NOVARTIS

Clinical Development

Remibrutinib (LOU064)

CLOU064A2201E1 / NCT04109313

An open-label, multicenter, extension study to evaluate the long-term safety and tolerability of LOU064 in eligible subjects with CSU who have participated in preceding studies with LOU064

Statistical Analysis Plan (SAP)

Author:	Statistician, [redacted]

Document type:	SAP Documentation
Document status:	Amendment v3.0
Release date:	13-Oct-2022
Number of pages:	30

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
9-Sep-2019	Prior to FPFV	Creation of final version	First version	NA
Jun-2021	[redacted]	Protocol amendment v2.0 Address comment from dry-run review Update the analysis visit window for eDiary assessment		Section 2.1.1.3 Update the assessment window for eDiary assessment (i.e. UAS7, [redacted]); Section 2.3.2 Add baseline characteristics; Section 2.5.1.1 Update the treatment emergent adverse event definition; Drop Table 2-2; Section 2.5.1.2 Update the CTCAE grade definition in Table 2-3 Section 2.5.1.3 Update the notable abnormality criterion in ECG; Section 2.5.1.4. Update the notable abnormality criterion in vital signs; Section 2.6.3 Drop the handling rule for duplicated UPDD entries; Section 2.13 text updated for more clarity on population included for IA2
Oct-22	Prior to final analysis	Update for protocol deviation		Additional details added to Section 2.3.1 for protocol deviation analysis

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Updates for demog and baseline characteristic		More details are added to clarify that sex, race and ethinicity collected from core study.
		Medical History		Urticaria related medical history summaries added Medical history and current medical condition listings are added
		Study treatment/compliance		More details are added for calculations of exposure (weeks), exposure (years) and exposure (100 subject years)
		[redacted]		[redacted]
		Section 2.4.2		Concomitant surgeries, medical procedures and non-drug therapies added Listing for Prior and concomitant medication included
		[redacted]		[redacted]
		[redacted]		[redacted]

Table of contents

List of abbreviations

[redacted]	[redacted]
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
b.i.d.	bis in diem/twice a day
BP	Blood Pressure
CSR	Clinical Study report
CSU	Chronic Spontaneous Urticaria
CV	Coefficient of Variation
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
ECG	Electrocardiogram
EOT	End of treatment period
EOS	End of study period
FAS	Full Analysis Set
GCP	Good Clinical Practice
HSS7	Weekly Hives Severity Score
Ig	Immunoglobulin
INR	International Normalized Ratio
IRT	Interactive Response Technology
ISS7	Weekly Itch Severity Score
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
[redacted]	[redacted]
QTcF	QT interval corrected by Fridericia's formula
SAE	Serious Adverse Event
SAF	Safety Analysis set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBL	Total bilirubin
ULN	Upper Limit of Normal
ULOQ	Upper Limit Of Quantification
UPDD	Urticaria Patient Daily Diary

1 Introduction

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

This document covers statistical and analytical plans [redacted] for the final analysis of all data collected up to end of the study for CLOU064A2201E1 study with reference to the study protocol.

[redacted]

1.1 Study design

This study is an open-label, single arm, multicenter, long-term safety and tolerability extension study for CSU patients who have participated in CLOU064A2201 or other preceding studies with LOU064 and fulfil the enrollment criteria for the extension study.

The study will consist of three periods: observational period (up to 12 weeks), treatment period (52 weeks), and follow-up period (4-16 weeks).

Approximately 250 patients will enroll into this extension study.

The following study periods will be considered for analysis:

- **Observational period** (Enrollment in observation period to end of observation period (up to Week 12))
- **Treatment period** (Enrollment in treatment period to Week 52 including follow-up visits for patients prematurely discontinued)
- **Entire study period** (Enrollment in treatment period to EoS (End of study) including follow-up visits for all patients)

1.2 Study objectives and endpoints

The purpose of this study is to evaluate long-term safety and tolerability as well as efficacy outcome of LOU064 in patients who have participated in a preceding study with LOU064 in CSU. [redacted]

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)

Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the long-term safety and tolerability of LOU064 in patients with CSU who have participated in preceding studies with LOU064.	• Safety endpoints will include but not be limited to: occurrence of treatment emergent (serious and non-serious) adverse events during the extension study
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of LOU064 when given without H1-antihistamines in patients with CSU with respect to change from baseline in UAS7, achieving controlled disease (defined by a UAS7≤6), and achieving complete response (defined by a UAS7=0) at Week 4 of treatment	• Change from baseline in UAS7 at Week 4 • UAS7≤6 response at Week 4 • UAS7=0 response at Week 4
• To evaluate the long-term efficacy of LOU064 in patients with CSU who have participated in previous studies with LOU064 with respect to maintaining or achieving controlled disease (defined by a UAS7≤6) over time	• UAS7≤6 response over time
• To evaluate the long-term efficacy of LOU064 in patients with CSU who have participated in preceding studies with LOU064 with respect to change from baseline in UAS7 over time	• Change from baseline in UAS7 over time

2 Statistical methods

Novartis will be performing [redacted] the final analysis. Statistical software R version 3.4.3 and SAS version 9.4 or later will be used.

2.1 Data analysis general information

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

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

[redacted]

2.1.1 General definitions

2.1.1.1 Study treatment

The following treatment groups will be presented:

- LOU064 100 mg b.i.d.
- Treatment free

2.1.1.2 Study Day 1 and Study Day for treatment period

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

For efficacy analysis, the day of enrollment in treatment period (visit 101) is defined as *Study Day 1* or *Day 1*.

Study days will be labeled relative to Day 1 for treatment period. 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/Enrollment] + 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/Enrollment], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1). The descriptor "Day 0" will not be used.

2.1.1.3 Assessment window for Study Week (eDiary)

The study weeks for assessment completed on eDiary are defined based on the study days starting with Day 1 (Enrollment in observational/treatment period Day).

For completers of treatment period, the study day for eDiary date will be calculated as [Date of Diary] – [Date of Enrollment] + 1 for post-baseline assessment and [Date of Diary] – [Date of Enrollment] 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. The analysis Week 52 score will be derived as Day -7 to Day -1 of actual Week 52 study visit day.

During the follow-up period, the study weeks for assessment completed on eDiary are defined based on the study days starting with Day 1 of follow-up period (actual Week 52 visit day). The study day for the eDiary date will be calculated as [Date of Diary] – [Date of Week 52 visit day] + 1. The analysis follow-up Week 1 to Week 16 will be derived based on the actual Week 52 study visit day as defined in Table 2-1.

For early discontinued patients, it is suggested to collect the eDiary data even after the patient discontinued from treatment per "Treatment policy strategy" (this part of data is named as "retrieved drop-out data"). The retrieved drop-out data will be included in the weekly score derivation per assessment window defined in Table 2-1.

Table 2-1 Assessment window for eDiary

Period	Analysis visit	Scheduled Visit Day	eDiary Assessment Window
Observational	OEnrollment	1	Day -7 to Day -1
	OWeek 1	-	Day 1 to Day 7
	OWeek 2	-	Day 8 to Day 14
	OWeek 3	-	Day 15 to Day 21
	OWeek 4	29	Day 22 to Day 28

	OWeek 5	-	Day 29 to Day 35
	OWeek 6	-	Day 36 to Day 42
	OWeek 7	-	Day 43 to Day 49
	OWeek 8	57	Day 50 to Day 56
	OWeek 9	-	Day 57 to Day 63
	OWeek 10	-	Day 64 to Day 70
	OWeek 11	-	Day 71 to Day 77
	OWeek 12	85	Day 78 to Day 84
Treatment	Baseline	1	Day -7 to Day -1
	Similar as in observational period.		
	Week 12	85	Day 78 to Day 84
	...		
	Week 16	113	Day 106 to Day 112
	...		
	Week 20	141	Day 134 to Day 140
	...		
	Week 28	197	Day 190 to Day 196
	...		
	Week 40	281	Day 274 to Day 280
	...		
	Week 52	365	Day 358 to Day 364 For completers, Day -7 to Day -1 of Week 52 study visit
Follow-up	Follow-up Week 1	393	Day 1 to Day 7 of Week 52 study visit
	...		
	Follow-up Week 4	421	Day 22 to Day 28 of Week 52 study visit
	...		
	Follow-up Week 12	477	Day 78 to Day 84 of Week 52 study visit

The baseline week is comprised of the 7 days prior to Day 1 (Day -7 to Day -1). The baseline UAS7 score for observational period could be different from the UAS7 score of the last visit for core study. The baseline UAS7 score for treatment period could be different from the UAS7 score of the last visit for observational period.

2.1.1.4 Baseline

Baseline for safety in treatment period is the last assessment (including unscheduled visits) obtained on or before the first dose day 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 Day 1 (Enrollment in treatment period Day) for UAS7 and other assessment on or prior enrollment in treatment period day.

For observational period, only baseline UAS7 score is applicable and defined in section 2.1.1.3. [redacted]

2.1.1.5 On-treatment

All safety events happened after first dose of study treatment and before minimum(last dose + 28days, end of study visit) will be considered on-treatment no matter during treatment period or follow-up period.

For AE summary for observational period, all adverse event happened after enrollment in observational period and before roll over to treatment period will be summarized.

2.2 Analysis sets

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

The **Safety Analysis Set** includes all subjects who received at least one dose of study treatment during the treatment period of this extension study.

For the observational period, the observational **Full Analysis Set (oFAS)** includes all subjects who enrolled in the observational period.

All enrolled subjects includes all subjects who enrolled in this extension study.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of screened and screen failures subjects will also be shown for all enrolled subjects. The reason for screen failure will be summarized.

The number of subjects in each analysis set will be presented by observational period based on oFAS and treatment period based on Safety set. The reason for excluded from any analysis set will be listed.

The number and percentage of patients enrolled in observational period, complete observation period or early discontinued from study during observational period will be presented based on oFAS. Similarly, the number and percentage of patients enrolled in treatment period, complete the treatment period or early discontinued from treatment/study will be presented based on SAF.

The number and percentage of patients who has experienced protocol deviations (PD) will be tabulated by deviation category for all patients. [redacted] Listing will be provided for all subjects enrolled.

2.3.2 Demographic and baseline characteristics

Demographics and baseline characteristics will be summarized for treatment period based on SAF and for observational period based on oFAS. Disease characteristics and relevant medical histories will also be presented based on SAF. Subject demographic and baseline characteristic data including sex, race and ethnicity that was collected as a part of the core study will be used in this extension study.

Listing will be provided for all subjects enrolled.

Summary statistics will be presented for continuous demographic and baseline characteristic variables for all patients.

Continuous variables:

- Age (years) (for A2201E1 study)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2
- Baseline UAS7 score/Enrollment UAS7 score
- [redacted]
- [redacted]
- Time since diagnosis of urticaria = (inform consent date – diagnosis date + 1)/365.25

The number and percentage of subjects in each category will be presented for categorical variables for all patients.

Categorical variables:

- Age categories (< 65, >= 65-<85years , >=85 years)
- Gender (from core study A2201)

- Race (from core study A2201)
- Ethnicity (from core study A2201)
- BMI groups (< 25, 25 - 30, >= 30 kg/m**2)
- Baseline UAS7 category (Mild disease: UAS7 6-<16; Moderate disease: UAS7 16-<28; Severe disease UAS7 28-42)/Enrollment UAS7 category
- [redacted]

2.3.3 Medical history

Relevant medical histories and current medical conditions before first dose of study treatment in the treatment period will be summarized by system organ class and preferred term according to MedDRA dictionary for SAF. Urticaria related medical history will be summarized separately for SAF.

All relevant medical histories and current medical conditions will be listed for all subjects enrolled. Cardiovascular history and family malignancy history for subjects developed malignancy during the treatment period will be listed for SAF

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

The analysis of study treatment data will be based on SAF.

2.4.1 Study treatment / compliance

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

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

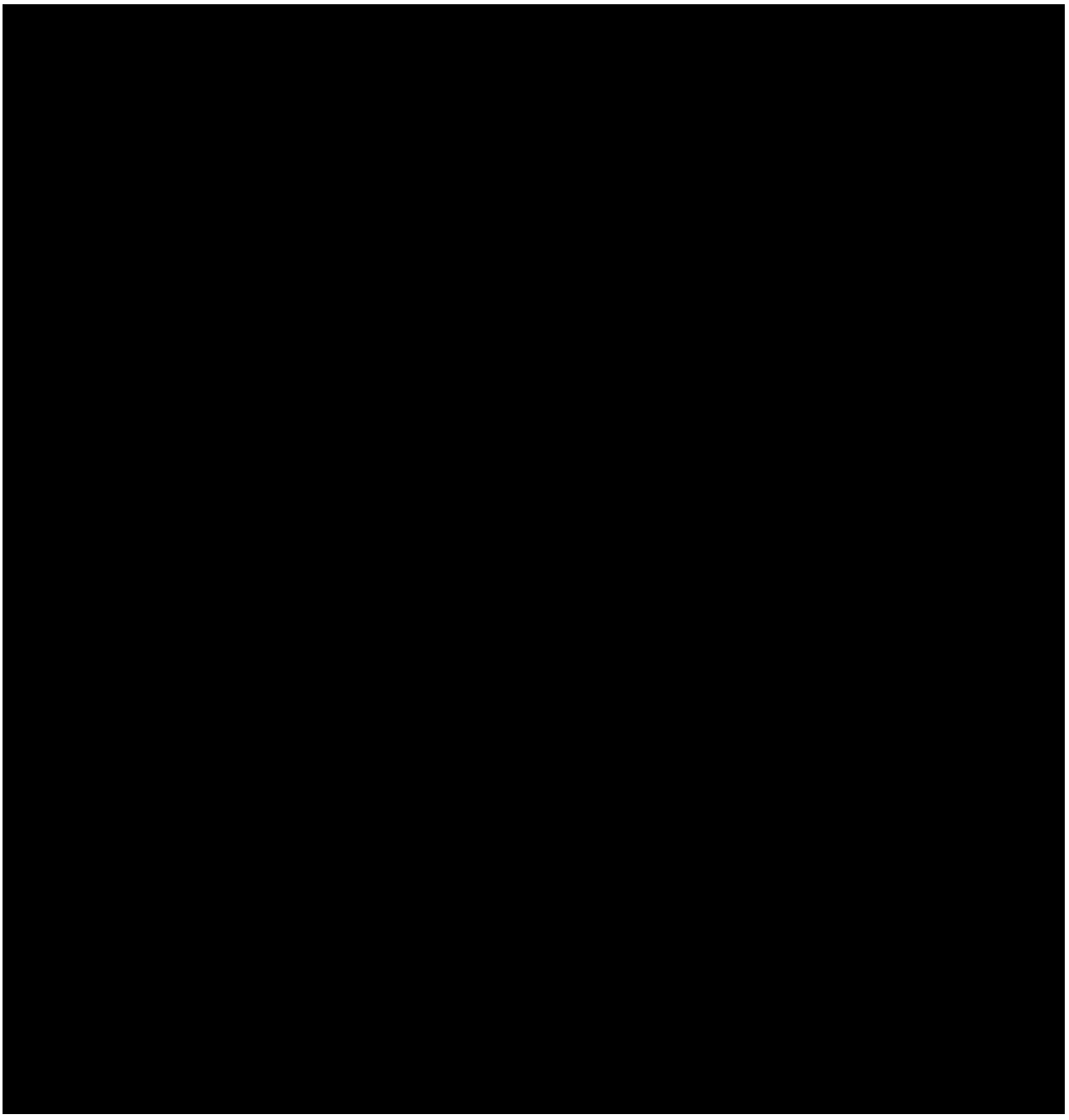
Duration of study for entire study period is defined as last study visit – enrollment in treatment period + 1.

Duration of exposure (weeks) = duration of exposure (days) / 7

Duration of exposure (years) = duration of exposure (days) / 365.25

Duration of exposure (100 subject years) = duration of exposure (years) / 100

The start date and end date of study treatment will be collected on eCRF and will be used to calculate the duration of exposure.



2.4.2 Prior, concomitant and post therapies

Prior, non-urticaria related concomitant medications and urticaria related concomitant medication or rescue medications during treatment period will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term for SAF. Additionally, concomitant surgeries, medical procedures and non-drug therapies by primary system organ class and preferred term will be preseted.

Concomitant medications are defined as any medication given at least once between the day of first dose of study treatment and the date of the last study visit.

Background medications and rescue medications during treatment period will be sumairzed separately by Anatomical Therapeutic Chemical (ATC) code and preferred term for SAF.

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

All relevant listings will be provided based on SAF for concomitant medication; concomitant surgeries, medical procedures and non-drug therapies.

2.5 Analysis of the primary objective

The primary objective of this study is to investigate the long-term safety and tolerability of LOU064 in subjects with CSU. The primary safety analysis will be analyzed using SAF.

2.5.1 Primary endpoint

2.5.1.1 Adverse events

All adverse events which newly start on the same day or after the first dose of study medication in the treatment period of this extension study OR worsen on the same day or after the first dose of study medication and within min(last dose + 28 days, end of study visit) will be considered as treatment emergent adverse event for this extension study.

Number and percentage of subjects having any treatment emergent adverse events during entire study period of the extension study, by system organ class and preferred term will be provided for:

- All adverse events
- Adverse events by maximum severity
- Drug related adverse events
- Serious Adverse events
- Adverse events leading to treatment discontinuation

Adverse events by standardized MedDRA Query (SMQ), System organ class (SOC) and preferred term will be provided. Separate summaries will be provided for deaths, SAEs, and other significant AEs leading to discontinuation.

If a subject reported more than one AE with the same preferred term, the AE with the greatest severity will be presented.

All adverse events will be listed for SAF.

Safety topic of special interest

Incidence rate for safety topic of special interest will be provided. The latest project eCRS will be used for reporting.

2.5.1.2 Laboratory data

Baseline is defined as last assessment (including unscheduled assessments) on or before the first dose day of treatment period.

Descriptive summary statistics for laboratory data (hematology and serum chemistry) will be provided at baseline and post-baseline by test category, parameter, and visit during the treatment period on SAF.

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

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

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

The number and percentage of subjects with CTCAE grade newly occurring or worsening after baseline will be presented.

Table 2-3 CTCAE grades for laboratory parameters to be analyzed

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

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

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

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

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

[redacted]

2.5.1.3 ECGs

Summary statistics will be provided for ECG parameters by visit/time. Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized.

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

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

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

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

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

2.5.1.4 Vital signs

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

Clinical notable vital sign values:

- Sitting pulse rate

- < 50 bpm and 25% decrease from baseline
- > 100 bpm and 25% increase from baseline

- systolic blood pressure
  - < 90 mmHg
  - ≥ 140 mmHg
- diastolic blood pressure
  - < 60 mmHg
  - ≥ 90 mmHg

2.5.2 Statistical hypothesis, model, and method of analysis

No hypothesis testing is planned for the primary objective.

2.5.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.5.4 Supportive analyses

Not applicable.

2.6 Analysis of the Secondary objective

2.6.1 Secondary endpoint

UAS7 score change from baseline at Week 4 and over time

Summary statistics for the absolute value, change and percent change from baseline in UAS7 will be presented for treatment period on SAF.

Summary statistics for the absolute value, change and percent change from baseline in HSS7 will be presented for treatment period on SAF.

Summary statistics for the absolute value, change and percent change from baseline in ISS7 will be presented for treatment period on SAF.

Controlled disease (UAS7≤ 6) at Week 4 and over time

The number and percentage of subjects achieved well controlled disease (UAS7≤ 6) will be summarized for treatment period on SAF [redacted] Figure will be provided.

Complete clinical response (UAS7 = 0) at Week 4

The number and percentage of subjects achieved complete clinical response (UAS7=0) will be summarized on SAF. [redacted]

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.6.3 Handling of missing values/censoring/discontinuations

The UAS7 is the sum of the average daily UAS over 7 days (range from 0 to 42). Note that the weekly score is derived according to the analysis week defined in Table 2-1.

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

- The weekly Urticaria Activity Score is the sum of both the HSS7 score and the ISS7 score and will be missing if at least one of them is missing.
- If a patient has at least 4 non-missing daily scores within the 7 days, then the weekly score for HSS or ISS will be calculated as the sum of the available eDiary scores of that week, divided by the number of non-missing days multiplied by 7.
- If there are less than 4 non-missing daily scores within the 7 days, then the weekly score for HSS or ISS will be missing for that week. Accordingly, no UAS7 can be calculated.

Non-responser imputation method

Missing values for binary response such as UAS7 = 0 response, UAS7 <= 6 response [redacted] in the secondary [redacted] analyses will be imputed by non-responder imputation method regardless of the reason for missingness.

For continuous variables such as UAS7 score, HSS7 score, ISS7 score, summary will be based on as observed data.

2.7 Safety analyses

2.7.1 Adverse event during observational period

Adverse event and serious adverse event during observational period will be summarized by primary system organ class and preferred term for oFAS.

2.7.2 Laboratory data

Abnormalities in urinalysis result will be listed.

2.7.3 Liver events

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

Table 2-4 Liver enzyme abnormalities

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>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)**

[redacted]

[redacted]

[redacted]

3 Sample size calculation

It is expected that approximately 250 subjects from CLOU064A2201 study will enroll in this extension study. Additional subjects may roll over from other not-yet specified studies.

[redacted]

[redacted]

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Partial dose date is not allowed in data collection.

5.1.2 AE date imputation

Impute AE end date:

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

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

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

Impute AE start date:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5.1.3 Concomitant medication date imputation

Impute concomitant medication (CM) end date:

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

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

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

Impute CM start date:

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

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

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

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

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

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

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

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

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

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

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

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

5.1.4 Prior therapies date imputation

See Section 5.1.3.

5.1.5 Other imputations

Diagnosis date imputation

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

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

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

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

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

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

5.2 AEs coding/grading

Not applicable.

5.3 Laboratory parameters derivations

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Table 5-1 Subject classification rule

Analysis Set	PD categories codes that cause subject to be excluded	Non-PD criteria that cause subjects to be excluded
Observational Full analysis set (oFAS)	*DVSPID: INCLxx; OTHxx-ICH-GCP*	*applicable.*
Safety analysis set (SAF)	*DVSPID: INCLxx; OTHxx-ICH-GCP; M-TRTxx*	*NA.*

INCLxx: ICF missing or not obtained.
OTHxx: Severe ICH-GCP non-compliance of study site
TRTxx: Subject enrolled but no study treatment was taken.

6 Reference