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LOU064/remibrutinib

Clinical Trial Protocol CLOU064A1301/NCT05048342

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 (BISCUIT)

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List of abbreviations

AAS	Angioedema Activity Score
AD	Atopic Dermatitis
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
b.i.d.	bis in die/twice a day
BCR	B cell receptor
BCRP	Breast Cancer Resistance Protein
BP	Blood Pressure
BTK	Bruton's Tyrosine Kinase
BTKi	Bruton's Tyrosine Kinase inhibitor
BUN	Blood Urea Nitrogen
CINDU	Chronic Inducible Urticaria
CIU	Chronic Idiopathic Urticaria
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
COA	Clinical Outcome Assessment
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CSU	Chronic Spontaneous Urticaria
CU	Chronic Urticaria
CV	Coefficient of Variation
CYP	Cytochrome P
DBP	Diastolic Blood Pressure
DIN	Drug Inducted Nephrotoxicity
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EDC	Electronic Data Capture
eDiary	Electronic Diary
eGFR	Estimated Glomerular Filtration Rate
[redacted]	[redacted]
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FAS	Full Analysis Set
FcγR	Fc gamma receptor
FcεR	Fc epsilon Receptor
[redacted]	[redacted]

[redacted]

FSH	Follicle stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
h	Hour
HBc	Hepatitis B core
HBcAb	Antibodies against hepatitis B core antigen (anti-HBcAg antibodies)
HBsAb	Antibodies against hepatitis B surface antigen (anti-HBsAg antibodies)
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCP	Healthcare Professional
HCV	Hepatitis C Virus
HCVAb	Hepatitis C Virus Antibody
HDL	High-Density Lipoprotein
hERG	Human ether a-go-go related gene
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
HSS	Hives Severity Score
HSS7	Weekly Hives Severity Score
i.v.	Intravenous
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISS	Itch Severity Score
ISS7	Weekly Itch Severity Score
[redacted]	[redacted]
[redacted]	[redacted]
KDIGO	Kidney Disease Improving Global Outcome
LC-MS/MS	Liquid Chromatography–Mass Spectrometry
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LTRA	Leukotriene Receptor Antagonists
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration

[redacted]

MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mg/d	Milligram per day
ml	Milliliter(s)
ms	Millisecond
MMRM	Mixed effect Model for Repeated Measurements
NOAC	Novel Oral Anti-Coagulant
NSAID	Nonsteroidal Anti-Inflammatory Drug
PC	Personal Computer
PCR	Protein-creatinine ratio
PD	Pharmacodynamic(s)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO	Patient Reported Outcomes
PT	Preferred Term
PT	Prothrombin Time
q.d.	Once a Day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RDO	Retrieved Drop Out
RNA	Ribonucleic Acid
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SiS	Sjogren's Syndrome
SMQ	Standardized MedDRA Query
SOC	System Organ Classes
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	[redacted]
UAS	Urticaria Activity Score
UAS7	Weekly Urticaria Activity Score
[redacted]	[redacted]
ULN	Upper Limit of Normal
UPDD	Urticaria Patient Daily Diary
UV	Ultraviolet
WHO	World Health Organization
WoCBP	Women of Child-Bearing Potential
[redacted]	[redacted]

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants.
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits

[redacted]

Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued, and no further assessments are planned
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations

[redacted]

	of interventions administered concurrently, e.g., as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 1 (06-JUL-2022)

Amendment rationale

This is the first amendment to be released for the CLOU064A1301 BISCUIT study. The main purpose of the amendment is to ensure the consistency across the program to reflect the recommendations from the US FDA and the feedback received from Health Authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) for both pivotal Phase 3 trials (CLOU064A2301 and CLOU064A2302, referred to as A2301 and A2302, respectively) to support remibrutinib for the treatment of CSU in Japan.

The main amendment in the pivotal Phase 3 studies is to implement recommendations from the US FDA regarding statistical analysis for covering intercurrent event handling for COVID-19 related reasons for treatment discontinuation and the use of the same covariates in both primary and secondary endpoints. So, in this study, the intercurrent event in statistical analysis was updated.

Furthermore, clarifications and corrections were made, and Section 4.5 Risks and benefits has been amended to include updates from the LOU064 Investigator Brochure Edition 9 (03-May-2022) as indicated below.

At the time of this amendment (V01) release, enrollment is ongoing with 40 patients screened and 28 patients treated.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Title : Study name “BISCUIT” for this study was added.
- Section 1.2: Deleted “planned” from the study CLOU064A2301
- [redacted]
- Section 2.1: Methods for handling of intercurrent events have been updated considering US FDA feedback for A2301 and A2302 studies.
- Section 2.2: Methods for handling of intercurrent events have been updated considering US FDA feedback for A2301 and A2302.
- Section 4.5: Risks and benefits has been amended to include updates from the LOU064 Investigator Brochure Edition 9. No change to risk-benefit assessment of the study.
- Section 5.2: Exclusion criteria 5 updated to clarify the disease of angioedema, exclusion criteria 13 and 18 updated to reflect the feedback received from Health Authorities, and exclusion criteria 19 updated to clarify maximum dose of clopidogrel.
- Section 6.2.2: Clarification that immunomodulating biologics are considered prohibited medication under immunosuppressive medications; prohibition period for live attenuated vaccines updated to reflect feedback from Health Authorities; maximum dose for long-term clopidogrel use added. Clarification that live attenuated vaccines are prohibited 6 weeks prior to randomization until at least 4 weeks after last dose of study treatment as

[redacted]

consistent with exclusion criteria and Investigator Brochure. Remibrutinib updated with study treatment for clarification.

- Section 6.6: Clarification that interruptions are permitted related to study treatment.
- Section 6.7.3: New section added regarding treatment of overdose, to align with the updated Novartis protocol template merged with the TransCelerate Common Protocol Template developed with input from industry, regulators, sites, CROs and IRBs
- Section 8: Order of assessments clarified.
- Table 8-1:Dispense participants' eDiary and Subject's eDiary review removed for Week 56/Safety FU/Study completion visit, considering eDiary completion ends at Week 52/Study discontinuation; Weight added at Baseline and Week 24 to allow for eGFR calculation; Rescue medication dispensation and usage removed from Week 56/Safety FU/Study completion visit, considering eDiary completion ends at Week 52/Study discontinuation; Footnotes 1, 3, and 7 updated for additional clarity; Footnote 4 updated to reflect feedback from Health Authorities; Footnotes 18, 19 and 20 added for clarity.
- Section 8.3.1: Duration of eDiary completion clarified.
- Table 8-8: Body temperature added to Physical Examination assessments to reflect feedback from Health Authorities in A2301 and A2302.
- Table 8-9: Hepatitis screening and Hepatitis re-activation monitoring amended as aligned with central laboratory testing procedures.
- [redacted]
- Section 9.1.1: Clarified that participant can request discontinuation from study treatment in writing or verbally; definition of severe/serious infections removed to reflect feedback from Health Authorities in A2301 and A2302.
- Section 9.1.2: Clarified that participant can request discontinuation from study in writing or verbally to reflect feedback from Health Authorities in A2301 and A2302.
- Section 9.2: Clarified that participant can request withdrawal of consent in writing or verbally to reflect feedback from Health Authorities in A2301 and A2302.
- Section 10.1.1: “Dose Reduced/increased” removed as dose modifications not permitted
- Section 10.1.3: Reporting timelines and follow-up for SAEs clarified to reflect feedback from Health Authorities.
- Section 10.3.2: Updated with the correct description.
- Section 12.4.3: Handling of intercurrent events amended, considering US FDA feedback for A2301 and A2302 studies.
- Section 12.4.5: AESI which becomes the object of sensitivity analysis clarified
- Section 12.5.1: Analysis method for absolute change from baseline in UAS7, ISS7 and HSS7 at Week 12 amended, considering US FDA feedback for A2301 and A2302 studies.
- [redacted]
- Section 15: Additional references added, and one reference removed to align with updated Investigator Brochure and Section 4.5.
- Section 16.1: QTcF increase ≥60 ms from baseline added to the definition of a notable QTc value for ECGs for clarification.

[redacted]

Additional minor changes (e.g., correction of typographical errors) have been incorporated directly in the protocol with track changes, even if not listed specifically in this section.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CLOU064A1301
Full Title	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 (BISCUIT)
Brief title	A Phase 3 study of safety and efficacy of remibrutinib in the treatment of chronic spontaneous urticaria in Japanese adults inadequately controlled by H1- antihistamines
Sponsor and Clinical Phase	Novartis Phase 3
Investigation type	Drug
Study type	Interventional
Purpose	The purpose of this study is to evaluate the safety and efficacy of remibrutinib (LOU064) 25 mg b.i.d in adult Japanese chronic spontaneous urticaria (CSU) participants inadequately controlled by second generation H1-antihistamines.
Primary Objective	The primary objective of this study is to evaluate the safety of remibrutinib (25 mg b.i.d.) during the 52-week treatment period. 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., on-treatment 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/concomitant medications?
Secondary Objectives	The secondary objective is to evaluate the efficacy of remibrutinib 25 mg b.i.d. by evaluation of: • Weekly Urticaria Activity Score (UAS7), Weekly Itch Severity Score (ISS7) and Weekly Hive Severity Score (HSS7) change from baseline at Week 12 • Proportion of participants who achieve UAS7 ≤ 6, Urticaria Activity Score (UAS) = 0 and Dermatology Life Quality Index (DLQI) = 0-1 at Week 12 • Proportion of participants who achieve UAS ≤ 6 at Week 2 • Proportion of participants who maintain disease activity control assessed as cumulative number of weeks with an UAS ≤ 6 response • Angioedema occurrence-free weeks assessed by the cumulative number of weeks with a weekly angioedema activity score (AAS7) = 0 response 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?
Study design	This is a Phase 3 multi-center, open-label, single arm study investigating the safety, tolerability and efficacy of remibrutinib (25 mg b.i.d.) in participants with CSU inadequately controlled by second generation H1-antihistamines. The study consists of three periods, the total study duration is up to 60 weeks: screening period of up to 4 weeks, open-label treatment period of 52 weeks, and a treatment free follow-up period of 4 weeks.
Rationale	The Phase 2b clinical trial CLOU064A2201 demonstrated clinical efficacy of remibrutinib 25 mg b.i.d. in the treatment of CSU patients with a fast onset of action and a favorable safety profile. For registration purposes, there is a relatively low number of Japanese CSU participants treated with the intended dose or higher during one year in studies CLOU064A2201E1 and CLOU064A2301. Therefore, the purpose of this study is to

[redacted]

	evaluate the safety and efficacy of remibrutinib (LOU064) in adult Japanese CSU participants inadequately controlled by second generation H1-antihistamines.
Study population	The study population will consist of approximately 70 Japanese male and female participants aged ≥ 18 years with CSU inadequately controlled by second generation H1-antihistamines.
Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study. • Male and female participants ≥18 years of age at the time of screening. • CSU duration for ≥ 6 months prior to screening (defined as the onset of CSU determined by the investigator based on all available supporting documentation). • Diagnosis of CSU inadequately controlled by second generation H1-antihistamines at baseline defined as: o The presence of itch and hives for ≥ 6 consecutive weeks prior to screening despite the use of second generation H1-antihistamines during this time period o UAS7 score (range 0-42) ≥ 16, ISS7 score (range 0-21) ≥ 6 and HSS7 score (range 0-21) ≥ 6 during the 7 days prior to baseline (Day 1) • Documentation of hives within three months before baseline (either at screening and/or at baseline; or documented in the participants' medical history). • Willing and able to complete an Urticaria Patient Daily Diary (UPDD) for the duration of the study and adhere to the study protocol • Participants must not have had more than one missing UPDD entry (either morning or evening) in the 7 days prior to baseline (Day 1).
Key Exclusion criteria	• Participants having a clearly defined predominant or sole trigger of their chronic urticaria (chronic inducible urticaria) including urticaria factitia (symptomatic dermographism), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria • Other diseases with symptoms of urticaria or angioedema, including but not limited to urticaria vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary angioedema, or drug-induced urticaria • Any other skin disease associated with chronic itching that might influence in the investigator's opinion the study evaluations and results, e.g., atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or psoriasis • Evidence of clinically significant cardiovascular (such as but not limited to myocardial infarction, unstable ischemic heart disease, New York heart association (NYHA) Class III/IV left ventricular failure, arrhythmia and uncontrolled hypertension within 12 months prior to Visit 1), neurological, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic, hematological disorders, gastrointestinal disease or immunodeficiency that, in the investigator's opinion, would compromise the safety of the participant, interfere with the interpretation of the study results or otherwise preclude participation or protocol adherence of the participant • Significant bleeding risk or coagulation disorders • History of gastrointestinal bleeding, e.g., in association with use of nonsteroidal anti-inflammatory drugs (NSAID), that was clinically relevant (e.g., for which intervention was indicated or requiring hospitalization or blood transfusion) • Requirement for anti-platelet medication, except for acetylsalicylic acid up to 100 mg/d or clopidogrel up to 75 mg/d. The use of dual anti-platelet therapy (e.g., acetylsalicylic acid + clopidogrel) is prohibited. • Requirement for anticoagulant medication (for example, warfarin or Novel Oral Anti-Coagulants (NOAC))

[redacted]

	• History or current hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or Aspartate Aminotransferase (AST)/ Alanine Aminotransferase (ALT) levels of more than 1.5 x upper limit of normal (ULN) or International Normalized Ratio (INR) of more than 1.5 at screening
Study treatment	LOU064 25 mg film-coated tablets
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.
Efficacy assessments	All efficacy measures are Patient Reported Outcomes (PROs): Electronic Diary (eDiary) assessments • Urticaria Patients Daily Diary (UPDD), which assesses: o Hives Severity Score (HSS) o Itch Severity Score (ISS) o Urticaria Activity Score (UAS) [redacted] o angioedema occurrence o number of calls to doctor, nurse or nurse practitioner • Angioedema Activity Score (AAS)
[redacted]	[redacted]
Key safety assessments	• Adverse event (AE) monitoring • Physical examinations • Vital signs • Monitoring of laboratory markers in blood and urine • Central electrocardiogram (ECG) monitoring
Other assessments	Other PROs assessments: • Dermatology Life Quality Index (DLQI) [redacted]
Data analysis	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.

[redacted]

	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) 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. In addition, a separate summary for deaths including on- treatment and post-treatment deaths will be provided. The number and the proportion (%) of participants with adverse events of special interest for remibrutinib (related to identified and potential risks) will be summarized. 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. The secondary (efficacy) variables during the study, including absolute change from baseline in UAS7 score at Week 12, will be summarized (by visit, if applicable).
Key words	BTK inhibitor; Chronic spontaneous urticaria; Urticaria activity score; Hives severity score; Itch severity score

[redacted]

1 Introduction

1.1 Background

Urticaria is classified into inducible and spontaneous urticaria in Japan. Spontaneous urticaria presents with hives occurring spontaneously without a direct cause. The Japanese Dermatological Association Guideline for the Treatment of Urticaria 2018 defines chronic spontaneous urticaria (CSU) as "urticaria persistent for ≥ 6 weeks after onset" (Hide et al 2018). The Western EAACI/GA^{2}LEN/EDF/WAO Guideline 2018 defines CSU, also known as chronic idiopathic urticaria (CIU) as the spontaneous occurrence of itchy wheals (hives), angioedema or both, lasting for at least 6 weeks (Zuberbier et al 2014, Zuberbier et al 2018). These Japanese and foreign guidelines use different terms, but these differences do not influence the respective diagnosis and, thus, describe the same disorder (Hide et al 2018).

The classic description of urticaria is a wheal and flare with a pale elevated lesion and surrounding erythema, ranging in size from a few millimeters to a few centimeters across, usually occurring in groups and often coalescing to form large confluent lesions. Wheals and angioedema in CSU involve the degranulation of mast cells, which release histamine, proteases and cytokines. These mediators induce vasodilation, increase vascular permeability, and stimulate sensory nerve endings leading to swelling, redness and itch (Kaplan et al 1978, Saini and Kaplan 2018).

CSU can be debilitating, is associated with intense itching and has a major impact on patient's quality of life, comparable to that of severe coronary artery disease (Greaves 2003, Powell et al 2007). The overall burden of CSU and CSU-associated angioedema for affected patients is substantial: CSU and its symptoms have a negative impact on numerous aspects of their daily life, including mental health, work productivity, sleep, partnership and family life (O'Donnell et al 1997, Maurer et al 2017, Gonçalo et al 2021).

Urticaria treatment aims at fully suppressing the symptoms of both itch and hives and occurrence of angioedema. All in all Japan and other countries share the same treatment strategy (Hide et al 2012).

Second generation Histamine H1 receptor antagonists (H1-antihistamines) are recommended as first-line treatment for patients with CSU but less than 40% of patients respond adequately (Guillén-Aguinaga et al 2016). While uptitration of second-generation H1-antihistamines up to 4-fold the approved dose is recommended by most CSU treatment guidelines as second-line therapy (Zuberbier et al 2018), the efficacy of uptitrated H1-antihistamines in CSU has not been studied in larger clinical trials and uptitration is considered off-label. The use of H2-antihistamines and Leukotriene Receptor Antagonists (LTRAs) has in the past been recommended by treatment guidelines for patients who remained symptomatic despite treatment with H1-antihistamines (Zuberbier et al 2009, Bernstein et al 2014, Hide et al 2018), although their use has not been well supported by clinical studies. In the latest version of the treatment guidelines (Zuberbier et al 2018), neither H2-antihistamines nor LTRAs are perceived to have sufficient evidence to maintain them as recommendable in the algorithm. Short courses of systemic corticosteroids are sometimes added to the treatment regimen, however they are not recommended in treatment guidelines for long-term use, as this would expose patients to the well-known risk of adverse effects associated with chronic systemic

corticosteroid use. In patients not responding adequately or intolerant to these treatment options, use of cyclosporine or other immunosuppressants is an option as experimental treatment. However, neither in Japan nor other countries has cyclosporine been approved and it is associated with renal insufficiency, hypertension and other clinically significant adverse reactions even at low doses. Thus, its use is limited to severe patients (Hide et al 2018). Omalizumab is an effective third-line therapy for CSU patients. However, less than 50% of patients treated with omalizumab reach complete control of signs and symptoms (Kaplan et al 2016). Therefore, there is a high unmet medical need for new treatment options for CSU patients inadequately controlled by H1-antihistamines.

Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase and member of the TEC kinase family. BTK is expressed in selected cells of the adaptive and innate immune system including B cells, macrophages, and mast cells/basophils. BTK is indispensable for signaling through the Fc epsilon receptor (FcεR1 for IgE), the activating Fc gamma receptors (FcγR for IgG), as well as the B cell antigen receptor (BCR) and therefore an important signaling node in the activation/ degranulation of B cells, macrophages, mast cells or basophils (Rip et al 2018).

BTK inhibitors (BTKi) like ibrutinib were first approved for the treatment of B cell malignancies (Hendriks et al 2014). Due to the above described role of BTK in adaptive as well as innate immune signaling and, associated with that, its role in immune-mediated diseases, targeting BTK is regarded as a promising new approach for the treatment of various immune-mediated conditions. [redacted]

Mast cells and basophils play a key role in the pathophysiology of CSU and it has been demonstrated that BTK inhibition leads to blockade of mast cell and basophil activation/degranulation in vitro and to reduced wheal sizes in skin prick tests with patients suffering from IgE-mediated allergies (Smiljkovic et al 2017, Regan et al 2017, Dispenza et al 2017). Thus, BTK inhibition is a promising therapeutic strategy for the treatment of CSU.

Remibrutinib (LOU064) is a low molecular weight compound for oral administration that covalently binds and inhibits BTK with high selectivity (Angst et al 2020, Gabizon and London 2020). In Phase 1, remibrutinib was well-tolerated at all doses without any dose-limiting toxicity and showed encouraging blood and skin pharmacodynamics with a favorable safety profile, fully supporting further development for diseases driven by mast cells, basophils and B cells, such as CSU (Kaul et al 2021). The Phase 2b clinical trial CLOU064A2201 primary endpoint analysis demonstrated clinical efficacy and a fast onset of action of remibrutinib in the treatment of CSU patients, as well as a favorable safety profile (for detailed information please refer to the Investigator`s Brochure (IB)).

Taken together, remibrutinib may offer a novel therapeutic approach for patients with CSU and is advanced to Phase 3 clinical development.

[redacted]

1.2 Purpose

The purpose of this study is to investigate the safety, tolerability and efficacy of remibrutinib (LOU064) in Japanese CSU patients inadequately controlled by H1-antihistamines. This study supports the registration of remibrutinib for the treatment of CSU in Japan.

Inadequate control of CSU by H1-antihistamines is defined as:

- The presence of itch and hives for ≥6 consecutive weeks prior to screening despite the use of second generation H1-antihistamines during this time period
- UAS7 score (range 0-42) ≥16, ISS7 score (range 0-21) ≥6 and HSS7 score (range 0-21) ≥6 during the 7 days prior to baseline (Day 1).

The effect of remibrutinib in patients with CSU inadequately controlled by H1-antihistamines was investigated in the Phase 2b dose-range finding study CLOU064A2201 and demonstrated efficacy in multiple remibrutinib dose groups compared to placebo. No safety concerns were identified in the remibrutinib groups. The long-term safety, tolerability and efficacy in participants who have completed the Phase 2b dose range finding study in CSU is investigated in the Phase 2b extension study CLOU064A2201E1. No safety concerns have been identified in this study either. Two Phase 3 studies CLOU064A2301 and CLOU064A2302 are intended to support the registration of remibrutinib for the treatment of patients with CSU in adults inadequately controlled by H1-antihistamines.

For the registration purpose, there is a relatively low number of Japanese CSU participants treated with the intended dose or higher during one year in studies CLOU064A2201E1 and CLOU064A2301. Therefore, the purpose of this CLOU064A1301 study is to evaluate the safety, tolerability and efficacy of remibrutinib in adult Japanese subjects with CSU, who remain symptomatic despite treatment by H1-antihistamines at locally label approved doses, for a duration of 52 weeks of treatment with remibrutinib and a post-treatment follow-up period of up to 4 weeks.

2 Objectives, endpoints and estimands

Table 2-1 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

[redacted]

Objectives	Endpoints
• 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
• 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]

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment). It summarizes at a population level what the outcomes would be in the same patients under different treatment conditions being compared.

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/ medication? (see Section 12.4.1).

[redacted]

The primary estimand on safety 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:** 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 100 mg/d 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 (pitavastatin, rosuvastatin, sulfasalazine and ubrogepan): Treatment policy strategy
   - Intake of other prohibited medication: Treatment policy strategy

* Assessment of confounder BCRP will be specified in the statistical analysis plan (SAP).

2.2 Secondary estimands

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? (see Section 12.5)

[redacted]

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 non-compliance (interruption), intake of rescue medication, or switch of background medication: 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: 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.

[redacted]

5. Handling of intercurrent events:

- Discontinuation of study treatment due to any reason, treatment non-compliance (interruption), intake of rescue medication, or switch of background medication: 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: 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 2-1.

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

3 Study design

This 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 participants with CSU inadequately controlled by second generation H1-antihistamines. The study consists of three periods, the total study duration is up to 60 weeks (Figure 3-1):

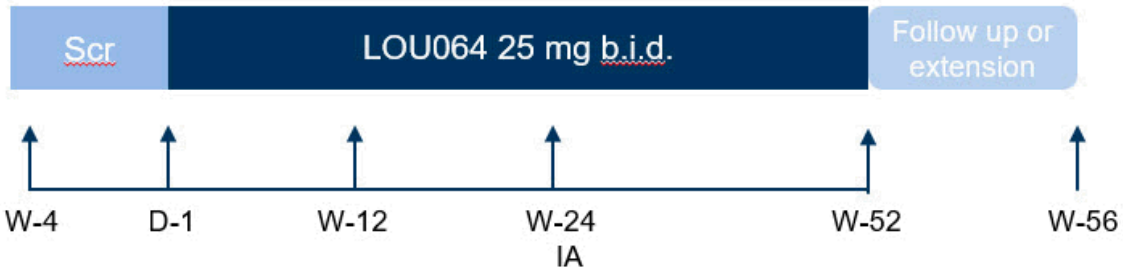
- **Screening period:** up to 4 weeks
- **Open-label treatment period:** 52 weeks of open-label treatment with remibrutinib (25 mg b.i.d.).
- **Follow-up period:** 4 weeks of treatment-free follow-up.

An interim analysis may be conducted after all participants have completed Week 24 or discontinued earlier. 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").

An extension study is being considered. Eligible participants may roll-over at Week 52 (after completing 52 weeks of treatment and all scheduled assessments planned at this visit). The details of the study design and procedures of the extension, if implemented, will be described in a separate protocol.

[redacted]

Figure 3-1 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

4 Rationale

4.1 Rationale for study design

The primary analysis of the Phase 2b dose-range finding study CLOU064A2201 demonstrated that treatment with remibrutinib 25 mg b.i.d. substantially improves signs and symptoms of CSU compared to placebo, in participants who have not adequately responded to prior treatment with H1-antihistamines and other CSU therapies including omalizumab. This Phase 3 study is designed to evaluate the safety, tolerability and efficacy of remibrutinib at a dose of 25 mg b.i.d. (as determined by the Phase 2b dose-range finding study CLOU064A2201, see also Section 4.2) in adult CSU patients. It is an open-label, single arm study that consists of three phases:

1. **Screening period**: the screening period of up to four weeks will allow the assessment of eligibility of participants and the determination of baseline disease activity.
2. **Open-label treatment period**: during this treatment period of 52 weeks, an open-label design without a comparator arm is considered adequate to evaluate long-term safety for CSU in Japanese participants and accepted by Japanese Health Authority. The treatment period will provide long-term safety and efficacy data to characterize the value of remibrutinib in CSU.
3. **Follow-up period**: a treatment-free follow-up period of four weeks at the end of the study will be implemented for all participants who do not enroll into the extension study (currently being considered). This allows the assessment of safety after treatment discontinuation as well as the dynamics of potential re-occurrence of CSU signs and symptoms after treatment discontinuation.

The study population consists of participants with CSU (UAS7 score ≥ 16, with HSS7 score ≥ 6 and ISS7 score ≥ 6), who have a duration of CSU of ≥6 months and who are inadequately controlled despite treatment with second generation H1-antihistamines at least at locally label approved dose. Importantly, patients who have inadequately responded to or did not tolerate anti-IgE biologic treatments are also eligible for this study. Thus, CSU patients with high unmet medical need are the target population for this study.

The primary endpoint of this study is overall safety, assessed as treatment-emergent adverse events during the study, as the number of Japanese CSU patients exposed to remibrutinib at the intended or higher dose in the global studies (CLOU064A2201, CLOU064A2201E1 and

CLOU064A2301) is expected to be limited for registration purpose. Therefore, this study is designed to obtain additional safety data of remibrutinib at 25 mg dosed for one year in Japanese CSU patients to support for the registration of remibrutinib in Japan.

UAS7, UAS7-based analysis (UAS7≤6 and UAS7=0), the assessment of the impact of remibrutinib treatment on itch (ISS7) and hives (HSS7), the assessment of the impact of remibrutinib treatment dermatology-related quality of life (DLQI-response of 0/1), and the assessment of the impact of remibrutinib treatment on the number of weeks without occurrence of angioedema (AAS7=0) were selected as secondary endpoints to further assess the efficacy of remibrutinib.

Assessing remibrutinib (25 mg b.i.d.) as add-on to background medication consisting of a locally label approved second generation H1-antihistamine follows recommendations of the current treatment guidelines (Zuberbier et al 2018).

For the primary safety estimand, applying a treatment policy strategy for all intercurrent events aims to collect all treatment-emergent adverse events occurring in the treatment period and follow-up period and assess remibrutinib as a CSU therapy (as an add-on to background medication) close to a "real-life" situation.

For the secondary efficacy estimand, applying a treatment policy strategy for treatment non-compliance, the use of rescue medication (a second generation H1-antihistamine that differs from the background medication), and most other intercurrent events aims to assess remibrutinib as a CSU therapy (as an add-on to background medication) close to a "real-life" situation. Only intercurrent events that are likely to impose a strong bias on the efficacy readout (such as use of highly effective biologics with a long half-life) will be handled using a composite strategy. Taken together, the study design will allow the investigation of long-term safety and efficacy of remibrutinib in Japanese CSU participants.

4.1.1 Rationale for choice of background therapy

Second-generation H1-antihistamines are chosen as background medication. Considering the add-on remibrutinib therapy, this reflects the current treatment guidelines to add a second- or third-line therapy to H1-antihistamine background therapy in CSU patients who are not adequately controlled by H1-antihistamines (Zuberbier et al 2018, Hide et al 2018).

4.2 Rationale for dose/regimen and duration of treatment

In this study, remibrutinib will be given at a dosing regimen of 25 mg b.i.d. for a duration of up to 52 weeks. A treatment duration of up to 52 weeks is in line with the current treatment guidelines (Zuberbier et al 2018) and in line with other current major Phase 3 trials in the CSU indication, e.g., with ligelizumab (NCT03580369 and NCT03580356). Therefore, it allows the collection of efficacy and safety data for remibrutinib over a treatment duration, which is applied in real-world clinical practice and which allows comparison to other Phase 3 trials in the same indication. Furthermore, a treatment duration of up to 52 weeks is covered by pre-clinical toxicity data and is used in the Phase 2b extension study CLOU064A2201E1.

The target population of this trial includes difficult-to-treat patients, such as patients with concomitant CINDU, a long disease history, and patients with prior inadequate response to anti-IgE biologics. In such cases a treatment duration of up to 52 weeks or more can be required. An

[redacted]

extension study is being considered and eligible participants will have the opportunity to roll over after completing 52 weeks of study treatment in this trial.

Based on the safety data from the completed and ongoing remibrutinib trials, the clinical safety profile of remibrutinib is favorable and supports the selected dose of 25 mg b.i.d. In the primary endpoint analysis of the dose-range finding Phase 2b study CLOU064A2201 (cut-off date at 14-Jan-2021), most AEs were mild in severity, without patterns of clustering or dose-dependency. Ongoing clinical safety review of CLOU064A2201E1, a long-term extension study of CLOU064A2201, with a 52-week treatment period with 100 mg remibrutinib b.i.d. did not reveal any safety signals. In addition, the clinical safety data from the completed Phase 1 studies, which tested doses of remibrutinib up to 600 mg q.d. and 200 mg b.i.d., was favorable and did not raise any concerns. For more detailed information on the safety profile of remibrutinib, please see Section 4.5 and the IB.

In the dose-range finding study CLOU064A2201, the efficacy of remibrutinib as an add-on to background therapy of second generation H1-antihistamines was assessed versus placebo for the following dose regimens: 10 mg q.d., 35 mg q.d., 100 mg q.d., 10 mg b.i.d., 25 mg b.i.d., 100 mg b.i.d. The treatment duration was 12 weeks and the primary endpoint was change in UAS7 score from baseline at Week 4. The key secondary endpoints were defined as change in UAS7 score from baseline at Week 12, change in UAS7 score from baseline over time, percentage of participants with UAS7 = 0 (complete absence of hives and itch) over time, and percentage of participants with UAS7 ≤6 (disease activity control) over time. At the time of the primary endpoint analysis, there were 301 participants (40-47 per arm) among 309 under full analysis set with a UAS7 score at Week 4, and 233 participants (29-37 per arm) with a UAS7 score at Week 12. The treatment groups were overall well balanced in terms of demography and baseline disease characteristics.

The study demonstrated clinical efficacy of remibrutinib in the treatment of CSU, with all tested doses showing superior efficacy over placebo at Week 4. A dose-response relationship was established for the q.d. and b.i.d. remibrutinib dosing regimens compared to placebo with respect to the change from baseline in UAS7 score at Week 4, with the dose-response plateau already achieved at 10 mg for q.d. dosing (=10 mg total daily exposure) and at 25 mg for b.i.d. dosing (=50 mg total daily exposure).

[redacted]

Figure 4-1 UAS7 score change from baseline over time estimated with a mixed-effect repeated measurement analysis, by treatment group (FAS)

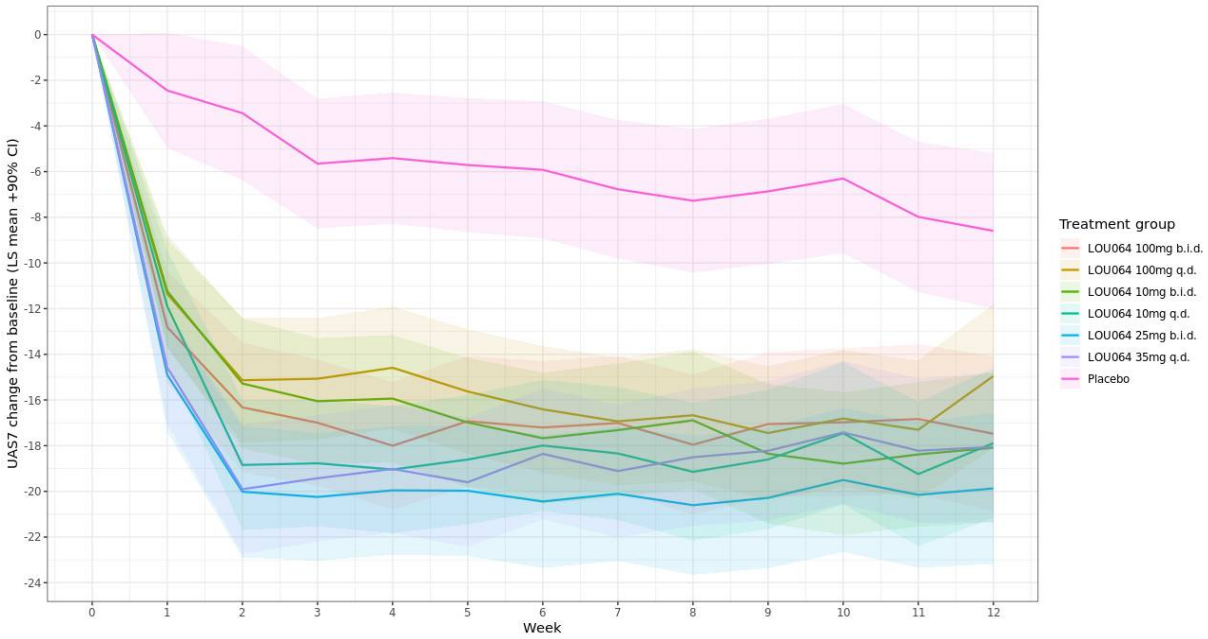
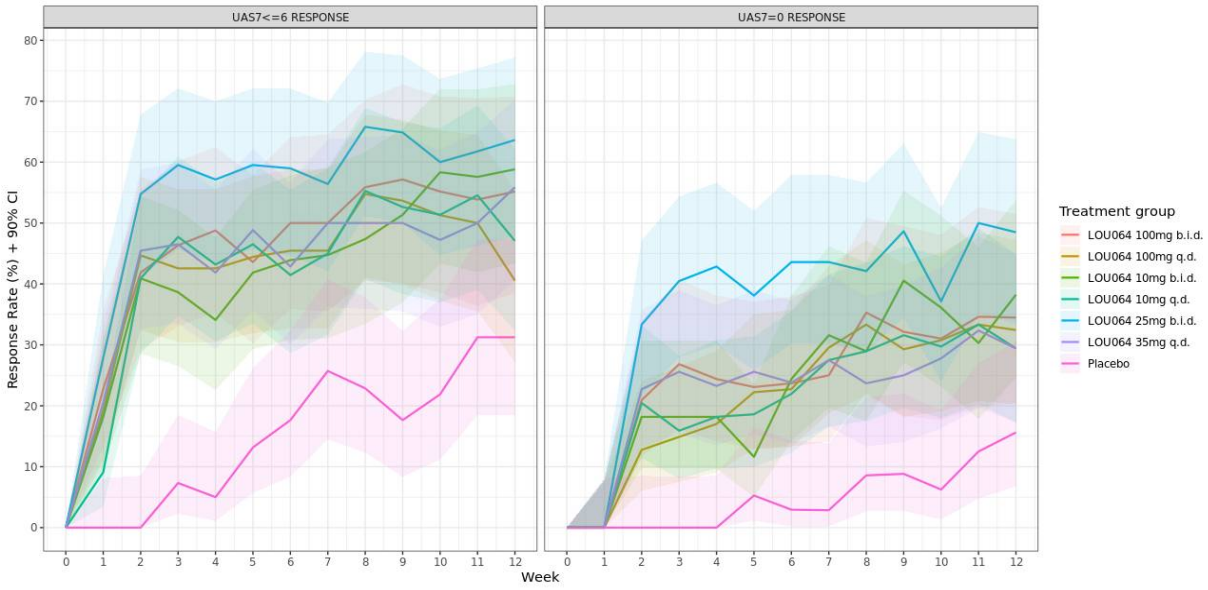


Figure 4-2 UAS7 = 0 and UAS7 <=6 response rate over time by treatment group (as observed) (FAS)



Assessing the higher hurdle UAS7 ≤ 6 (disease activity control) and UAS7 = 0 (total absence of itch and hives) response rates enabled further differentiation between the tested doses (Figure 4-1 and Figure 4-2): At Week 4, the remibrutinib 25 mg b.i.d dosing regimen achieved numerically higher UAS7 ≤ 6 response rates than all other tested doses: 55.8% on25 mg b.i.d. compared to 43.2%, 40.9%, 42.6%, 34.1%, 44.4%, 4.8% on 10 mg q.d., 35 mg q.d., 100 mg q.d., 10 mg b.i.d., 100 mg b.i.d., placebo (non-responder imputation). In line with that, the

25 mg b.i.d. dosing regimen also achieved considerably higher UAS7=0 response rates than all other tested doses at Week 4: 41.9% on 25 mg b.i.d compared to 18.2%, 22.7%, 17.0%, 18.2%, 22.2%, 0.0% on 10 mg q.d., 35 mg q.d., 100 mg q.d., 10 mg b.i.d., 100 mg b.i.d, placebo (non-responder imputation). The numerically higher efficacy of the 25 mg b.i.d. dosing regimen compared to all other doses was observed consistently over time, with higher UAS7 ≤ 6 and UAS7 = 0 response rates from Week 2 throughout Week 12 (Figure 4-2). Furthermore, the 25 mg b.i.d. dosing regimen showed the fastest onset of action, with high response rates already achieved at Week 2 (Figure 4-2).

At Week 12, the UAS7 ≤ 6 and UAS7 = 0 response rates for placebo-treated participants were relatively high (31.3% and 15.7%), reflecting the fluctuating nature of CSU (Figure 4-2). While still showing numerical superiority, the q.d. dosing regimens (10 mg q.d., 35 mg q.d., 100 mg q.d.) showed a tendency towards weaker differentiation vs placebo in UAS7 ≤ 6 and UAS7 = 0 response at Week 12 (UAS7 ≤ 6: 43.2%, 40.9%, 42.6%; UAS7 = 0: 29.4%, 29.4%, 32.4%) (as observed), whereas the 25 mg b.i.d. regimen was able to maintain a notable difference (UAS7 ≤ 6: 63.6%, UAS7 = 0: 48.5%). B.i.d. dosing is also supported from a pharmacokinetics, pharmacodynamics and mode-of-action perspective, in order to ensure sustained BTK inhibition over 24 hours, considering the relatively fast turnover of the covalent BTK-remibrutinib complex in tissue (see IB for details).

Taken together, all tested remibrutinib dosing regimens demonstrated superior efficacy in treating signs and symptoms of CSU compared to placebo, when assessing the mean change from baseline in UAS7. However, when analyzing higher hurdle efficacy endpoints with higher discriminatory power (UAS7 ≤ 6 or UAS7 = 0) and later time points with higher placebo response rates, the 25 mg b.i.d. treatment regimen showed notably higher efficacy than the other tested regimens, especially than the q.d. regimens.

A lower b.i.d. dose (10 mg b.i.d.) or once daily dosing (35 mg q.d.) does not enable participants to achieve the maximum efficacy which can be achieved with 25 mg b.i.d. dosing, especially when considering the UAS7 ≤ 6 and UAS7 = 0 response rates. At the same time, higher dosing regimens, such as 100 mg b.i.d., are not required to reach maximum efficacy.

As the safety data also support the 25 mg b.i.d. dosing regimen (see Section 4.5 and the IB) with a favorable safety profile and no dose-dependent safety signals, remibrutinib 25 mg b.i.d. was selected as the optimal dose for this study.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

One interim analysis may be conducted for the purpose of submission to Health Authorities for marketing authorization approval. This interim analysis is planned when all participants have completed their Week 24 visit or discontinued early.

Additional 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

[redacted]

projects in general, or in case of any safety concerns. These interim analyses are not expected to have any impact on the conduct or scientific integrity of the study. Refer to the interim analyses Section 12.7 for further details.

4.5 Risks and benefits

Signs and symptoms of CSU are a direct consequence of mast cell degranulation with release of inflammatory mediators including histamine (Ferrer 2015, Saini and Kaplan 2018). BTK is a cytoplasmic tyrosine kinase that is indispensable for FcεR1 signaling and a central signaling kinase in mast cell activation. It has been demonstrated that BTK inhibition can effectively inhibit mast cell activation and reduce wheal sizes in skin prick tests (Regan et al 2017; Dispenza et al 2018; Kaul et al 2019). In Phase 1, remibrutinib was well-tolerated at all doses without any dose-limiting toxicity and showed encouraging blood and skin pharmacodynamics with a favorable safety profile, fully supporting further development for diseases driven by mast cells, basophils, or B cells, such as CSU. Furthermore, remibrutinib has been shown to effectively reduce wheal size in skin prick tests (Kaul et al 2021). The Phase 2b clinical trial CLOU064A2201 (primary endpoint analysis) demonstrated clinical efficacy of remibrutinib in the treatment of CSU patients with a fast onset of action and a favorable safety profile.

Based on this data, 25 mg b.i.d. has been selected as the optimal dosing regimen for the treatment of CSU patients. Treatment with remibrutinib 25 mg b.i.d. resulted in a substantial reduction of the UAS7 score, which measures frequency/intensity of hives and itch, the two key symptoms defining the burden of CSU for affected participants. The benefit for CSU patients treated with remibrutinib 25 mg b.i.d. was also reflected by substantial improvements in health-related quality of life (HRQoL), as measured by the DLQI score (see Investigator's Brochure (IB) for details).

BTK inhibition is a new therapeutic principle for the treatment of CSU that significantly differs from currently available treatment options in terms of its mode of action and route of administration. Remibrutinib may therefore offer a treatment option for patients with contraindications against or inadequate response to approved treatment options for CSU including anti-IgE directed biologics. These patients, for whom a high unmet need for new treatments exists, are part of the eligible patient population of this study. In the above-mentioned Phase 2b trial CLOU064A2201, remibrutinib showed a rapid onset of action already after the first week of treatment, which is of significant benefit for CSU patients, who often have a high current symptom burden. Furthermore, the oral route of administration of remibrutinib offers additional convenience compared to injectable biologics.

Taken together, the benefit for study participants is that treatment with remibrutinib could substantially improve their CSU signs and symptoms and lead to a better quality of life.

The available clinical safety experience has documented favorable safety and tolerability of remibrutinib. As of 10-Mar-2022, approximately 903 participants (healthy volunteers and patients suffering from CSU, asthma, Sjogren's Syndrome, atopic dermatitis (AD), and relapsing multiple sclerosis) have been exposed to remibrutinib at doses ranging from 0.5 mg to 600 mg, placebo or comparator. A maximum tolerated dose has not been identified.

[redacted]

In the final analysis of the Phase 2b trial CLOU064A2201 in patients with CSU, 309 participants (safety set (SAF)) received remibrutinib at doses/regimens up to 100 mg b.i.d. for up to 12 weeks. Most adverse events (AEs) were mild in severity, without clustering of specific AEs and no apparent dose-related pattern was identified. The most frequent AEs were reported in the following System Organ Classes (SOC): Infections and infestations (24.0% in any remibrutinib arm vs 21.4% in placebo arm), Skin and subcutaneous tissue disorders (16.9% vs 4.8%), Nervous system disorders (13.1% vs 16.7%), and Gastrointestinal disorders (11.2% vs 11.9%). The most frequent AEs (defined by MedDRA Preferred Term (PT)), occurring in ≥ 5% of participants in either any remibrutinib or placebo arm) were:

- Headache: 9.7% in any remibrutinib arm vs. 14.3% in placebo arm
- Nasopharyngitis: 8.6% in any remibrutinib arm vs. 7.1% in placebo arm
- Chronic spontaneous urticaria: 6.0% in any remibrutinib arm vs. 2.4% in placebo arm (the events of CSU were flares primarily reported by participants during the treatment-free follow-up period).

In interim analysis 2 (IA2; cut-off May-2021) of the Phase 2b long-term open-label extension trial CLOU064A2201E1, data from 183 CSU participants enrolled with a median exposure to remibrutinib 100 mg b.i.d. of 35.14 weeks showed a similar safety profile to that in the core CLOU064A2201 study. Most AEs were non-serious, mild in severity, and did not lead to treatment discontinuation. The most common SOCs (≥ 10% of subjects) were Infections and infestations (23%), Skin and subcutaneous tissue disorders (17.5%), Gastrointestinal disorders (14.2%), and Nervous systems disorders (10.4%). The 3 most commonly reported PTs were headache (6.6%), COVID-19 (4.9%), and diarrhea (4.9%). Based on the mode of action of remibrutinib, pre-clinical safety information, drug-drug-interaction studies, and the review of currently available literature as well as safety information of approved BTK inhibitors (e.g., ibrutinib, acalabrutinib and zanubrutinib), the following potential risks of remibrutinib have been identified (see below). Of note, many safety risks identified for ibrutinib and acalabrutinib, two BTK inhibitors approved for the treatment of B cell malignancies (mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstroem´s macrogloblinemia), are less likely related to the pharmacology of BTK inhibition, but rather to the underlying hemato-oncologic diseases being treated and their associated comedications and complications, such as tumor lysis syndrome, second primary malignancies, etc. Therefore, when comparing the safety risks between the approved BTK inhibitors and remibrutinib, the underlying condition of the treated patient population must be taken into consideration. Furthermore, ibrutinib and acalabrutinib have a different target selectivity profile compared to remibrutinib (Angst et al 2020).

- *Infections:* BTK is an important signaling kinase downstream of cell surface receptors and expressed in a number of cell types of the adaptive and innate immune system, including B cells, macrophages, basophils and mast cells. Thus, administration of remibrutinib might be associated with an increased risk for infections and participants should be monitored for signs and symptoms of infections and be evaluated promptly. In the completed and ongoing clinical trials with remibrutinib, infections were well balanced between the remibrutinib and placebo arms. Most of the infections observed were mild to moderate and did not lead to a change in study treatment. In the final analysis of the Phase 2b study CLOU064A2201, infection rates (defined as MedDRA SOC Infections and infestations) were comparable between any remibrutinib arm (24.0%) and the placebo arm

[redacted]

(21.4%). Most infections reported in the remibrutinib arms were mild in severity and did not lead to treatment discontinuation. All participants in remibrutinib clinical trials are monitored closely for signs and symptoms of infections while in the trial. Patients with a known history of chronic recurrent or active ongoing infections are excluded from the trial (refer to Section 5.2 for details). In addition, the use of live attenuated vaccines should be avoided 6 weeks before study treatment and during the study until at least 4 weeks after the last dose of the study treatment (see Section 6.2.2).

- *Response to vaccination*: In general, immunomodulatory treatments may diminish vaccine efficacy (Farez et al 2019). BTK inhibition is expected to affect the response to vaccinations and result in reduced vaccination efficacy. Due to its immunomodulatory effects, treatment with remibrutinib might be associated with reduced efficacy of vaccinations. There are limited data available on vaccination response in patients treated with BTK inhibitors and primarily reported in patients with hematologic malignancies (Pleyer et al 2021, Weber et al 2021). In ongoing studies with remibrutinib, participants are advised to complete necessary vaccination before starting treatment with remibrutinib. If necessary, vaccination with non-live vaccines is allowed during the study.
- *Effect on platelet function - risk for bleeding*: BTK is a signaling molecule in one of several platelet activation pathways, and clinically relevant effects of remibrutinib on platelet functions were observed in the remibrutinib preclinical toxicology program. The mode of action by which remibrutinib could potentially cause bleeding is currently not fully understood. In vitro assessments suggest a target-related impact on platelets, similar to effects induced by the BTK inhibitor ibrutinib, which has been shown to inhibit clot retraction (Bye et al 2015).
- In CSU, in the completed core CLOU064A2201 Phase 2b study, 18 (6.7%) non-serious bleeding events were reported in any remibrutinib arm compared to one event on placebo (2.4%); none of the AEs was serious or severe. All the bleeding AEs reported were mild, except 2 moderate AEs: gingival bleeding and hematuria. Two bleeding events (petechiae and hematuria) led to study treatment discontinuation. There were no notable clinically relevant abnormalities for coagulation parameters, hemoglobin levels or platelet counts noted in these studies. In the interim analysis of the open-label long-term (up to 52 weeks) extension trial CLOU064A2201E1, the rate of bleeding events (4.4%) was comparable to that seen in the core trial; all events were non-serious, and all but 2 events (purpura and heavy menstrual bleeding in the setting of leiomyoma) were mild in severity. Potential effects of remibrutinib on hemostasis should be monitored both clinically and by standard, validated laboratory measures including complete blood count and standard coagulation parameters. Clinical monitoring should focus on skin (bruising, petechiae) and mucosa (e.g., gastro-intestinal (GI) tract bleeding including gingival, rectal, and conjunctival bleeding). Patients with a known history of bleeding disorders, or with a history of clinically relevant gastrointestinal bleeding and patients requiring anti-platelet or anticoagulant therapy (other than aspirin up to 100 mg/d or clopidogrel up to 75 mg/d) are excluded from the trial; the use of dual anti-platelet therapy (e.g., acetylsalicylic acid + clopidogrel) is prohibited (see details in Section 5.2 and Section 6.2.2). In case of a significant bleeding event, study treatment must be discontinued immediately. Please refer to the current IB for further details.

[redacted]

- *Effects on QT interval*: Remibrutinib is a mild inhibitor of the human ether-a-go-go related gene (hERG) channel (IC50 = 1.4 µM; unbound Cmax-based average safety margin of 43-fold based on 100 mg b.i.d. in humans), without affecting other ion channels in a relevant manner. Close ECG monitoring via Holter recordings in the first in human studies (CLOU064X2101 and CLOU064X1101) documented a minor exposure-dependent increase in QTcF with no outliers (i.e., QT-interval with a frequency correction according to Fridericia (QTcF) > 480 ms or increases equal or greater than 60 ms) up to the maximal dose of 600 mg. At the projected supratherapeutic exposure calculated based on the observed Cmax at 25 mg b.i.d., assuming severe organ impairment and comedication with a strong CYP3A4 inhibitors such as ritonavir ("worst case" scenario), the calculated mean QTcF effect is 2.580 ms which is well below the threshold of 5 ms to rule out a relevant QT-effect. The predicted upper 90% confidence limit of the QTcF changes is well below 10 ms, the regulatory pharmacologic effect threshold for cardiac repolarization, indicating a low probability of clinically significant repolarization effects even at 2-fold higher exposure than that of the "worst-case" scenario. In the interim and final analyses of ongoing and completed Phase 2 studies in participants with CSU, Sjogren's Syndrome and asthma, no notable trend was observed for the change of ECG over time; no finding in ECG recordings or AEs suggestive of pro-arrhythmic events were noted. Patients with a history of major cardiovascular events are excluded from the trial. In addition, triplicate sequential ECG monitoring is implemented in the study to monitor potential effects of remibrutinib on QTc and other ECG parameters.
- *Myelomodulation*: Treatment-emergent grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in participants with hematologic malignancies treated with ibrutinib and acalabrutinib. Again, the underlying hemato-oncologic diseases of these participants and their frequent association with such events should be taken into consideration here. All cytopenias reported in the final analysis of CLOU064A2201 were mild. Participants are closely monitored for signs and symptoms of cytopenia while in the trial, and those with a history of hematological disorders or with markedly altered hematologic parameters at baseline are excluded from the study (see details in Section 5.2).
- *Drug-drug interactions*: Oxidative metabolism is the major clearance pathway of remibrutinib and expected to be predominantly mediated by CYP3A4 with minor contribution of other CYP450 enzymes (e.g., CYP2C9, CYP1A1). At the dose used in this study (25 mg remibrutinib b.i.d.), co-administration of CYP3A4 inhibitors (even of strong ones) will not result in exposure levels of remibrutinib that are associated with clinically relevant QT prolongation. Likewise, co-administration of even strong CYP3A4 inhibitors with 25 mg remibrutinib b.i.d. will not increase exposure levels of remibrutinib beyond exposure levels that can be reached with 100 mg remibrutinib b.i.d., a dose that was well-tolerated in CLOU064A2201 and was not associated with any safety signals, based on the interim analysis. Therefore, only co-administration of strong CYP3A4 inhibitors is prohibited in this study. Concomitant administration of moderate and strong inducers of CYP3A4 is also prohibited during the study (see Table 6-2). Remibrutinib can be co-administered with oral contraceptives such as ethinylestradiol or levonorgestrel without a major impact on their exposure and efficacy. Remibrutinib has been shown to inhibit some efflux and uptake transporters (such as P-glycoprotein, OATP1B, Mate1, OAT3, organic

[redacted]

cation transporter 1 and BCRP). However at a dose of 25 mg b.i.d. only inhibition of BCRP remains as a minor risk which is planned to be investigated in a clinical drug-drug interaction study. Therefore, concomitant administration of remibrutinib with respective BCRP substrates with a small safety margin may be administered with caution (see Table 6-3).

- *Reproductive toxicity*: Remibrutinib is not genotoxic or mutagenic in *in vitro* or *in vivo* studies. No effects on fertility or embryo-fetal development were observed in rats up to the highest dose, while in rabbits a no-observed-adverse-effect-level at 100 mg/kg/day was established. At doses ≥300 mg/kg/day, body weight loss, marked low food consumption, and moribundity were noted, as well as a higher incidence of external fetal malformations (see details in IB). For the approved BTK inhibitors, embryo-fetal toxicity in animals is reported (see national prescribing information). Highly effective methods of contraception must be practiced. Women of child-bearing potential will be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the trial and must agree that in order to participate in the trial they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

For detailed information on potential risks associated with remibrutinib, please refer to the IB.

In summary, CSU patients with inadequate response to H1-antihistamines (and other available treatment options if applicable) participating in this clinical trial may significantly benefit from treatment with remibrutinib. Additionally, this trial will help to improve the understanding of remibrutinib in the management of CSU and potentially enable the development of a novel, innovative, oral drug that could improve the quality of life of CSU patients beyond the limited treatment modalities currently available. Potential risks are mitigated as far as possible by compliance with inclusion/exclusion criteria, study procedures, very close clinical and laboratory monitoring, periodic review of safety data by an independent Data Monitoring Committee (DMC), and study drug discontinuation rules. As with investigational drugs in general, not all safety risks are known. Participants and investigators participating in this trial will be informed should important new safety information become available.

Considering all aspects, the risk-benefit assessment fully supports this trial with remibrutinib 25 mg b.i.d.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

[redacted]

5 Study Population

The study population will consist of approximately 70 eligible female and male adult participants with CSU inadequately controlled by second generation H1-antihistamines (at least at local label approved dose).

The screen failure rate is estimated to be 30%, meaning approximately 100 participants are expected to be screened.

Participants who drop out after they have entered into the treatment period will not be replaced.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Male and female participants ≥18 years of age at the time of screening
3. CSU duration for ≥ 6 months prior to screening (defined as the onset of CSU determined by the investigator based on all available supporting documentation)
4. Diagnosis of CSU inadequately controlled by second generation H1-antihistamines at the time of baseline (Day 1) defined as:
   - The presence of itch and hives for ≥6 consecutive weeks prior to screening despite the use of second generation H1-antihistamines during this time period
   - UAS7 score (range 0-42) ≥16, ISS7 score (range 0-21) ≥ 6 and HSS7 score (range 0-21) ≥ 6 during the 7 days prior to baseline (Day 1)
5. Documentation of hives within three months before baseline (either at screening and/or at baseline; or documented in the participants' medical history)
6. Willing and able to complete an UPDD for the duration of the study and adhere to the study protocol
7. Participants must not have had more than one missing UPDD entry (either morning or evening) in the 7 days prior to baseline (Day 1)

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

Evaluation of participant eligibility for laboratory parameters listed below must be based on central laboratory results. In case eligibility criteria are not met for specific laboratory parameters, these may be re-tested a maximum of once during the screening period.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible participants.

1. Use of other investigational drugs within 5 half-lives, or within 30 days (for small molecules) prior to Screening or until the expected PD effect has returned to baseline (for biologics), whichever is longer; or longer if required by local regulations
2. Previous use of remibrutinib or other BTK inhibitors
3. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes

[redacted]

4. Participants having a clearly defined predominant or sole trigger of their chronic urticaria (chronic inducible urticaria) including urticaria factitia (symptomatic dermographism), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria.

5a. Other diseases with symptoms of urticaria or angioedema, including but not limited to urticaria vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary angioedema, or drug-induced urticaria

6. Any other skin disease associated with chronic itching that might influence in the investigator's opinion the study evaluations and results, e.g., atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or psoriasis

7. Participants taking medications prohibited by the protocol (See Table 6-2)

8. Known history or evidence of ongoing alcohol or drug abuse within the last 6 months before baseline

9. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases

10. Pregnant or nursing (lactating) women

11. Women of child-bearing potential (WoCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days after stopping of study treatment. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception [redacted]

    In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

    are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the

[redacted]

case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

12. Major surgery within 8 weeks prior to screening or planned surgery for the duration of the study

13a. History of live attenuated vaccine within 6 weeks prior to baseline or requirement to receive these vaccinations at any time during the study

14. Evidence of clinically significant cardiovascular (such as but not limited to myocardial infarction, unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, arrhythmia and uncontrolled hypertension within 12 months prior to Visit 1), neurological, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic, hematological disorders, gastrointestinal disease or immunodeficiency that, in the investigator's opinion, would compromise the safety of the participant, interfere with the interpretation of the study results or otherwise preclude participation or protocol adherence of the participant

15. Uncontrolled disease states, such as asthma, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids

16. Hematology parameters at screening:
    - Hemoglobin: < 10 g/dL
    - Platelets: < 100 000/mm^3
    - Leucocytes: <3 000/mm^3
    - Neutrophils: < 1 500/mm^3

17. Significant bleeding risk or coagulation disorders

18a. History of gastrointestinal bleeding, e.g., in association with use of nonsteroidal anti-inflammatory drugs (NSAIDs), that was clinically relevant (e.g., for which intervention was indicated or requiring hospitalization or blood transfusion)

19a. Requirement for anti-platelet medication, except for acetylsalicylic acid up to 100 mg/d or clopidogrel up to 75 mg/d. The use of dual anti-platelet therapy (e.g., acetylsalicylic acid + clopidogrel) is prohibited.

20. Requirement for anticoagulant medication (e.g., warfarin or Novel Oral Anti-Coagulants (NOAC))

21. History or current hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or Aspartate Aminotransferase (AST)/ Alanine Aminotransferase (ALT) levels of more than 1.5 x upper limit of normal (ULN) or International Normalized Ratio (INR) of more than 1.5 at screening

22. History of renal disease, creatinine level above 1.5x ULN, or estimated Glomerular Filtration Rate (eGFR) <45 ml/min (using the Cockcroft-Gault equation) at screening

23. Evidence of an ongoing Hepatitis C infection (e.g., defined by the detection of hepatitis C-ribonucleic acid (HCV-RNA) at screening) and/or an ongoing Hepatitis B infection (defined by the detection of Hepatitis B virus surface antigen (HBsAg) and/or hepatitis B virus (HBV)-DNA at screening; participants who are positive for anti-hepatitis B core

[redacted]

(HBc) antibodies but who are negative for antibodies against HBsAg and HBV-DNA can be included into the study if they agree to monitoring for HBsAg and HBV-DNA re-activation).

24. Known or suspected ongoing, chronic or recurrent infectious disease including but not limited to opportunistic infections (e.g., tuberculosis, atypical mycobacterioses, listeriosis or aspergillosis) and/or known positivity for Human Immunodeficiency Virus (HIV) infection.

6 Treatment

6.1 Study treatment

Investigational drug will be dispensed at assigned treatment visits as described in Table 8-1 after baseline.

6.1.1 Investigational and control drugs

Novartis Global Clinical Supply (GCS) will provide the following Investigational Medicinal Product (IMP) supplies in appropriately open labeled bottles (Table 6-1).

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
LOU064 25 mg	Film coated tablet	Oral use	Open-label	Novartis Pharma AG

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

Participants will take background medication (second generation H1-antihistamines at locally label approved doses) with a stable regimen during the study (Section 6.2.1). For rescue medication, see Section 6.2.4.

6.1.3 Treatment arms/group

Participants will be treated at Day 1 to remibrutinib 25 mg b.i.d. Each participant will take one film-coated tablet in the morning and one film-coated tablet in the evening [redacted]

6.1.4 Treatment duration

The planned duration of treatment is 52 weeks. Participants may discontinue from study treatment earlier at the discretion of the investigator or the participant, e.g., due to adverse events (see Section 9.1) or lack/loss of efficacy. Eligible participants may roll over at Week 52 into the extension study currently being considered (after completing all scheduled assessments planned at these visits). The details of the study design and procedures of the extension, if implemented, will be described in a separate protocol.

[redacted]

There are total of 9 dispensing visits per participant in the trial in the open-label period. The last dispensing visit occurs at Week 40.

6.2 Other treatments

6.2.1 Concomitant therapy

Throughout the study, participants **must** take a second generation H1-antihistamine at a locally label approved dose (background therapy). Background therapy should not be changed until the Week 12 visit and should only be changed thereafter if medically required (i.e., adverse reactions that are attributable to background therapy as per investigator judgment). For detailed information on the background medication, refer to the corresponding national prescribing information.

Prior medication for treatment of CSU will be recorded in the Electronic Case Report Forms (eCRF). In addition, all concomitant medication at screening and prior medication that has been terminated within 4 weeks prior to screening will be recorded. The investigator should instruct the participant to notify the study site about any new medications (including medications that are not related to the treatment of CSU) he/she takes after the participant was enrolled into the study, ideally before initiating a new treatment.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate eCRFs.

Each concomitant medication must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before treating a participant or allowing a new medication to be started. If the participant is already started the study treatment, contact Novartis to determine if the participation in the study should be continued.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed during the specified time period.

Table 6-2 Prohibited Medication

Medication	Prohibition period	Action taken
Biologics for treatment of CSU (including omalizumab and ligelizumab)	4 months prior to the first administration of study treatment until end of treatment[1]	Discontinue biologic treatment and closely monitor for potential associated adverse events.
Routine (more than 3 doses over 5-day period) oral corticosteroids	30 days prior to screening until end of treatment **Oral corticosteroids are only allowed as an additional rescue therapy for CSU AFTER Week 12**, on an as-needed basis for unbearable symptoms as per Section 6.2.4. Other preparations of corticosteroids with limited systemic exposure for non-CSU indications (e.g., intra-nasal or any	Discontinue routine corticosteroids if medically justifiable and closely monitor for potential associated adverse events. If discontinuation of routine corticosteroids is not possible, discontinue study treatment.

[redacted]

Medication	Prohibition period	Action taken
	topical corticosteroids) can be used on an as-needed basis.	
i.v./IM/IA corticosteroids	30 days prior to screening until end of treatment[1].	Discontinue i.v./IM/IA corticosteroids if medically justifiable and closely monitor for potential associated adverse events. If discontinuation of i.v./IM/IA corticosteroids is not possible, discontinue study treatment.
Leukotriene antagonists (including montelukast and zafirlukast)	From screening until end of treatment[1]	Discontinue Leukotriene antagonists and closely monitor for potential associated adverse events.
H2-antihistamines	From screening until end of treatment[1]	Discontinue H2-antihistamines and closely monitor for potential associated adverse events.
First-generation antihistamines	From screening until end of treatment[1]	Discontinue first-generation antihistamines and closely monitor for potential associated adverse events.
Second generation antihistamines **other than** the participant's defined background medication and rescue medication	From 7 days prior to the first administration of study treatment until end of treatment[1]	Discontinue all second-generation H1-antihistamines but the defined background and rescue medication and closely monitor for potential associated adverse events.
Other immunosuppressive/immunomodulating medication with or without known effect on CSU including but not limited to hydroxychloroquine, methotrexate, cyclosporine A, cyclophosphamide, tacrolimus and mycophenolate mofetil	30 days or 5 half-lives (whichever is longer) prior to screening until end of treatment[1]	Discontinue immunosuppressive/ immunomodulating medication if medically justifiable and closely monitor for potential associated adverse events. If discontinuation not possible, discontinue study treatment.
Intravenous (i.v.) immunoglobulins or plasmapheresis	30 days prior to screening until end of treatment[1]	Discontinue i.v. immunoglobulins or plasmapheresis if medically justifiable and closely monitor for potential associated adverse events. If discontinuation not possible, discontinue study treatment.
Ultraviolet (UV) therapy	From screening until end of treatment[1]	Discontinue UV therapy and closely monitor for potential associated adverse events.
Any other therapy intended for the treatment of urticaria including but not limited to herbal therapies	From 2 weeks prior to the first administration of study treatment until end of treatment[1]	Discontinue any therapy intended for the treatment of urticaria and closely monitor for potential associated adverse events.
Live attenuated vaccines	6 weeks prior to baseline until at least 4 weeks after last dose of study treatment	Discontinue study treatment.
Strong inhibitors of CYP3A4	From 2 weeks prior to the first administration of study treatment until end of treatment[1]	Discontinue CYP3A4 inhibitor if medically justifiable and closely monitor for potential associated adverse events. If discontinuation

[redacted]

Medication	Prohibition period	Action taken
		not possible, discontinue study treatment
Moderate and strong inducers of CYP3A4	From 2 weeks prior to the first administration of study treatment until end of treatment[1]	Discontinue CYP3A4 inducers if medically justifiable and closely monitor for potential associated adverse events. If discontinuation not possible, discontinue study treatment.
Anticoagulant medication (e.g., warfarin, or NOAC)	From screening until end of treatment[1]	Only if medically justifiable, discontinue anticoagulant medication and interrupt study medication until anticoagulant effects have ended. Otherwise discontinue study treatment. Closely monitor coagulation parameters and associated adverse events. Clinical monitoring should focus on skin (bruising, petechiae) and mucosa (e.g., gastro-intestinal tract bleeding including gingival and rectal, or conjunctival bleeding). In case of a significant bleeding event, study treatment must be discontinued immediately.
Anti-platelet medication except for acetylsalicylic acid up to 100 mg/d or clopidogrel up to 75 mg/d. The use of dual anti-platelet therapy (e.g., acetylsalicylic acid + clopidogrel) is prohibited.	From screening until end of treatment[1]	Only if medically justifiable, discontinue anti-platelet medication and interrupt study medication until anti-platelet effects have ended. Otherwise discontinue study treatment. Closely monitor coagulation parameters and associated adverse events. Clinical monitoring should focus on skin (bruising, petechiae) and mucosa (e.g., gastro-intestinal tract bleeding including gingival and rectal, or conjunctival bleeding). In case of a significant bleeding event, study treatment must be discontinued immediately.

[1] The day when patient receives the last study treatment dose (i.e., on Week 52 or in case of early treatment discontinuation the day of last dose of study treatment).

6.2.3 Permitted concomitant therapy requiring caution and/or action

Remibrutinib has been shown to inhibit the BCRP transporter at the intestinal level. As a consequence, co-administration with remibrutinib can lead to exposure increases are under the curve of >1.5-fold. Therefore, concomitant administration of remibrutinib with respective BCRP substrates (e.g., pitavastatin, rosuvastatin, sulfasalazine and ubrogepan) may be accomplished with caution. BCRP substrates with a small safety margin may be administered 2 hours before or after remibrutinib (staggered dosing).

[redacted]

Table 6-3 Permitted concomitant therapy requiring caution and/or action

Medication	Period	Guidance
Oral BCRP substrates that may have increased exposure when co-administered with remibrutinib (pitavastatin, rosuvastatin, sulfasalazine and ubrogepan)	1 day prior to dosing with remibrutinib until end of treatment	Use with caution, replace medication or administer 2hr before or after remibrutinib (staggered dosing)

6.2.4 Rescue medication

H1-antihistamines: In addition to being used as background medication, second generation H1-antihistamines are allowed as rescue medication, used on an as needed basis for participants with CSU flare-ups of unbearable symptoms during screening, treatment and follow-up periods. The selection of the rescue medication H1-antihistamine should be made only once for an individual participant and recorded in the source document. For each individual participant, **the H1-antihistamine used as rescue medication must differ from the H1-antihistamine used as background medication**. The daily dose of H1-antihistamine **rescue** medication should **not** exceed 4-fold of the approved dose, as recommended by the current urticaria treatment guidelines (Zuberbier et al 2018). For detailed information on the rescue medication, refer to the corresponding national prescribing information. A change of the rescue medication for an individual participant is only permitted in case of adverse reactions that are, in the judgment of the investigator, attributable to rescue medication.

Oral corticosteroids: Prior to Week 12, any corticosteroid use for CSU is prohibited. After Week 12, participants will be permitted to use oral corticosteroids such as prednisone or its equivalent, as rescue medication if needed for CSU flare-ups of unbearable symptoms. The selection of the oral corticosteroid to be used as rescue medication after Week 12, should be made only once for an individual participant. A switch of oral corticosteroids as rescue medication for an individual is not permitted except due to an AE. **Rescue oral corticosteroid use will be limited to 3 days in a 30 day period and a maximum of 9 days in total after Week 12** to avoid any confounding suppression of signs and symptoms of CSU. The recommended dose is 20 - 50 mg prednisone or equivalent per day, which is in line with the current urticaria treatment guidelines (Zuberbier et al 2018).

Rescue medication will be sourced locally. Use of H1-antihistamine rescue medication only for CSU must be recorded in the eDiary by the participant (number of tablets taken) and the name and dose will be captured on the appropriate eCRF. All relevant information for oral corticosteroid rescue therapy will be captured in the appropriate eCRF.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (Section 6.1.1).

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the Interactive Response Technology (IRT) and obtaining the medication number(s).

[redacted]

The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1-month supply. In this case, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/home nursing to the participant's home at the time of a planned on-site visit will occur for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until it is safe for the participant to visit the site again.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during regular monitoring visits, and at the completion of the trial.

Participants will be asked to return all unused study treatment and packaging at each site visit during the study and at the end of the study, or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the field monitor or to the Novartis address provided in the investigator folder at each site.

6.3.1.2 Handling of other treatment

Not applicable.

[redacted]

6.3.2 Instruction for prescribing and taking study treatment

Every participant should take one film-coated tablet of remibrutinib 25 mg in the morning and in the evening, respectively, with a 12-hour interval at approximately the same time every day. The study medication may be taken with or without a meal but participants should adhere to their choice throughout the study. If taken without food, the study medication should be taken with a glass of water (250 milliliters (mL)) at least 2 hours after the last meal and 1 hour before the next meal. Participants should be instructed to swallow whole tablets and not to chew or break them.

[redacted]

If vomiting occurs during the course of treatment, participants should not take the study treatment again before the next scheduled dose.

Participants should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 6 hours after the approximate time of the usually morning/evening dosing. That dose should be omitted and the participant should continue treatment with the next scheduled dose.

H1-antihistamines taken as either as background medication or rescue medication, respectively, should be taken according to the local treatment instructions.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.4.2 Treatment assignment, randomization

No randomization will be performed in this study due to a single arm study design. All participants whose eligibility has been confirmed will receive remibrutinib 25 mg b.i.d.

6.5 Treatment blinding

Not applicable.

[redacted]

6.6 Dose escalation and dose modification

Investigational or other study treatment dose adjustments are not permitted.

Study treatment interruptions are permitted in order to manage the following events:

- Management of bleeding events: in case of planned surgery with clinical significant bleeding risk, interruption of study treatment 7 days before the surgery is required; after recovery, participant may re-start study treatment after 7 days.
- Management of participants in case of Hepatitis B re-activation (new appearance of detectable HBV-DNA or positive HBsAg): participants should start antiviral treatment according to local clinical practice and interrupt study treatment until HBV-DNA and HBsAg reach an undetectable level, and then re-start study treatment.

Study treatment interruption for other than the above reasons is only permitted if, in the opinion of the investigator, a participant is deemed to be at a significant safety risk unless administration of investigational treatment is temporarily interrupted. In such cases study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be re-started at the next scheduled visit after resolution of the safety risk.

6.6.1 Follow-up for toxicities

Not applicable.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using tablet counts (if applicable) and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

[redacted]

6.7.2 Emergency breaking of assigned treatment code

Since this is an open label study, this is not applicable.

6.7.3 Treatment of overdose

No clinical data are available to assess the risk of overdose. Based on preclinical data, it is concluded that remibrutinib has a low potential to cause acute toxicity, e.g., in case of accidental overdosing. Single and multiple ascending doses of remibrutinib up to 600 mg were studied in healthy volunteers with no dose-limiting toxicities identified. With the 25 mg b.i.d. dose used in this study, the potential of remibrutinib to cause acute toxicity is assessed as low.

[redacted]

There is no specific antidote to remibrutinib; therefore, adverse events will be managed symptomatically according to standard of care and applicable clinical guidelines.

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 good clinical practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
  - [redacted]
  - [redacted]

[redacted]

- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

[redacted]

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that, in order to participate in the study, they must adhere to the contraception requirements.

[redacted]

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

[redacted]

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

For participants who discontinue from study treatment refer to Section 9.1.1.

Participants who discontinue from the study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit, if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

The preferred sequence of assessments during study visits is PRO completion, ECG collection, followed by vital signs, and blood sampling.

[redacted]

Table 8-1 Assessment Schedule

Period	Screening	Treatment												Follow-up	Unscheduled
Visit Name	Screening	Baseline[1]	Week 2[1]	Week 4	Week 8	Week 12[1]	Week 16	Week 20	Week 24	Week 32	Week 40	Early treatment discontinuation	Week 52/Study discontinuation[1]	Week 56/Safety FU/Study completion	Unscheduled visit
Days	-28 to -1	1	15	29	57	85	113	141	169	225	281	-	365	394	-
Informed consent	X														
[redacted]															
IRT transaction	X	X		X	X	X	X	X	X	X	X	X	X		
Inclusion / Exclusion criteria	X	X													
Demography	X														
Pregnancy and assessments of fertility[2]	XS	S		S	S	S	S	S	S	S	S	S	S	S	S
Evidence of urticaria	S	S													
Hepatitis screen	X														
Relevant medical history	X														
Dispense participants' eDiary[3]	S											S	S		
CSU History and prior urticaria treatment	X														

[redacted]

Period	Screening	Treatment												Follow-up	Unscheduled
Visit Name	Screening	Baseline[1]	Week 2[1]	Week 4	Week 8	Week 12[1]	Week 16	Week 20	Week 24	Week 32	Week 40	Early treatment discontinuation	Week 52/Study discontinuation[1]	Week 56/Safety FU/Study completion	Unscheduled visit
Days	-28 to -1	1	15	29	57	85	113	141	169	225	281	-	365	394	-
Cardiovascular history	X														
Physical Examination[4]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Height and Weight[5]	X	S				X			S			X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X	X	X[6]			X[6]			X			X	X[6]	X	X
Subject's eDiary review[7]		S	S	S	S	S	S	S	S	S	S	S	S		S
DLQI[8]		X		X		X			X			X	X		X
[redacted]															
Study drug dispensation		X		X	X	X	X	X	X	X	X				
Background medication dispensation and compliance assessment[18]	X	X		X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Period	Screening	Treatment												Follow-up	Unscheduled
Visit Name	Screening	Baseline[1]	Week 2[1]	Week 4	Week 8	Week 12[1]	Week 16	Week 20	Week 24	Week 32	Week 40	Early treatment discontinuation	Week 52/Study discontinuation[1]	Week 56/Safety FU/Study completion	Unscheduled visit
Days	-28 to -1	1	15	29	57	85	113	141	169	225	281	-	365	394	-
Rescue medication dispensation and usage[10]	X	X		X	X	X	X	X	X	X	X	X	X		
[redacted]															
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X	X		X		X			X		X	X	X	X	X
[redacted]															
Hepatitis B re-activation monitoring[14]				X	X	X	X	X	X	X	X	X	X	X	X
HIV testing[15]	S														
[redacted]															

[redacted]

Period	Screening	Treatment												Follow-up	Unscheduled
Visit Name	Screening	Baseline[1]	Week 2[1]	Week 4	Week 8	Week 12[1]	Week 16	Week 20	Week 24	Week 32	Week 40	Early treatment discontinuation	Week 52/Study discontinuation[1]	Week 56/Safety FU/Study completion	Unscheduled visit
Days	-28 to -1	1	15	29	57	85	113	141	169	225	281	-	365	394	-
[redacted]															
Eligibility assessment for extension study[19]													S		
Trial Feedback Questionnaire[20]		X							X					X[17]	
Prior and Concomitant medication/non-drug therapies	X														
Adverse Events	X														
Study completion information	X														

[1] Participant to come fasting for ≥8h (ideally overnight) to visits: Baseline, Week 2, Week 12 and Week 52
[2] Serum pregnancy test and fertility assessment will be done at Screening. Urine pregnancy test to be completed every 4 weeks by WoCBP from Baseline through to Study completion visit. At Weeks 28, 36, 44 and 48 test may be performed at home - sites must contact participants to obtain test results. Any positive or undetermined test result must be confirmed by a serum pregnancy test done by central lab and results received electronically. Urine pregnancy results are reported as source.
[3] Participants eDiary will be returned to site at either Week 52/study discontinuation
[4] Complete physical exam at screening, short physical exam at all subsequent visits including body temperature monitoring (per local practice)
[5] Height collected at screening visit only
[6] pre and post dose
[7] eDiary includes UPDD (Urticaria Patient Daily Diary) with UAS (Urticaria Activity Score, part of UPDD) and AAS (Angioedema Activity Score), eDiary to be completed from screening to Week 52/study discontinuation.
[8] Completed in the patient's eDiary during site visit. Order of completion: DLQI - [redacted] All questionnaires should be completed prior to

[redacted]

Period	Screening	Treatment												Follow-up	Unscheduled
Visit Name	Screening	Baseline[1]	Week 2[1]	Week 4	Week 8	Week 12[1]	Week 16	Week 20	Week 24	Week 32	Week 40	Early treatment discontinuation	Week 52/Study discontinuation[1]	Week 56/Safety FU/Study completion	Unscheduled visit
Days	-28 to -1	1	15	29	57	85	113	141	169	225	281	-	365	394	-

any other physician assessment.

[redacted]

[14] Hepatitis B re-activation monitoring only for participants who were HBsAg negative and HBcAb (anti-HBc) positive with a negative HBV DNA test at Screening.
[15] HIV test will be performed only when required an allowed by local regulations.

[redacted]

[17] The last response should be performed at Week 56 as study completion. However, if participants enroll the extension study, this should be done at the timing of Week 52.

[18] Dispensation for background medication covers prescription, dispensation and/or instruction of the participant on dosing and use of background medication and protocol requirements, considering different procedures for the provision of background medication at investigational sites. At Week 56/Safety FU/Study completion visit only compliance to be checked.

[19] Only for participants who have completed Week 52 visit, not applicable at Study discontinuation visit

[20] Trial Feedback Questionnaire is not considered study data and will be received electronically outside the clinical database

[redacted]

8.1 Screening

Screening and re-screening

Participants will have a screening period of 7 up to a maximum of 28 days to establish eligibility for the study.

Once all eligibility criteria have been assessed and the participant is eligible for enrollment in the study the baseline visit can be scheduled (this may be prior to the maximum 28 day screening period duration).

Evaluation of participant eligibility for laboratory parameters listed in Section 5.2 must be based on central laboratory results. In case eligibility criteria are not met for specific laboratory parameters, these may be re-tested a maximum of once during the screening period.

If for any reason a participant is a screen failure, the participant may be re-screened. Re-screening is only allowed once. There is no restriction on how much time must pass from the date of screen failure to the date of re-screening.

If a participant re-screens for the study, then they must sign a new ICF and be issued a new participant number prior to any screening assessment being conducted for the participant under the new screening subject number. The investigator/qualified site staff will record if the participant was re-screened on the re-screening eCRF and any applicable screening numbers the participant was issued prior to the current screening number.

The date of the new informed consent signature must be entered on the informed consent eCRF to correspond to the new screening subject number. For re-screening, all screening assessments must be performed per protocol.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible prior to start the study treatment will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event (SAE) during the screening phase (see SAE section for reporting details). If the participant fails to enter the treatment phase, the IRT must be notified within 2 days of the screen fail that the participant was not enter the treatment phase.

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Baseline CSU activity will be assessed using the eDiary from Day -7 to Day -1.

[redacted]

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Participant demographic and baseline characteristic data to be collected at screening on all enrolled participants:

- Demography (age, sex, race and ethnicity) information on racial and ethnicity will be collected and analyzed to document that the Japanese participants are recruited.
- Relevant medical history (including evaluation of inclusion/exclusion criteria, evidence of urticaria, CSU history and cardiovascular history) and current medical condition present before signing the informed consent. Where possible, diagnoses, and not symptoms, will be recorded.
- Data on participants' family history of malignancies will be collected on the respective eCRF page, only when a participant has a malignancy event reported during the study, to assess possible risk factors related to any malignancies.
- Prior urticaria treatment and background therapy
- All concomitant medication at screening and prior medication that has been terminated within 4 weeks prior to screening
- Furthermore, the following assessments will be performed:
  - Physical examination, height and weight
  - Vital signs including blood pressure and pulse
  - 12-lead ECG
  - Laboratory evaluations (e.g., Clinical Chemistry, Hematology, Urinalysis, Coagulation Panel)
  - Pregnancy Test for all pre-menopausal women

8.3 Efficacy

8.3.1 eDiary assessments

All participants will be provided with an electronic device (eDiary) that contains the following Patient Reported Outcomes (PRO) assessments: UPDD and AAS.

Site and participants will receive appropriate training and guidance on the use of the eDiary and will receive clear instructions on the completion of the assessments. Investigators need to review the eDiary at every visit.

Assessments will be completed twice daily (UPDD), once daily (AAS, if triggered by opening question within the UPDD) from screening to Week 52/study discontinuation or until early treatment discontinuation visit for participants who decline to continue the assessments.

In general, participants complete eDiary questionnaires at home and independent of study visits. Participants will be instructed to complete eDiary entries after they took their study medication throughout the treatment period.

The DLQI, [redacted] questionnaires will be administered during respective visits on site and should be completed prior to any other study specific procedure [redacted]. Site personnel must allow participants to complete the questionnaire

[redacted]

on their own without any assistance from the site staff. In the case that participants cannot come to site (see Section 4.6), the DLQI, [redacted] will be available on their electronic device.

8.3.1.1 Urticaria Patient Daily Diary (UPDD)

UPDD includes Urticaria Activity Score (UAS) which assesses twice daily severity of itch and number of hives, use of rescue medication, sleep and activity interference, angioedema occurrence, its management and records the calls to a healthcare professional (HCP). The components are presented in the Table 8-2 and the relevant weekly scores are described below.

Table 8-2 UPDD

Diary component	When assessed
Urticaria Activity Score (UAS) • Itch severity • Number of hives	Morning and evening
Sleep interference	Morning
Daily activity interference	Evening
Rescue medication use	Evening
Angioedema: • Whether patient had an episode • If patient had an episode, how did they manage it	Evening
Contact health care provider	Evening

8.3.1.1.1 Weekly Hives Severity Score (HSS7)

The hives (wheals) severity score, defined by number of hives, will be recorded by the participant twice daily in their eDiary, on a scale of 0 (none) to 3 (> 12 hives/12 hours; Table 8-3). A weekly score (HSS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0 - 21.

Table 8-3 Hives Severity Score

Score	Hives (Wheals) (every 12 hours)
0	None
1	1-6 hives/12 hours
2	7-12 hives/12 hours
3	>12 hives/12 hours

8.3.1.1.2 Weekly Itch Severity Score (ISS7)

The severity of the itch will be recorded by the participant twice daily in their eDiary, on a scale of 0 (none) to 3 (severe) (Table 8-4). A weekly score (ISS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0 - 21.

[redacted]

Table 8-4 Itch Severity Score

Score	Pruritus (Itch) (every 12 hours)
0	None
1	Mild (minimal awareness, easily tolerated)
2	Moderate (definite awareness, bothersome but tolerable)
3	Severe (difficult to tolerate)

8.3.1.1.3 Weekly Urticaria Activity Score (UAS7)

The UAS7 is the sum of the HSS7 score and the ISS7 score. The possible range of the weekly UAS7 score is 0 – 42 (highest activity).

[redacted]

8.3.1.1.7 Angioedema occurrence

Angioedema occurrence is recorded once daily in the evening in the eDiary by the participant. Reporting the occurrence of angioedema will be used as opening question for the assessment of the AAS (see Section 8.3.1.2). Actions and/or treatments related to those angioedema occurrences will be also recorded in the eDiary as follows (multiple answers possible):

[redacted]

- Did nothing
- Took some prescription or non-prescription medication
- Called my doctor, nurse or nurse practitioner
- Went to see my doctor, nurse or nurse practitioner
- Went to the emergency room at the hospital
- Was hospitalized.

8.3.1.1.8 Number of calls to doctor or nurse

The number of calls to doctor, nurse or nurse practitioner because of the participant's skin condition will be recorded once daily in the eDiary by the participant.

8.3.1.2 Angioedema Activity Score (AAS)

AAS is recorded once daily in the evening in the eDiary by the participant. This validated tool assesses occurrence of episodes of angioedema. As an opening question, the occurrence of angioedema in the UPDD (see Section 8.3.1.1.7) will be used. If participants answer this opening question in the UPDD with "no", AAS score for this day is 0. If "yes" is the answer to the opening question in the UPDD, the participant will continue to answer questions about the duration, severity and impact on daily functioning and appearance of the angioedema (see Appendix 5). A score between 0 and 3 is assigned to every answer field. The AAS score in this study will be reported as weekly AAS (AAS7). Minimum and maximum possible AAS7 scores are 0−105. A higher score means higher severity.

8.3.2 Other Patient Reported Outcomes (PRO) assessments

8.3.2.1 Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item (grouped in 6 domains) dermatology-specific quality of life (QoL) measure (Finlay and Khan 1994). The DLQI was validated for patients aged 16 and above. Participants rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives thinking about the previous 7 days.

An overall score is calculated and ranges from 0 to 30 (higher score meaning worse disease-related QoL). Domain scores are calculated for: Symptoms and Feelings (0-6), Daily Activities (0-6), Leisure (0-6), Work and School (0-3), Personal Relationships (0-6), Treatment (0-3).

The overall DLQI score range was split into score bands (Hongbo et al 2005) and validated in terms of their meaning/relevance to patients as follows:

Table 8-7 DLQI score bands and impact on patient's life

DLQI band	Significance of score
0-1	No effect on patient's life
2-5	Small effect on patient's life
6-10	Moderate effect on patient's life
11-20	Very large effect on patient's life
21-30	Extremely large effect on patient's life

[redacted]

A DLQI score of > 10 is relevant for a very large impact on patients' life and justification for a biologic prescription for example in psoriasis (Finlay 2005). The DLQI questionnaires are completed at visits detailed in Table 8-1 in the eDiary. The DLQI should be completed prior to any other assessment and prior to administration of investigational medication.

[redacted]

[redacted]

8.3.3 Appropriateness of efficacy assessments

UAS7: The UAS7 score is a unified, simple, well-established and validated tool, recommended by the current urticaria guidelines for the assessment of disease activity and treatment response in real-world clinical practice as well as in clinical trials with urticaria patients (Młynek et al 2008, Hawro et al 2018, Zuberbier et al 2018). It is based on the assessment of the two key urticaria signs and symptoms, wheals and pruritus, which are documented by the patient, making this score especially valuable. The use of the UAS7 facilitates comparison of study results across different trials, since it is used in other major Phase 3 trials in the CSU indication as well (e.g., with ligelizumab).

AAS7: The AAS7 score is a unified, simple and validated tool, recommended by the current urticaria guidelines for the assessment of disease activity and treatment response in patients with angioedema (Weller et al 2013, Zuberbier et al 2018). The use of the AAS7 facilitates comparison of study results across different trials, since it is used in other major Phase 3 trials in the CSU indication as well (e.g., with ligelizumab).

[redacted]

8.3.4 Other assessments: evidence of urticaria

The investigator must confirm the presence of urticaria (i.e., the presence of hives) in each participant before starting the study treatment by direct physical examination. In the absence of active disease at the screening and/or baseline visit, the following will be acceptable: (a) a clearly identifiable photograph of the participant that is no older than 3 months showing the presence of urticaria, (b) the investigator must have seen the participant with active CSU in the past 3 months, or (c) the presence of hives/wheals must have been documented in the medical

[redacted]

record of the participant by a physician trained in the management of urticaria in the past 3 months.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-8 Physical assessments

Assessment	Specification
Physical examination	A complete physical examination (performed at Screening) will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, neurological and body temperature measurement (per local practice). If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam (performed at all visits except Screening) will include the examination of general appearance, assessment of the skin for signs of urticaria and other skin lesions, body temperature measurement (per local practice) and vital signs (blood pressure (BP) [systolic blood pressure (SBP) and diastolic blood (DBP)] and pulse). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include BP and pulse measurements. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g., OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Section 16.1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens detailed in this section (Table 8-9) unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

If participants cannot visit the site for protocol specified safety lab assessments (per Section 4.6), an alternative lab (local) collection may be used.

Clinically notable laboratory findings are defined in Section 16.1.

[redacted]

Clinically significant abnormalities must be recorded on the relevant section of the eCRF capturing medical history/current medical conditions/AEs.

Table 8-9 Laboratory assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, [in the case of clinically significant anemia the following parameters will be assessed: Ery. Mean Corpuscular Hemoglobin (MCH), Ery. Mean Corpuscular Hemoglobin Concentration (MCHC), Ery. Mean Corpuscular Volume (MCV)], Platelets, Erythrocytes, Leukocytes, and Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin, Alkaline phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine, Creatine Kinase (CK), Direct Bilirubin, Indirect Bilirubin (in case of clinically significant elevation), Total Bilirubin, Total Cholesterol, Low Density Lipoprotein (LDL) Cholesterol, High Density Lipoprotein (HDL) Cholesterol, Total Protein, Triglycerides, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase C-reactive protein (CRP), estimated Glomerular Filtration Rate (eGFR): in all patients at screening, baseline, Weeks 12, 24 and 52 and when deemed necessary by the investigator at any other visits than those listed. Fasting glucose assessed at baseline, Weeks 2, 12 and 52.
Urinalysis	Done on site: Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Hepatitis screening	Hepatitis B screening: Antibodies against Hepatitis B virus core antigen (HBcAb or anti-HBc); antibodies against Hepatitis B virus surface antigen (HBsAb or anti-HBs); Hepatitis B virus surface antigen (HBsAg). Hepatitis B virus-Deoxyribonucleic acid (HBV-DNA, only in participants who are positive for HBcAb or anti-HBc). The study site may refer to local guidelines for hepatitis B monitoring. Hepatitis C screening: Hepatitis C virus antibodies (anti-HCVAb) and Hepatitis C-Ribonucleic acid (HCV-RNA, only in participants who are positive for anti-HCVAb)
Hepatitis B re-activation monitoring	Only in participants who are positive for HBcAb (anti-HBc positive) and negative for HBsAb and HBV-DNA at screening: HBsAg, HBV-DNA. The study site may refer to local guidelines for hepatitis B re-activation monitoring.
HIV testing	HIV test performed at screening, only when required by local regulations.
Additional tests	[redacted] Follicle-stimulating hormone (FSH) (for female participants with unclear fertility status)
Pregnancy Test	Serum / Urine pregnancy test for WoCBP (refer to Section 8.4.3)

8.4.2 Electrocardiogram (ECG)

ECGs must be recorded according to the ECG investigator manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Triplicate 12-lead ECGs are to be collected approximately 2 minutes apart for central analysis. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each participant. At Weeks 2, 12 and 52 pre and post-dose assessments should be collected (refer to Table 8-1), post dose assessment should be measured [redacted]

[redacted] and the mean QTcF value for each timepoint will be calculated from the triplicate ECGs for each participant.

All ECGs, including unscheduled safety ECGs with clinically relevant findings collected during the study needs to be transmitted to the central ECG laboratory for review.

A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 450 ms (males)/ 460 ms (females)), a copy of the assessment is sent to the core laboratory for expedited review if applicable, and the ECG is repeated to confirm the diagnosis. If the participant is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

If participants cannot visit the site for protocol specified safety ECG assessments (per Section 4.6), an alternative machine (local) may be used.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing at screening (serum), at baseline (Day 1, before administration of study medication (urine)), and every 4 weeks thereafter (urine). Where the visit interval is greater than 4 weeks, or in the case that the participants cannot visit the site, the participants will be provided with urine pregnancy tests kits to be used at home. Results must be provided to the investigator at the next scheduled visit. Participants should be instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment.

A positive urine pregnancy test needs to be confirmed with a serum test. Where a home urine pregnancy test is positive the participant must contact the investigator and return to site for a serum pregnancy test, in the case that participants cannot visit the site an alternative (local lab) can be used. If positive the participant must be discontinued from study treatment.

A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., following country-specific measures).

Additional pregnancy testing might be performed if requested by local requirements.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or bilateral tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

[redacted]

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Appropriateness of safety measurements

The selected safety monitoring assessments (including laboratory assessments covering clinical chemistry, hematology, coagulation status [redacted] as well as clinical and physical assessments, triplicate ECG monitoring and general AE assessments) are reliable and well-established standard measures which allow valid and close safety monitoring of the trial´s patient population, with regards to their disease, to the compound they are treated with, remibrutinib, and also to their overall medical safety.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Trial Feedback Questionnaire

This study includes an optional anonymized questionnaire, the 'Trial Feedback Questionnaire' for trial participants to provide feedback on their clinical trial experience at 3 timepoints at the start, during and at the end of the trial. Individual trial participant responses will not be reviewed by investigators. Responses may be used by the sponsor to understand where improvements can be made in the clinical trial process. This questionnaire does not ask questions about the trial participant's disease, symptoms, treatment effect or adverse events and therefore is not considered as trial data.

In the case that participants cannot come to site (see Section 4.6), these questionnaires would be available on their electronic device.

[redacted]

[redacted]

[redacted]

[redacted]

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the protocol planned completion of study drug administration) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant decision (request in writing or verbally)
- Pregnancy
- Use of prohibited treatment requiring study treatment discontinuation as detailed in Table 6-2 or discontinuation of highly effective methods of contraception as detailed in Section 5.2
- Any situation in which continued study participation might result in a safety risk to the participant

[redacted]

- Emergence of the following AEs:
  - any adverse events that in the judgement of investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study, including:
    - hypersensitivity reactions,
    - severe/serious infections
    - clinically significant spontaneous bleeding events
    - new confirmed diagnosis of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer)
  - Platelets < 75 000/mm3
  - Abnormal renal laboratory results requiring discontinuation (see Section 16.3)
  - Abnormal liver laboratory results requiring discontinuation (see Section 16.2)
  - Any other laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
  - Participant received a live virus vaccination during the study

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

All participants who discontinue from study treatment prematurely should complete the Early treatment discontinuation visit at the time of treatment discontinuation.

For participants who discontinue from study treatment prior to Week 12, where possible they should be requested to return for visits after the Early treatment discontinuation visit as per the Assessment Schedule (Table 8-1) up to and including the Week 12 timepoint. At the Week 12 timepoint the study discontinuation visit should be performed [redacted] If the participant declines to continue with assessments as per the visit schedule up to Week 12, then they should complete the safety follow-up visit after the Early treatment discontinuation visit.

Participants who discontinue from study treatment after Week 12 should complete the safety follow-up visit indicated in the Assessment Schedule (Table 8-1) whenever possible.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

[redacted]

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason, including participant's decision (requested in writing or verbally).

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent /opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing or verbally (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

[redacted]

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, enrolls into the planned extension study following completion of the 52 week treatment period or, in the event of an early study termination decision, the date of that decision.

Participants who complete participation in the 52 week treatment period of this trial may be eligible to receive remibrutinib as part of an extension study (under development) if they meet the eligibility criteria defined in the extension study protocol.

The extension study will require endorsement as per local laws and regulations.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. Following instruction from Novartis, investigators must contact the participant to schedule the study discontinuation and study completion visits (as appropriate) and provide instruction regarding study drug intake. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study.

[redacted]

Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade.
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Drug interrupted/permanently discontinued

6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

[redacted]

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. See Section 16.1, Section 16.2 and Section 16.3 for alert ranges for laboratory and other test abnormalities.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

[redacted]

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred (see Section 10.1.5).

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, then local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the electronic serious adverse event (eSAE) (with paper backup if required). Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

1. Screen Failures (e.g., a participant who is screened but is not treated): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis with 24 hours of learning of its occurrence.
2. Treated Participants: SAEs collected between time participant signs ICF until 30 days after the participant has discontinued from study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, then local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to

[redacted]

inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the Targeted Follow-up pregnancy - Infant status form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (European Medicines Agency definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

[redacted]

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections (Section 10.1.1 and Section 10.1.2).

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1 in Section 16.2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2 and Table 16-3. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1 and Section 16.2), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include, based on investigator's discretion:
  - serology tests, imaging and pathology assessments, hepatologist’s consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

[redacted]

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Any one of the following:
  - Urine protein-creatinine ratio (PCR) ≥1 g/g or ≥100 mg/mmol, OR
  - New onset dipstick proteinuria ≥ 3+, OR
  - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events as defined in Table 16-4 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-5.

10.3 Committees

10.3.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.3.2 Steering Committee

A steering committee has been established comprising medical and scientific experts who are not members of the DMC, and Novartis representatives from the Clinical Trial Team.

The steering committee will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The steering committee will review the initial protocol and protocol amendments as appropriate. Together with the clinical trial team, the steering committee will also develop recommendations for publications of study results including authorship rules.

[redacted]

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, scheduled visit, screen failures and study completion, as well as data about all study treatment(s) dispensed to the participant will be tracked using an Interactive Response Technology (IRT). The system will be supplied by Novartis, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eCRFs)

[redacted]

with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

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

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The following analysis sets will be used in this study.

Safety Set: 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.

[redacted]

12.2 Participant demographics and other baseline characteristics

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

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized as frequencies and percentage combined by system organ class and preferred term for the Safety Set.

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.

12.3 Treatments

The Safety Set will be used for the analyses below.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in weeks to remibrutinib will be summarized.

The duration of exposure to study treatment will be computed without excluding temporary treatment interruptions.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the ATC classification system.

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 the study medication 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.

12.4 Analysis supporting primary objectives

This section will detail the statistical analysis of the primary (safety) estimand.

12.4.1 Definition of primary endpoints

The assessment of safety is based on all safety outcomes including reported adverse events or routine assessments such like vital signs, lab parameters or ECG measures. The estimand framework cannot be explicitly applied to all parameters. However, it may be useful to apply the estimand framework for treatment-emergent AEs.

In the majority of cases the assessments are not performed after permanent treatment discontinuation but the data collection are continued until end of safety follow-up period. For

[redacted]

the sake of consistency, main estimands defined for treatment-emergent AEs should follow the same logic.

The broad clinical question to be addressed is then: what is the safety of LOU064 while participant is still on-treatment, i.e., has not yet discontinued for any reasons?

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? (see Section 2.1)

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.

12.4.2 Statistical model, hypothesis, 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) 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.

In addition, a separate summary for deaths including on-treatment and post-treatment deaths will be provided.

The number and the proportion (%) of participants with adverse events of special interest for remibrutinib (related to identified and potential risks) will be summarized.

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

All 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.

[redacted]

12.4.3 Handling of intercurrent events of primary estimand

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

- 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), 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. Data collected after these events will be used for analysis (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: Data collected after these events will be used for analysis (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/d 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 (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: Data collected after these events will be used for analysis (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: Data collected after these events will be used for analysis (Treatment policy strategy).

* Assessment of confounder BCRP will be specified in the SAP.

12.4.4 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.

12.4.5 Sensitivity analyses

If unexpectedly high incidence of adverse events of special interest (AESI) is observed, then sensitivity analysis may be performed for the AESI.

The following sensitivity analysis may be 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.

[redacted]

- Intake of strongly confounding prohibited medication (e.g., biologics treatment, cyclosporine, systemic corticosteroids): 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/d 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 (pitavastatin, rosuvastatin, sulfasalazine and ubrogepan): only measurements prior to intake of these medications will be used for analysis (While on treatment strategy).

* Assessment of confounder BCRP will be specified in the SAP.

12.4.6 Supplementary analysis

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

12.5 Analysis supporting secondary objectives

This section will detail the statistical analysis of the secondary (efficacy) estimands (see Section 2.2).

12.5.1 Efficacy and/or Pharmacodynamic endpoints

Definition of secondary endpoints

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 at Week 12 after treatment in adult participants with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second-generation H1-antihistamine, regardless of treatment discontinuation for any reason or intake of a different second-generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication use as an unfavorable outcome?

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.

Other secondary endpoints are listed in the Table 2-1.

Statistical model, hypothesis, and method of analysis

The secondary (efficacy) variables during the study, including absolute change from baseline in UAS7 score at Week 12, will be summarized (by visit, if applicable).

Baseline for efficacy 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.

[redacted]

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.

The analyses will be performed based on the data after the missing data imputation for the intercurrent events have been performed.

Handling of intercurrent events of secondary estimand

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

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

- 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, cyclosporine after Week 8, systemic corticosteroids after Week 8): 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, or non-response for binary endpoints) (Composite strategy (irrespective of potential occurrence of other intercurrent events)).
- 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).

Handling of missing values not related to intercurrent event

The UAS7 score is derived from the sum of the HSS7 score and the ISS7 score. The HSS7 and ISS7 score will be derived by adding up the daily HSS and ISS scores of the 7 days preceding the visit, respectively. The daily score (HSS and ISS) will be calculated by averaging the morning and evening HSS and ISS score, respectively. 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.

For each weekly score from the UPDD (i.e., HSS7, ISS7), if one or more of the daily scores are missing, the following principles will be applied to handle the missing data:

- The weekly UAS7 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 (morning or evening) scores within the 7 days prior to the study visit, 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.

[redacted]

- If there are less than 4 non-missing daily scores within the prior 7 days, then the weekly score for HSS or ISS will be considered as missing for that week. Accordingly, no UAS7 can be calculated.

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.

Sensitivity analyses

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

Supplementary analyses

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

12.5.2 Safety endpoints

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).

Adverse events

See the Section 12.4.

Vital signs

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

12-lead ECG

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

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

Clinical laboratory evaluations

All laboratory data will be listed by participant and visit and if normal ranges are available abnormalities will be flagged. Summary statistics for the change from baseline will be provided by visit. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

[redacted]

[redacted]

Dermatology Life Quality Index (DLQI)

An overall score will be calculated according to the scoring manual.

For DLQI total score, summary statistics will be provided for absolute change from baseline as well as for percent change from baseline by visit.

The proportion of participants achieving DLQI = 0-1 will be provided by visit.

Angioedema Activity Score (AAS)

For AAS7 score, summary statistics will be provided for absolute change from baseline as well as for percent change from baseline over time, in participants with angioedema at baseline (AAS7 >0) and in all participants.

The proportion of participants achieving AAS7 = 0 will be provided over time.

The cumulative number of weeks achieving AAS7 = 0 response between baseline and Week 12 will be derived based on the AAS eDiary and UPDD diary. A weekly AAS7 score will be derived by adding up the daily scores of the 7 days preceding the visit, and ranges from 0 to 105. If the AAS7 assessment is missing, it will be considered as a non-response for the cumulative number of weeks that participants achieve AAS7 = 0 response calculation.

For angioedema burdened days, summary statistics will be provided for absolute change from baseline as well as for percent change from baseline over time.

[redacted]

[redacted]

12.7 Interim analyses

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. Timing of this interim analysis may be changed from Week 24 depending on the time of the submission, and will be documented in the SAP.

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

12.8 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

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screened in order to collect approximately 70 participants who enter the treatment period and to collect a total of approximately 60 completed participants.

12.8.1 Primary endpoint

Not applicable.

12.8.2 Secondary endpoints

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

[redacted]

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk-based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures, and are performed according to written Novartis processes.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication
- Individual study results - after CSR publication
- Trial Feedback Questionnaires - 3 timepoints: at the start, during and at the end of the trial.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

[redacted]

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following specific criteria have been identified for this study. Should these criteria be met, a re-test must be done within 5 days after the first assessment. Discontinuation of the study treatment should be considered if the abnormal hematology parameter is confirmed:

- Hemoglobin: < 10 g/dl
- Platelets: < 75 000/mm3
- Leukocytes: < 3 000/mm3
- Neutrophils: < 1 500/mm3

For all other laboratory assessments, the central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory report (which the investigator should review and sign-off) and the investigator will report any values considered clinically significant in the eCRF.

Refer to Section 16.2 for clinically notable laboratory values for hepatotoxicity.

Refer to Section 16.3 for clinically notable laboratory values for nephrotoxicity.

Notable values for vital signs and change from baseline will be summarized.

Notable values are defined as follows:

- heart rate of < 50 or > 100 bpm
- systolic blood pressure of < 90 and ≥ 140 mmHg
- diastolic blood pressure of < 60 and ≥ 90 mmHg.

For ECGs, a notable QTc value is defined as an absolute QTc (Fridericia's) interval of greater than 450 ms for males or greater than 460 ms for females QTcF increase of ≥60 ms compared to baseline QTcF value – all such ECGs will be flagged by the central CRO's cardiologist and require assessment for clinical relevance by the investigator.

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16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ULN: upper limit of normal

Table 16-2 Follow up requirements for liver laboratory triggers: ALT, AST and TBL

		Action Taken		
Trigger	**Liver Symptoms**	**Monitoring**	**Follow-up Monitoring**	**Study Medication**
ALT				
ALT > 3 ULN TBL normal, or no change for participants with Gilbert's syndrome	None	Measure ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH in 48-72 hours	Follow up for symptoms	Continue dosing
ALT > 5 x ULN for more than two weeks TBL normal, or no change for participants with Gilbert's syndrome	None	Measure ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH in 48-72 hours	Follow-up for symptoms Initiate close monitoring and workup for competing etiologies	Interrupt Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline
ALT > 8 x ULN TBL normal, or no change for participants with Gilbert's syndrome	None	Measure ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH in 48-72 hours	Follow-up for symptoms Initiate close monitoring and workup for competing etiologies	Interrupt Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline
ALT > 3 x ULN TBL > 2 x ULN (or INR > 1.5) For patients with	None	Measure ALT, AST, ALP, GGT, TBL, INR, albumin, CK,	Follow-up for symptoms Initiate close monitoring and	Interrupt Study drug can be restarted only if another etiology is

[redacted]

		Action Taken		
Trigger	**Liver Symptoms**	**Monitoring**	**Follow-up Monitoring**	**Study Medication**
Gilbert's syndrome: Doubling of direct bilirubin		and GLDH in 48-72 hours	workup for competing etiologies	identified and liver enzymes return to baseline
ALT > 3 x ULN TBL normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	Measure ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH in 48-72 hours	Follow-up for symptoms Initiate close monitoring and workup for competing etiologies	Interrupt Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline
Total Bilirubin (isolated)				
>1.5 – 3.0 ULN		Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[1] to ≤ Grade 1 or to baseline	Continue dosing
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)		Repeat LFT within 48-72 hours Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution[1] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)	Interrupt
> 10 x ULN		Hospitalize the participant Establish causality Record the AE and contributing factors(e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[1] (frequency at investigator discretion)	Discontinue treatment immediately
General Clinical Symptoms				
Any AE potentially indicative of a liver toxicity including: (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia		Establish causality Record the AE and contributing factors(e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion	Consider study treatment interruption or discontinuation

[1] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death

Alb: Albumin, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CK: Creatinine kinase, CRF: Case report form, GGT: Gamma-glutamyl transferase, GLDH: glutamate dehydrogenase, INR: International Normalized Ratio, LFTs: Liver function tests, Med Hx: medical history, PT: Prothrombin time, TBL: Total bilirubin, ULN: upper limit of normal

[redacted]

Table 16-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 - 3.0 ULN	- Maintain treatment- Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 (≤ 1.5 ULN) or to baseline
> 3 - 10 x ULN (in the absence of known Gilbert syndrome)	- Interrupt treatment - Repeat LFT within 48-72 hours - Hospitalize if clinically appropriate - Establish causality - Record the AE and contributing factors(e.g., conmeds, med hx, lab) in the appropriate CRF	- Monitor LFTs weekly until resolution to ≤ Grade 1 (≤ 1.5 ULN) or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) - Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	- Discontinue the study treatment immediately - Hospitalize the participant - Establish causality - Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity	- Consider study treatment interruption or discontinuation - Hospitalization if clinically appropriate- Establish causality- Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

[redacted]

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow -up within 2-5 days; increase fluid intake before assessment if appropriate • Repeat follow-up (every 2-5 days) until creatinine is <125% of baseline value
Serum creatinine increase ³ 50 % [1]	• Consider causes and possible interventions and initiate renal investigation • Repeat assessment within 24-48 h if possible • Interruption of study drug • Close follow-up (every 24-48 h), consider participant hospitalization and specialized treatment until creatinine is <125% of baseline value
New onset dipstick proteinuria ≥ 3[1]	• Consider causes and possible interventions
When urine proteins are measured as a follow-up of positive urine dipstick measurements:Protein-creatinine ratio (PCR) ≥ 1 g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3[1] on urine dipstick	• Assess and document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[1] Corresponds to KDIGO criteria for Acute Kidney Injury

Whenever a renal event is identified, a detailed participant history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, eg, dehydration due to delirium, tumor lysis

[redacted]

Table 16-5 Renal event follow-up

FOLLOW-UP OF RENAL EVENTS
Assess, document and record in the CRF: • Urine dipstick and sediment microscopy evidence of Drug-Induced Nephrotoxicity (DIN): crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
Monitor participant regularly (frequency at investigator's discretion) until: • Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.
Analysis of urine markers in samples collected over the course of the DIN event