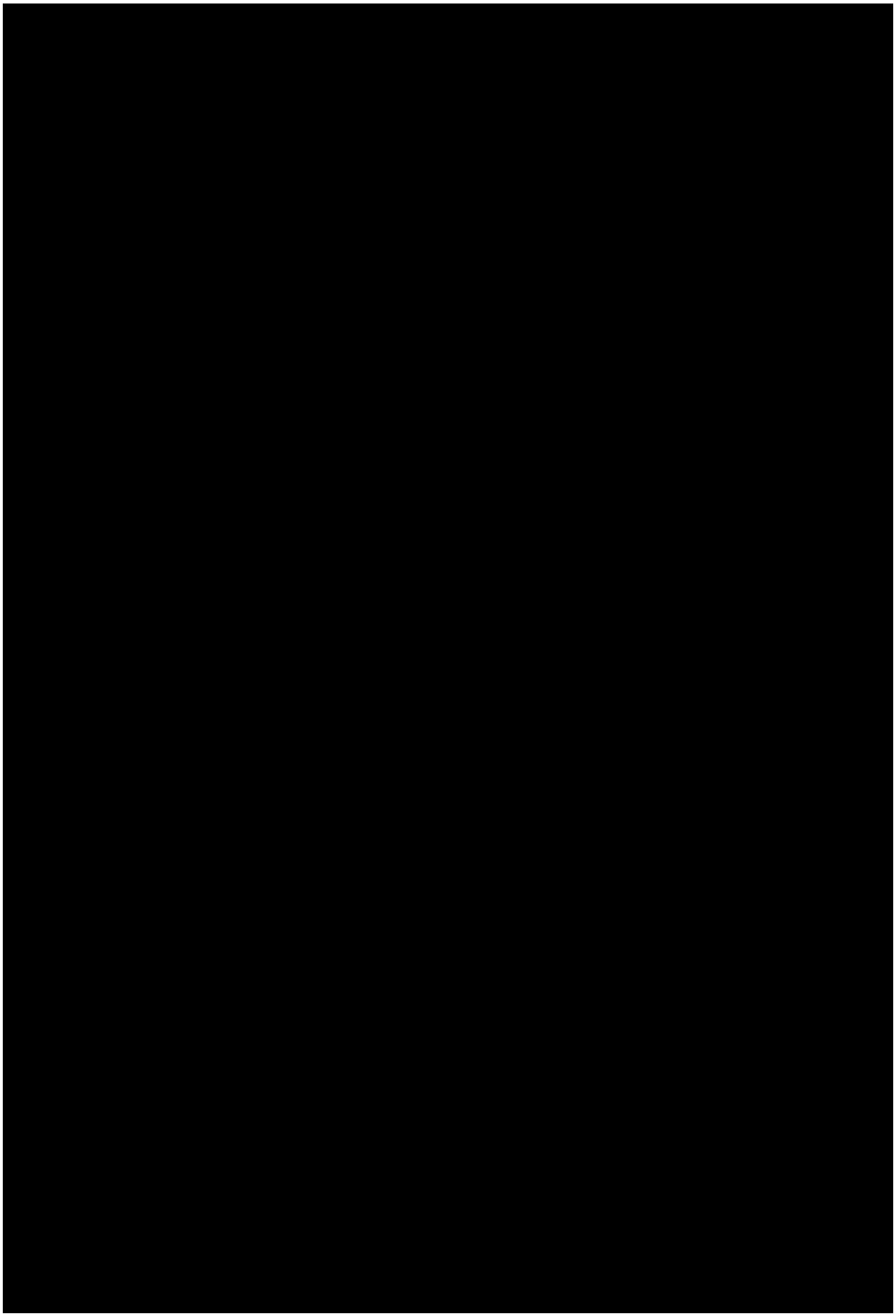
$$L = \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

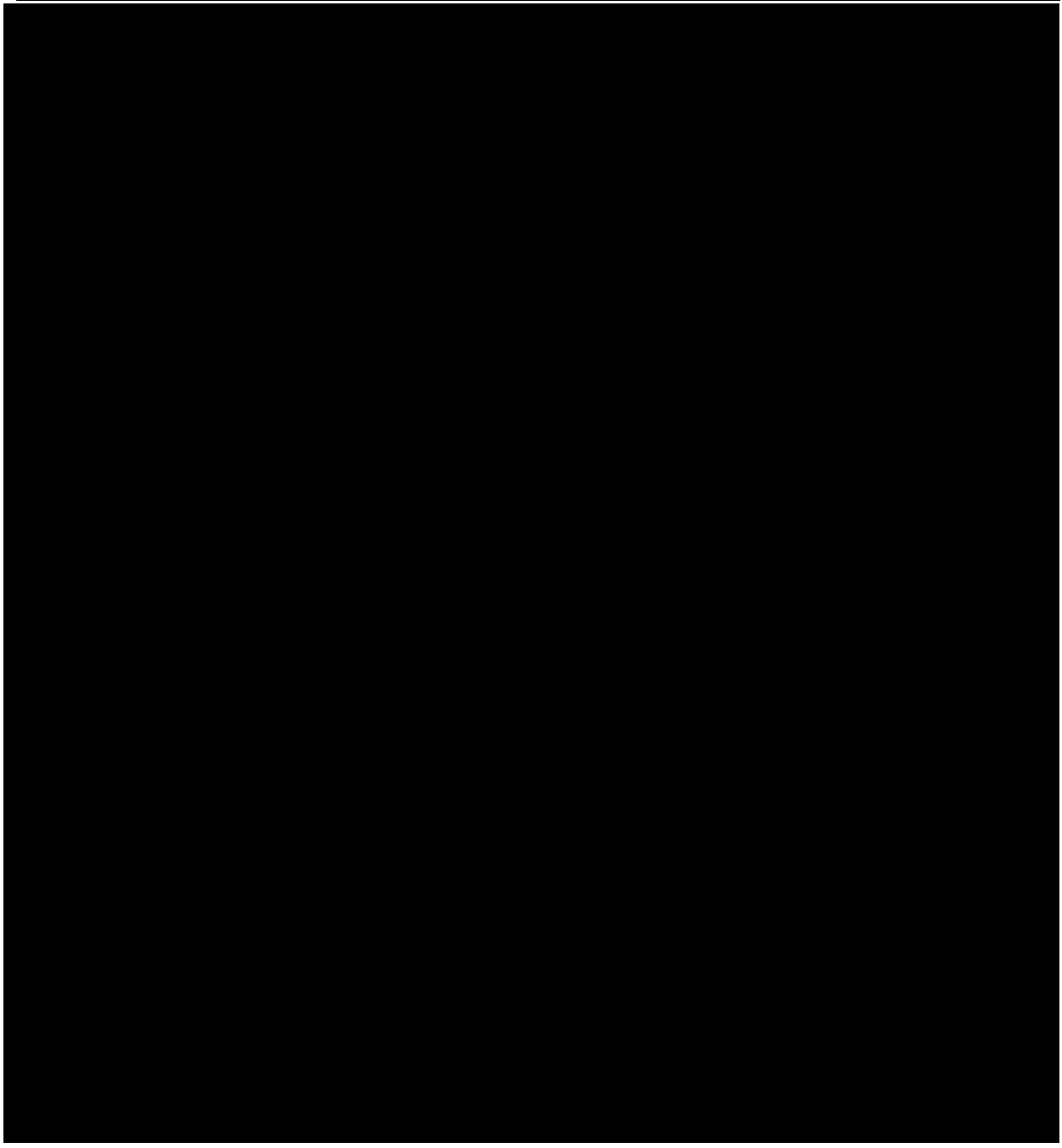
and the upper limit is for $p < 1, (U = 1 \text{ for } p = 1),$

$$U = \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq-1)}}{2(n+z^2)}\right).$$

Note: if L > (100 x p) then L = (100 x p) and if U < (100 x p) then U = (100 x p).







5.5 Rule of exclusion criteria of analysis sets

Table 5-2 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
Enrolled analysis set		Not enrolled/Mis-enrolled/serious GCP violation at site
FAS		Not in the enrolled analysis set;
SAF		Not in the enrolled analysis set; No study drug taken

* Written informed consent must be obtained before any assessment is performed.

6 Reference

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