NOVARTIS

Clinical Development

LOU064/Remibrutinib

CLOU064A2302 / NCT05032157

A multicenter, randomized, double-blind, placebo-controlled Phase 3 study of remibrutinib (LOU064) to investigate the efficacy, safety and tolerability for 52 weeks in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
23-Nov-2021	Prior to FPFV	Creation of final version	N/A - First version	NA
21-Jun-2022	Prior to the primary analysis	Protocol amendment V01 Adress the comments from TFL shell review	SAP Amendment 1	[redacted] Section 1.2.1, Section 1.2.2, Section 2.5.1.3, Section 2.5.1.6, Section 2.5.2.1, Section 2.6.1.6 update the handling of intercurrent events Section 2.1.1.5 update the assessment window for weekly scores from eDiary data, update the assessment window for the assessments performed at study visit [redacted] [redacted] Section 2.5.1.5, Section 2.6.1.5 remove the tipping point analysis as sensitivity analysis Section 2.5.2.2 add details of MMRM Section 2.7.1 specify narrow SMQ search Section 2.7.3 add the handling of local laboratory data for urinalysis, Add the summary table of maximum change for Hematology and Serum chemistry Add the description of newly occurring and worsening abnormality Add the analysis of renal alert criteria Section 2.10 remove the treatment difference from by-visit summary [redacted] Add the summary table by treament and visit

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				[redacted] Section 6 add the reference
28-Mar-2023	Prior to the primary analysis	Add new safety analyses Add details for implementation of statistical modeling analyses and missing data imputation	SAP Amendment 2	Section 2.2.2 list subgroup analyses to be reported outside of CSR Section 2.4.2 combine the summary of concomitant medications for urticaria and non-urticaria Section 2.5.1.1 add the handling of duplicated data in eDiary Section 2.5.1.4 add details for the handling of missing values, imputation steps Section 2.5.2.1 change the imputation method for missing response variables Section 2.5.2.2 add details for the offset variable on negative binomial regression model Section 2.7.1 add new analysis for infections and infestations (SOC) Section 2.7.1.1 add new analyses for the selected AESIs Section 2.7.3 add the handling of urinalysis central laboratory data Update the CTCAE grade based on internal guidance (Version 5.0) Add graphical presentation for liver enzyme test abnormalities Section 5.4.1.1, Section 5.4.2.1, Section 5.4.2.3 add details for implementation of statistical modeling analyses Section 5.4.2.5 new section of exposure adjusted occurrence rate

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 5.4.2.6 new section of confidence interval for proportion of binary data Section 5.4.3 added details for implementation of multiple imputation
27-Apr-2023	Prior to the primary analysis	Add estimand up to Week 24 on the primary and secondary endpoints based on FDA feedback (from March 2023). Add lab parameters with CTCAE grades.	SAP amendment 3	Section 1 Update the version of edit check specifications. Section 1.2 Add the statement that for China registration, scenario with UAS7 score as the primary efficacy endpoint will be adopted. Section 2.1.1.1 Add long term efficacy analysis beyond Week 24. Section 2.1.1.4 Update the definition of on - treatment period at final analysis. Section 2.1.1.5 Update the assessment schedule of weight in Table 2-6 and the assessment window of weight in Table 2-9. [redacted] Section 2.2.2 Add pre-COVID/post-COVID analyses for China subgroup analyses. Section 2.3.2 Update text: “Previous exposure to anti-IgE biologics for CSU (Yes, No).” Section 2.7.3 Add lab parameters of creatinine kinase, total cholesterol, triglycerides, amylase, and lipase with CTCAE grades. Update text: “For the combination criteria of parameters, except potential Hy’s Law case, all the elevations must occur at the same post-baseline timepoint.” Update the notable criteria of serum creatinine as “increase 25% – <50% (%change from baseline), increase ≥ 50%” in Table 2-17. Section 2.7.4.1 Update QTcF (Fridericia’s) interval change from baseline. Section 2.10 Update PRO analyses to include efficacy analyses beyond Week 24 at primary analysis. [redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
30-June-2023	Prior to the primary analysis	Add detailed descriptions on multiple imputation	SAP amendment 4	List of abbreviations: Add CIR and CR. Section 1 Update the version of edit check specifications. Section 2.1.1.5: The start date of eDiary data after Week 24 is updated to the Date of Day 1 of open-label period. Section 2.3.2: Add definition of categorized Duration of CSU in the categorical variables. Section 2.4.1: Include Placebo group in the Entire study period for primary analysis; Update the definition of Last study visit in Tables 2-10 and 2-11. Section 2.7.4.1, Section 2.7.4.2 and Section 2.10: Add description on the handling of scheduled and unscheduled visits for by-visit summary tables for corresponding assessments. Section 5.4.1.1: Add text “If the computation of the MMRM model takes extreme amount of time, the ddfm=bw option could be considered.” Section 5.4.2.6 Update text to clarify that confidence invervals based on the score method including continuity correction are used for observed response rate and adverse event incidence rate. Section 5.4.3: Add more details on multiple imputations, including the macros we will use and the imputation steps, with example codes. Section 6: Reference are sorted in alphabetical order.
24-Jan-2024	Prior to the final analysis	Correction and clarification	SAP amendment 5	Section 1 Update the version of edit check specifications. Section 1.2.1, section 1.2.2, and section 2.6.1.6 Add “or participants non-compliant to treatment prior to Week 12” for consistency.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 2.1.1.4 Add a sentence to clarify the on-treatment double-blind period for safety assessments. Section 2.1.1.5 Update the assessment schedule of weight in Table 2-6 and the assessment window of weight in Table 2-9. Section 2.4.1 Footnote for the definition of last study visit is updated for clarification. Section 2.4.2 For the analysis of rescue medication in oral corticosteroids, remove "by dose per tablet" for correction. Section 2.7.3 Update CTCAE grade for neutrophil count decrease and lymphocyte count decreased according to updated internal CTCAE guidance. Clarify that local laboratory data will not be included in the by-visit summary tables. Add "Box plots for selected parameters will be provided by treatment group and study period." Section 2.7.4.1 Add for completeness: "A shift table from baseline to the worst post-baseline value will be presented based on the overall ECG interpretation." Section 2.7.4.1 and section 2.7.4.2 Add for clarification: "For notable summary tables, all post-baseline visits including unscheduled visits will be considered in the analysis." Section 2.11 Add for clarification: "In the figures of immunoglobulins, normal range will be presented. If multiple normal ranges are available for a parameter, most frequent ranges will be presented." [redacted]

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AAS	Angioedema Activity Score
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
b.i.d.	bis in die/twice a day
BUN	Blood Urea Nitrogen
[redacted]	[redacted]
CIR	Copy Increments in Reference
CR	Copy Reference
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CSU	Chronic Spontaneous Urticaria
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
EAIR	Exposure Adjusted Incidence Rate
EAOR	Exposure Adjusted Occurrence Rate
eDiary	Electronic Diary
[redacted]	[redacted]
FAS	Full Analysis Set
GGT	Gamma-glutamyl transferase
HDL	High-Density Lipoprotein
HLGT	Hight Level Group Term
HLT	High Level Term
HSS	Hives Severity Score
HSS7	Weekly Hives Severity Score
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
INR	International Normalized Ratio
IRT	Interactive Response Technology
ISS	Itch Severity Score
ISS7	Weekly Itch Severity Score
J2R	Jump to Reference
MAR	Missing At Random
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
MMRM	Mixed effect Model for Repeated Measurements
NovDTD	Novartis Drug and Therapy Dictionary

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO	Patient Reported Outcomes
PT	Preferred Term
QTcF	QT interval corrected by Fridericia's formula
RAS	Randomized Set
RAP	Reporting & Analysis Process
RDO	Retrieved Drop Out
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, Listings
UAS	Urticaria Activity Score
UAS7	Weekly Urticaria Activity Score
[redacted]	[redacted]
ULN	Upper Limit of Normal
UPDD	Urticaria Patient Daily Diary
[redacted]	[redacted]

1 Introduction

Data will be analyzed by Novartis according to the data analysis Section 12 of the CLOU064A2302 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 24) if conducted, and the final analysis of CLOU064A2302 study with reference to:

- the study protocol Version 01
- the case report form (CRFs) Version 6.0
- the LOU064A master analysis plan (MAP) Version 2.0
- [redacted]

[redacted]

A separate statistical analysis plan for the program DMC will be prepared.

1.1 Study design

Study CLOU064A2302 is a global Phase 3 multicenter, randomized, double-blind, parallel-group, placebo-controlled study investigating the efficacy, safety and tolerability of remibrutinib (25 mg b.i.d.) in adult participants with Chronic Spontaneous Urticaria (CSU) inadequately controlled by second generation H1-antihistamines.

The study consists of four periods, the total study duration is up to 60 weeks:

- **Screening period**: up to 4 weeks.
- **Double-blind treatment period**: 24 weeks of double-blind treatment with remibrutinib (25 mg b.i.d.) or placebo.
- **Open-label treatment period**: 28 weeks of open-label treatment with remibrutinib (25 mg b.i.d.).
- **Follow-up period**: 4 weeks of treatment-free follow-up (only for participants who do not enroll into the CLOU064A2303B extension study).

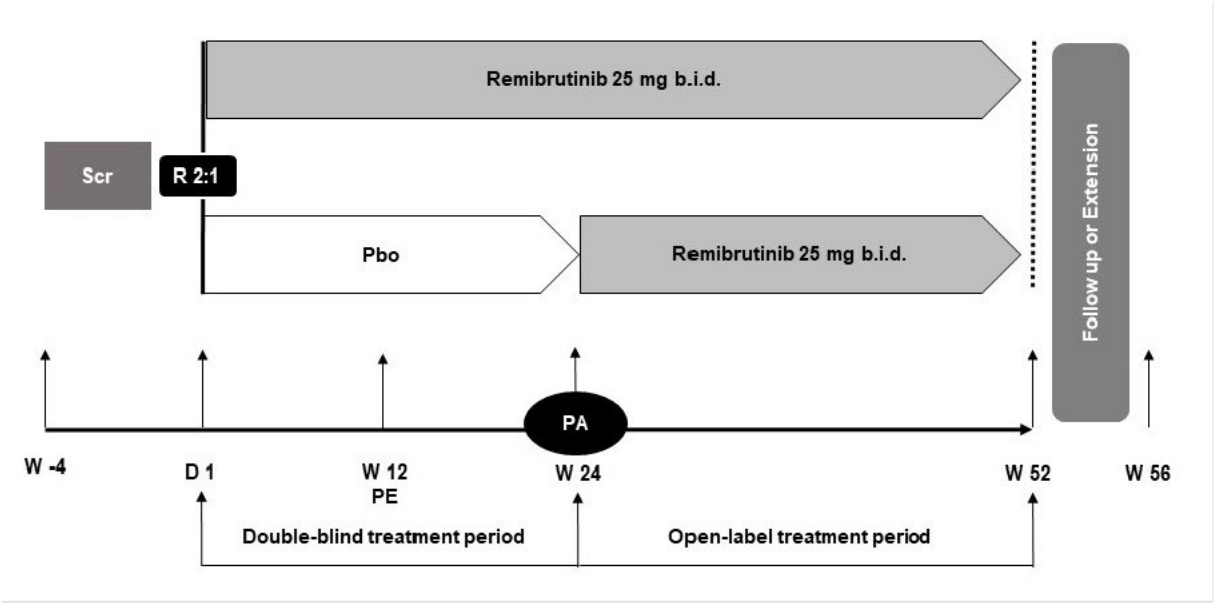
Approximately 450 participants will be randomized in a 2:1 ratio (300 in treatment arm and 150 in the placebo arm) stratified by prior exposure to anti-IgE biologics for CSU and by geographic region to the following arms:

- **LOU064 25 mg b.i.d.**: 25 mg LOU064 twice daily
- **Placebo**: LOU064 matching placebo twice daily

Maximum number of participants with prior exposure to anti-IgE biologics for CSU will be limited to approximately 30% of the total study population.

All participants will be on a stable, locally label approved standard dose of a second generation H1-antihistamine ("background therapy") throughout the entire study (starting a minimum of 7 days prior to randomization until the end of the study). To treat unbearable symptoms of CSU, participants will be allowed to use another second generation H1-antihistamine on an as-needed basis ("rescue therapy").

Figure 1-1 Study Design



D1: Day 1, b.i.d.: bis in die/twice a day, mg: milligram(s), Pbo: placebo, PA: Primary Analysis, PE: Primary Endpoint, Scr: Screening, W: Week

A primary analysis may be conducted when all participants have completed their Week 24 visit or discontinued early and when a minimum of 150 participants across both Phase 3 pivotal studies, CLOU064A2301 and CLOU064A2302 (a second nearly identical Phase 3 study conducted in parallel) have completed the treatment period at Week 52. After the primary analysis and/or after all participants have entered the open label treatment period, additional optional interim analyses may be conducted.

A final analysis will be performed when all participants have completed the study or discontinued early.

1.2 Study objectives, endpoints and estimands

There are two primary objective scenarios based on regional regulatory precedent and Health Authorities' feedback. These two primary objective scenarios will be tested in two distinct testing strategies (Table 1-1 and Table 1-2). Distinctions in the secondary objectives reflect the corresponding scenario: the primary objective in one scenario is presented as secondary objective(-s) in another. The other secondary [redacted] objectives are identical in both scenarios. To support China registration, scenario with UAS7 score as the primary efficacy endpoint listed in Table 1-1 will be adopted.

Table 1-1 Objectives and related endpoints – Scenario with UAS7 as the primary efficacy endpoint

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that remibrutinib (25 mg b.i.d.) is superior to placebo in CSU with respect to change from baseline in UAS7 at Week 12	• Absolute change from baseline in UAS7 at Week 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To demonstrate that a greater proportion of participants achieve disease activity control (UAS7 ≤ 6) at Week 12 who are treated with remibrutinib (25 mg b.i.d.) compared to placebo-treated participants	• Achievement of UAS7 ≤ 6 (yes/no) at Week 12
• To demonstrate that a greater proportion of participants achieve complete absence of hives and itch (UAS7 = 0) at Week 12 who are treated with remibrutinib (25 mg b.i.d.) compared to placebo-treated participants	• Achievement of UAS7 = 0 (yes/no) at Week 12
• To demonstrate the superiority of remibrutinib (25 mg b.i.d.) treated participants with respect to a reduction from baseline in the weekly itch severity score at Week 12 compared to placebo-treated participants	• Improvement of severity of itch, assessed as absolute change from baseline in ISS7 score at Week 12
• To demonstrate the superiority of remibrutinib (25 mg b.i.d.) treated participants with respect to a reduction from baseline in the weekly hive severity score at Week 12 compared to placebo-treated participants	• Improvement of severity of hives, assessed as absolute change from baseline in HSS7 score at Week 12
• To demonstrate that a greater proportion of participants achieve UAS7 ≤ 6 at Week 2 who are treated with remibrutinib (25 mg b.i.d.) compared to placebo-treated participants	• Achieving early onset of disease activity control, as defined as achievement of UAS7≤ 6 (yes/no) at Week 2
• To demonstrate that a greater proportion of participants who are treated with remibrutinib (25 mg b.i.d.) achieve DLQI = 0-1 at Week 12 compared to placebo-treated participants	• No impact on participants' dermatology-quality of life, as defined by achievement of DLQI = 0-1 (yes/no) at Week 12
• To demonstrate that remibrutinib (25 mg b.i.d.) treated participants maintain disease activity control (defined as UAS7≤6) for more weeks compared to placebo treated participants over 12 weeks	• Achieving sustained disease activity control, assessed as cumulative number of weeks with an UAS7≤6 response between baseline and Week 12

Objective(s)	Endpoint(s)
• To demonstrate that remibrutinib (25 mg b.i.d.) treated participants have more angioedema occurrence-free weeks over 12 weeks compared with placebo-treated participants	• Number of weeks without angioedema, assessed by the cumulative number of weeks with an AAS7 = 0 response between baseline and Week 12
• To demonstrate the safety and tolerability of remibrutinib (25 mg b.i.d.)	• Occurrence of treatment emergent adverse events and serious adverse events during the study

[redacted]

Objective(s)	Endpoint(s)
[redacted]	

Table 1-2 Objectives and related endpoints - Scenario with ISS7 and HSS7 as the co-primary efficacy endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that remibrutinib (25 mg b.i.d.) is superior to placebo in CSU with respect to change from baseline in ISS7 and HSS7 at Week 12	• Absolute change from baseline in ISS7 at Week 12 • Absolute change from baseline in HSS7 at Week 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To demonstrate that remibrutinib (25 mg b.i.d.) is superior to placebo in CSU with respect to change from baseline in UAS7 at Week 12	• Absolute change from baseline in UAS7 at Week 12
• To demonstrate that a greater proportion of participants achieve disease activity control (UAS7 ≤ 6) at Week 12 who are treated with remibrutinib (25 mg b.i.d.) compared to placebo-treated participants	• Achievement of UAS7≤ 6 (yes/no) at Week 12
• To demonstrate that a greater proportion of participants achieve complete absence of hives and itch (UAS7 = 0) at Week 12 who are treated with remibrutinib (25 mg b.i.d.) compared to placebo-treated participants	• Achievement of UAS7 = 0 (yes/no) at Week 12
• To demonstrate that a greater proportion of participants achieve UAS7 ≤ 6 at Week 2 who are treated with remibrutinib (25 mg b.i.d.) compared to placebo-treated participants	• Achieving early onset of disease activity control, as defined as achievement of UAS7≤ 6 (yes/no) at Week 2
• To demonstrate that a greater proportion of participants who are treated with remibrutinib (25 mg b.i.d.) achieve DLQI = 0-1 at Week 12 compared to placebo-treated participants	• No impact on participants' dermatology quality of life as defined by achievement of DLQI = 0-1 (yes/no) at Week 12.
• To demonstrate that remibrutinib (25 mg b.i.d.) treated participants maintain disease activity control (defined as UAS7≤6) for more weeks compared to placebo treated participants over 12 weeks	• Achieving sustained disease activity control, assessed as cumulative number of weeks with an UAS7≤6 response between baseline and Week 12
• To demonstrate that remibrutinib (25 mg b.i.d.) treated participants have more angioedema occurrence-free weeks over 12 weeks compared with placebo-treated participants	• Number of weeks without angioedema, assessed by the cumulative number of weeks with an AAS7= 0 response between baseline and Week 12
• To demonstrate the safety and tolerability of remibrutinib (25 mg b.i.d.)	• Occurrence of treatment emergent adverse events and serious adverse events during the study

Objective(s)	Endpoint(s)
[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).

Primary estimand for scenario with UAS7 as primary efficacy endpoint

The primary clinical question of interest is: What is the effect of remibrutinib treatment versus placebo on the change from baseline in UAS7 score after 12 weeks treatment in adult participants with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of discontinuation from study treatment for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication as an unfavourable outcome?

The primary estimand is described by the following attributes:

1. **Population**: participants with inadequately controlled CSU despite treatment with second generation H1-antihistamine who have CSU duration ≥ 6 months, a UAS7 score ≥ 16, ISS7 ≥ 6 and HSS7 score ≥ 6 in the last 7 days prior to randomization.
2. **Endpoint:** Change in UAS7 from baseline at Week 12.
3. **Treatment of interest:** the randomized study treatment (remibrutinib 25 mg b.i.d. or placebo) regardless of treatment compliance, with background medication of locally label approved dose second generation H1-antihistamine, and a different second generation H1-antihistamine as rescue medication.
4. **Summary Measurement:** the mean difference between treatment groups.
5. **Handling of intercurrent events:**

- Discontinuation of study treatment due to any reason: Treatment policy strategy
- Intake of strongly confounding prohibited medication (e.g. biologics treatment at any time before Week 12, cyclosporin after Week 8, systemic corticosteroids after Week 8): Composite strategy (irrespective of potential occurrence of other intercurrent events)
- Intake of rescue medication, switch of background medication, intake of other prohibited medication, or participants non-compliant to treatment prior to Week 12: Treatment policy strategy

Primary estimand for scenario with ISS7/HSS7 as co-primary efficacy endpoints

The primary clinical question of interest is: What is the effect of remibrutinib treatment versus placebo on the co-primary endpoints change from baseline in ISS7 score and change from baseline in HSS7 score after treatment in adult participants with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of discontinuation from study treatment for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication as an unfavourable outcome?

The primary estimand is described by the following attributes:

1. **Population**: participants with inadequately controlled CSU despite treatment with second generation H1-antihistamine who have CSU duration ≥ 6 months, a UAS7 score ≥ 16, ISS7 ≥ 6 and HSS7 score ≥ 6 in the last 7 days prior to randomization.
2. **Endpoint (co-primary):** Change in ISS7 from baseline at Week 12 and change in HSS7 from baseline at Week 12.
3. **Treatment of interest:** the randomized study treatment (remibrutinib 25 mg b.i.d. or placebo) regardless of treatment compliance, with background medication of locally label approved dose second generation H1-antihistamine, and a different second generation H1-antihistamine as rescue medication.
4. **Summary Measurement:** the mean difference between treatment groups.
5. **Handling of intercurrent events:**
   - Discontinuation of study treatment due to any reason: Treatment policy strategy
   - Intake of strongly confounding prohibited medication (e.g, biologics treatment at any time before Week 12, cyclosporin after Week 8, systemic corticosteroids after Week 8): Composite strategy (irrespective of potential occurrence of other intercurrent events)
   - Intake of rescue medication, switch of background medication, intake of other prohibited medication, or participants non-compliant to treatment prior to Week 12: Treatment policy strategy

1.2.2 Secondary estimand(s)

Secondary estimand on the secondary endpoint UAS7 ≤ 6 response at week 12

The secondary clinical question of interest is: What is the effect of remibrutinib treatment versus placebo on the UAS7 ≤ 6 response after 12 weeks treatment in adult participants with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of treatment discontinuation for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication as an unfavourable outcome?

The secondary estimand is described by the following attributes:

1. **Population**: patients with inadequately controlled CSU despite treatment with second generation H1-antihistamine who have CSU duration ≥6 months, a UAS7 score ≥ 16, ISS7 score ≥ 6 and HSS7 score ≥ 6 in the last 7 days prior to randomization.
2. **Endpoint:** UAS7 ≤ 6 response at Week 12.
3. **Treatment of interest:** the randomized study treatment (remibrutinib 25 mg b.i.d. or placebo) regardless of treatment compliance, with background medication of locally label approved dose second generation H1-antihistamine, and a different second generation H1-antihistamine as rescue medication.
4. **Summary Measurement:** the odds ratio between treatment groups.
5. **Handling of intercurrent events:**
    - Discontinuation of study treatment due to any reason: Treatment policy strategy
    - Intake of strongly confounding prohibited medication (e.g, biologics treatment at any time before Week 12, cyclosporin after Week 8, systemic corticosteroids after Week 8): Composite strategy (irrespective of potential occurrence of other intercurrent events)
    - Intake of rescue medication, switch of background medication, intake of other prohibited medication, or participants non-compliant to treatment prior to Week 12: Treatment policy strategy

Secondary estimand on the secondary endpoint UAS7 = 0 response at week 12

Similar Estimand approach will be implemented for UAS7= 0 as for UAS7 ≤ 6.

Other secondary estimand on the other secondary endpoints as defined in Table 1-1 and Table 1-2.

Similar Estimand approach will be implemented for these endpoints as the primary Estimand or co-primary Estimand.

2 Statistical methods

2.1 Data analysis general information

The statistical analysis will be performed by Novartis personnel, using SAS Version 9.4 or above.

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.

The p-values will be presented as one-sided with level of significance 2.5%. 95% confidence intervals will be displayed and will always be two-sided.

The primary analysis may be conducted when all participants have completed their Week 24 visit or discontinued early and when a minimum of 150 participants across both Phase 3 pivotal studies (A2301 and A2302) have completed the 52 week treatment period. Details are given in this document.

The final analysis will be performed based on the final database lock when all participants have completed the study or discontinued early.

2.1.1 General definitions

2.1.1.1 Analysis period and treatment groups

Primary analysis

When the primary analysis is conducted, the efficacy analysis will include visits up to Week 24 and include the primary endpoint at Week 12. Long term efficacy analysis including all data available at the cut-off date (beyond Week 24) will be evaluated in addition.

The safety analysis will be conducted at the time of primary analysis. This analysis will include separate analysis for the double-blind period (comparing LOU064 vs placebo up to Week 24) and the entire study period data available at the cut-off date (including beyond Week 24). The safety data during all periods of double blind, open label and safety follow up will be included.

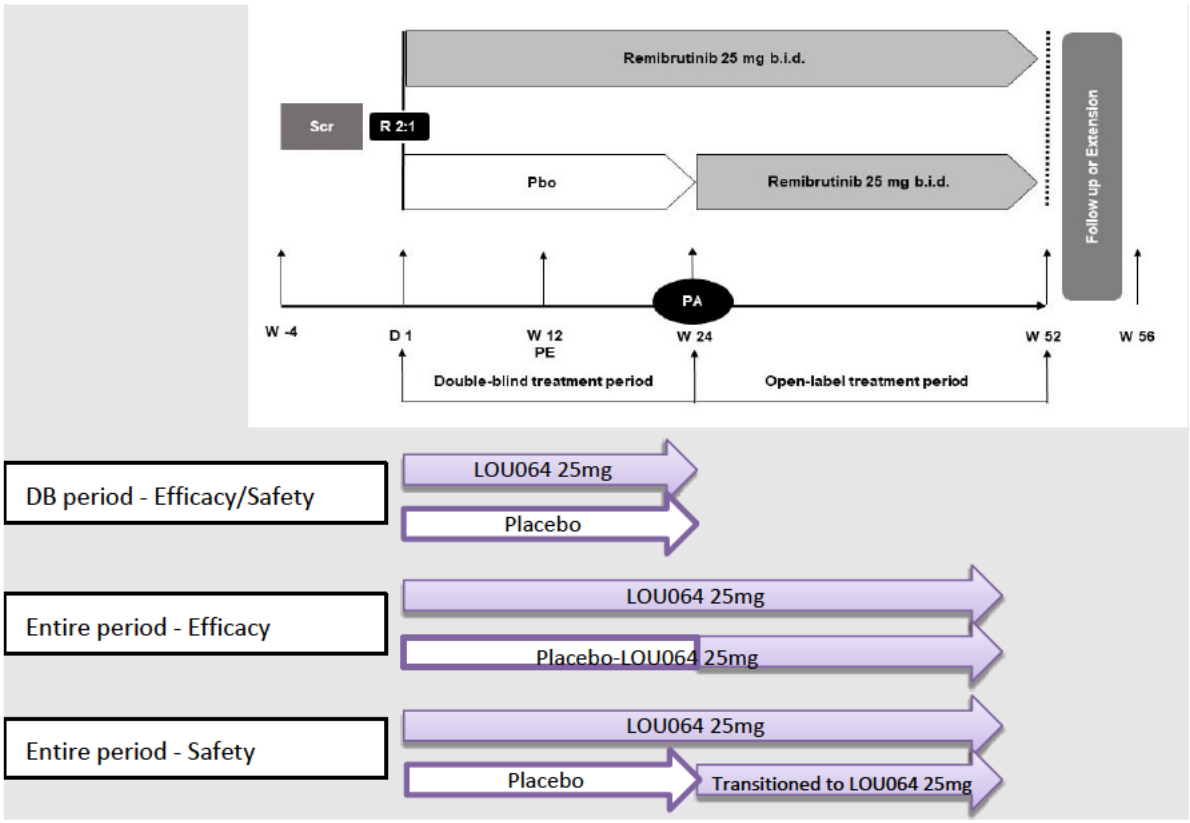
The treatment groups and the data to be used for primary analysis are provided in Table 2-1.

Table 2-1 Treatment groups for primary analysis

Endpoint	Study period	Treatment group	Details
Efficacy	Double blind	LOU064 25mg	Participants initially randomized to LOU064 Efficacy from baseline up to Week 24 Note: the primary endpoint is at Week 12
		Placebo	Participants initially randomized to placebo Efficacy from baseline up to Week 24 Note: the primary endpoint is at Week 12
	Entire study	LOU064 25mg	Participants initially randomized to LOU064

Endpoint	Study period	Treatment group	Details
	(DB period + OL period)		Efficacy from baseline up to cut-off
		Placebo - LOU064 25mg	Participants initially randomized to placebo regardless of entering into OL period, i.e., including participants who discontinued during DB period and not entered into OL period, participants who entered into OL period and switched to LOU064. Efficacy from baseline up to cut-off
Safety	Double blind	LOU064 25mg	Participants initially randomized to LOU064 Safety from baseline up to Week 24
		Placebo	Participants initially randomized to placebo Safety from baseline up to Week 24
	Entire study (DB period + OL period + FW period)	LOU064 25mg	Participants initially randomized to LOU064 Safety from baseline up to cut-off
		Placebo	Participants initially randomized to placebo Safety from baseline up to Week 24
		Transitioned to LOU064 25mg	Participants initially randomized to placebo and switched to LOU064 Safety after switching to LOU064 up to cut-off

DB: double-blind, OL: open-label, FW: follow-up



Final analysis

Final efficacy and safety analyses will be conducted on the entire study period (all periods of double blind, open label and safety follow up).

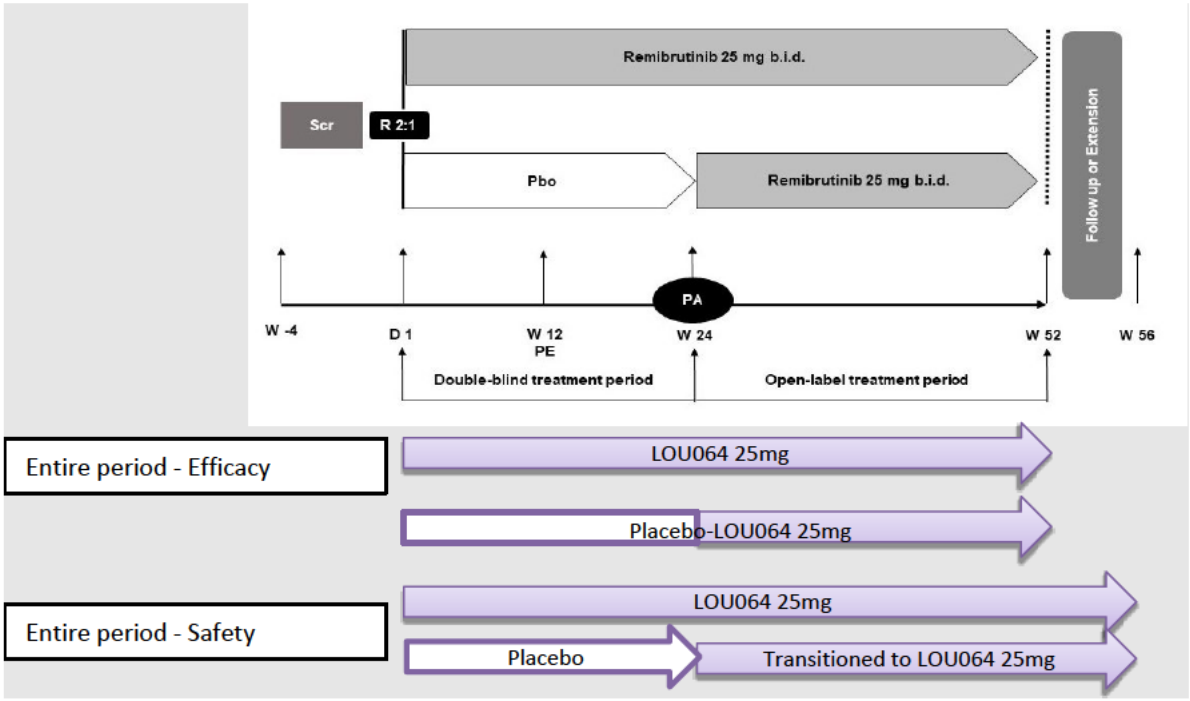
The treatment groups and the data to be used for final analysis are shown in Table 2-2.

Please note: efficacy analysis for "Placebo – LOU064 25mg "treatment group will be provided for all participants initially randomized to placebo regardless of entering the open-label treatment. The efficacy data from baseline to Week 24 will be assessed under placebo. The data after the first dose of LOU064 will be assessed under LOU064 25mg treatment, but separated from the LOU064 25mg treatment group (participants initially randomized to LOU064). Safety analysis for "Transitioned to LOU064" group will be conducted using safety data after switching to LOU064 25 mg treatment.

Table 2-2 Treatment groups for final analyses

Endpoint	Period	Treatment group	Details
Efficacy	Entire study (DB period + OL period)	LOU064 25mg	Participants initially randomized to LOU064 Efficacy from baseline to Week 52
		Placebo - LOU064 25mg	Participants initially randomized to placebo regardless of entering into OL period, i.e. including participants who discontinued during DB period and not entered into OL period, participants who entered into OL period and switched to LOU064. Efficacy from baseline up to Week 52. Note: the data from baseline to Week 24 is under placebo, the data after the first dose of LOU064 is under LOU064 25mg
Safety	Entire study (DB period + OL period + FW period)	LOU064 25mg	Participants initially randomized to LOU064 Safety from baseline up to the end of study
		Placebo	Participants initially randomized to placebo Safety from baseline up to Week 24
		Transitioned to LOU064 25mg	Participants initially randomized to placebo and switched to LOU064 25mg Safety after switching to LOU064 up to the end of study

DB: double-blind, OL: open-label, FW: follow-up



2.1.1.2 Baseline and post-baseline definitions

Baseline for safety (in treatment period) 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 (in treatment period) is comprised of the 7 days prior to the randomization day for weekly scores (UAS7, HSS7, ISS7, AAS7, [redacted] etc.). For other assessments (DLQI, [redacted] etc.), baseline is the assessment on or before the randomization day.

2.1.1.3 Study Day 1 and Study Day

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

For efficacy analysis, the day of randomization is defined as 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 (for safety)/Randomization (for efficacy)] + 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 (for safety)/Randomization (for efficacy)], 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.

2.1.1.4 On-treatment period for safety assessment

The On-treatment period is defined as the period from the first date of dose intake of treatment to the last date of dose intake + a period of time accounting for remaining exposure to drug in relation to the potential pharmacodynamic effects of remibrutinib. It is the reference period for safety analyses on adverse events, laboratory, vital signs, etc.

Remibrutinib has a short half-life (5hrs). Due to the covalent-binding mode, pharmacodynamic effects, including target inhibition in tissues and cells is to be taken into account for determining the follow-up time after the last study drug dose, which is beyond 5 half-lives'. As a conservative measure, 28 days was selected.

Double blind period

The on-treatment DB period will be defined as

- starting from the date of the first actual dose intake of DB treatment and
- ending at the minimum between (i) the date of the last actual dose intake of DB treatment plus 4 weeks (28 days) or (ii) the end of DB period

The end of DB period is minimum of (one day before the date of the first actual dose intake of OL treatment, or the date of study discontinuation, or safety follow-up).

For the participants who entered open-label period more than 28 days later than the last actual dose intake of DB treatment, their end date of on-treatment DB period is defined as one day before the date of the first actual dose intake of OL treatment.

The safety assessment performed at the visit on the day of the first actual dose intake of OL treatment belongs to DB period, assuming that this assessment is performed before the actual dose intake of OL treatment.

This definition will be applied to both of LOU064 25mg treatment group and placebo group.

Entire study period

At the primary analysis, for LOU064 25mg group, the on-treatment period for entire study period will be defined as

- starting from the date of the first actual dose intake of LOU064 treatment
  i.e., the first day of LOU064 DB treatment
- ending at the minimum between (i) the date of the last actual dose intake of LOU064 treatment plus 4 weeks (28 days) or (ii) the end of study

The end of study is either the date of Week 52 visit, or study discontinuation, or study completion, or safety follow-up visit or cut-off date of primary analysis, depending on participant's status.

For Transitioned to LOU064 25mg group, the on-treatment period for entire study period will be defined as

- starting from the date of the first actual dose intake of LOU064 treatment (i.e., the first day of LOU064 OL treatment)

- ending at the minimum between (i) the date of the last actual dose intake of LOU064 OL treatment plus 4 weeks (28 days) or (ii) the end of study

The end of study is either the date of Week 52 visit, or study discontinuation, or study completion, or safety follow-up visit or cut-off date of primary analysis, depending on participant's status.

For Placebo group, the definition of on-treatment period is same as the on-treatment DB period.

At the final analysis, **for LOU064 25mg group**, the on-treatment period for entire study period will be defined as

- starting from the date of the first actual dose intake of LOU064 treatment (i.e., the first day of LOU064 DB treatment) and
- ending at the minimum between (i) the date of the last actual dose intake of LOU064 treatment plus 4 weeks (28 days), or (ii) the end of study

The end of study is either the date of Week 52 visit, or study discontinuation, or study completion, or safety follow-up visit.

For Transitioned to LOU064 25mg group, the on-treatment period for entire study period will be defined as

- starting from the date of the first actual dose intake of LOU064 treatment (i.e., the first day of LOU064 OL treatment) and
- ending at the minimum between (i) the date of the last actual dose intake of LOU064 treatment plus 4 weeks (28 days), or (ii) the end of study

The end of study is either the date of Week 52 visit, or study discontinuation, or study completion, or safety follow-up visit.

For Placebo group, the definition of on-treatment period is same as the on-treatment DB period.

2.1.1.5 Assessment window

Assessment window for weekly scores (e.g. UAS7, ISS7, HSS7, etc.) from eDiary data

For completers (i.e. participants completed Week 52 study treatment), the study weeks for assessment completed on eDiary up to Week 24 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 23 of the treatment period will be derived based on scheduled visit day as defined in Table 2-3. eDiary data on or before Day -1 of actual Week 24 study visit will be used for weekly score calculation up to Week 23.

The analysis Week 24 score will be derived as Day -7 to Day -1 of actual Week 24 study visit day.

After Week 24 until Week 51, weekly score will be derived based on the study days starting with Day 1 of open-label period (i.e., Date of first study treatment in open-label period). The study day for the eDiary date will be calculated as [Date of Diary] – [Date of Day 1 of open-label period] + 1. The analysis Week 25 through Week 51 of the treatment period will be derived based on scheduled visit day as defined in Table 2-3. eDiary data on or before Day -1 of actual Week 52 study visit will be used for weekly score calculation up to Week 51.

The analysis Week 52 score will be derived as Day -7 to Day -1 of actual Week 52 study visit day.

Table 2-3 Assessment window for weekly scores based on eDiary (for completers)

Analysis period	Analysis visit	Scheduled Visit Day	eDiary Assessment Window
Double-blind	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 78 to Day 84
	Week 13	-	Day 85 to Day 91
	Week 14	-	Day 92 to Day 98
	Week 15	-	Day 99 to Day 105
	Week 16	113	Day 106 to Day 112
	Week 17	-	Day 113 to Day 119
	Week 18	-	Day 120 to Day 126
	Week 19	-	Day 127 to Day 133

	Week 20	141	Day 134 to Day 140
	Week 21	-	Day 141 to Day 147
	Week 22	-	Day 148 to Day 154
	Week 23	-	Day 155 to Day 161
	Week 24	169	Day -7 to Day -1 of Week 24 study visit
Open label	Week 25	-	Day 1 (Date of first study treatment in open-label period) to Day 7 of open-label period
	Week 26	-	Day 8 to Day 14 of open-label period
	Week 27	-	Day 15 to Day 21 of open-label period
	Week 28	-	Day 22 to Day 28 of open-label period
	Week 29	-	Day 29 to Day 35 of open-label period
	Week 30	-	Day 36 to Day 42 of open-label period
	Week 31	-	Day 43 to Day 49 of open-label period
	Week 32	225	Day 50 to Day 56 of open-label period
	Week 33	-	Day 57 to Day 63 of open-label period
	Week 34	-	Day 64 to Day 70 of open-label period
	Week 35	-	Day 71 to Day 77 of open-label period
	Week 36	-	Day 78 to Day 84 of open-label period
	Week 37	-	Day 85 to Day 91 of open-label period
	Week 38	-	Day 92 to Day 98 of open-label period
	Week 39	-	Day 99 to Day 105 of open-label period
	Week 40	281	Day 106 to Day 112 of open-label period
	Week 41	-	Day 113 to Day 119 of open-label period
	Week 42	-	Day 120 to Day 126 of open-label period

	Week 43	-	Day 127 to Day 133 of open-label period
	Week 44	-	Day 134 to Day 140 of open-label period
	Week 45	-	Day 141 to Day 147 of open-label period
	Week 46	-	Day 148 to Day 154 of open-label period
	Week 47	-	Day 155 to Day 161 of open-label period
	Week 48	-	Day 162 to Day 168 of open-label period
	Week 49	-	Day 169 to Day 175 of open-label period
	Week 50	-	Day 176 to Day 182 of open-label period
	Week 51	-	Day 183 to Day 189 of open-label period
	Week 52	365	Day -7 to Day -1 of Week 52 study visit

Note: Week 52 study visit is during treatment epoch. eDiary data on this day will not be taken into the analysis.

For participants early discontinued study treatment prior to Week 12, it is suggested to collect the eDiary data even after the participant discontinued from treatment per "Treatment policy strategy" (this part of data is named as "retrieved drop-out data"). The retrieved drop-out (RDO) data will be included in the weekly score derivation until Week 12, when treatment policy strategy is used for estimands.

For participants who discontinued the study treatment earlier than Week 24, assessment will follow rules as defined in Table 2-4 **up to Week 24**. After Week 25, weekly scores will not be derived even when the eDiary data are collected.

Table 2-4 Assessment window for weekly scores based on eDiary (for early treatment discontinued participants earlier than Week 24)

Analysis period	Analysis visit	Scheduled Visit Day	eDiary Assessment Window
Double blind	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 78 to Day 84
	Week 13	-	Day 85 to Day 91
	Week 14	-	Day 92 to Day 98
	Week 15	-	Day 99 to Day 105
	Week 16	113	Day 106 to Day 112
	Week 17	-	Day 113 to Day 119
	Week 18	-	Day 120 to Day 126
	Week 19	-	Day 127 to Day 133
	Week 20	141	Day 134 to Day 140
	Week 21	-	Day 141 to Day 147
	Week 22	-	Day 148 to Day 154
	Week 23	-	Day 155 to Day 161
	Week 24	169	Day 162 to Day 168
No further analysis visit			

For participants who discontinued study treatment after Week 24, assessment will follow the rules as defined in Table 2-5 **up to Week 52.**

Table 2-5 Assessment window for weekly scores based on eDiary (for early treatment discontinued participants after Week 24)

Analysis period	Analysis visit	Scheduled Visit Day	eDiary Assessment Window
Double blind	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 78 to Day 84
	Week 13	-	Day 85 to Day 91
	Week 14	-	Day 92 to Day 98
	Week 15	-	Day 99 to Day 105
	Week 16	113	Day 106 to Day 112
	Week 17	-	Day 113 to Day 119
	Week 18	-	Day 120 to Day 126
	Week 19	-	Day 127 to Day 133
	Week 20	141	Day 134 to Day 140
	Week 21	-	Day 141 to Day 147
	Week 22	-	Day 148 to Day 154
	Week 23	-	Day 155 to Day 161
	Week 24	169	Day -7 to Day -1 of Week 24 study visit

Open label	Week 25	-	Day 1 (Date of first study treatment in open-label period) to Day 7 of open-label period
	Week 26	-	Day 8 to Day 14 of open-label period
	Week 27	-	Day 15 to Day 21 of open-label period
	Week 28	-	Day 22 to Day 28 of open-label period
	Week 29	-	Day 29 to Day 35 of open-label period
	Week 30	-	Day 36 to Day 42 of open-label period
	Week 31	-	Day 43 to Day 49 of open-label period
	Week 32	225	Day 50 to Day 56 of open-label period
	Week 33	-	Day 57 to Day 63 of open-label period
	Week 34	-	Day 64 to Day 70 of open-label period
	Week 35	-	Day 71 to Day 77 of open-label period
	Week 36	-	Day 78 to Day 84 of open-label period
	Week 37	-	Day 85 to Day 91 of open-label period
	Week 38	-	Day 92 to Day 98 of open-label period
	Week 39	-	Day 99 to Day 105 of open-label period
	Week 40	281	Day 106 to Day 112 of open-label period
	Week 41	-	Day 113 to Day 119 of open-label period
	Week 42	-	Day 120 to Day 126 of open-label period
	Week 43	-	Day 127 to Day 133 of open-label period
	Week 44	-	Day 134 to Day 140 of open-label period
	Week 45	-	Day 141 to Day 147 of open-label period

	Week 46	-	Day 148 to Day 154 of open-label period
	Week 47	-	Day 155 to Day 161 of open-label period
	Week 48	-	Day 162 to Day 168 of open-label period
	Week 49	-	Day 169 to Day 175 of open-label period
	Week 50	-	Day 176 to Day 182 of open-label period
	Week 51	-	Day 183 to Day 189 of open-label period
	Week 52	365	Day 190 to Day 196 of open-label period
No further analysis visit			

Assessment window for the assessments performed at study visit (e.g. DLQI, [redacted], safety assessment except AEs etc.) until Week 52

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, and study discontinuation (SD) visit. **ETD visit, SD 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).

The assessment window is based on the study assessment schedule. For participants initially randomized to placebo and switched to LOU064, the date of first OL study treatment will be considered. The assessments under placebo treatment will not be remapped to the visits during OL period and the assessments under LOU064 treatment will not be remapped to the visits during DB period.

The protocol defined assessment schedule is shown in Table 2-6. For ECG, at Week 2, 12, 52 and SD visit pre and post-dose assessments will be collected. ETD visit can be remapped to Week 24 only, and SD visit can be remapped to Week 2, 12 and 52.

Table 2-6 Assessment schedule

Visit Name	BSL	week 2	week 4	week 8	week 12	week 16	week 20	week 24	week 32	week 40	week 52	ETD	SD
Scheduled visit Day	1	15	29	57	85	113	141	169	225	281	365	-	-
Vital Signs Clinical Chemistry* Hematology Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X		X		X			X		X	X	X	X
[redacted]													
Weight					X						X	X	X
ECG	X	X[2]			X[2]			X			X[2]	X	X[2]
DLQI	X		X		X			X			X	X	X
[redacted]													

X: to be recorded, BSL: baseline, ETD: early treatment discontinuation, SD: study discontinuation

[1] only post-baseline assessments

[2] pre and post dose

* C-reactive protein (CRP), estimated Glomerular Filtration Rate (eGFR): assessed at screening, baseline, weeks 12, 24 and 52. Fasting glucose assessed at baseline, weeks 2, 12 and 52.

Table 2-7 shows the assessment windows for the assessments collected at every visit (i.e., Vital signs, Clinical Chemistry, Hematology, Urinalysis).

If more than one assessment fall into the interval,

- Then if there is the scheduled visit recorded in eDiary or eCRF, this visit will be chosen.
- If no, the earliest visit day will be chosen.

For example, when a participant discontinued study treatment after completing Week 2 and Week 4, and ETD visit occurred on Day 35 and SD visit occurred on Day 80, the ETD visit will be mapped to Week 8 and SD visit will be remapped to Week 12.

If a participant visited the site earlier than scheduled visit day, e.g., Week 4 on Day 25, ETD visit on Day 29, ETD visit will be remapped to Week 4. As the participant already performed Week 4 scheduled visit, the remapped Week 4 (ETD visit) will not be used.

If a participant visited the site late than scheduled visit day, e.g.,Week 4 on Day 25, ETD visit on Day 58, SD visit on Day 85, both ETD visit and SD visit will be remapped to Week 12. In this case, ETD visit will be used as Week 12, and Week 8 will be missing.

Table 2-7 Assessment window for vital signs, clinical chemistry, hematology, urinalysis until Week 52

Assessment visit	Scheduled Visit Day	Assessment Window
Week 2	15	Day 2 to Day 15
Week 4	29	Day 16 to Day 29
Week 8	57	Day 30 to Day 57
Week 12	85	Day 58 to Day 85
Week 16	113	Day 86 to Day 113
Week 20	141	Day 114 to Day 141
Week 24	169	Day 142 to Day 169
Week 32	225	Day 170 to Day 225
Week 40	281	Day 226 to Day 281
Week 52	365	Day 282 to Day 365

For the assessments which are not collected at every visit (e.g., DLQI), assessment window will be combined. For example, DLQI is collected at Week 4, Week 12, Week 24 and Week 52. The assessment window will be combined as follows:

Table 2-8 Assessment window for DLQI until Week 52

Assessment visit	Scheduled Visit Day	Assessment Window
Week 4	29	Day 2 to Day 29
Week 12	85	Day 30 to Day 85
Week 24	169	Day 86 to Day 169
Week 52	365	Day 170 to Day 365

Table 2-9 shows the assessment windows of days for each assessment.

Table 2-9 Assessment windows by assessment

Assessment Visit	week 2	week 4	week 8	week 12	week 16	week 20	week 24	week 32	week 40	week 52
Scheduled visit Day	15	29	57	85	113	141	169	225	281	365
Vital Signs Clinical Chemistry Hematology Urinalysis	2-15	16-29	30-57	58-85	86-113	114-141	142-169	170-225	226-281	282-365
Coagulation Panel	2-29		30-85		86-169			170-281		282-365
[redacted]										
Weight	2-85				86-365					
ECG	2-15	16-85			86-169			170-365		
DLQI	2-29		30-85		86-169			170-365		
[redacted]										

2.2 Analysis sets

The following analysis sets will be used in this trial:

- The **Randomized Analysis Set (RAS)** consists of all randomized participants, regardless of whether or not they receive a dose of study drug. Participants will be analyzed according to the treatment they are assigned.
- The **Full Analysis Set (FAS)** comprises all participants to whom study treatment has been assigned by randomization. FAS will be used for all efficacy variables, unless otherwise stated. Mis-randomized participants (mis-randomized in IRT) will be included in the Randomized set but will be excluded from FAS.

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

- The **Safety Set (SAF)** includes all participants who received at least one dose of study treatment, whether or not being randomized. Participants will be analyzed according to the study treatment received. The safety set will be used in the analysis of all safety variables. The actual treatment will be defined as the treatment received over the study. In case of error in dispensation, the actual treatment will correspond to the treatment which was given most often.

For the rule of exclusion criteria of analysis sets, see Appendix 5-5.

2.2.1 Subgroup of interest

To explore the impact of disease characteristics at baseline on the efficacy, subgroup analysis will be provided on:

- UAS7 (for co-primary endpoints ISS7/HSS7) change from baseline over time
- Achievement of UAS7≤6 over time
- Achievement of UAS7=0 over time

[redacted]

The definition of subgroups are following,

[redacted]

- Duration of CSU defined as Time since diagnosis of urticaria, informed consent date – diagnosis date + 1 (≤1 year, >1 to 3 years, >3 to 5 years, >5years)

[redacted]

Subgroup analyses will be performed for the primary endpoint and secondary endpoints using the randomization strata subgroups. If the actual stratum is different to the assigned stratum in IRT, the actual stratum will be used in the analysis.

Randomization strata

- Previous exposure to anti-IgE biologics (Yes/No)
- Geographic region (LaCAN (Latin America, Caribbean and Canada), RE (Region Europe), China, US, AMEA (Asia, Middle East & Africa)

2.2.2 Subgroup analyses to be reported outside of CSR

In addition, to support local regulatory requirements, analysis of key efficacy and safety data for Chinese patients (Geographic region=China) (only required for China submission) will be performed. The following endpoints will be summarized and/or analyzed using similar methods as described in below sections, if not marked with special symbol.

- Patient disposition
- Exposure

- Demographics
- Disease characteristics
- Selected efficacy endpoints
- [redacted]
- Laboratory data
- ECG
- Vital signs
- Adverse events*

* Some of the outputs are only needed for Chinese subgroup analyses. The specific outputs under each endpoint will be specified in the TFLs.

To assess the potential impact due to COVID occurred after the new COVID policy was released in China, additional safety analyses will be perform by pre-COVID and post-COVID period, which is cut-off by Dec 7th, 2022. The following analysis will be provided by periods for Chinese population.

- Exposure
- Adverse events (TEAE and AESI)

For the analyses of adverse events by COVID periods, the exposure adjusted incidence rate (EAIR) summary table will be provided.

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 of 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 Randomized set who completed the study treatment period, who discontinued the study treatment and the reason for treatment discontinuation will be presented for each treatment group and all participants (total) by study period. LOU064 25 mg and Placebo treatment groups will be presented for DB period, LOU064 25 mg and Placebo-LOU064 25mg treatment groups will be presented for entire period.

The number and percentage of participants in the Randomized 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 (Randomized, FAS and Safety) will be presented for each treatment group and all participants (total) by study period (as presented in Table 2-1 and Table 2-2). 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 for each treatment group and all participants (total). The summary of overall important PDs (including COVID-19 related PDs), important COVID-19 related PDs will be provided by study period for the Randomized set.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for each initially randomized treatment group (LOU064 25mg, Placebo) and for all participants (total) for the Randomized 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
- Baseline UAS7 score
- Baseline ISS7 score
- Baseline HSS7 score
- Baseline AAS7 score
- Baseline DLQI score
- Duration of CSU, defined as Time since diagnosis of urticaria (years) = (informed consent date – diagnosis date + 1)/365.25

Categorical variables:

- Age categories (≥18 - <65, ≥ 65 - <85 years , ≥85 years)
- Gender
- Race
- Ethnicity
- BMI groups (< 25, 25 - <30, ≥ 30 kg/m^2)
- Baseline UAS7 category (Mild disease: 6 < UAS7 <16; Moderate disease: 16 ≤ UAS7 <28; Severe disease 28 ≤ UAS7 ≤ 42)
- Baseline AAS7 = 0 response (Yes, No)
- Previous exposure to anti-IgE biologics for CSU (Yes, No)

- Geographic region (China, AMEA, US, LaCAN, RE)
- Previous experience of Angioedema (Yes, No)
- [redacted]
- [redacted]
- Duration of CSU groups, defined as categorical groups of duration of CSU (≤1 year, >1 to 3 years, >3 to 5 years, >5 years)

Relevant medical histories and current medical conditions at baseline will be summarized combined by system organ class and preferred term, by treatment group initially randomized treatment group (LOU064 25mg, Placebo) for the Randomized set.

- CSU related history (CSU, Urticaria related history, [redacted])
- 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.

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 to LOU064 25mg and placebo will be summarized by treatment group and by study period (DB period and entire study period).

Primary analysis

For double-blind period, the duration of exposure/study in weeks and total duration in years (subject-years) to **LOU064 25 mg and placebo** will be summarized by treatment group (LOU064 25mg and Placebo).

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 - <16 weeks, ≥16 weeks - <20 weeks, ≥20 weeks - <24 weeks, ≥24 weeks) will be displayed.

For entire study period, the duration of exposure/study in weeks and total duration in years (subject-years) to **LOU064 25 mg** will be summarized by treatment group (LOU064 25 mg, Placebo, Transitioned to LOU064 25 mg)

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 - <16 weeks, ≥16 weeks - <20 weeks, ≥20 weeks - <24 weeks, ≥24 weeks - <32 weeks, ≥32 weeks - <40 weeks, ≥40 weeks - <52 weeks and ≥52 weeks) will be displayed.

Table 2-10 Definitions of first dose of study treatment, last dose of study treatment, last study visit for primary analysis

Study period	Treatment group	First dose of study treatment	Last dose of study treatment	Last study visit
Double blind	LOU064 25mg	Date of first dose intake in DB period	Date of last dose intake in DB period	Minimum (one day before the date of Week 24 study visit, the date of study discontinuation/safety follow-up)
	Placebo	Date of first dose intake in DB period	Date of last dose intake in DB period	Minimum (one day before the date of week 24 study visit, the date of study discontinuation/safety follow-up)
Entire study	LOU064 25mg	Date of first dose intake in DB period	Date of last dose intake in DB/OL period	Minimum (Week 52/the date of study discontinuation/study completion/safety follow-up, cut-off date of primary analysis)*
	Placebo	Date of first dose intake in DB period	Date of last dose intake in DB period	Minimum (one day before the date of week 24 study visit, the date of study discontinuation/safety follow-up)
	Transitioned to LOU064 25mg	Date of first dose intake in OL period	Date of last dose intake in OL period	Minimum (Week 52/ the date of study discontinuation/study completion/safety follow-up, cut-off date of primary analysis)*

DB: Double blind, OL: Open label

*: If both Week 52 and study completion visits are present, the date of study completion will be used

Final analysis

For entire study period, the duration of exposure/study in weeks and total duration in subject years to **LOU064 25 mg and placebo** will be summarized by treatment group (LOU064 25 mg, Placebo, Transitioned to LOU064 25 mg)

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 - <16 weeks, ≥16 weeks - <20 weeks, ≥20 weeks - <24 weeks, ≥24 weeks - <32 weeks, ≥32 weeks - <40 weeks, ≥40 weeks - <52 weeks and ≥52 weeks) will be displayed.

Table 2-11 Definitions of first dose of study treatment, last dose of study treatment, last study visit for final analysis

Study period	Treatment group	First dose of study treatment	Last dose of study treatment	Last study visit
Entire study	LOU064 25mg	Date of first dose intake in DB period	Date of last dose intake in DB/OL period	Maximum (Week 52/the date of study discontinuation/study completion/safety follow-up)
	Placebo	Date of first dose intake in DB period	Date of last dose intake in DB period	Minimum (one day before the date of week 24 study visit/the date of study discontinuation/safety follow-up)
	Transitioned to LOU064 25mg	Date of first dose intake in OL period	Date of last dose intake in OL period	Maximum (Week 52/ the date of study discontinuation/study completion/safety follow-up)

DB: Double blind, OL: Open label

2.4.2 Prior, concomitant and post therapies

Medications will be identified using the NovDTD 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, preferred term for initially randomized treatment group (LOU064 25mg, Placebo) in the Randomized set.

Concomitant medications (excluding background or rescue medications) will be summarized by ATC code, preferred term for study period and treatment group in the Safety set.

Background medications will be summarized by ATC code, preferred term, and dose per administration for study period and treatment group in the Randomized set.

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

Rescue medication: oral corticosteroids will be summarized by ATC code and preferred term for study period and treatment group 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 for initially randomized treatment group (LOU064 25mg, Placebo) in the Randomized set. Concomitant non-drug therapies/procedures will be summarized for study period and treatment group in the Safety set.

2.5 Analysis plan for the scenario with UAS7 as the primary efficacy endpoint

2.5.1 Analysis supporting primary objective

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

2.5.1.1 Primary endpoint

The primary clinical question of interest is: What is the effect of remibrutinib treatment versus placebo on the change from baseline in UAS7 score at Week 12 after treatment in adult participants with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of treatment discontinuation for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication as an unfavourable outcome?

The primary efficacy endpoint is the absolute change from baseline in **UAS7 score at Week 12**, which is the UAS7 score at Week 12 minus the UAS7 score at baseline. The UAS7 is the sum of the HSS7 score and the ISS7 score, and ranges from 0-42. Weekly scores (HSS7 and ISS7 scores) will be derived by adding up the average daily scores of the 7 days preceding the visit.

Derivation of UAS7

HSS and ISS are recorded by the participant twice daily (morning, evening) in their eDiary, on scale of 0 to 3.

The daily score of HSS and ISS will be calculated by averaging the morning and evening HSS and ISS score, respectively (possible range 0-3). If one of the morning or evening scores is missing, the non-missing score for that day (morning or evening) will then be used as the daily score. If both of the morning and evening scores are missing, the daily score for that day will be missing.

If the questionnaires in eDiary are completed more than once per session (morning, evening) on the same day, then the worst score will be used for that day.

HSS7 and ISS7

The weekly score of HSS and ISS (HSS7 and ISS7) will be derived by adding up the daily HSS and ISS scores of the 7 days preceding the visit, respectively (please refer to the assessment window in Section 2.1.1.5). If one or more of the daily scores are missing, the following principles will be applied to handle the missing data:

- If a participant has at least 4 non-missing daily scores within the 7 days, HSS7 or ISS7 will be calculated as the sum of the available 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, HSS7 or ISS7 will be considered as missing for that week.

UAS7

The UAS7 score will be derived from the sum of the HSS7 score and the ISS7 score when both HSS7 and ISS7 are non-missing. If at least one of them is missing, the UAS7 will be missing.

2.5.1.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis test for the primary endpoint being tested is that the absolute change from baseline in UAS7 score at Week 12 in remibrutinib is not superior to the placebo group i.e.:

H_{01}: $\mu_{\text{remibrutinib}} \geq \mu_{\text{Placebo}}$ versus H_{A1}: $\mu_{\text{remibrutinib}} < \mu_{\text{Placebo}}$

where μ is the mean change from baseline in UAS7 at Week 12.

A linear mixed model with repeated measures (MMRM) will be used to estimate treatment differences for change from baseline in UAS7 score at Week 12, based on the FAS. The MMRM model will include treatment group, baseline UAS7 score, randomization strata variables, week and both interaction of treatment by week and interaction of baseline UAS7 score by week as fixed effects. Repeated measures within participant are modeled using an unstructured covariance of the error terms. Additional important covariates may be added to the model. For the primary analysis, data up to Week 12 will be used in the model. The treatment difference LOU064 25 mg – placebo at Week 12 will be estimated using the LS mean and 95% CI, and p-value for treatment comparison will be presented.

The detailed testing strategy including the primary endpoint analysis is provided in Section 2.5.2.1.

2.5.1.3 Handling of intercurrent events

Participants who discontinue from study treatment early due to any reason will be encouraged to stay in the study following the procedures. Every effort will be made to continue to follow participants who discontinued from study treatment up to Week 12. These are considered as Retrieved drop out (RDO) participants.

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

1. Discontinuation of study treatment prior to Week 12 due to any reason:

   A treatment policy strategy will be applied and these intercurrent events will be ignored. Data collection will be maintained and available measurements post-treatment discontinuation will be used as if they had been obtained under the treatment assigned at randomization. i.e, RDO data collected after study treatment discontinuation will be used for analysis. In case of missing values, a multiple imputation approach will be applied (see Section 2.5.1.4 for details).
2. Intake of rescue medication as per protocol, or switch of background medication, or intake of other prohibited medication (except for strongly confounding prohibited medication listed below), or participants non-compliant (dose interruption) to treatment prior to Week 12:

   A treatment policy strategy will be applied in the same way as described above. Data collected after these events will be used for analysis.
3. Intake of strongly confounding prohibited medication:
   - Biologics treatment at any time before Week 12 (as identified by PD M-COMD03)
   - Cyclosporin after Week 8 to Week 12 (as identified by PD M-COMD04)
   - Systemic corticosteroids after Week 8 to Week 12 (as identified by PD M-COMD04)

   A composite strategy will be applied. Measurements after this event will be excluded from the analysis and will be imputed using the worst value of the endpoint (i.e., 42 for UAS7).

2.5.1.4 Handling of missing values

Missing data imputation will be performed for the analyses when using statistical model.

Handing of missing RDO data

If no RDO data was collected after study treatment permanent discontinuation, missing data will be imputed based on the following rules:

- For participants in the active treatment arms, if sufficient RDO data, missing data will be imputed using MI based on observed RDO data in the corresponding active arm. If not feasible (e.g., very limited RDO data), missing data will be imputed based on observed data in the placebo arm under the assumption of jump to reference (J2R) using MI.
- For participants in the placebo arm, if sufficient RDO data, missing data will be imputed using MI based on observed RDO placebo arm data. If not feasible (e.g., very limited RDO data), missing data will be imputed using MI under the MAR assumption based on the observed placebo arm data.

Handling of other missing data

If there is any missing data prior to Week 12, the missing data will be handled following the MAR assumption.

The detailed steps for handling of the intercurrent events and analyses are described below.

Step 1: Identify the participants with intercurrent events.

Step 2: For participants with intercurrent event 1 (Discontinuation of study treatment prior to Week 12 due to any reasons), determine the imputation strategy based on the amount of RDO data.

- Calculate the percentage of RDO data available at Week 12 in participants with intercurrent event 1 by treatment group
- If >=50 % of participants had RDO data at Week 12, consider RDO data is sufficient
- If <50% of participants had RDO data at Week 12, consider RDO data is not sufficient

Step 3: Perform the missing data imputation.

- For participants with intercurrent event 3 (Intake of strongly confounding prohibited medication), set missing at all visits after the event
- Perform the missing data imputation under MI framework according to the imputation strategy on Step 2. At the same time, missing data imputation of other missing data (i.e., non RDO data) will also be performed. The details on MI are described in Section 5.4.3
- Replace the values at all visits after the intercurrent event 3 with the worst value

Step 4: Perform the analysis.

2.5.1.5 Sensitivity analyses

The following sensitivity analysis will be performed for the primary estimand to assess the robustness of the estimation in the presence of deviations from the assumptions specified in the primary analysis. The sensitivity analysis will be implemented with the same target population, the primary variables and the summary measure as for the primary estimand, but using the different assumptions or handling of intercurrent events.

Sensitivity analysis: The change from baseline in UAS7 score up to week 12 will be imputed using zero (i.e., no clinical improvement from baseline) for the intercurrent event of "Intake of strongly confounding prohibited medication (e.g. biologics treatment at any time before Week 12, cyclosporin after Week 8 to Week 12, systemic corticosteroids after Week 8 to Week 12)" handled with composite strategy.

2.5.1.6 Supplementary analyses

Supplementary estimand

The clinical question of interest is: What is the effect of remibrutinib treatment versus placebo on the change from baseline in UAS7 score after 12 weeks treatment in adult patients with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of treatment discontinuation

for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication, and as if strongly confounding prohibited medication was not taken?

The supplementary estimand is described by the following attributes:

1. **Population**: patients with inadequately controlled CSU despite treatment with second generation H1-antihistamine who have CSU duration ≥6 months, a UAS7 score ≥16, ISS7 score ≥6 and HSS7 score ≥6 in the last 7 days prior to randomization.

2. **Endpoint:** Change in UAS7 from baseline at Week 12.

3. **Treatment of interest:** the randomized study treatment (remibrutinib 25 mg b.i.d. or placebo) regardless of treatment compliance, with background medication of local approved second generation H1-antihistamine, and a different second generation H1-antihistamine as rescue medication.

4. **Summary Measurement:** the mean difference between treatment groups.

5. **Handling of intercurrent events:**

- Discontinuation of study treatment prior to Week 12 due to any reason: **Treatment policy strategy** (same as in Section 2.5.1.3)
- Intake of rescue medication as per protocol, or switch of background medication, or intake of other prohibited medication (except for strongly confounding prohibited medication listed below), or participants non-compliant to treatment prior to Week 12: **Treatment policy strategy** (same as in Section 2.5.1.3)
- Intake of strongly confounding prohibited medication (e.g. biologics treatment at any time before Week 12, cyclosporin after Week 8 to Week 12, systemic corticosteroids after Week 8 to Week 12): **Hypothetical strategy** will be applied irrespective of potential occurrence of other intercurrent events. Measurements after this event will be excluded from the analysis and will be imputed via a modeling approach.
    - For participants in the active treatment arms, hypothetical data will be imputed using multiple imputation under missing at random (MAR) assumptions using LOU064 data.
    - For participants in the placebo arm, hypothetical data will be imputed using multiple imputation under MAR assumptions using Placebo data.

For detailed data handling, please see Section 2.5.1.3 and Section 2.5.1.4.

2.5.2 Analysis supporting secondary objectives

2.5.2.1 Secondary endpoint(s)

The secondary endpoints of the scenario with UAS7 as the primary efficacy endpoint are as follows:

1. Disease activity control at Week 12, assessed as % of participants achieving UAS7 ≤ 6.
2. Complete absence of hives and itch at Week 12, assessed as % of participants achieving UAS7 =0.

3. Improvement of severity of itch at Week 12, assessed as absolute change from baseline in ISS7 score.
4. Improvement of severity of hives at Week 12, assessed as absolute change from baseline in HSS7 score.
5. Disease activity control at Week 2, assessed as proportion of participants achieving UAS7 ≤ 6.

For derivation of UAS7, HSS7 and ISS7 scores, please see Section 2.5.1.1. The response variables (e.g., UAS7 ≤ 6) will be derived using the corresponding weekly score.

6. No impact on participants' dermatology quality of life at Week 12, assessed as proportion of participants achieving DLQI = 0-1.

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.

7. Cumulative number of weeks that participants achieve UAS7 ≤ 6 responses between baseline and Week 12.

The cumulative number of weeks achieving UAS7 ≤ 6 response between baseline and Week 12 will be derived based on the eDiary (possible range 0-12).

8. Cumulative number of weeks that participants achieve AAS7 = 0 responses between baseline and Week 12.

The cumulative number of weeks achieving AAS7 = 0 response between baseline and Week 12 will be derived based on the AAS eDiary (possible range 0-12). The AAS7 = 0 response will be derived using the weekly score as described below.

Derivation of AAS7 score: A weekly AAS7 score will be derived by adding up the daily scores (possible ranges 0 to 15) of the 7 days preceding the visit, and ranges from 0 to 105 (please refer to the assessment window in Section 2.1.1.5). If one or more of the daily scores are missing, the following principles will be applied to handle the missing data: If a participant has at least 4 non-missing daily scores within the 7 days, ASS7 will be calculated as the sum of the available 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, ASS7 will be considered as missing for that week.

Secondary estimand

For each secondary endpoint, the following secondary estimand will be considered:

The secondary clinical question of interest is: What is the effect of remibrutinib treatment versus placebo on secondary endpoints after 12 weeks treatment in adult participants with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of treatment discontinuation for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication as an unfavourable outcome?

The secondary estimand is described by the following attributes:

1. **Population**: patients with inadequately controlled CSU despite treatment with second generation H1-antihistamine who have CSU duration ≥6 months, a UAS7 score ≥ 16, ISS7 score ≥ 6 and HSS7 score ≥ 6 in the last 7 days prior to randomization.
2. **Endpoint:** see below
3. **Treatment of interest:** the randomized study treatment (remibrutinib 25 mg b.i.d. or placebo) regardless of treatment compliance, with background medication of locally label approved dose second generation H1-antihistamine, and a different second generation H1-antihistamine as rescue medication.
4. **Summary Measurement:** see below
5. **Handling of intercurrent events:** the intercurrent events are the same for the primary endpoint as described in Section 2.5.1.3. For the handling of intercurrent events, please see below.

Table 2-12 Estimand attributes for secondary endpoints

Endpoint	Summary measurement	Handing of intercurrent event
UAS7 ≤ 6 at Week 12	Odds ratio between treatment groups	A treatment policy strategy: RDO data or data collected after the IE will be used. In case of missing values of RDO data, derivation based on the multiply imputed UAS7 described in Section 2.5.1.3 will be applied. A composite strategy: UAS7 response after the intercurrent event will be excluded and UAS7 ≤ 6 will be derived from imputed UAS7 score using the worst value (i.e., 42).
UAS7 = 0 at Week 12	Odds ratio between treatment groups	Same as UAS7 ≤ 6 at Week 12.
ISS7 score change from baseline to Week 12	Mean difference between treatment groups	Same as the primary estimand, see Section 2.5.1.3
HSS7 score change from baseline to Week 12	Mean difference between treatment groups	Same as the primary estimand, see Section 2.5.1.3
UAS7 ≤ 6 at Week 2	Odds ratio between treatment groups	Same as UAS7 ≤ 6 at Week 12.

Endpoint	Summary measurement	Handing of intercurrent event
		Note: As this endpoint is for the score at W2, some intercurrent events, e.g. intake of strongly confounding prohibited medication, will not be considered.
DLQI 0/1 at Week 12	Odds ratio between treatment groups	Same as UAS7 ≤ 6 at Week 12. In case of missing values of RDO data, derivation based on the multiply imputed DLQI score with same approach as UAS7 will be applied.
Cumulative number of weeks with an UAS7 ≤6 response between baseline and Week 12	Ratio of response rate between treatment groups	Same as UAS7 ≤ 6 at Week 12. Derivation based on the multiply imputed UAS7 described in Section 2.5.1.3 will be applied. .
Cumulative number of weeks with an AAS7= 0 response between baseline and Week 12	Ratio of response rate between treatment groups	Same as UAS7 ≤ 6 at Week 12. Derivation based on the multiply imputed AAS7 with same approach as UAS7 will be applied.

2.5.2.2 Statistical hypothesis, model, and method of analysis

Statistical hypothesis and testing strategy

The following null hypotheses (H_0) will be tested against the respective alternative hypotheses (H_A) in a closed testing procedure (Bretz et al 2009), thus controlling the family-wise type I error which is set to 0.025 (one-sided):

Primary:

UAS7 score change from baseline at Week 12

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

where μ is the mean change from baseline in UAS7 at Week 12

Secondaries:

- **UAS7 ≤ 6 at Week 12**

H_{02}: $p_{remibrutinib} \leq p_{Placebo}$ versus H_{A2}: $p_{remibrutinib} > p_{Placebo}$

where p is the proportion of participants achieving UAS7≤6 at Week 12,

- **UAS7 = 0 at Week 12**

H_{03}: $p_{remibrutinib} \leq p_{Placebo}$ versus H_{A3}: $p_{remibrutinib} > p_{Placebo}$

where p is the proportion of participants achieving UAS7=0 at Week 12,

- **ISS7 score change from baseline at Week 12**

H_{04}: $\mu_{remibrutinib} \geq \mu_{Placebo}$ versus H_{A4}: $\mu_{remibrutinib} < \mu_{Placebo}$

where μ is the mean change from baseline in ISS7 at Week 12,

- **HSS7 score change from baseline at Week 12**

H_{05}: $\mu_{remibrutinib} \geq \mu_{Placebo}$ versus H_{A5}: $\mu_{remibrutinib} < \mu_{Placebo}$

where μ is the mean change from baseline in HSS7 at Week 12,

- **UAS7 ≤ 6 at Week 2**

H_{06}: $p_{remibrutinib} \leq p_{Placebo}$ versus H_{A6}: $p_{remibrutinib} > p_{Placebo}$

where p is the proportion of participants achieving UAS7 ≤6 at Week 2,

- **DLQI = 0/1 at Week 12**

H_{07}: $p_{remibrutinib} \leq p_{Placebo}$ versus H_{A7}: $p_{remibrutinib} > p_{Placebo}$

where p is the proportion of participants achieving DLQI = 0/1 at Week 12,

- **Cumulative number of weeks with an UAS7 ≤6 response between baseline and Week 12**

H_{08}: $\mu_{remibrutinib} \leq \mu_{Placebo}$ versus H_{A8}: $\mu_{remibrutinib} > \mu_{Placebo}$

where μ is the mean cumulative number of weeks that participants achieve UAS7 ≤6 response between baseline and Week 12,

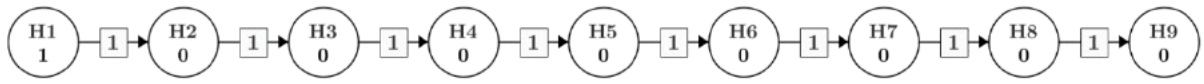
- **Cumulative number of weeks with an AAS7= 0 response between baseline and Week 12**

H_{09}: $\mu_{remibrutinib} \leq \mu_{Placebo}$ versus H_{A9}: $\mu_{remibrutinib} > \mu_{Placebo}$

where μ is the mean cumulative number of weeks that participants achieve AAS7=0 response between baseline and Week 12,

A graphical representation of the testing strategy is presented in Figure 2-1

Figure 2-1 Testing strategy with UAS7 as the primary endpoint



The value inside the circle represents the significance level. The arrow and value inside the square represent the "alpha-propagation".

The first hypothesis is tested with full level alpha (0.025 one-sided). If significant, the second hypothesis is tested with full-level alpha; otherwise, the testing procedure stops. The testing is strictly hierarchical, so that null hypotheses can be tested along the pre-defined order at the level assigned until a null hypothesis cannot be rejected, at which point the testing stops. Furthermore, the testing strategy reflects the separation of primary and secondary endpoints, so that hypotheses related to secondary endpoints will only be tested if the null hypothesis related to the primary endpoint is rejected.

Statistical model and method of analysis

1. **UAS7 ≤ 6 at Week 12**

The proportion of participants with UAS7 ≤ 6 at Week 12 will be analyzed using a logistic regression model including treatment group, region, prior exposure to anti-IgE biologics and baseline UAS7 score as covariate.

2. **UAS7 = 0 at Week 12**

The proportion of participants with UAS7 = 0 at Week 12 will be analyzed using a logistic regression model including treatment group, region, prior exposure to anti-IgE biologics and baseline UAS7 score as covariate.

3. **ISS7 score change from baseline at Week 12**

The absolute change from baseline in ISS7 score at Week 12 will be analyzed using MMRM modeling including treatment group, baseline ISS7 score, randomization strata variables, week and both interaction of treatment by week and interaction of baseline ISS7 score by week as fixed effects.

4. **HSS7 score change from baseline at Week 12**

The absolute change from baseline in HSS7 score at Week 12 will be analyzed using MMRM modeling including treatment group, baseline HSS7 score, randomization strata variables, week and both interaction of treatment by week and interaction of baseline HSS7 score by week as fixed effects.

5. **UAS7 ≤ 6 at Week 2**

The proportion of participants with UAS7 ≤ 6 at Week 2 will be analyzed using a logistic regression model including treatment group, region, prior exposure to anti-IgE biologics and baseline UAS7 score as covariate.

6. **DLQI = 0/1 at Week 12**

The proportion of participants with overall DLQI scores ≤ 1 at Week 12 will be analyzed using a logistic regression model which includes treatment group, region, prior exposure to anti-IgE biologics and baseline DLQI score.

7. **Cumulative number of weeks with an UAS7 ≤6 response between baseline and Week 12**

The cumulative number of weeks achieving UAS7 ≤ 6 response between baseline and Week 12 will be modelled using a negative binomial regression model with log link, using treatment group, region, and prior exposure to anti-IgE biologics. The patient's time in the treatment period up to Week 12 (natural log of proportion of time in treatment period, i.e., natural log of [number of weeks with the response variable in treatment period/12 weeks]) is used as an offset variable to obtain the UAS7 ≤ 6 rate, adjusted for the varying lengths of patient's time in the randomized treatment period.

8. **Cumulative number of weeks with an AAS7= 0 response between baseline and Week 12**

The cumulative number of weeks achieving AAS7 = 0 response between baseline and Week 12 will be modelled using a negative binomial regression model with log link, using treatment

group, region, prior exposure to anti-IgE biologics and baseline AAS7 = 0 status. The patient's time in the treatment period up to Week 12 (natural log of proportion of time in treatment period, i.e., natural log of [number of weeks with the response variable in treatment period/12 weeks]) is used as an offset variable to obtain the AAS7=0 rate, adjusted for the varying lengths of patient's time in the randomized treatment period.

2.5.2.3 Handling of intercurrent events

See Section 2.5.2.1

2.5.2.4 Handling of missing values

See Section 2.5.1.4 for missing data of continuous variables. Missing data of response variables will be derived using the multiply imputed data for corresponding continuous variables.

2.5.2.5 Sensitivity analyses

Not applicable

2.5.2.6 Supplementary analyses

For binary variables (UAS7 $\leq$ 6 at Week 12, UAS7 = 0 at Week 12, UAS7 $\leq$ 6 at Week 2, DLQI 0/1 at Week 12), the treatment difference adjusting covariates as region, prior exposure to anti-IgE biologics and baseline UAS7 score will be provided.

2.6 Analysis plan for the scenario with ISS7 and HSS7 as the co-primary efficacy endpoints

2.6.1 Analysis supporting primary objective(s)

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

2.6.1.1 Primary endpoints

Primary estimand for scenario with ISS7 and HSS7 as the co-primary efficacy endpoints

The primary clinical question of interest is: What is the effect of remibrutinib treatment versus placebo on the change from baseline in ISS7 score and change from baseline in HSS7 score at Week 12 after treatment in adult participants with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of treatment discontinuation for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication as an unfavorable outcome?

The co-primary efficacy endpoints are the absolute change from baseline in **ISS7 score at Week** 12 and absolute change from baseline in **HSS7 score at Week 12**, which is the ISS7 score (respectively HSS7 score) at Week 12 minus the ISS7 score (respectively HSS7 score at baseline). The weekly scores ISS7 and HSS7 range from 0-21, and will be derived by adding up the average daily scores of the 7 days preceding the visit.

Derivation of primary endpoints

See Section 2.5.1.1

2.6.1.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis test for the co-primary endpoints tests the union null hypothesis that the absolute change from baseline in ISS7 score at Week 12 in remibrutinib is not superior to the placebo group or the absolute change from baseline in HSS7 score at Week 12 in remibrutinib is not superior to the placebo group i.e.:

H_{01a}: $\mu_{\text{remibrutinib}} \geq \mu_{\text{Placebo}}$ versus H_{A1a}: $\mu_{\text{remibrutinib}} < \mu_{\text{Placebo}}$

where μ is the mean change from baseline in ISS7 at Week 12.

H_{01b}: $\mu_{\text{remibrutinib}} \geq \mu_{\text{Placebo}}$ versus H_{A1b}: $\mu_{\text{remibrutinib}} < \mu_{\text{Placebo}}$

where μ is the mean change from baseline in HSS7 at Week 12.

The union null hypothesis is rejected if both elementary null hypotheses (H_{01a}, H_{01b}) are rejected.

A linear mixed model with repeated measures (MMRM) will be used to estimate treatment differences for change from baseline in ISS7 score (respectively HSS7) at Week 12, based on the FAS. The MMRM model will include treatment group, baseline ISS7 score (respectively HSS7), randomization strata variables, week and both interaction of treatment by week and interaction of baseline ISS7 score (respectively HSS7) by week as fixed effects. Repeated measures within participant are modeled using an unstructured covariance of the error terms. Additional important covariates may be added to the model. For the primary analysis, data up to Week 12 will be used in the model. The treatment difference LOU064 25 mg – placebo at Week 12 will be estimated using the LS mean and 95% CI, and p-value for treatment comparison will be presented.

The detailed testing strategy including the primary endpoint analysis is provided in Section 2.6.2.2.

2.6.1.3 Handling of intercurrent events

See Section 2.5.2.1

2.6.1.4 Handling of missing values

See Section 2.5.1.4

2.6.1.5 Sensitivity analyses

The following sensitivity analysis will be performed for the primary estimand to assess the robustness of the estimation in the presence of deviations from the assumptions specified in the primary analysis. The sensitivity analysis will be implemented with the same target population, the primary variables and the summary measure as for the primary estimand but using the different assumptions or handling of intercurrent events.

Sensitivity analysis: The change from baseline in ISS7 and HSS7 score up to Week 12 will be imputed using zero (i.e. no clinical improvement from baseline) for the intercurrent event of "Intake of strongly confounding prohibited medication (e.g. biologics treatment at any time before Week 12, cyclosporin after Week 8 to Week 12, systemic corticosteroids after Week 8 to Week 12)" handled with composite strategy.

2.6.1.6 Supplementary analyses

Supplementary estimand

The clinical question of interest is: What is the effect of remibrutinib treatment versus placebo on the change from baseline in ISS7 score and change from baseline in HSS7 score at Week 12 after treatment in adult participants with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of treatment discontinuation for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication, and as if strongly confounding prohibited medication was not taken?

The supplementary estimand is described by the following attributes:

1. **Population**: patients with inadequately controlled CSU despite treatment with second generation H1-antihistamine who have CSU duration ≥6 months, a UAS7 score ≥16, ISS7 score ≥6 and HSS7 score ≥6 in the last 7 days prior to randomization.

2. **Endpoint:** Change in ISS7 from baseline at Week 12 and change in HSS7 from baseline at Week 12.

3. **Treatment of interest:** the randomized study treatment (remibrutinib 25 mg b.i.d. or placebo) regardless of treatment compliance, with background medication of local approved second generation H1-antihistamine, and a different second generation H1-antihistamine as rescue medication.

4. **Summary Measurement:** the mean difference between treatment groups.

5. **Handling of intercurrent events:**

- Discontinuation of study treatment due to any reason, treatment non-compliance (dose interruption): **Treatment policy strategy** (same as in Section 2.5.1.3)
- Intake of rescue medication, switch of background medication, intake of other prohibited medication, or participants non-compliant to treatment prior to Week 12: **Treatment policy strategy** (same as in Section 2.5.1.3)
- Intake of strongly confounding prohibited medication (e.g. biologics treatment at any time before Week 12, cyclosporin after Week 8 to Week 12, systemic corticosteroids after Week 8 to Week 12): **Hypothetical strategy** (irrespective of potential occurrence of other intercurrent events) (same as in Section 2.5.1.6)

For detailed data handling, please see Section 2.5.1.3 and Section 2.5.1.4.

2.6.2 Analysis supporting secondary objectives

2.6.2.1 Secondary endpoint(s)

The secondary endpoints of the scenario with ISS7 and HSS7 as the co-primary efficacy endpoints as follows:

1. Improvement of UAS7 at Week 12, assessed as absolute change from baseline in UAS7 score at Week 12
2. Disease activity control at Week 12, assessed as % of participants achieving UAS7 ≤ 6.
3. Complete absence of hives and itch at Week 12, assessed as % of participants achieving UAS7 =0.
4. Disease activity control at Week 2, assessed as proportion of participants achieving UAS7 ≤ 6.
5. No impact on participants' dermatology quality of life at Week 12, assessed as proportion of participants achieving DLQI = 0-1.
6. Cumulative number of weeks that participants achieve UAS7 ≤ 6 responses between baseline and Week 12.
7. Cumulative number of weeks that participants achieve AAS7 = 0 responses between baseline and Week 12.

For derivation of each endpoint, please see Section 2.5.2.1.

Secondary estimand

See Section 2.5.1.1 for UAS7 score change from baseline at Week 12, and Section 2.5.2.1 for others.

2.6.2.2 Statistical hypothesis, model, and method of analysis

Statistical model, hypothesis, and method of analysis for scenario with ISS7/HSS7 as the co-primary efficacy endpoints

Testing strategy

The following null hypotheses (H_0) will be tested against the respective alternative hypotheses (H_A) in a closed testing procedure (Bretz et al 2009), thus controlling the family-wise type I error which is set to 0.025 (one-sided):

Co-Primary:

- **ISS7 score change from baseline at Week 12**
- **HSS7 score change from baseline at Week 12**

H_{01a}: $\mu_{remibrutinib} \geq \mu_{Placebo}$ versus H_{A1a}: $\mu_{remibrutinib} < \mu_{Placebo}$

where μ is the mean change from baseline in ISS7 at Week 12.

H_{01b}: $\mu_{remibrutinib} \geq \mu_{Placebo}$ versus H_{A1b}: $\mu_{remibrutinib} < \mu_{Placebo}$

where μ is the mean change from baseline in HSS7 at Week 12.

The union null hypothesis is rejected if both elementary null hypotheses (H_{01a}, H_{01b}) are rejected.

Secondaries:

- **UAS7 score change from baseline at Week 12**

H_{02}: $\mu_{remibrutinib} \geq \mu_{Placebo}$ versus H_{A2}: $\mu_{remibrutinib} < \mu_{Placebo}$

where μ is the mean change from baseline in UAS7 at Week 12,

- **UAS7 ≤ 6 at Week 12**

H_{03}: $p_{remibrutinib} \leq p_{Placebo}$ versus H_{A3}: $p_{remibrutinib} > p_{Placebo}$

where p is the proportion of participants achieving UAS7≤6 at Week 12,

- **UAS7 = 0 at Week 12**

H_{04}: $p_{remibrutinib} \leq p_{Placebo}$ versus H_{A4}: $p_{remibrutinib} > p_{Placebo}$

where p is the proportion of participants achieving UAS7=0 at Week 12,

- **UAS7≤ 6 at Week 2**

H_{05}: $p_{remibrutinib} \leq p_{Placebo}$ versus H_{A5}: $p_{remibrutinib} > p_{Placebo}$

where p is the proportion of participants achieving UAS7≤6 at Week 2,

- **DLQI = 0/1 at Week 12**

H_{06}: $p_{remibrutinib} \leq p_{Placebo}$ versus H_{A6}: $p_{remibrutinib} > p_{Placebo}$

where p is the proportion of participants achieving DLQI = 0/1 at Week 12,

- **Cumulative number of weeks with an UAS7≤6 response between baseline and Week 12**

H_{07}: $\mu_{remibrutinib} \leq \mu_{Placebo}$ versus H_{A7}: $\mu_{remibrutinib} > \mu_{Placebo}$

where μ is the mean cumulative number of weeks that participants achieve UAS7≤6 response between baseline and Week 12,

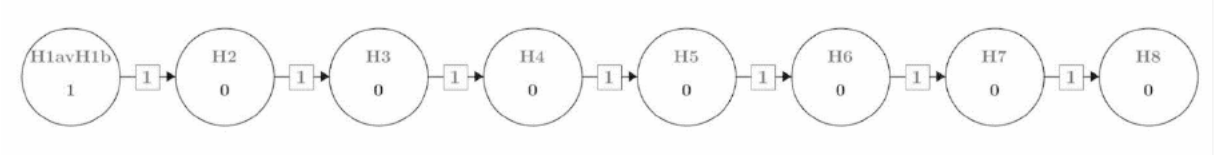
- **Cumulative number of weeks with an AAS7= 0 response between baseline and Week 12**

H_{08}: $\mu_{remibrutinib} \leq \mu_{Placebo}$ versus H_{A8}: $\mu_{remibrutinib} > \mu_{Placebo}$

where μ is the mean cumulative number of weeks that participants achieve AAS7=0 response between baseline and Week 12,

A graphical representation of the testing strategy is presented in Figure 2-2.

Figure 2-2 Testing strategy with ISS7/HSS7 as the co-primary endpoints



The value inside the circle represents the significance level. The arrow and value inside the square represent the "alpha-propagation".

The first two hypotheses are tested: both H_{1a} and H_{1b} are tested with full level alpha (0.025 one-sided) and only if both are rejected, then H_2 hypothesis is tested with full-level alpha; otherwise, the testing procedure stops. The testing is strictly hierarchical, so that null hypotheses can be tested along the pre-defined order at the level assigned until a null hypothesis cannot be rejected, at which point the testing stops. Furthermore, the testing strategy reflects the separation of primary and secondary endpoints, so that hypotheses related to secondary endpoints will only be tested if both null hypotheses related to the co-primary endpoints are rejected.

Statistical model and method of analysis

See Section 2.5.1.2 for UAS7 score change from baseline at Week 12, and Section 2.5.2.2 for others.

2.6.2.3 Handling of intercurrent events

See Section 2.5.1.3 for UAS7 score change from baseline at Week 12, and Section 2.5.2.1 for others.

2.6.2.4 Handling of missing values

See Section 2.5.2.4

2.6.2.5 Sensitivity analyses

Not applicable.

2.6.2.6 Supplementary analyses

See Section 2.5.2.6

2.7 Safety analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group and 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 2.1.1.4.

2.7.1 Adverse events (AEs)

All information obtained on adverse events will be listed by treatment group and 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 by study period in the following ways:

- by treatment group, primary system organ class and preferred term.
- by treatment group, primary system organ class, preferred term and maximum severity.
- by treatment group, 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 by study period and treatment group.

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 bid starting from the most common event. The cut-off of 3% can be re-evaluated based on 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 by treatment group for the double-blind period and for the entire study period. The rate estimates will be reported with exact Poisson 95% CIs (Garwood 1936, Sahai and Khurshid 1993). Please see Section 5.4.2.4 for details.

For infections and infestations (SOC), the number (and percentage) of participants with this event will be summarized by treatment group, SOC, HLGT, HLT and PT for the double-blind period and the entire study period.

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 analysis	Double blind	• LOU064 25mg • Placebo	Crude incidence EAIR	Crude incidence
	Entire study	• LOU064 25mg • Placebo • Transitioned to LOU064 25mg (under LOU064 treatment)	Crude incidence EAIR	Crude incidence
Final analysis	Entire study	• LOU064 25mg • Placebo • Transitioned to LOU064 25mg (under LOU064 treatment)	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 for study period and treatment group. Exposure adjusted incidence rate will also be provided by treatment group for the double-blind period and the entire study period.

In addition, for the selected AESIs (Infections, Bleeding, Cytopenias), the number of AESI events will be summarized by safety topic of interest (i.e., risk name) for study period and treatment group.

Summaries will also include the exposure adjusted occurrence rate and the corresponding 95% CI, the number of events per participant, time to onset of first event, duration of the events, the severity of the events, the outcome of events, treatment related events, the action taken with the study treatment for each event and duration of study drug interruption for events leading to study drug interruption.

- Exposure Adjusted Occurrence Rate (EAOR) will be calculated as follows:

EAOR = 100* total number of events / total exposure subject-time (years)

The exact Poisson 95% CIs (Garwood 1936, Sahai and Khurshid 1993) will be used. Please see Section 5.4.2.5 for details.

For duration of study drug interruption (in days), once the events leading to study drug interruption are selected, the drug interruption occurred within 7 days of the event onset date will be considered. If there are more than one interruption, only the first interruption will be considered.

For the selected AESIs (Infections, Bleeding, Cytopenias), during the double-blind period, the number of events (per risk name), EAOR, and number of participants at risk occurring between 0-≤4 weeks, 4-≤12 weeks, 12-<24 weeks will be displayed by treatment group.

2.7.1.2 Requirements of ClinicalTrials.gov and EudraCT

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent AEs: non-serious AEs with an incidence greater than 3% , 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 3% can be re-evaluated based on 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 treatment group, 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 be listed and be included in the notable summary tables, but will not be included in the by-visit summary tables.

For Urinalysis, handling of data will depend on country (China, non-China) as follows:

- Non-China participants

  For those who have only local laboratory data, local data will be included in the summary tables;

  For those who have both of local and central laboratory data, local data will be included in the summary tables;

  For those who have only central laboratory data, central data will be included in the summary tables.

  Both of local and central data can be listed.

- China participants

  For those who have only central laboratory data, central data will be included in the summary tables;

  For those who have both of local and central laboratory data, central data will be included in the summary tables;

  For those who have only local laboratory data, local data will be included in the summary tables.

  Both of local and central data can be listed.

For by-visit summary tables, scheduled visits (including remapped visits following the assessment window in Section 2.1.1.5) 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 analysis	Double blind	• LOU064 25mg • Placebo	X (up to Week 24)	X (up to Week 24 including unscheduled visits of Week 24)
	Entire study	• LOU064 25mg • Placebo • Transitioned to LOU064 25mg (under LOU064 treatment)	X (after Week 24)	X
Final analysis	Entire study	• LOU064 25mg • Placebo • Transitioned to LOU064 25mg (under LOU064 treatment)	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 study period, laboratory test and treatment group. 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 by treatment group during the double-blind period.

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 study period, laboratory test and treatment group.

Box plots for selected parameters will be provided by treatment group and study period.

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 2-15: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, creatinine kinase, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total cholesterol, triglycerides, amylase, and lipase.

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 and will be presented by study period and treatment group.

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
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	<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
INR increased	INR	>1.2 - 1.5	>1.5 - 2.5	>2.5	-
Creatinine increased	Serum creatinine	>ULN-1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Creatinine kinase increased	Serum creatinine kinase	>ULN-2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 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
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
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
Amylase increased	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
Lipase increased	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 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, 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 during is worse than baseline.

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

In addition, for liver enzyme test abnormalities,

For participants meeting the criteria [ALT or AST >5x ULN] or [ALT or AST>3xULN & TBL >2xULN & ALP <2xULN], graphical case (per participant) representation to include graph of liver enzymes over time (ALT, AST, TBL, ALP, based on xULN) with treatment exposure and concomitant medications.

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
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 treatment group, participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by study period, treatment group and visit/time.

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.

A shift table from baseline to the worst post-baseline value will be presented based on the overall ECG interpretation.

Newly occurring observations of 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%

For by-visit summary tables, scheduled visits (including remapped visits following the assessment window in Section 2.1.1.5) 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.

2.7.4.2 Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities (and relevant changes) will be flagged. Summary statistics will be provided by study period, treatment group and 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 newly occurring clinically notable vital signs changes from baseline will be presented. Clinically notable vital sign results are provided in Table 2-18 below.

Table 2-18 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria
Systolic blood pressure (mmHg)	< 90 mmHg
	≥ 140 mmHg
Diastolic blood pressure (mmHg)	< 60 mmHg
	≥ 90 mmHg
Pulse (bpm)	< 50 bpm
	> 100 bpm

For by-visit summary tables, scheduled visits (including remapped visits following the assessment window in Section 2.1.1.5) 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.

[redacted]

2.10 Patient-reported outcomes

At the primary analysis and the final analysis, the values from baseline to the end of study will be summarized for LOU064 25 mg and Placebo-LOU064 25 mg treatment groups.

[redacted]

Dermatology Life Quality Index (DLQI)

For the following DLQI assessments, summary statistics will be presented by treatment group for the FAS.

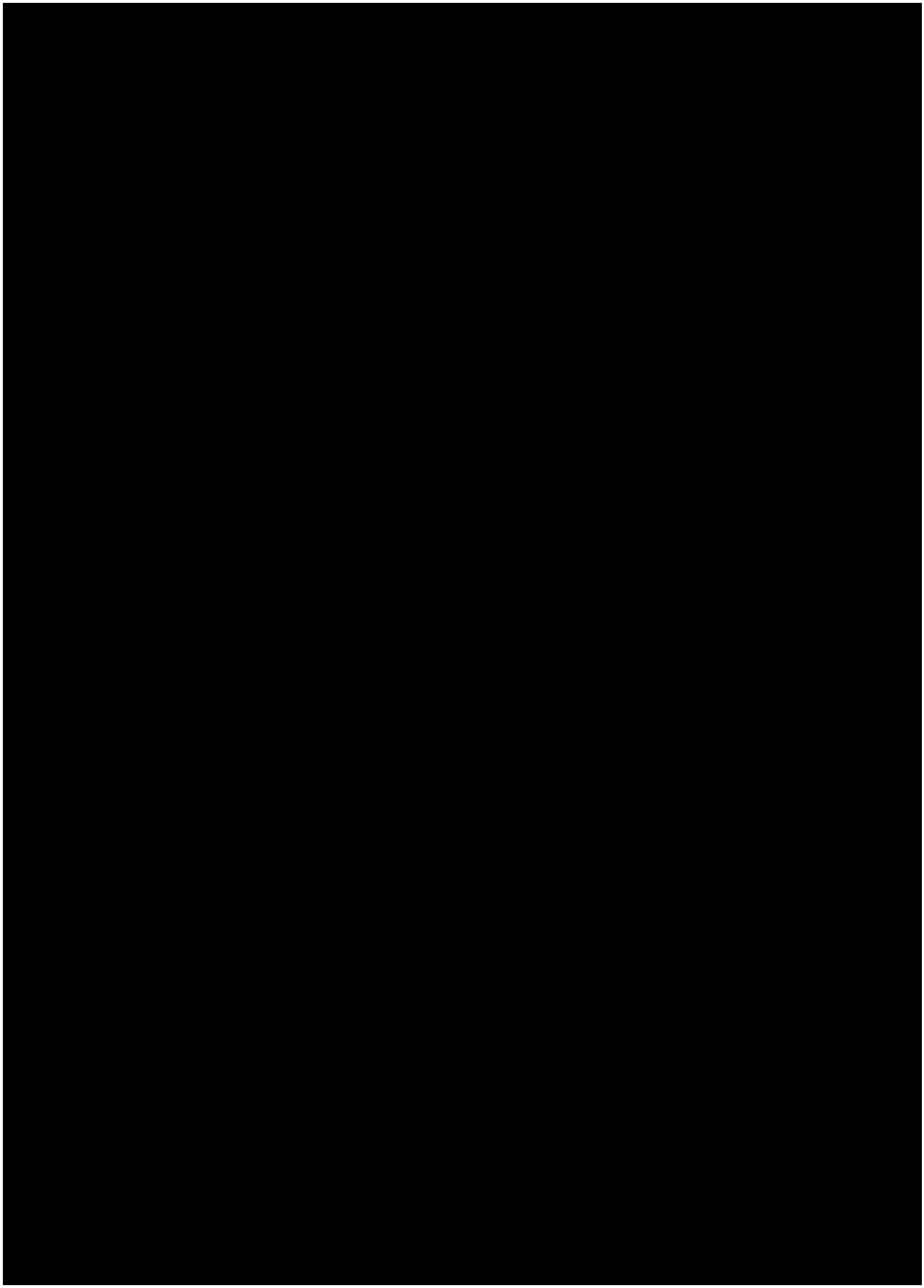
[redacted]

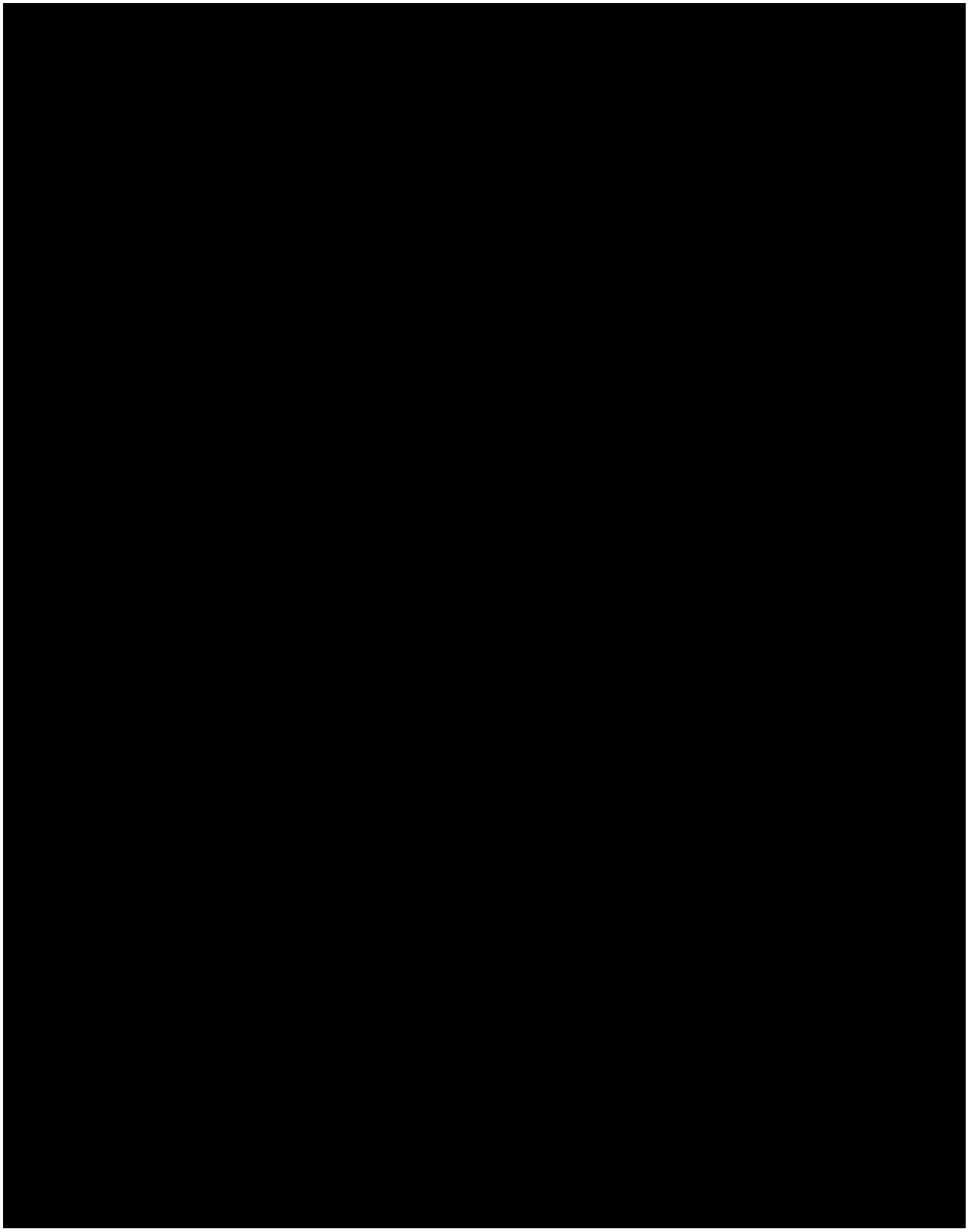
- DLQI = 0-1: the proportion of participants achieving DLQI = 0-1 response [redacted].

Angioedema Activity Score (AAS)

For the following AAS assessments based on AAS eDiary, summary statistics will be presented by treatment group for the FAS. Please see Section 2.5.2.1 for derivation of AAS7 score and AAS7 = 0 response.

[redacted]





2.13 Interim analysis

A primary analysis may be conducted when all participants have completed their Week 24 visit or discontinued early and when a minimum of 150 participants across both Phase 3 pivotal studies (A2301 and A2302) have completed the treatment period. The minimum of 150 participants reaching week 52 should enable analysis on a minimum of 100 participants exposed to remibrutinib for 52 weeks, considering the initial randomization to either the remibrutinib or the placebo arm (2:1). The results of the primary analysis will further inform decision-making for the remibrutinib development program. Formal testing of the primary endpoint and key secondary endpoints will only be performed at the primary analysis time point; thus, no adjustment for multiplicity is required.

After the primary analysis and/or after all participants entered the open-label treatment period, additional optional interim analyses may be conducted at the discretion of the Sponsor to

support potential Health Authority requests and interactions (these interim analyses are not expected to have any impact on the conduct or scientific integrity of the study). The decision to conduct optional interim analyses and the timing of these analyses will be documented in the Statistical Analysis Plan prior to the conduct of any interim analysis. These interim analyses will be performed and interpreted by members of the Novartis clinical team.

3 Sample size calculation

3.1 Primary endpoint(s)

In order to fulfill registration and ICH E1 requirements on the number of participants treated for 6 months and 12 months in the development program, a sample size of 300 participants in the active arm and 150 in the placebo arm is targeted. Hence, the total sample size is 450 randomized participants.

From an efficacy point of view, the sample size justification is based on UAS7 change from baseline (for scenario with one primary endpoint), ISS7 and HSS7 change from baseline (for scenario with co-primary endpoints) and achievement of UAS7≤6 and UAS7=0 at Week 12. To avoid assigning an unnecessary large number of participants to placebo, participants will be randomized in a 2:1 ratio to remibrutinib 25 mg b.i.d. and placebo arms, respectively.

All calculations were performed with nQuery Advisor 8.4.1.0 and Ri386 4.0.2 softwares.

For scenario with UAS7 as the primary efficacy endpoint

UAS7 change from baseline at Week 12

Approximately 10% drop-out is expected at week 12, thus with 270 participants in the active arm and 135 participants in the placebo arm, this gives a nominal power of more than >99% to detect a difference between remibrutinib and placebo if the mean change of UAS7 from baseline to Week 12 is at least 10 in favor of remibrutinib, with common standard deviation of approximately 12 (based on the primary endpoint analysis of Phase 2b study (CLOU064A2201)), based on a t-test, assuming type I error 0.025 (one-sided).

For scenario with ISS7/HSS7 as the co-primary efficacy endpoints

ISS7 change from baseline at Week 12

Approximately 10% drop-out is expected at week 12, thus with 270 participants in the active arm and 135 participants in the placebo arm, this gives a nominal power of more than >99% to detect a difference between remibrutinib and placebo if the mean change of ISS7 from baseline to Week 12 is at least 4 in favor of remibrutinib, with common standard deviation of approximately 6 (based on the primary endpoint analysis of Phase 2b study (CLOU064A2201)), based on a t-test, assuming type I error 0.025 (one-sided).

HSS7 change from baseline at Week 12

Approximately 10% drop-out is expected at week 12, thus with 270 participants in the active arm and 135 participants in the placebo arm, this gives a nominal power of more than >99% to detect a difference between remibrutinib and placebo if the mean change of HSS7 from baseline to Week 12 is at least 4 in favor of remibrutinib, with common standard deviation of approximately 6 (based on the primary endpoint analysis of Phase 2b study (CLOU064A2201)), based on a t-test, assuming type I error 0.025 (one-sided).

With 300 participants in the active arm and 150 participants in the placebo arm randomized in this study, this gives a power of more than >90% to detect a difference between remibrutinib and placebo in both mean change of ISS7 and HSS7 from baseline to Week 12 when correlation

between endpoints is 0 (conservative assumption, as higher the correlation is, higher the power is).

3.2 Secondary endpoint(s)

Achievement of UAS7 = 0 at Week 12

Similarly, with approximately 10% drop-out at week 12, then with 270 participants in the active arm and 135 participants in the placebo arm, this gives a nominal power of more than >99% to detect a difference between remibrutinib and placebo arm assuming a proportion of complete response (UAS7=0) of 0.35 in the remibrutinib arm and of 0.10 in the placebo arm, based upon a 2-group continuity corrected $\chi 2$ test with a 0.025 one-sided significance level.

Achievement of UAS7 ≤6 at Week 12

Similarly, with approximately 10% drop-out at week 12, then with 270 participants in the active arm and 135 participants in the placebo arm, this gives a nominal power of more than >99% to detect a difference between remibrutinib and placebo arm assuming a proportion of disease activity control response (UAS7≤6) of 0.53 in the remibrutinib arm and of 0.15 in the placebo arm, based upon a 2-group continuity corrected $\chi 2$ test with a 0.025 one-sided significance level.

The primary and secondary endpoints analyses are planned to use the multiple testing strategy to control the family-wise error at α=0.025 (one-sided). It is considered, however, this hierarchical approach could impact the sample size compared to the separate endpoint approach, which depends on how the recycled alpha will be used. In both scenarios, the "family-wise" power (power to reject all null hypotheses) is >90% when correlation between endpoints is 0 (Higher the correlation is, higher the power is).

4 Change to protocol specified analyses

No change.

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.

5.1.4 Concomitant therapies

Please see Section 5.1.3.

5.1.5 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

5.4.1 Analysis supporting primary objective(s)

5.4.1.1 Mixed model with repeated measures

For the primary efficacy endpoints (change from baseline in UAS7 or ISS7 or HSS7), a linear mixed model with repeated measures (MMRM) will be used to estimate treatment differences, based on the FAS. The MMRM model will include treatment group, the corresponding baseline score, actual randomization strata variables, week and both interaction of treatment by week and interaction of the corresponding baseline score by week as fixed effects. Repeated measures within subject are modeled using an unstructured covariance of the error terms.

The primary analysis will be performed based on the data after the missing data imputation for the intercurrent events have been performed. All data up to Week 12 will be included in the MMRM model for primary analysis.

The SAS procedure proc mixed will be used for this analysis with the following code:

```
ods output DIFFS=diff LSMeans=mean ConvergenceStatus=conv_mmrm1;
proc mixed data=..... covtest;
by _imputation_;
class subject group week region antige;
model change=baseline group week region antige group*week baseline*week/s
ddfm=kr cl;
repeated week/ type=UN subject=subject r;
lsmeans group*week /cl diff;
run;
```

where change = change from baseline UAS7 score
baseline = baseline UAS7 score
group = plannedtreatment group
(1 = LOU064 2 = Placebo)
week = study week
region = geographic region
antige = prior exposure to anti-IgE biologics
subject = subject
imputation = the index for imputation times

Note that the *mean* and *diff* datasets created will include all the treatment interactions for each week. The estimates for the right weeks, e.g. Week 12, and right treatment comparisons, e.g. LOU064 vs Placebo, should be subsetted by taking "week = **12** and _week=**12**" and "group= **1** and _group=**2**".

If the computation of the MMRM model takes extreme amount of time, the ddfm=bw option could be considered. If the model with an unstructured covariance matrix does not converge, SAS will give a warning as "Unable to make hessian positive definite" or "Unable to Converge". Meanwhile, the Status variable in the "convest" dataset created will take on the value 1 or 2. In this case, the compound-symmetry structure should be used.

Rubin's Rule:

Rubin's Rule will be applied to combine the multiple sets of estimates to produce the overall estimates, standard error, confidence interval and p-values.

The SAS procedure proc mianalyze will be used for this analysis with the following code:

```
proc mianalyze data=mean(where=(week=12));
by group;
ModelEffects estimate;
stderr stderr;
ods output ParameterEstimates=est_mean;
run;

proc mianalyze data=diff(where=(week=12 & _week=12));
by group _group;
ModelEffects estimate;
stderr stderr;
ods output ParameterEstimates=est_diff;
run;
```

where *est_mean* includes the results for LS mean in each group, and *est_diff* includes the results for the treatment difference between groups.

If the datasets between imputations are identical after multiple imputation step, which will cause the SAS procedure proc mianalyze not runnable, the dataset with _imputation_=1 will be used to create the results.

5.4.2 Analysis supporting secondary objective(s)

5.4.2.1 Logistic regression

Binary outcome variables including UAS7=0 "Complete Response" or UAS7≤6 "Disease control" will be evaluated using a logistic regression model with treatment, and actual randomization strata variables (i.e. geographic region and prior exposure to anti-IgE biologics). Odds ratios will be computed for treated participants with response relative to control participants utilizing the logistic regression model fitted.

The odds ratio will be calculated such that an odds ratio > 1 is favorable for LOU064 drug. The SAS procedure PROC LOGISTIC will be used for this analysis with the following code:

```
proc logistic data = ...;
by_imputation_;
class trt01p antige region/ param = glm;
model response (event = '1') = trt01p antige region baseline;
estimate "LOU064 vs Placebo" trt01p 1 -1;
```

```
ods output ESTIMATEs=estimates;

run;
```

If separation occurs, the Firth's method will be implemented using the firth option in the MODEL statement.

The SAS procedure PROC MIANALYZE will be used to combine the results. The odds ratios and the 95% confidence interval for the odds ratio will be generated using an exponential transformation of the model estimates.

5.4.2.2 Covariate adjustment for treatment difference with binary outcome variable

For binary outcome variables, the treatment difference and the corresponding 95 % confidence interval will be provided besides odds ratios.

FDA guidance introduces the following steps for one statistically reliable method of covariate adjustment for treatment difference with binary outcome (Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products, Guidance for Industry, Draft guidance, May 2021).

5.4.2.3 Negative binomial regression

Count variable including the cumulative number of weeks achieving AAS7= 0 response between baseline and Week 12 or the cumulative number of weeks achieving UAS7≤6 response will be modelled using a negative binomial regression model with log link, using treatment group, randomization strata factors (i.e. geographic region and prior exposure to anti-IgE biologics, and baseline AAS7=0 status (for AAS7 = 0 response only). The patient's time in the treatment period up to Week 12 (natural log of proportion of time in treatment period, i.e., natural log of [number of weeks with the response variable in treatment period/12 weeks]) is used as an offset variable. The patient's time in the treatment period up to Week 24 (natural log of proportion of time in treatment period, i.e., natural log of [number of weeks with the response variable in treatment period/24 weeks]) is used as an offset variable.

If the AAS7 = 0 (respectively UAS7≤6) assessment is missing, it will be considered as a non-response for the cumulative number of weeks that participants achieve AAS7= 0 response calculation (respectively UAS7≤6).

The negative binomial model accounts for any over dispersion that may result from assuming a Poisson distribution by allowing a different Poisson rate for each patient and assuming that these rates as a set are distributed across participants according to a gamma distribution.

The SAS procedure PROC GENMOD will be used for this analysis with the following code:

```
proc genmod data=...;
      by impnb;
      class trt01p antige region/ param = glm;
      model count = baseline trt01p antige region/ DIST= NEGBIN LINK= LOG
offset=offset;
      lsmeans trt01p / cl exp diff ilink e OM;
      estimate "LOU064 v.s pbo" trt01p 1 -1;
```

```
      ods output Estimates=estimates LSMeans=lsmeans;
run;
```

where baseline = baseline AAS7=0 status (for AAS7 = 0 response only).

The SAS procedure PROC MIANALYZE will be used to combine the results. The risk ratio and the 95% confidence intercal for the risk ratio will be generated using an exponential transformation of the model estimates.

5.4.2.4 Exposure adjusted incidence rate and 100*(1-α)% confidence interval

It will be assumed that for each of n participants in a clinical trial the time t_j (j=1,...,n) to the first occurrence of a certain event is observed, or if the event was not experienced, the (censored) time to the end of the observation period. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where $T=\sum_{j=1}^{n} t_j$ and D is the number of participants with at least one event. Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit $L=\frac{0.5c_{\alpha/2,2D}}{T}$ for D>0, 0 otherwise,

Upper confidence limit $U=\frac{0.5c_{1-\alpha/2,2D+2}}{T}$

where $c_{\alpha,k}$ is the α^{th} quantile of the Chi-square distribution with k degrees of freedom.

5.4.2.5 Exposure adjusted occurrence rate and 100*(1-α)% confidence interval

It will be assumed that for each of n participants in a clinical trial the time t_j (j=1,...,n) is the observation period. The number of occurrences of the event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where $T=\sum_{j=1}^{n} t_j$ and D is total number of events. Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit $L=\frac{0.5c_{\alpha/2,2D}}{T}$ for D>0, 0 otherwise,

Upper confidence limit $U = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$

where $C_{\alpha,k}$ is the α^{th} quantile of the Chi-square distribution with k degrees of freedom.

5.4.2.6 Confidence interval for proportion of binary data

Confidence intervals for proportion of binary data including observed response rate and adverse event incidence rate 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 (SAS: z = PROBIT(1-α/2), n as total number of subjects (i.e. number of subjects in the denominator), 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 $p < 1, (U = 1 \text{ for } p = 1),$

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

5.4.3 Multiple imputations

Multiple imputation is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Rubin (1987) presented rules how to combine the multiple sets of estimates to produce overall estimates and confidence intervals that adequately incorporate missing data uncertainty. The multiple imputation analysis will be imputed based on the individual treatment arm information.

Missing values for UAS7/HSS7/ISS7/AAS7/DLQI will be imputed separately. The imputation is done on the original post-baseline score and the imputation model will include treatment group, the corresponding baseline score, actual randomization strata variables, week and both interaction of treatment by week and interaction of the corresponding baseline score by week. The number of imputations is 100. The imputed values may exceed possible range of variables. In this case, the imputed values which exceed possible maximum value (e.g., 42 for UAS7) will be replaced with the maximum value, the imputed values which exceed possible minimum value (e.g., 0 for UAS7) will be replaced with the minimum value.

Multiple imputation will be implemented using the RMConjPlus20 and RefBTBV04 SAS macro. The macros are available from the website of London school of Hygiene & tropical

medicine (LSHTM) on https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data. The purpose and activities of each of the two macros is described below. For more details of these two macros please see "The RMConjPlus and RefbTbV SAS macros" by James H. Roger (2023) at https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data.

The %RefBTBV SAS macro is used to set up the design matrix for reference-based imputation. This macro creates an input data set for %RMConjPlus by generating the required Treatment*Visit part of the design matrix based on the chosen reference-based imputation method (J2R, CIR, CR, etc.).

The %RMConjPlus SAS macro is applied for reference-based imputation (J2R in this study) where an individual patient's means model for those on active treatment is modified after trial withdrawal to closer represent the reference (placebo) arm (Carpenter, 2013). The imputation is done by two stages. In stage 1, it fits a Bayesian Repeated Measures model where there are a fixed number of visits. A multivariate Normal model is assumed with a series of one or more unstructured covariance matrices. Each subject uses only one of these matrices. Data within subject are related while data between subjects are assumed independent. In stage 2, it builds a set of imputed values for missed observations directly as part of the MCMC process using an pre-specified imputation model (J2R in this study).

This is example code to implement the primary analysis:

```
%RefbTBV(
Data= inputdata,
Out=RefB_Out,
Subject= usubjid,
Visit= week,
OnTreatment= OT,
Treatment= group,
Method= Mymethod,
Reference= Placebo);
```

where usubjid = unique subject identifier
week =study week
group= planned treatment group
(1 = LOU064 2 = Placebo)
OT = indicator of on/off treatment status
Mymethod = Method used to impute missing data. For example, this could be specified as J2R to indicate that Jump to reference is used to impute missing data for LOU064 patients who discontinued treatment and MAR otherwise, where Placebo is used as reference.

```
%RMConjPlus(
   Data=RefB_Out ,
   OUT_Imp= out_imp,
   Subject=usubjid,
   Visit=week,
   Response=aval,
   Model=&RefbTbV base*week antige region,
   Class=week group antige region,
```

```
   seed=23012,
   Nimpute=100
);
```

Where usubjid = unique subject identifier
week =study week
aval = UAS7 weekly score
base = baseline UAS7 score
antige = prior exposure to anti-IgE biologics
region = geographic region
&RefbTbV = design matrix generated from RefbTBV macro.

If the imputation model has warnings regarding auto-correlation, a larger number of autocorlag parameter could be specified (e.g., autocorlag=70 in the RMConjPlus macro). Any missing baseline values will be multiply imputed using baseline characteristics variables before putting into the %RefBTBV and %RMConjPlus using Proc MI. The example code for imputing baseline of DLQI is shown below:

```
proc mi data= dlqi_base_imp out=dlqi_regpmm nimpute = 100 seed = 23012;
class group sex antige region;
FCS regpmm(base/details);
var age sex group antige region base ;
run;
```

Where group= planned treatment group
(1 = LOU064 2 = Placebo)
age = age at screening of study participants
sex = gender of study participants
antige = prior exposure to anti-IgE biologics
region = geographic region
base = baseline DLQI score

5.5 Rule of exclusion criteria of analysis sets

Table 5-1 Criteria leading to exclusion from analysis sets

Analysis Set	Protocol deviations* that cause a participant to be excluded	Non-PD criteria that cause a participantto be excluded
RAS	P-INCL01B-ICF not signed	Not randomized
FAS	P-INCL01B-ICF not signed	Not in RAS;
	M-OTH12-ICH-GCP non compliance	Mistakenly randomized and no double-blind study drug taken
SAF	P-INCL01B-ICF not signed	Not dosed
	M-OTH12-ICH-GCP non compliance	

P-INCL01B-ICF not signed: Written informed consent was not signed or missing
M-OTH12-ICH-GCP non-compliance: Severe ICH-GCP non-compliance of study site

* Reference from the edit check specifications Version 14.0. The latest version should be considered at time of the analysis.

[redacted]

6 Reference

Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products, Guidance for Industry, Draft guidance, May 2021.Altrichter S, et al (2021) Total IgE as Marker for Chronic Spontaneous Urticaria, Allegy Asthma Immunol Res. 2021 Mar; 13 (2): 206-218.

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