NOVARTIS

Clinical Development

LOU064/remibrutinib

CLOU064A1301

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

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Amendment 4
Release date:	9-Jan-2024
Number of pages:	54

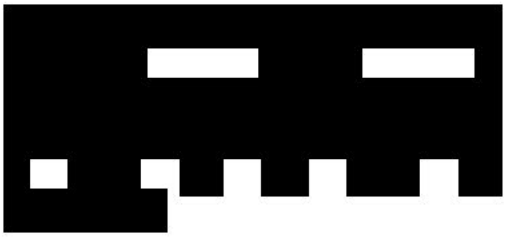
Template Version 4.0, Effective from 23-Apr-2021

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
16-Dec-2021	Prior to FPFV	Creation of final version	N/A – First version	NA
22-Jul-2022	Prior to the primary analysis	Protocol amendment 1 To align with LOU064A2301 and LOU064A2302 studies	SAP Amendment 1	Section 1 update reference document version [redacted] Section 1.2.1, Section 1.2.2, Section 2.5.3, Section 2.6.3 update the handling of intercurrent events Section 2.1.1.4 update the assessment window for weekly scores from eDiary data, update the assessment window for the assessments performed at study visit Section 2.2 Added acronym for safety set [redacted] [redacted] Section 2.4.2 update the medication dictionary Section 2.5.2 specify narrow SMQ search Section 2.5.5 Specify the subject to sensitivity analysis

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 2.7.2 delete the summary table of death 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 [redacted] [redacted] Section 2.12 add details for reference Section 5.4.2 delete description about multiple imputation Section 5.5 Change "Safety Set" to "SAF" [redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
10-Apr-2023	Prior to the primary analysis	In general the SAP was amended to align with LOU064A2301 and LOU064A2302 studies Adress the discrepancy between SAP and TFL shells Add new safety analyses	SAP Amendment 2	Section 1 update reference document version Section 2.4.2 combine the summary of concomitant medications for urticaria and non-urticaria Section 2.5.2 add analyses of exposure adjusted incidence rates for adverse events and serious adverse events Section 2.6.1 add the handling of duplicated data in eDiary 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 [redacted] Section 2.12 add detail of the conversion factor document Section 5.4.1.1 new section of exposure adjusted incidence rate Section 5.4.1.2 new section of confidence interval for proportion of binary data [redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 6 add reference related to calculation methods for exposure adjusted incidence rate and the 95% CI Add reference related to calculation methods for confidence interval for proportion of binary data
1-Jun-2023	Prior to the primary analysis	In general the SAP was amended to align with LOU064A2301 and LOU064A2302 studies Add lab parameters with CTCAE grades	SAP Amendment 3	Section 1 update the version of reference document Section 1.1 add the statement of the data to be evaluated in interim analysis Section 2.1.1.4 update the assessment window of weight in Table 2-6  Section 2.2 add definition of Screened Set as Analysis sets Section 2.3.2 add categorical variables Section 2.5.2 add new analysis for infections and infestations (SOC) Section 2.6.2 delete the statement of analysis after the missing data imputation

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 2.7.3 add lab parameters with CTCAE grades Clarify the criteria of potential Hy's Law case Update the notable criteria of Serum creatinine Section 2.7.4 update the condition of clinically notable changes of ECG and vital sign tables
9-Jan-2024	Prior to final DBL	In general the SAP was amended to align with LOU064A2301 and LOU064A2302 studie Remove the word "EudraCT"	SAP Amendment 4	Section 1 update the version of reference document Section 2.7.3 update the definition of the combination criteria of parameters Section 2.7.3 update CTCAE grade for neutrophil count decrease and lymphocyte count decreased according to updated internal CTCAE guidance." Section 2.7.1.2 remove the word "EudraCT" because this study does not register for EudraCT

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List of abbreviations

AAS	Angioedema Activity Score
AAS7	Weekly 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
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
BSL	Baseline
CI	Confidential Interval
[redacted]	[redacted]
cm	Centimeter(s)
CM	Concomitant Medication
COVID-19	Coronavirus Disease 2019
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CSU	Chronic Spontaneous Urticaria
CTCAE	Common Terminology Criteria for Adverse Event
CU	Chronic Urticaria
CV	Coefficient of Variation
CYP	Cytochrome P
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRS	Electronic Case Retrieval Strategy
eDiary	Electronic Diary
[redacted]	[redacted]
ETD	Early Treatment Discontinuation
FAS	Full Analysis Set
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HSS	Hives Severity Score
HSS7	Weekly Hives Severity Score
hrs	Hours

ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
Ig	Immunoglobulin
INR	International Normalized Ratio
ISS	Itch Severity Score
ISS7	Weekly Itch Severity Score
IU	International Unit
kg	Kilogram(s)
LLN	Lower Limit of Normal-range
LLOQ	Lower Limit of Quantification
MAP	Master Analysis Plan
MAR	Missing At Random
MedDRA	Medical dictionary for regulatory activities
m	Meter(s)
mg	Milligram(s)
mL	Milliliter(s)
PD	Protocol Deviation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO	Patient Reported Outcomes
PT	Preferred Term
QTcF	QT interval corrected by Fridericia's formula
RDO	Retrieved Drop Out
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SD	Study Discontinuation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings Shells document
UAS	Urticaria Activity Score
UAS7	Weekly Urticaria Activity Score
[redacted]	[redacted]
ULN	Upper Limit of Normal-range

ULOQ	Upper Limit of Quantification
UPDD	Urticaria Patient Daily Diary
[redacted]	[redacted]
[redacted]	[redacted]

1 Introduction

Data will be analyzed by Novartis according to the data analysis Section 12 of the CLOU064A1301 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 an interim analysis at Week 24 if conducted, and the final analysis of CLOU064A1301 study with reference to:

- the study protocol Version 01
- the case report forms (CRFs) Version 6.0
- the LOU064A master analysis plan (MAP) Version 2.0

[redacted]

A separate SAP for the program Data Monitoring Committee (DMC) will be prepared.

1.1 Study design

Study CLOU064A1301 is a single country, multicenter, open-label, single arm Phase 3 study investigating the safety, tolerability and efficacy of remibrutinib (25 mg b.i.d.) in Japanese adult participants with Chronic Spontaneous Urticaria (CSU) inadequately controlled by second-generation H1-antihistamines.

The study consists of three periods, the total study duration is up to 60 weeks (Figure 1-1):

- **Screening period**: up to 4 weeks
- **Open-label treatment period**: 52 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 extension study)

Approximately 70 adult participants will be enrolled in the treatment period.

An interim analysis may be conducted when all participants have completed their Week 24 visit or discontinued early. The interim analysis at the time of this Week 24 database lock would be utilized for the purpose of submission to Health Authorities for marketing authorization approval. When the interim analysis is conducted, all data available at the cut-off data (beyond Week 24) will be evaluated in both efficacy and safety analysis.

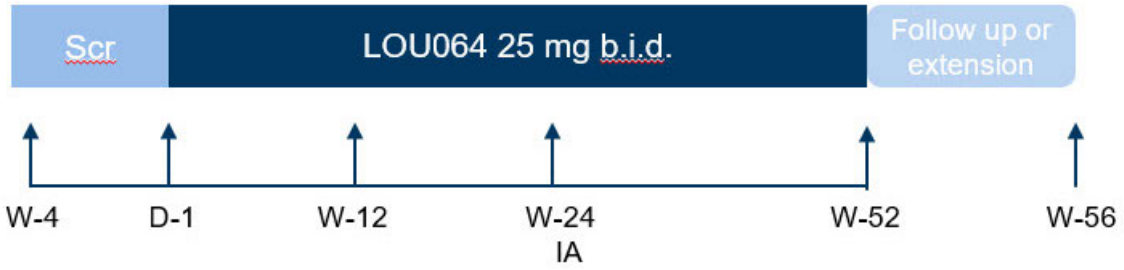
Additional optional interim analyses may be conducted at the discretion of the Sponsor to support decision making concerning the current clinical study, the Sponsor's clinical development projects in general, or in case of any safety concerns. The decision to conduct the

additional optional interim analyses and the timing/data to be reviewed will be documented in the SAP prior to the conduct of any additional optional interim analysis.

The final analysis will be conducted on all participants' data at the time the trial ends regardless of the interim analysis.

All participants will be on a stable, local label approved dose of a second-generation H1-antihistamine ("background therapy") throughout the entire study (starting a minimum of 7 days prior to baseline 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



D-1: Day 1, b.i.d.: bis in die/twice a day, IA: interim analysis, mg: milligram(s), Scr: Screening, W: Week

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
• To evaluate the safety of remibrutinib (25 mg b.i.d.) in CSU patients	• Overall safety data, assessed as treatment emergent adverse events during the study
Secondary objectives	**Endpoints for secondary objectives**
• To evaluate the efficacy of remibrutinib (25 mg b.i.d.) by evaluation of:	
◦ Change from baseline in UAS7 at Week 12	• Absolute change from baseline in UAS7 at Week 12
◦ Proportion of participants achieve disease activity control (UAS7 ≤ 6) at Week 12	• Achievement of UAS7≤ 6 (yes/no) at Week 12
◦ Proportion of participants achieve complete absence of hives and itch (UAS7 = 0) at Week 12	• Achievement of UAS7 = 0 (yes/no) at Week 12
◦ Change from baseline in ISS7 at Week 12	• Absolute change from baseline in ISS7 score at Week 12
◦ Change from baseline in HSS7 at Week 12	• Absolute change from baseline in HSS7 score at Week 12
◦ Proportion of participants achieve disease activity control (UAS7 ≤ 6) at Week 2	• Achieving early onset of disease activity control, as defined as achievement of UAS7≤ 6 (yes/no) at Week 2

Objectives	Endpoints
• Proportion of participants achieve DLQI = 0-1 at Week 12	• No impact on participants' dermatology-quality of life, as defined by achievement of DLQI = 0-1 (yes/no) at Week 12
• Maintain disease activity control assessed as cumulative number of weeks with UAS7 ≤ 6 response	• Achieving sustained disease activity control, assessed as cumulative number of weeks with an UAS7≤6 response between baseline and Week 12
• Angioedema occurrence-free weeks assessed by the cumulative number of weeks with AAS7 = 0 response	• Number of weeks without angioedema, assessed by the cumulative number of weeks with an AAS7= 0 response between baseline and Week 12
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

1.2.1 Primary estimand(s)

Primary estimand on safety as primary endpoint

The primary clinical question of interest regarding safety as the primary endpoint is: What is the effect of remibrutinib treatment on the incidence of treatment-emergent adverse events (i.e., events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) 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, non-compliance (interruption) to treatment, switch of background medication or intake of a different second-generation H1-antihistamine as rescue medication/ confounding prohibited medication?

The primary estimand on safety is described by the following attributes:

1. **Population:** participants with inadequa]tely controlled CSU despite treatment with second-generation H1-antihistamine treatment who have CSU duration ≥6 months, a UAS7 score ≥16, ISS7 score ≥6 and HSS7 score ≥6 in the last 7 days prior to start of treatment.
2. **Endpoint:** incidence of treatment-emergent adverse events.

3. **Treatment of interest:** the study treatment (remibrutinib 25 mg b.i.d.) regardless of treatment compliance (discontinuation/interruption), with background medication of local approved second-generation H1-antihistamine, and a different second-generation H1-antihistamine as rescue medication.
4. **Summary Measurement:** the number and the proportion of participants with at least one treatment-emergent adverse event.
5. **Handling of remaining intercurrent events:**
   - Discontinuation of study treatment due to any reason: data collection will be maintained in the follow-up period. The data collected after these events will be used for analysis.
   - Treatment non-compliance (interruption), intake of rescue medication, or switch of background medication: ignore, i.e., data collection will be maintained and available measurements post-intercurrent event will be used as if they had been obtained under the treatment: Treatment policy strategy
   - Intake of strongly confounding prohibited medication (e.g., biologics treatment, cyclosporine, systemic corticosteroids): Treatment policy strategy
   - Administration of medications affecting the evaluation of potential risks, including: (a) anticoagulant/anti-platelet medications (other than acetylsalicylic acid up to 100mg/day or clopidogrel); (b) live attenuated vaccines; (c) strong cytochrome P (CYP) 3A4 inhibitors; (d) moderate/strong CYP3A4 inducers, (e) Oral breast cancer resistance protein (BCRP) substrates that may have increased exposure when co-administered with remibrutinib (defined as pitavastatin, rosuvastatin, sulfasalazine and ubrogepan): Treatment policy strategy
   - Intake of other prohibited medication: Treatment policy strategy

1.2.2 Secondary estimand(s)

Secondary estimand on efficacy as secondary endpoint: change from baseline in UAS7 score at Week 12

The secondary clinical question of interest regarding efficacy as secondary endpoint, change from baseline in UAS7 score at Week 12 is: What is the effect of remibrutinib treatment on the change from baseline in UAS7 score after 12 weeks of 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 or intake of a different second-generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication use as an unfavorable outcome?

The secondary estimand on efficacy as secondary endpoint, change from baseline in UAS7 score at Week 12 is described by the following attributes:

1. **Population:** participants with inadequately controlled CSU despite treatment with second-generation H1-antihistamine treatment who have CSU duration ≥6 months, a UAS7 score ≥16, ISS7 score ≥6 and HSS7 score ≥6 in the last 7 days prior to start of treatment.
2. **Endpoint:** change in UAS7 from baseline at Week 12.

3. **Treatment of interest:** the study treatment (remibrutinib 25 mg b.i.d.) 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 change from baseline.
5. **Handling of remaining intercurrent events:**
   - Discontinuation of study treatment due to any reason: Treatment policy strategy
   - Treatment non-compliance (interruption), switch of background medication, or intake of rescue medication as per protocol prior to Week 12: Treatment policy strategy
   - Intake of strongly confounding prohibited medication (e.g., biologics treatment at any time before Week 12, cyclosporine after Week 8, systemic corticosteroids after Week 8): Composite strategy (irrespective of potential occurrence of other intercurrent events)
   - Intake of other prohibited medication prior to Week 12: Treatment policy strategy

Secondary estimand on efficacy as secondary endpoint: UAS7 ≤6 response at Week 12 (Week 2, if applicable)

The secondary clinical question of interest regarding efficacy as secondary endpoint, UAS7 ≤6 response at Week 12 is: What is the effect of remibrutinib treatment on the UAS7 ≤6 response after 12 weeks of 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 or intake of a different second-generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication as an unfavorable outcome?

The secondary estimand on efficacy as secondary endpoint, UAS7 ≤6 response at Week 12 is described by the following attributes:

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

Secondary estimand on efficacy as secondary endpoint: UAS7=0, DLQI=0-1 and AAS7=0 response at Week 12

Similar estimand approach will be implemented for these endpoints as for the UAS7 ≤6 response at Week 12.

Secondary estimand on efficacy as other secondary endpoints as defined in Table 1-1.

Similar estimand approach will be implemented for these endpoints as for the change from baseline in UAS7 score at Week 12.

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, and maximum.

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

The interim analysis may be conducted when all participants have completed their Week 24 visit or discontinued early. If the interim analysis is conducted, data available at the cut off date (including beyond Week 24) will be used for the analysis. The data cut off date for Week 24 interim analysis will be the date of Week 24 visit for the last participant completing Week 24 visit. For efficacy analyses, the data up to Week 24 visit for each individual participant will be included. For safety analyses and other summaries, all available data until the cut off date will be included.

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

The "LOU064 25mg" will be used as treatment group name in this study.

2.1.1 General definitions

2.1.1.1 Baseline and post-baseline definitions

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

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

2.1.1.2 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 enrollment in treatment period 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)/day of the enrollment in the treatment period (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)/enrollment in the treatment period (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.

2.1.1.3 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.

The on-treatment period lasts from the date of first administration of study treatment to 28 days after the date of the last actual administration of the study treatment or the end of study where the end of study is either of the date of study discontinuation, or study completion, or safety follow-up completion or cut-off date, depending on participant's status.

2.1.1.4 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 52 are defined based on the study days starting with Day 1 (day of the enrollment in treatment period). The study day for the eDiary date will be calculated as [Date of Diary] – [Date of day of the enrollment in treatment period] + 1 for post-baseline assessment and [Date of Diary] – [Date of day of the enrollment in treatment period] for baseline assessment.

The analysis Week 1 through Week 51 of the treatment period will be derived based on scheduled visit day as defined in Table 2-1. 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.

The analysis follow-up Week 1 to Week 4 will be derived based on the actual Week 52 study visit day as defined in Table 2-1.

Table 2-1 Assessment window for weekly scores based on eDiary (for completers)

Study period	Analysis visit	Scheduled visit day	eDiary assessment window
Treatment	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
	Week 25	-	Day 169 to Day 175
	Week 26	-	Day 176 to Day 182
	Week 27	-	Day 183 to Day 189
	Week 28	-	Day 190 to Day 196
	Week 29	-	Day 197 to Day 203
	Week 30	-	Day 204 to Day 210
	Week 31	-	Day 211 to Day 217
	Week 32	225	Day 218 to Day 224
	Week 33	-	Day 225 to Day 231
	Week 34	-	Day 232 to Day 238
	Week 35	-	Day 239 to Day 245
	Week 36	-	Day 246 to Day 252
	Week 37	-	Day 253 to Day 259
	Week 38	-	Day 260 to Day 266
	Week 39	-	Day 267 to Day 273
	Week 40	281	Day 274 to Day 280
	Week 41	-	Day 281 to Day 287
	Week 42	-	Day 288 to Day 294
	Week 43	-	Day 295 to Day 301
	Week 44	-	Day 302 to Day 308
	Week 45	-	Day 309 to Day 315

	Week 46	-	Day 316 to Day 322
	Week 47	-	Day 323 to Day 329
	Week 48	-	Day 330 to Day 336
	Week 49	-	Day 337 to Day 343
	Week 50	-	Day 344 to Day 350
	Week 51	-	Day 351 to Day 357
	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 in 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 52, assessment will follow rules as defined in Table 2-2 **up to Week 52**. After Week 52, weekly scores will not be derived even when the eDiary data are collected.

Table 2-2 Assessment window for weekly scores based on eDiary (for early treatment discontinued participants earlier than Week 52)

Study period	Analysis visit	Scheduled visit day	eDiary assessment window
Treatment	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
	Week 25	-	Day 169 to Day 175
	Week 26	-	Day 176 to Day 182
	Week 27	-	Day 183 to Day 189
	Week 28	-	Day 190 to Day 196
	Week 29	-	Day 197 to Day 203
	Week 30	-	Day 204 to Day 210
	Week 31	-	Day 211 to Day 217
	Week 32	225	Day 218 to Day 224
	Week 33	-	Day 225 to Day 231
	Week 34	-	Day 232 to Day 238
	Week 35	-	Day 239 to Day 245
	Week 36	-	Day 246 to Day 252
	Week 37	-	Day 253 to Day 259

	Week 38	-	Day 260 to Day 266
	Week 39	-	Day 267 to Day 273
	Week 40	281	Day 274 to Day 280
	Week 41	-	Day 281 to Day 287
	Week 42	-	Day 288 to Day 294
	Week 43	-	Day 295 to Day 301
	Week 44	-	Day 302 to Day 308
	Week 45	-	Day 309 to Day 315
	Week 46	-	Day 316 to Day 322
	Week 47	-	Day 323 to Day 329
	Week 48	-	Day 330 to Day 336
	Week 49	-	Day 337 to Day 343
	Week 50	-	Day 344 to Day 350
	Week 51	-	Day 351 to Day 357
	Week 52	365	Day 358 to Day 364
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 early treatment discontinuation (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 consider as baseline).

The assessment window is based on the study assessment schedule. The assessment schedule defined in the protocol is shown in Table 2-3. Note for Electrocardiogram (ECG), at Week 2, 12, 52 and SD visit pre and post dose assessments will be performed. ETD visit can be remapped to Week 24 only, and SD visit can be remapped to Week 2, 12 and 52.

Table 2-3 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
Electrocardiogram (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

[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.

The Table 2-4 shows the assessment window for the assessments performed at every visits (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 and 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 and 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 2-4 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 etc.), 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 Table 2-5.

Table 2-5 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 2-6 show the assessment windows of days for each assessment.

Table 2-6 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]										
Electrocardiogram (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 study.

Screened Set: **The Screened Set includes all participants who had signed an informed consent form and had a screening visit.**

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

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

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

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 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, > 5 years)*

[redacted]

* The subgroup categorization may be re-assessed and re-defined in the TFLs (Tables, Figures, Listings Shells document) if one subgroup has 5 or less participants.

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 Safety Set who completed the study treatment period, who discontinued the study treatment and the reason for treatment discontinuation will be presented.

The number and percentage of participants in the Safety Set who completed the study (including follow-up period), who discontinued the study and the reason for discontinuation will be presented as well.

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

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

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively on the Safety Set.

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

Continuous variables:

- Screening Age (years)
- Screening Height (cm)
- Screening Weight (kg)
- Body mass index (BMI) calculated as (body weight at screening in kilograms) / (height at screening 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, ≥ 85 years)
- Gender
- Race
- Ethnicity
- BMI groups (< 25, 25 -< 30, ≥ 30 kg/m^2)

- Baseline UAS7 categories (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)
- Previous experience of Angioedema (Yes, No)
- [redacted]
- [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, > 5 years)
- [redacted]

The following relevant medical histories and current medical conditions at baseline will be summarized combined by system organ class and preferred term on the Safety 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 and the duration of 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 to study treatment will be computed without excluding temporary treatment interruptions.

The duration of exposure and duration of study in weeks to LOU064 25mg will be summarized.

The number of participants with the duration of exposure and the duration of 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.

2.4.2 Prior, concomitant and post therapies

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

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

The Safety Set will be used for the analyses described in this section.

Prior urticaria medications and prior non-urticaria medications will be summarized separately by ATC code and preferred term.

Concomitant medications (excluding background or rescue medications) will be summarized by ATC code and preferred term.

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

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

Rescue medication: oral corticosteroids will be summarized by ATC code and preferred term.

In addition, prior/concomitant significant non-drug therapies/procedures will be summarized separately by primary system organ class and preferred term of MedDRA dictionary.

2.5 Analysis supporting primary objective(s)

2.5.1 Primary endpoint(s)

The primary clinical question of interest regarding safety as primary endpoint is: What is the effect of remibrutinib treatment on the incidence of treatment-emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) 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, non-compliance (interruption) to treatment, switch of background medication or intake of a different second-generation H1-antihistamine as rescue medication/ confounding prohibited medication?

The primary (safety) endpoint (variable) is the number and the proportion of participants with treatment-emergent adverse event. The treatment-emergent adverse event is defined as event started during on-treatment period or event present prior to start of treatment but increased in severity based on preferred term. The on-treatment period lasts from the date of first administration of study treatment to 28 days after the date of the last actual administration of the study treatment or the end of study where the end of study is either of the date of study discontinuation, or study completion, or safety follow-up completion or cut-off date, depending on participant's status.

2.5.2 Statistical hypothesis, model, and method of analysis

The number and the proportion (%) of participants with the treatment-emergent adverse events will be summarized in the following ways:

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

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

The most common adverse events reported (≥5% for each preferred term or ≥5% for each SMQ) will be presented in descending frequency according to its incidence starting from the most common event. The cut-off of 5% can be re-evaluated based on number of participants with 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 by severity table, 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.

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 treatment-emergent adverse events.

The number and the proportion (%) of participants with AESI will be summarized by safety topic of interest (i.e., risk name) and preferred term.

In addition, for adverse events, serious adverse events and AESI exposure adjusted incidence rates will be estimated 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 5.4.1 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.

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

All analyses for the primary (safety) endpoint will be performed descriptively. No statistical hypothesis is set for the primary (safety) endpoint in this study.

For all safety analyses, the Safety Set will be used.

2.5.3 Handling of intercurrent events

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

- Discontinuation of study treatment due to any reasons:
  data collection will be maintained in the follow-up period. Participants with these events will be encouraged to stay in the study following the procedures. Every effort will be made to continue to follow participants with these events up to study end. The data collected after these events will be used for analysis.
- Treatment non-compliance (interruption), switch of background medication, or intake of rescue medication as per protocol:
  ignore, i.e., data collection will be maintained and available measurements post-intercurrent event will be used as if they had been obtained under the treatment (Treatment policy strategy).
- Intake of strongly confounding prohibited medication (e.g., biologics treatment, cyclosporine, systemic corticosteroids):
  ignore, i.e., data collection will be maintained and available measurements post-intercurrent event will be used as if they had been obtained under the treatment (Treatment policy strategy).
- Administration of medications affecting the evaluation of potential risks, including: (a) anticoagulant/anti-platelet medications (other than acetylsalicylic acid up to 100 mg/day or clopidogrel); (b) live attenuated vaccines; (c) strong CYP3A4 inhibitors; (d) moderate/strong CYP3A4 inducers, (e) Oral BCRP substrates that may have increased exposure when co-administered with remibrutinib (defined as pitavastatin, rosuvastatin, sulfasalazine and ubrogepan):
  ignore, i.e., data collection will be maintained and available measurements post-intercurrent event will be used as if they had been obtained under the treatment (Treatment policy strategy).
- Intake of other prohibited medication:
  ignore, i.e., data collection will be maintained and available measurements post-intercurrent event will be used as if they had been obtained under the treatment (Treatment policy strategy).

2.5.4 Handling of missing values not related to intercurrent event

No imputation will be done for missing data. All available data will be used for the analyses.

2.5.5 Sensitivity analyses

If unexpectedly high incidence of adverse events of special interest (AESI) is observed, i.e., if incidence of AESI is greater than the one reported in the final analysis of A2201E1 study +20%, then sensitivity analysis will be performed for the AESI.

The following sensitivity analysis maybe performed on AESI, to assess the causality between the occurrence of AESI and medications. The sensitivity analysis will be implemented with the same target population, on AESI variable and the summary measure as for the primary estimand, but using the different assumptions or handling of intercurrent events.

- Intake of strongly confounding prohibited medication (e.g., biologics treatment (as identified by PD M-COMD03 and/or M-COMD03B), cyclosporine (as identified by PD M-COMD04 and/or M-COMD04B), systemic corticosteroids (as identified by PD M-COMD02B and/or M-COMD04 and/or M-COMD05)) : only measurements prior to intake of these prohibited medications will be used for analysis (While on treatment strategy).
- Intake of medications affecting the evaluation of potential risks, including: (a) anticoagulant/anti-platelet medications (other than acetylsalicylic acid up to 100 mg/day or clopidogrel) (as identified by PD M-COMD07); (b) live attenuated vaccines (as identified by PD M-COMD07); (c) strong CYP3A4 inhibitors (as identified by PD M-COMD07); (d) moderate/strong CYP3A4 inducers (as identified by PD M-COMD07), (e) Oral BCRP substrates that may have increased exposure when co-administered with remibrutinib (defined as pitavastatin, rosuvastatin, sulfasalazine and ubrogepan) (as identified by the name of concomitant medications entered in CRFs): only measurements prior to intake of these medications will be used for analysis (While on treatment strategy).

2.5.6 Supplementary analyses

No supplementary analysis is planned for the primary (safety) endpoints.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

The secondary clinical question of interest regarding efficacy as secondary endpoints is: What is the effect of remibrutinib treatment on secondary efficacy endpoints 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 or intake of a different second-generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication use as an unfavorable outcome?

The secondary estimand on efficacy as secondary endpoints is described by the following attributes:

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

2. **Endpoint:** see below.
3. **Treatment of interest:** the study treatment (remibrutinib 25 mg b.i.d.) 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:** see Table 2-7 below.
5. **Handling of remaining intercurrent events:** see Section 2.6.3.

One of the secondary (efficacy) endpoints (variables) 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 2.1.1.4). 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.

Other secondary endpoints are as follows:

- Disease activity control at Week 12, assessed as proportion of participants achieving UAS7 ≤6
- Complete absence of hives and itch at Week 12, assessed as proportion of participants achieving UAS7 =0
- Improvement of severity of itch at Week 12, assessed as absolute change from baseline in ISS7 score
- Improvement of severity of hives at Week 12, assessed as absolute change from baseline in HSS7 score
- Disease activity control at Week 2, assessed as proportion of participants achieving UAS7 ≤6

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

- 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.

- Cumulative number of weeks that participants achieving UAS7 ≤6 response 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). If the UAS7 score for a week is missing, it will be considered as a non-response for that week for the cumulative number of weeks that participants achieve UAS7 ≤6 response calculation.

- Cumulative number of weeks that participants achieving AAS7 =0 response 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

A weekly AAS7 score will be derived by adding up the daily scores (possible range 0-15) of the 7 days preceding the visit, and ranges from 0 to 105 (please refer to the assessment window in Section 2.1.1.4). 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, AAS7 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, AAS7 will be considered as missing for that week. If the AAS7 score for a week is missing, it will be considered as a non-response for that week for the cumulative number of weeks that participants achieve AAS7 =0 response calculation.

Table 2-7 Estimand attributes for secondary endpoints

Endpoint	Summary measurement
UAS7 score change from baseline to Week 12	Mean change from baseline
UAS7 ≤6 at Week 12	Number and proportion of participants with UAS7 ≤6 response at Week 12
UAS7 =0 at Week 12	Number and proportion of participants with UAS7 =0 response at Week 12
ISS7 score change from baseline to Week 12	Mean change from baseline
HSS7 score change from baseline to Week 12	Mean change from baseline
UAS7 ≤6 at Week 2	Number and proportion of participants with UAS7 ≤6 response at Week 2
DLQI =0-1 at Week 12	Number and proportion of participants with DLQI =0-1 response at Week 12
Cumulative number of weeks with an UAS7 ≤6 response between baseline and Week 12	Mean of cumulative number of weeks with an UAS ≤6 response between baseline and Week 12
Cumulative number of weeks with an AAS7 =0 response between baseline and Week 12	Mean of cumulative number of weeks with an AAS7 =0 response between baseline and Week 12

2.6.2 Statistical hypothesis, model, and method of analysis

The secondary (efficacy) variables during the study, listed in Table 2-7, will be summarized.

All analyses for the secondary (efficacy) endpoints will be performed descriptively. No statistical hypothesis is set for the secondary (efficacy) endpoints in this study.

For all efficacy analyses, the FAS will be used.

2.6.3 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 RDO participants. If no RDO data was collected after study treatment permanent discontinuation, missing data will be handled without imputation and all available data will be used for the analysis.

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

- Discontinuation of study treatment prior to Week 12 due to any reason: ignore, i.e., data collection will be maintained and available measurements post-treatment discontinuation will be used as if they had been obtained under the treatment: RDO data collected after study treatment discontinuation will be used for analysis (Treatment policy strategy).
- Treatment non-compliance (interruption), switch of background medication, or intake of rescue medication as per protocol prior to Week 12: ignore, i.e., data collected after these events will be used for analysis (Treatment policy strategy).
- Intake of strongly confounding prohibited medication (e.g., biologics treatment at any time before Week 12 (as identified by PD M-COMD03), cyclosporine 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)): measurements after this event will be excluded from the analysis and will be imputed using the worst value of the endpoint (e.g., 42 for UAS7 score at Week 12, 21 for ISS7 or HSS7 score) (Composite strategy (irrespective of potential occurrence of other intercurrent events)). Note: for the endpoint of UAS7 ≤6 at Week 2, intake of cyclosporine or systemic corticosteroids will not be considered.
- Intake of other prohibited medication prior to Week 12: ignore, i.e., Data collected after these events will be used for analysis (Treatment policy strategy).

2.6.4 Handling of missing values

See Section 2.6.1 for the derivation of the each variable.

If there is any intermittent missing data not due to any of the intercurrent events as we defined above, the missing data will be handled without imputation and all available data will be used for the analysis.

2.6.5 Sensitivity analyses

No sensitivity analysis is planned for the secondary (efficacy) estimands.

2.6.6 Supplementary analyses

No supplementary analysis is planned for the secondary (efficacy) estimands.

2.7 Safety analyses

For all safety analyses, the Safety Set will be used.

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 2.1.1.3.

2.7.1 Adverse events (AEs)

See Section 2.5.

2.7.1.1 Adverse events of special interest / grouping of AEs

See Section 2.5.2.

2.7.1.2 Requirements of ClinicalTrials.gov

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

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 AEs 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

Death including on-treatment and post-treatment deaths will be listed.

2.7.3 Laboratory data

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

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

For Urinalysis, local laboratory data will be included in the summary tables. For participants who have only central laboratory data, central data will be used in the summary tables. Both of local and central data will be listed. For by-visit summary tables, scheduled visits (including remapped visits following the assessment window in Section 2.1.1.4) 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.

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

For continuous variables, descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test. Change from baseline will only be summarized for participants with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value.

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

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

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

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Event (CTCAE) grades (version 5.0), given in Table 2-8: hemoglobin, platelets, white blood cells, neutrophils, lymphocytes, prothrombin time-international normalized ratio (INR), 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, and 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.

Table 2-8 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	Platelets	<LLN-75,000/mm^3	<75,000-50,000/mm^3	<50,000-25,000/mm^3	<25,000/mm^3

White blood cell count decreased	White blood cells	<LLN-3000/mm^3	<3000-2000/mm^3	<2000-1000/mm^3	<1000/mm^3
Neutrophil count decreased	Neutrophils	<2000-1500/mm^3	<1500-1000/mm^3	<1000-500/mm^3	<500/mm^3
Lymphocyte count decreased	Lymphocytes	<1500-800/mm^3	<800-500/mm^3	<500-200/mm^3	<200/mm^3
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
ALT 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
AST 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
ALP 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.

Note: The comparison with baseline is not considered for derivation of LAB CTC grade due to Novartis CTCAE V5 implementation guide.

To evaluate potential drug-induced liver injury, newly occurring liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-9. 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 is worse than baseline.

Similarly, participants meeting specific renal alert criteria at any post-baseline will be summarized according to Table 2-10.

In addition to 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, will be provided if any case.

Table 2-9 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 2-10 Specific renal alert criteria

Parameter	Notable criteria
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

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

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

The number and percentage of participants with newly occurring of the following criteria after baseline will be summarized:

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

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

For by-visit summary tables, scheduled visits (including remapped visits following the assessment window in Section 2.1.1.4) 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.

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 2-11 below.

Table 2-11 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 notable summary tables, all post-baseline visits including unscheduled visits will be considered in the analysis.

[redacted]

2.10 Patient-reported outcomes (PROs)

[redacted]

[redacted]

Dermatology Life Quality Index (DLQI)

For the following DLQI assessments, summary statistics will be presented on the FAS. The DLQI consists of 10-items, and the total score of the DLQI is calculated based on the developers' rules (possible range 0-30). For the total score derivation, if there was only one item left unanswered, the score of that item is imputed to 0 and then the total score is calculated accordingly. If there were two or more items left unanswered, then the total score is considered as missing. If the total score is missing, it will be handled without imputation and all available data will be used for the analysis.

[redacted]

- DLQI = 0-1: the proportion of participants achieving DLQI = 0-1 response by visit

Angioedema Activity Score (AAS)

For the following AAS assessments based on AAS eDiary, summary statistics will be presented on the FAS. See Section 2.6.1 for derivation of AAS7 score and AAS7 =0 response.

[redacted]

[redacted]

[redacted]

[redacted]

2.13 Interim analysis

See Section 1.1.

3 Sample size calculation

Since CSU is a chronic disease, and remibrutinib is expected to be administered over a long period, safety in long-term treatment needs to be confirmed. "Regarding sample size and treatment period required to assess safety at the clinical study stage of a new drug anticipated to be administered for a non-fatal disease over a long period" (Notification No. 592 of the Pharmaceuticals and Cosmetics Division, Pharmaceutical Affairs Bureau, MHLW, dated 24-May-1995), this notification requires to collect safety data of at least 100 Japanese patients who receive the drug over one year. CLOU064A2201E1 study was planned to collect efficacy and safety data of about 33 Japanese CSU participants exposed to remibrutinib greater than or equal to the application dose for one year and CLOU064A2301 study was planned to collect efficacy and safety data of about 15 Japanese CSU participants exposed to remibrutinib of the application dose for one year. Therefore, this study CLOU064A1301, is designed to obtain safety data of approximately 70 Japanese CSU participants exposed to remibrutinib at the application dose for one year. Since approximately 30% screening failure rate and approximately 15% dropout rate are expected, approximately 100 patients will need to be screened in order to collect approximately 70 participants who enter the treatment period and to collect a total of approximately 60 completed participants.

4 Change to protocol specified analyses

No change from protocol specified analysis.

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

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

Imputation for 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 < the treatment start date then AE start reference date = min (informed consent date, earliest visit date)
- Else AE start reference date = the treatment start date

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

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

- If the AE start date 'month' is missing, the imputed AE start date is set to the mid-year point (01JulYYYY)
- Else if the AE start date 'month' is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY)

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

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

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

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

- And the AE start date 'month' is missing, the imputed AE start date is set to the AE reference start date + 1 day
- Else if the AE start date 'month' is less than the treatment start date 'month', the imputed AE start date is set to the mid-month point (15MONYYYY)
- Else if the AE start date '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 the (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 the imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

Imputation for concomitant medication (CM) end date:

1. If the CM end date 'day' is missing and the CM end date 'month' and 'year' are not missing, the imputed CM end date is set to the earlier of the (treatment end date and last day of the month).

2. If the CM end date 'day' and 'month' are missing and the CM end date 'year' is not missing, the imputed CM end date is set to the earlier of the (treatment end date and end of the year (31DECYYYY)).

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

Imputation for CM start date:

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

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

- If the CM start date 'month' is missing, the imputed CM start date is set to the mid-year point (01JulYYYY)
- Else if the CM start date 'month' is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY)

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

- If the CM start date 'month' is missing, the imputed CM start date is set to the year start point (01JanYYYY)
- Else if the CM start date 'month' is not missing, the imputed CM start date is set to the month start point (01MONYYYY)

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

- And the CM start date 'month' is missing or the CM start date 'month' is equal to the treatment start date 'month', the imputed CM start date is set to one day prior to the treatment start date.
- Else if the CM start date 'month' is less than the treatment start date 'month', the imputed CM start date is set to the mid-month point (15MONYYYY)
- Else if the CM start date '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 the imputed CM start date should be set to the (imputed) CM end date.

5.1.4 Concomitant therapy date imputation

Same rule as for concomitant medication in Section 5.1.3.

5.1.5 Other imputations

First diagnosis date imputation

1. If the first diagnosis date 'day' and 'month' are missing and 'year' is not missing:

- If the first diagnosis date 'year' is equal to the inform consent date 'year', the imputed first diagnosis date is set to the year start point (01JanYYYY)
- Else the imputed first diagnosis date is set to the mid-year point (01JulYYYY)

2. If the first diagnosis date 'day' is missing and 'month' and 'year' are not missing:

- If the first diagnosis date 'month' and 'year' are equal to the inform consent date 'year' and 'month', then the imputed first diagnosis date is set to the month start point (01MONYYYY)
- Else 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 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 $U = \frac{0.5c_{1-\frac{\alpha}{2},2D+2}}{T}$

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

5.4.1.2 Confidence interval for proportion of binary data

Confidence intervals for proportion of binary data including 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 $p > 0$, ($L = 0\ for\ p = 0$),

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

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

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

5.4.2 Analysis supporting secondary objective(s)

Not applicable.

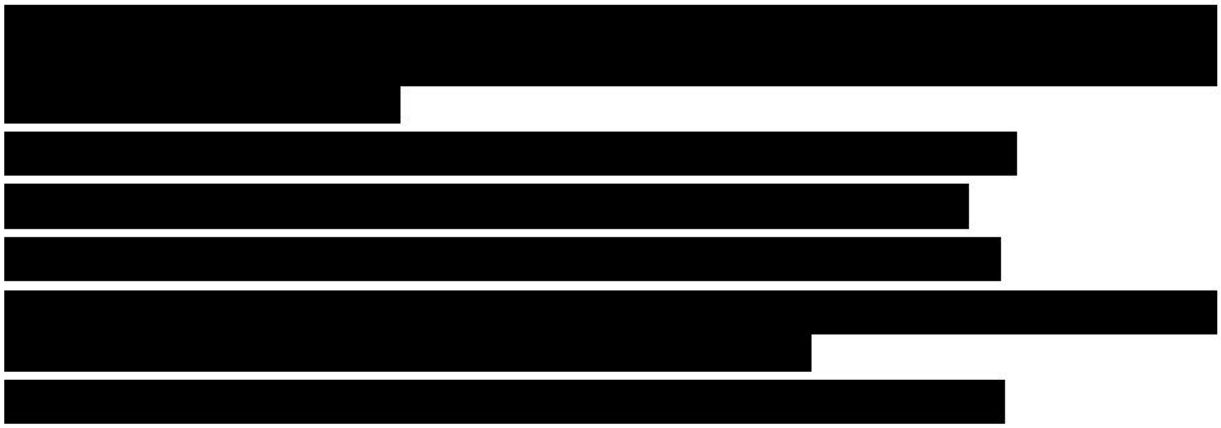
5.5 Rule of exclusion criteria of analysis sets

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 subject to be excluded
FAS	P-INCL01B-ICF not signed M-OTH12-ICH-GCP non-compliance	No assigned treatment and No dosed
SAF	P-INCL01B-ICF not signed M-OTH12-ICH-GCP non-compliance	No dosed

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

[redacted]



6 Reference

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