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Novartis Research and Development

Clinical Trial Protocol Title:

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

Clinical Trial Protocol Number: CLOU064A2305 / NCT05795153

Version Number: 00 (Original Protocol)

Compound: LOU064

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

Study Phase: III

Sponsor Name: Novartis

Regulatory Agency Identifier Numbers: EudraCT - 2022-002838-13, IND-131325

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1 Protocol summary

1.1 Summary

Protocol Title:

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

Brief Title:

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

Purpose:

The purpose of this study is to assess the effect of remibrutinib 25 milligrams (mg) b.i.d. open label on systolic blood pressure (SBP) measured as a change in 24-hour average SBP from baseline to Week 4 assessed by ambulatory blood pressure monitoring (ABPM); and to evaluate the overall safety and efficacy over 12 weeks in participants with chronic spontaneous urticaria (CSU) inadequately controlled by H1-antihistamines (H1-AH).

Study Indication /Medical Condition:

Chronic spontaneous urticaria (CSU)

Treatment type:

Drug

Study type:

Interventional

Table 1-1 Objectives, Endpoints, and Estimands

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

• To evaluate changes in daytime and nighttime average SBP over Week 4	• The change in the measured ABPM daytime and nighttime weighted average SBP at Week 4
• To evaluate changes in daytime and nighttime average DBP at Week 4	• The change in the measured ABPM daytime and nighttime weighted average DBP at Week 4
• To evaluate the safety and tolerability of remibrutinib 25 mg b.i.d.	• Occurrence of treatment emergent adverse events and serious adverse events (SAEs) during the study, evaluation of laboratory and vital signs data

Trial Design:

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

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

At the end of the treatment phase, participants have the option to continue in an extension study (CLOU064A2303B) if approved in the country and at the site.

This study will be included in the program level 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.

Brief Summary:

The primary objective of the study is to rule out an increase of >3mmHg in 24-hour average Systolic Blood Pressure at steady state (Week 4) compared to baseline. ABPM was chosen for the blood pressure assessment in this trial as recommended by the FDA for drugs intended for chronic use (Assessment of Pressor Effects of Drugs Guidance for Industry (FDA 2022)). It allows the observation over a 24-hour period and the measure of an individual's blood pressure throughout an entire day. This ABPM study will be performed in a patient population similar to the ongoing Phase 3 studies.

The study duration will be up to 20 weeks. The treatment duration will be up to 12 weeks and the visit frequency will be once every 4 weeks with additional 2 visits for application of the ABPM device before baseline and Week 4 visits.

Treatment of interest:

Participants will be treated with remibrutinib 25 mg b.i.d.

Number of Participants:

Approximately, 136 participants will be enrolled in the study.

Key Inclusion criteria:

- Signed informed consent must be obtained prior to participation in the study
- Male and female adult participants ≥ 18 years of age
- 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-AH 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-AH during this time period.
  - Weekly Urticaria Activity Score (UAS7) score (range 0-42) ≥ 16, Weekly Itch Severity Score (ISS7) score (range 0-21) ≥ 6 and Weekly Hives Severity Score (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 (Day 1); 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 two missing UPDD entry (either morning or evening) in the 7 days prior to baseline (Day 1).

Key Exclusion criteria:

- Participants unable to tolerate 24-hour ambulatory blood pressure measurement using automatic ABPM device
- Ongoing or past history of hypertension and/or SBP ≥140 or ≤90 OR DBP ≥90 or ≤60 mmHg at screening
- Known history or evidence of ongoing alcohol or drug abuse within the last 6 months before baseline (Day 1)
- Participants working night shifts
- Participants with an arm circumference greater than 50cm
- Participants taking/requiring medications prohibited by the protocol (including those known to interfere with blood pressure assessments in the study)
- [redacted]
- [redacted]
- Evidence of clinically significant cardiovascular, 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

Treatment Groups:

All participants will receive open-label remibrutinib 25 mg b.i.d.

Data Monitoring/Other Committee:

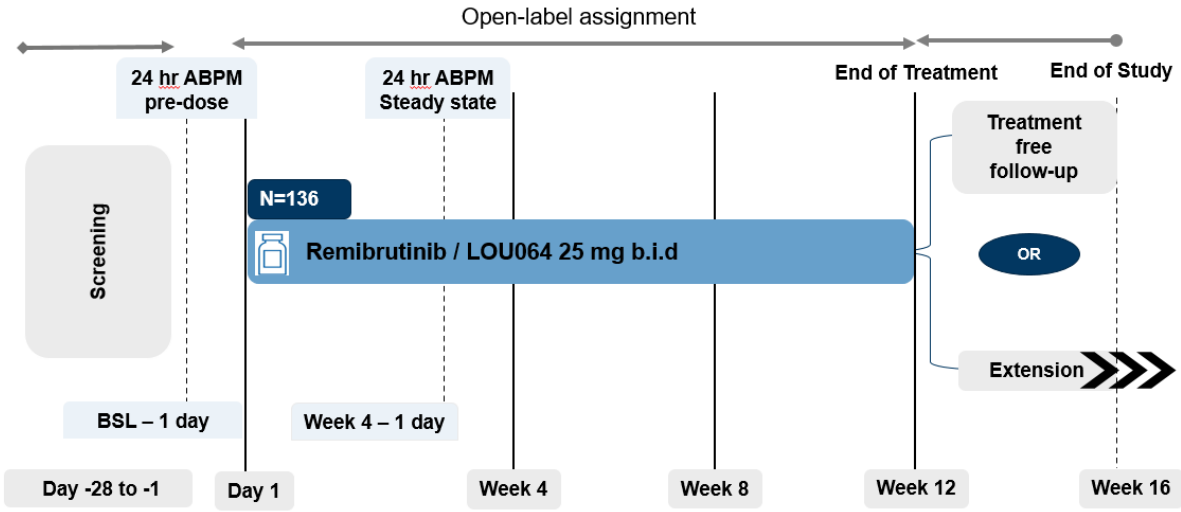
Yes (see Section 10.1.4 Committees Structure)

Key words

BTK inhibitor; Ambulatory Blood Pressure Monitoring, Chronic spontaneous urticaria; Urticaria activity score; Hives severity score; Itch severity score

1.2 Schema

Figure 1-1 Study Design



N= Number of treated participants; **BSL**: Baseline; **hr**: hour; **ABPM**: Ambulatory Blood Pressure Monitoring; **b.i.d**.: twice a day.

1.3 Schedule of activities (SoA)

The SoA lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. 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.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment are to complete the end of treatment visit as soon as possible, and attend the follow-up visit as indicated in the SoA.

Participants who discontinue from study 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 events and concomitant medications not previously reported must be recorded on the case report form (CRF).

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural and man-made disaster or geopolitical instability, 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 allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the investigator delegates tasks to an off-site healthcare professional, the investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-2 Assessment Schedule

Period	Screening		Treatment						Follow-up /End of Study	Unscheduled visit
Visit Name	Screening Visit 1[1]	Screening Visit 2	Baseline	Week 4 -1 day	Week 4[1]	Week 8	Week 12/ End of Treatment	Early Treatment Discontinuation	Week 16	Unscheduled visit
Days	-28 to -1	-4 to -1	1	28	29	57	85	-	113	-
Informed consent	X									
[redacted]										
IRT transaction	X		X		X	X	X	X		
Inclusion / Exclusion criteria	X	X	X							
Demography	X									
Pregnancy and assessments of fertility[2]	S		S		S	S	S	S	S	S
Evidence of urticaria	S									
Hepatitis screen[3]	X									
Relevant medical history	X									
CSU History and prior urticaria treatment	X									
Cardiovascular history	X									
Family malignancy history (CRF to be completed if participant develops malignancy during the study)	X	X	X	X	X	X	X			X
Physical Examination[4]	S	S	S	S	S	S	S	S	S	S
Vital Signs	X	X	X	X	X	X	X	X	X	X
Height and Weight[5]	X						X			X
Electrocardiogram (ECG)	X		X		X		X			X

Period	Screening		Treatment						Follow-up /End of Study	Unscheduled visit
Visit Name	Screening Visit 1[1]	Screening Visit 2	Baseline	Week 4 -1 day	Week 4[1]	Week 8	Week 12/ End of Treatment	Early Treatment Discontinuation	Week 16	Unscheduled visit
Days	-28 to -1	-4 to -1	1	28	29	57	85	-	113	-
Dispense participants' eDiary[6]	S									
Subject's eDiary review[7]	[redacted]									
[redacted]										
Study drug dispensation			X		X	X				
Background medication dispensation and compliance assessment[9]	X	X	X	X	X	X	X	X	X	X
Rescue medication dispensation and usage	X	X	X	X	X	X	X			
[redacted]										
Clinical Chemistry	X		X		X		X	X	X	X
Hematology	X		X		X		X	X	X	X
[redacted]										
Urinalysis	X		X		X		X	X	X	X
[redacted]										
Hepatitis B re-activation monitoring[11]			X		X	X	X	X	X	X
[redacted]										
ABPM device installation		X		X						
ABPM device return			X		X					
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X

Period	Screening		Treatment						Follow-up /End of Study	Unscheduled visit
Visit Name	Screening Visit 1[1]	Screening Visit 2	Baseline	Week 4 -1 day	Week 4[1]	Week 8	Week 12/ End of Treatment	Early Treatment Discontinuation	Week 16	Unscheduled visit
Days	-28 to -1	-4 to -1	1	28	29	57	85	-	113	-
Adverse Events	X	X	X	X	X	X	X	X	X	X
HIV screen[13]	X									

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Participant to come fasting for ≥8 hours (h) (ideally overnight) for Screening Visit 1 and Week 4.
[2] Serum pregnancy test and fertility assessment will be done at Screening. Urine pregnancy test to be completed every 4 weeks by WoCBP from Day 1 through to Study completion visit. Any positive or undetermined test result must be confirmed by a serum pregnancy test done by central lab and results received electronically. In the case that participant cannot visit the site an alternative (local lab) can be used. Urine pregnancy results are reported as source.
[3] To include Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV)
[4] Complete physical exam at screening, short physical exam at all subsequent visits
[5] Height collected at screening visit only
[6] Participants eDiary will be returned to site at either Week 12 or study discontinuation
[7] [redacted]
[redacted]
[9] 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 Follow-up visit only compliance to be checked
[redacted]
[11] Hepatitis B re-activation monitoring only for participants who were Hepatitis B virus surface antigen (HBsAg) negative and HBcAb (anti-HBc) positive with a negative HBV Deoxyribonucleric Acid (DNA) test at Screening.
[redacted]
[13] Optional, depending on local requirements

2 Introduction

2.1 Study rationale

The purpose of this study is to assess the effect of remibrutinib 25 mg b.i.d. open label on SBP measured as a change in 24-hour weighted average SBP from baseline to Week 4 assessed by ambulatory blood pressure monitoring (ABPM); and to assess overall safety and efficacy over 12 weeks in participants with chronic spontaneous urticaria (CSU) inadequately controlled by H1-AH.

2.2 Background

CSU, also known as Chronic Idiopathic Urticaria (CIU), is defined as the spontaneous occurrence of itchy wheals (hives), angioedema or both, lasting for at least 6 weeks (Zuberbier et al 2014, Saini, Kaplan 2018, Zuberbier et al 2021). 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 disease activity states of CSU are commonly defined as complete control, well controlled, mild, moderate and severe (Stull et al 2017).

Second generation H1-AH are recommended as first-line treatment for patients with CSU, including up-titration to 4-fold the approved dose (Zuberbier et al 2021). Omalizumab is an effective second-line therapy for CSU patients as an add-on therapy to antihistamines at the licensed dose of 300 mg every 4 weeks subcutaneously (Zuberbier et al 2021). Cyclosporine, as a 3rd line option, is an immunosuppressive drug associated with a high incidence of adverse effects (Zuberbier et al 2021). Finally, short courses of systemic corticosteroids are sometimes added to the treatment regimen, but they are not recommended for long-term use due to the well-known adverse effects. Therefore, there is a high unmet medical need for new treatment options for CSU patients inadequately controlled by H1-AH.

Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase and member of the TEC kinase family and is expressed in selected cells of the adaptive and innate immune systems. BTK is indispensable for signaling through the Fc epsilon receptor (FcεR1 for IgE), the activating Fc gamma receptors (FcγR for IgG) and the B cell antigen receptor (BCR), important signaling nodes in the activation/degranulation of B cells, macrophages, mast cells or basophils (Rip et al 2018). Targeting BTK is regarded as a promising new approach for the treatment of various immunomediated conditions, including CSU. BTK inhibitors (BTKi) like ibrutinib were first approved for the treatment of B cell malignancies (Hendriks et al 2014) and certain safety concerns are described for one or more of the compounds: risk of infections, potential myelomodulating effects, risk for bleeding and also, for ibrutinib, cardiovascular effects, including cardiac failure and hypertension. Notably, the risk of hypertension has not been seen with newer more selective approved BTK inhibitors, acalabrutinib and zanubrutinib. Based on the current understanding, effects on cardiovascular system with ibrutinib, including hypertension and cardiac failure could be explained by off-target kinase inhibition effects, e.g., blocking ERBB2/HER2 by ibrutinib results in cardiomyocyte dysfunction and reduced heart contractile efficiency (Estupiñán et al 2021).

Remibrutinib is a low molecular weight compound for oral administration that covalently binds and inhibits BTK with high selectivity (Angst et al 2020, Gabizon, London 2020). Remibrutinib is seen to offer a novel therapeutic approach for patients with CSU and is currently being investigated in two pivotal Phase 3 clinical trials (CLOU064A2301 and CLOU064A2302) with treatment duration up to 52 weeks. In completed (CLOU064A2201) and interim analysis of an ongoing open-label extension (CLOU064A2201E1) Phase 2 remibrutinib clinical studies in CSU (which allowed inclusion of patients with medical history of hypertension), no safety concern on elevated blood pressure was noted in the analysis of adverse events and vital signs.

Elevated blood pressure increases the risk of adverse cardiovascular events and death and characterizing the off-target blood pressure effects of drugs became an important component of regulatory benefit-risk assessment and post-marketing clinical decision-making. In February 2022, the US Food and Drug Administration (FDA) released revision 1 of the draft Assessment of Pressor Effects of Drugs Guidance for Industry intended to advise sponsors on the premarketing assessment of a drug's effect on blood pressure. In the draft Guidance, FDA recommends the use of ambulatory blood pressure (BP) monitoring (ABPM) rather than routine clinic blood pressure measurement for drugs intended to be used chronically (12 weeks or more) as ABPM provides more accurate measurements of BP throughout the day. This study is planned to address the question of the potential pressor effect of remibrutinib 25 mg b.i.d on BP, as assessed by measuring the change in 24-hour average SBP between baseline and at Week 4 as assessed by ABPM.

2.3 Benefit/Risk assessment

Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase that is indispensable for FcεR1 signaling and a central signaling kinase in mast cell activation. In Phase 1, remibrutinib was well-tolerated at all doses without any dose-limiting toxicity (DLT) and showed encouraging blood and skin pharmacodynamics with a favorable safety profile. The Phase 2b clinical trial CLOU064A2201 demonstrated clinical efficacy of remibrutinib in the treatment of CSU patients with a fast onset of action and a favorable safety profile. Based on these data, 25 mg b.i.d. has been selected as the optimal dosing regimen for the Phase 3 trials. 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. 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. Furthermore, the oral route of administration of remibrutinib offers additional convenience compared to injectable biologics.

The available clinical safety experience has demonstrated favorable safety and tolerability of remibrutinib. [redacted]

In the final analysis of the Phase 2b trial CLOU064A2201 in patients with CSU, 309 participants (safety set) 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. Serious events reported with remibrutinib were rare (1.9%), and no deaths were reported. Remibrutinib was also well tolerated with AEs leading to discontinuation being also rare, reported in 2.6% of patients receiving any remibrutinib. The most frequent adverse events were reported in System Organ Classes (SOC) Infections and infestations (24.0% any remibrutinib dose 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%). Overall, AEs by SOC were balanced between any remibrutinib and placebo groups, with the exception of SOC Skin and subcutaneous tissue disorders - the difference in this SOC was primarily driven by events of chronic spontaneous urticaria (see below). The most frequent AEs (defined by MedDRA (Medical dictionary for regulatory activities) 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 chronic spontaneous urticaria were flares primarily reported by participants during the treatment-free follow-up period)

In interim analysis 2 (IA2; cut-off May-2021) of the ongoing Phase 2b long-term open-label extension trial CLOU064A2201E1 data from 183 CSU patients enrolled with a median exposure to remibrutinib 100 mg b.i.d. of 35.14 weeks showed 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%), Coronavirus disease 2019 (COVID-19) (4.9%), and diarrhea (4.9%). No notable trends in vital signs, including assessment of SBP and DBP values was evident.

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), [redacted]. No major concerns with regards to the mentioned risks was notable in remibrutinib completed and ongoing clinical trials to date, including long-term exposure in Phase 2b open-label extension study CLOU064A2201E1. Corresponding eligibility and monitoring criteria are set to safeguard participants in this clinical trial. 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 macroglobulinemia), 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).

Women of child-bearing potential and sexually active males 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 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 current Investigator Brochure (IB).

In summary, CSU patients with inadequate response to H1-AH (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 effects of remibrutinib on BP. Risks mentioned above 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.

3 Objectives, endpoints, and estimands

Table 3-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoints for primary objective**
• To rule out an increase of >3mmHg in 24-hour average SBP at steady state (Week 4) compared to baseline, measured by ABPM.	• the change in the ABPM-measured 24-hour weighted average SBP at Week 4 compared to baseline
Secondary objectives	**Endpoint(s) for secondary objectives**
• To evaluate changes in 24-hour average SBP at steady state (Week 4) compared to baseline	• the change in the ABPM-measured 24-hour weighted average SBP at Week 4 compared to baseline
• To evaluate changes in 24-hour average DBP at steady state (Week 4) compared to baseline	• the change in the measured ABPM 24-hour weighted average DBP at Week 4 compared to baseline
• To evaluate changes in daytime and nighttime average SBP at 4 weeks.	• the change in the measured ABPM daytime and nighttime weighted average SBP at Week 4
• To evaluate changes in daytime and nighttime average DBP at 4 weeks.	• the change in the measured ABPM daytime and nighttime weighted average DBP at Week 4
• To evaluate the safety and tolerability of remibrutinib 25 mg b.i.d.	• Occurrence of treatment emergent adverse events and serious adverse events (SAEs) during the study, evaluation of laboratory and vital signs data

Objectives	Endpoints
[redacted]	

3.1 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).

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

The primary estimand is described by the following attributes:

1. **Population**: participants without ongoing or past history of hypertension and with 90< SBP <140mmHg, 60< DBP<90 mmHg at screening, with inadequately controlled CSU despite treatment with second generation H1-AH who have CSU duration ≥ 6 months, a UAS7 score ≥ 16, ISS7 ≥ 6 and HSS7 score ≥ 6 in the last 7 days prior to Baseline (Day 1).
2. **Endpoint:** change from baseline in 24-hour weighted average SBP at Week 4.
3. **Treatment of interest:** the study treatment (remibrutinib 25 mg b.i.d.).
4. **Summary Measurement**: the mean change from baseline.
5. **Handling of intercurrent events**:
    - Discontinuation of study treatment due to any reason prior to Week 4: participants will be excluded from the analysis
    - Intake of prohibited antihypertensive treatment prior to Week 4 (see Section 6.8.2): Composite strategy (irrespective of potential occurrence of other intercurrent events). Measurements after this event will be excluded from the analysis and will be imputed using an increase of 3mmHg in 24-hour average SBP from baseline at Week 4.

3.2 Secondary estimands

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

The secondary estimand attributes are identical to the ones described in Section 3.1.

Secondary estimand on the secondary endpoints

Similar Estimand approach will be implemented for Change from baseline in 24-hour weighted average DBP at Week 4 as for Change from baseline in 24-hour weighted average SBP at Week 4.

Similar Estimand approach will be implemented for Change from baseline in daytime weighted average SBP at Week 4 as for Change from baseline in daytime weighted average SBP at Week 4.

Similar Estimand approach will be implemented for Change from baseline in nighttime weighted average SBP at Week 4 as for Change from baseline in nighttime weighted average SBP at Week 4.

Similar Estimand approach will be implemented for Change from baseline in daytime weighted average DBP at Week 4 as for Change from baseline in daytime weighted average DBP at Week 4.

Similar Estimand approach will be implemented for Change from baseline in nighttime weighted average DBP at Week 4 as for Change from baseline in nighttime weighted average DBP at Week 4.

4 Study design

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

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

At the end of the treatment phase, participants have the option to continue in an extension study (CLOU064A2303B) if approved in the country and at the site.

4.1 Overall design

Refer to Section 1.2 Schema for study design figure.

All participants will be on a stable, local label-approved standard dose of a second generation H1-AH ("background therapy") throughout the entire study (starting at screening until the end of the study). In addition to that, to treat unbearable symptoms of potential CSU flares, participants will be allowed to use another second generation H1-AH on an as-needed basis ("rescue therapy").

Screening period:

The screening period of up to 4 weeks allows for the assessment of eligibility, determination of baseline disease activity and wash-out of prohibited medications (please see prohibited medications Table 6-4 and Table 6-5).

Treatment period:

At baseline, all eligible participants will be assigned to **remibrutinib 25 mg b.i.d.**: After a baseline 24 hour ABPM measurement, all participants will receive remibrutinib 25 mg b.i.d. for 12 weeks.

Participants who complete the treatment period at Week 12 are invited to roll-over to the Phase 3 extension study CLOU064A2303B, where they, if eligible, enter Epoch 2 of the extension study.

Participants who do not roll over to the extension study proceed to the follow-up period.

Follow-up period:

There will be a 4-week, treatment-free, safety follow-up period (for patients who do **not** roll-over to the extension study CLOU064A2303B).

Remote procedures:

Not applicable

4.2 Scientific rationale for study design

The primary objective of the study is to rule out an increase of >3mmHg in 24-hour average SBP at steady state (Week 4) compared to baseline, as assessed by evaluation of change from baseline in 24-hour average SBP pressure at Week 4 measured by ABPM.

This Phase 3 study is based on prior experience with remibrutinib in completed and ongoing studies in adult CSU patients. The analysis of the Phase 2b dose-range finding study CLOU064A2201 demonstrated that treatment with remibrutinib 25 mg b.i.d. over 12 weeks substantially improved the signs and symptoms of CSU compared to placebo, in participants who have not adequately responded to prior treatment with H1-AH and other CSU therapies. No safety signals on mean increase of SBP or DBP was notable in this study. One Phase 2 extension study (CLOU064A2201-E1) and two Phase 3 randomized, placebo-controlled studies (CLOU064A2301 and CLOU064A2302) are ongoing to confirm and further evaluate the efficacy and safety of remibrutinib at a dose of 25 mg b.i.d. given up to 52 weeks in adult CSU patients.

ABPM was chosen for the blood pressure assessment in this trial as recommended by the FDA for drugs intended for chronic use (Assessment of Pressor Effects of Drugs Guidance for Industry (FDA 2022)). It allows the observation over a 24-hour period and the measure of an individual's blood pressure throughout an entire day besides other benefits. Since ABPM studies with duration shorter than 12 weeks suggest there is little or no change on placebo, it is not required to have a placebo group in this proposed short duration study. The ABPM study will be performed in a patient population similar to the ongoing Phase 3 studies. Participants will be treated for 12 weeks to enable an assessment of the treatment response to evaluate the benefit risk for each patient for the optional long-term treatment in the extension study.

4.3 Justification for dose

The analysis of the Phase 2b dose-range finding study CLOU064A2201 demonstrated that treatment with remibrutinib 25 mg b.i.d. substantially improved the signs and symptoms of CSU compared to placebo, in participants who have not adequately responded to prior treatment with H1-AH and other CSU therapies. One Phase 2 extension study (CLOU064A2201-E1) and two Phase 3 randomized, placebo-controlled studies (CLOU064A2301 and CLOU064A2302) are ongoing to confirm and further evaluate the efficacy and safety of remibrutinib at a dose of 25 mg b.i.d. in adult CSU patients.

Based on the safety data from the completed and ongoing remibrutinib trials, the clinical safety profile of remibrutinib is favorable and supported the whole dose range studied in the Phase 2 program (10mg q.d.-100mg b.i.d.), including the selected dose of 25 mg b.i.d. In the final analysis [redacted] In

addition, the clinical safety data from the completed [redacted]
For more detailed information on the safety profile of remibrutinib, see protocol (Section 2.3) and the LOU064 IB. In the [redacted] 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. [redacted]

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. [redacted]

4.3.1 Rationale for choice of background therapy

Second-generation H1-AH are chosen as background medication. Considering the add-on remibrutinib therapy, this reflects the current treatment guidelines, which recommend to add a second or third-line therapy to H1-AH background therapy in CSU patients who are not adequately controlled by H1-AH (Zuberbier et al 2021).

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

Not applicable

4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster and man-made disaster or geopolitical instability), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. 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.

4.6 Purpose and timing of interim analyses/design adaptations

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

4.7 End of study definition

Study completion is defined as when the last participant finishes their last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator.

5 Study population

The study population will consist of approximately 136 adult participants with CSU inadequately controlled by second generation H1-AH.

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 adult 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-AH 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-AH 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 (Day 1); or documented in the participants` medical history).
6. Willing and able to complete an Urticaria Patient Daily Diary (UPDD) for the duration of the study and adhere to the study protocol.
7. Participants must not have had more than two 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.

1. Use of other investigational drugs within 5 half-lives or within 30 days (for small molecules) prior to Screening or until the expected pharmacodynamic (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.
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.
5. Ongoing or past history of hypertension and/or SBP ≥140 or ≤90 and/or DBP ≥90 or ≤60 mmHg at screening.
6. Participants unable to tolerate 24-hour ambulatory blood pressure measurement prior to baseline.
7. Participants with an arm circumference greater than 50cm.
8. Other diseases with symptoms of urticaria or angioedema, including but not limited to urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary angioedema, or drug-induced urticaria.
9. 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.
10. Participants taking/requiring medications prohibited by the protocol (see Table 6-4 and Table 6-5).
11. Known history or evidence of ongoing alcohol or drug abuse within the last 6 months before baseline (Day 1).
12. Participants working night shifts.
13. 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.
14. Pregnant or nursing (lactating) women.
15. 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 the last dose of study drug). 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 6 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, or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral or hormonal contraception, women should have been stable on the same pill or medication for a minimum of 3 months before taking investigational drug.

Women 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 tubal ligation at least 6 weeks ago. In the 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 ICF.

16. Major surgery within 8 weeks prior to screening or planned surgery for the duration of the study.
17. History of live attenuated vaccine use within 6 weeks prior to baseline (Day 1) or requirement to receive these vaccinations at any time during the study.
18. 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 ongoing 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.
19. Uncontrolled disease states, such as asthma, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids.
20. Hematology parameters at screening:
    - Hemoglobin: < 10 g/dl
    - Platelets: < 100 000/mm^3
    - Leucocytes: < 3 000/mm^3
    - Neutrophils: < 1 500/mm^3
21. Significant bleeding risk or coagulation disorders.
22. History of gastrointestinal bleeding.

[redacted]

25. 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.
26. History of renal disease, creatinine level above 1.5x ULN, or estimated Glomerular Filtration Rate (eGFR) <45 milliliters (ml)/min (using the Cockcroft-Gault equation) at screening.
27. Evidence of an ongoing Hepatitis C infection (e.g., defined by the detection of HCV-RNA at screening) and/or an ongoing Hepatitis B infection (defined by the detection of HBsAg and/or HBV-DNA at screening; participants who are positive for anti-HBc antibodies but who are negative for HBsAG and HBV-DNA can be included into the study if they agree to monitoring for HBsAg and HBV-DNA re-activation).
28. 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. HIV antigen/antibody tests will be performed to determine HIV status if required and allowed according to local regulations at screening.

5.3 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Participants who sign an informed consent form and are subsequently found to be ineligible prior to inclusion in the trial will be considered as screen failures. 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 during the screening period (see SAE Section 8.6.3 for reporting details). If the participant fails to be included, the investigator/ designated site personnel update the IRT system within 2 days of the screen fail that the participant was not included in the trial. Data and samples collected from participants prior to screen failure may still be analyzed.

Participants who are included in the trial and fail to start treatment, e.g., participants included in error, will be considered an early terminator. The reason should be recorded on the appropriate Case Report Form.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once (refer Section 8.1).

In the case where a safety laboratory assessment at screening and/or initial baseline is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to

inclusion. If the repeat value remains outside of the specified range, the participant must be excluded from the study. ABPM may be repeated, if initial assessment failed, within 4 days prior to baseline visit.

5.3.1 Replacement policy

Not applicable.

5.3.2 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 rescreened. The Participant No. consists of the Site Number (Site 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 rescreen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

5.4 Lifestyle considerations

For the duration of the study, participants should be informed and reminded of the restrictions outlined in this section. In general, it is recommended to avoid major changes in lifestyle, including avoiding the use and/or major change in the use of substances (See Section 5.4.1 below) or change in physical activities for the period of ABPM assessment (from Screening to Week 4).

5.4.1 Caffeine, alcohol, and tobacco

The intake of substances potentially affecting blood pressure should generally be avoided from the first (Screening Visit 2) until second (Week 4) ABPM measurements. Excessive use of alcohol or caffeine; use of certain substances, such as certain herbs, traditional medicine, cannabis or drugs for recreational use; are the examples of such substances and should be avoided. If the participant is consuming alcohol or caffeine (in the low-risk levels, e.g., according to local guidelines and practices) or is a smoker, the ongoing use of such substances, e.g., alcohol, or caffeine, or nicotine should not variate significantly during the study, particularly up until completion of the second ABPM measurement (Week 4).

5.4.2 Activity

No strenuous physical exercise (e.g., weight training, aerobics, football) until 24 hours before start and until the completion of ABPM measurement (both at Screening Visit 2 and Week 4-1 Day assessment).

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

Novartis Global Clinical Supply (GCS) will supply the following Investigational Medicinal Product (IMP) in the trial in appropriately labeled bottles:

Table 6-1 Investigational drug

Investigational Drug	Treatment Form or Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
LOU064 25 mg (remibrutinib)	Film coated tablets	Oral use	Open label, Patient specific kit	Novartis Pharma AG (global)

No other supplies apart from these will be provided by GCS.

6.1.1 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

Participants will continue to take their background therapy (H1-AH at local label-approved doses) with a stable regimen during the study (Section 6.8.1.1).

6.1.2 Treatment arms/group

All participants are assigned to remibrutinib.

6.1.3 Treatment duration

The planned treatment duration of the study is 12 weeks. Participants may discontinue from study treatment earlier at the discretion of the investigator or the participant, e.g., due to AEs (see Section 7) or lack/loss of efficacy. See Section 6.6 for information on continued access to study treatment after the end of the study.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under Table 6-1 Investigational drug section.

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 IRT and obtaining the medication number(s). 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 4.5, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster and man-made disaster or geopolitical instability 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's supply. In this case, regular phone calls or virtual contacts (every 2 weeks or more frequently if needed) will occur between the site and the participant 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 the participants can resume visits at the study site.

6.2.1 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 or designated site staff 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 site or remote monitoring visits, and at the completion of the trial.

If study treatment is administered at home, e.g. oral medication, participants will be asked to return all unused study treatment and packaging 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 Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.2.2 Handling of other treatment

Not applicable.

6.2.3 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 for the 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 usual morning/evening dosing. That dose should be omitted, and the participant should continue treatment with the next scheduled dose.

H1-AH taken either as background medication or as rescue medication, respectively, should be taken according to the locally labeled treatment instructions.

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

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

All participants will be assigned to remibrutinib 25 mg b.i.d.

At baseline visit (Day 1), all eligible participants will be included in the trial via Interactive Response Technology (IRT). The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a participant number to the participant, which is retained for the participant throughout his/her participation in the trial.

As this is an open-label study a separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

6.3.2 Treatment blinding

Not applicable.

6.3.3 Emergency breaking of assigned treatment code

Not applicable.

6.4 Study 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 pill

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.

6.4.1 Recommended treatment of adverse events

At present, there is insufficient information to provide specific recommendations regarding treatment of AEs apart from management of a significant bleeding event.

In case of a significant bleeding event, remibrutinib must be discontinued immediately. Please refer to the current version of IB for more details.

Medication used to treat AEs must be recorded on the appropriate eCRF.

6.5 Dose modification

Investigational study treatment dose adjustments and/or interruptions are not permitted.

6.5.1 Dose escalation guidelines

Dose adjustments are not foreseen in this study.

6.5.1.1 Starting dose

The dose level of remibrutinib 25 mg b.i.d., is foreseen for the whole study treatment duration.

6.5.2 Definitions of dose limiting toxicities (DLTs)

No dose-limiting toxicities were identified for remibrutinib. For the management of liver function test and renal function test abnormalities, refer to Table 10-2,Table 10-3, Table 10-4 and Table 10-5 as well as Section 10.5 and Section 10.6 respectively.

6.5.3 Dose modifications

Investigational or other study treatment dose adjustments are not foreseen in the study. For the management (including study treatment interruption and discontinuation) of liver function test and renal function test abnormalities, refer to Section 10.5 and Section 10.6 respectively.

Study treatment interruptions are permitted in order to manage the AEs if in the opinion of the investigator it is warranted to avoid risks resulting from the continuous study treatment administration in a trial participant. In such cases, study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be restarted after resolution of the safety risk. In addition, study treatment interruption is recommended in the following events/cases:

- [redacted].
- [redacted].

[redacted].

Study treatment interruptions (interruption date and re-start date) must be captured on the appropriate eCRF.

6.5.3.1 Dose adjustments for QTcF prolongation

In case of QTcF >500 msec or QTcF prolongation >60 msec from screening

- Assess the quality of the ECG recording and the QT value and repeat if needed
- Determine serum electrolyte levels (in particular hypokalemia, hypomagnesemia).
- Review concomitant medication use for other causes for QT prolongation (refer to qtdrugs.org for known QT prolonging drugs) and for drugs with the potential to increase the risk of drug exposure related QT prolongation i.e., concomitant use of CYP3A4 inhibitors.
- Check treatment compliance

After confirming ECG reading at site, if QTcF > 500 msec or QTcF prolongation >60 msec from screening

- Assess the benefit-risk of continued study treatment administration and evaluate if study treatment interruption is warranted
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed > 500 msec:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify clinical conditions that could potentially prolong the QT as per the ECG and QTc Clinical Safety Standards Guidelines.
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec
- After resolution to ≤ 480 msec and if the study treatment was interrupted, consider re-introducing treatment and increase ECG monitoring (i.e., at least every study visit):
  - If QTcF recurs > 500 msec, consult study medical monitor and evaluate benefit-risk for continued study treatment for the participant.

6.5.4 Follow-up for toxicities

Follow-up criteria for clinically notable laboratory values and vital signs is provided in Section 10.3. Follow up requirements for liver and renal events are provided in Section 10.5 and Section 10.6, respectively. For management of notable ECG abnormalities, see Section 6.5.3.1.

6.5.4.1 Follow up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 2 x baseline] OR [AST or ALT >3.0 U/L], whichever occurs first combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed to be the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, Gamma-glutamyl transferase (GGT), prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Perform relevant examinations (Ultrasound or Magnetic resonance imaging (MRI), Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule-out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis). The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-2 provides guidance on specific clinical and diagnostic assessments which can be performed to rule-out possible alternative causes of observed LFT abnormalities.

Table 6-2 Guidance on specific clinical and diagnostic assessments to be performed to rule-out possible alternative causes of observed Liver Function Tests (LFT) abnormalities

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, Mean Corpuscular Volume (MCV), CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 years old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes mellitus / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" (i.e., >50% likely), if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant" and thus, meet the definition of SAE and should be reported as a SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Continued access to study treatment after the end of the study

A Phase 3b extension study (CLOU064A2303B) will allow participants from CLOU064A2305 to join once they have received the last dose of study treatment.

6.6.1 Post trial access

Participants who complete participation in the 12-week treatment period of this trial may be eligible to receive remibrutinib as part of an open-label extension study if they meet the eligibility criteria defined in the extension study protocol.

The open-label extension will require endorsement in participating countries and sites as per local laws and regulations.

6.7 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 due to low solubility and highly under-proportional exposure increase at doses >100 mg b.i.d. 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, see IB.

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

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.

6.7.1 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 (EMA 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. Study treatment errors and uses outside of what is foreseen in the protocol, 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. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

Throughout the study, participants must take a second-generation H1-AH at a local label-approved standard dose (background therapy). For detailed information on the background medication, refer to the corresponding country-specific prescribing information. Even if up-titration is specified in the national prescribing information, this is not allowed per protocol. Background therapy should not be changed during the study.

All concomitant medication at screening will be recorded in the eCRF. 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 drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

Prior medication for treatment of CSU will be recorded in the eCRF. In addition to all concomitant medication at screening, prior medication that has been terminated within 4 weeks prior to screening will be recorded.

[redacted]

6.8.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed after enrollment.

Table 6-4 Prohibited medications (From Screening to EOS)

Medications	Prohibition period	Action taken during study
Biologics for treatment of CSU (including omalizumab and ligelizumab)	From screening until EOS	Discontinue biologic treatment and closely monitor for potential associated adverse events
Intravenous (i.v.)/Intramuscular (IM)/Intraarticular (IA) corticosteroids	From screening until EOS	Discontinue i.v./IM/IA corticosteroids if medically justifiable and closely monitor for potential associated adverse events. If

Medications	Prohibition period	Action taken during study
		discontinuation of i.v./IM/IA corticosteroids is not possible, discontinue study treatment.
Leukotriene antagonists (including montelukast and zafirlukast)	From screening until EOS	Discontinue Leukotriene antagonists and closely monitor for potential associated adverse events.
H2-antihistamines	From screening until EOS	Discontinue H2-antihistamines and closely monitor for potential associated adverse events.
First-generation antihistamines	From screening until EOS	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 screening until EOS	Discontinue all second-generation H1-AH 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	From screening until EOS	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	From screening until EOS	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 EOS	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 screening until EOS	Discontinue any therapy intended for the treatment of urticaria and closely monitor for potential associated adverse events.
[redacted]		

Medications	Prohibition period	Action taken during study
[redacted]		

Table 6-5 Prohibited medications (From Screening From screening until Week 4 ABPM assessment is completed)

Medications	Prohibition period	Action taken during study
Routine (more than 3 doses over a 5-day period) oral corticosteroids	From screening until Week 4 ABPM assessment is completed: Oral corticosteroids as an additional rescue therapy for CSU are NOT allowed Other preparations of corticosteroids with limited systemic exposure for non-CSU indications (e.g., intranasal or any topical corticosteroids) can be used on an as-needed basis.	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.
Herbal supplements (e.g., Ma Huang [ephedra], St. John's wort [with MAO inhibitors, yohimbine, arnica, ginseng, guarana]) with a BP effect	From screening until Week 4 ABPM assessment is completed	Discontinue any therapy with a BP effect and closely monitor for potential associated adverse events
[redacted]		

Medications	Prohibition period	Action taken during study
[redacted]		

6.8.3 Rescue medicine

H1-antihistamines: In addition to being used as background medication, second generation H1-AH are allowed as rescue medication, used on an as needed basis for participants with CSU flare-ups of unbearable symptoms.

For each individual participant, the H1-AH used as rescue medication must differ from the H1-AH used as background medication. The daily dose of H1-AH rescue medication should not exceed 4-fold of the approved dose, as recommended by the current Urticaria treatment guidelines (Zuberbier et al 2021). For detailed information on the rescue medication, refer to the corresponding national prescribing information. Rescue medication should not be used for 24 hours before and during the ABPM measurements.

Oral corticosteroids:

Participants will be permitted to use oral corticosteroids such as prednisone or its equivalents, as rescue medication if needed for CSU flare-ups of unbearable symptoms after the Week 4 ABPM assessment is completed. The selection of the oral corticosteroid to be used as rescue medication 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 5 days in a 30-day period and a maximum of 10 days during each (Re-)treatment period, to avoid chronic corticosteroid exposure and confounding suppression of signs and symptoms of CSU. The recommended dose is 20 - 50 mg prednisone or equivalent per day, as suggested by the current urticaria treatment guidelines (Zuberbier et al 2021).

Rescue medication will be sourced locally. Use of H1-AH rescue medication only for CSU must be recorded in the Electronic Diary (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.

6.8.4 Considerations for concomitant and prohibited medications and substances potentially affecting blood pressure assessment

The purpose of this study is to assess the effect of remibrutinib 25 mg b.i.d. on SBP measured by ABPM at baseline and Week 4 visits. It's important to minimize the impact of other parameters, such as lifestyle (see Section 5.4.1), and concomitant medications on blood pressure measurements. The use of certain medication (see Table 6-4,Table 6-5, Section 6.8.2) is not allowed until Week 4 or for the whole duration of the study.

Starting 24 hours before the first (screening visit 2) ABPM assessment visit and throughout Week 4 visit, particularly 24 hours before and during the 24-hour ABPM measurement at visits, participants should be instructed not to do any major change and amend to their lifestyle and concomitant medications.

This includes avoiding excessive exercise, change in nutrition pattern (i.e., type and amount of consumed food, use of diets), use of nutritional supplements, change in the consumption of alcohol and caffeine (this should be within low-risk limits throughout the study) and change in the smoking habit.

Also, background therapy for treatment of CSU should not be changed and rescue medications should not be used during the 24 hour-period before and during ABPM measurement (Section 6.8.1).

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration, if any) 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/guardian decision (requested in writing or verbally)
- Pregnancy
- Use of prohibited treatment requiring study treatment discontinuation as per recommendations in the prohibited treatment Section 6.8.2 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
- Following emergency unblinding

- Emergence of the following adverse events:
  - any adverse events that in the judgement of investigator, taking into consideration the participant's overall status, prevent 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)
- Abnormal laboratory and instrumental findings, including platelet counts < 75 000/mm3 (see Section 10.3)
- Abnormal renal laboratory results requiring discontinuation (see Section 10.6)
- Abnormal liver laboratory results requiring discontinuation (see Section 10.5)
- Any 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 assessments listed under Early Treatment Discontinuation visit at the time of treatment discontinuation (as per the Assessment Schedule Table 1-1).

If a participant declines to continue with assessments as per the visit schedule, he/she will remain in the study for a 4-week treatment-free safety follow up, then complete the safety follow-up visit and exit the study.

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.

7.2 Participant discontinuation from the study

Discontinuation from the study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 SoA. Participants who discontinue study during the treatment should complete Early Treatment Discontinuation visit and follow-up visits.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data
  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 as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g., to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

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/exercise data privacy rights and record this information. The investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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/exercise data privacy rights should be made as detailed in Section 1.3.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants'

data privacy rights), 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.

7.5 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to):

- 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 treatment development in this indication

The Sponsor may terminate this study prematurely, either in its entirety or at any study site.

Reasons for early termination (but not limited to):

- Failure by the participant and/or the study site to comply with the protocol (e.g., noncompliance), the requirements of the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator/ failure of the investigator to enter study participants at an acceptable rate
- Recommendations from applicable board(s) after review of safety data based on the number and/or severity of suspected unexpected serious adverse reactions (SUSARs)/SAEs/AEs in the study, or new data becoming available, which raise concern about the safety profile of the study treatment.
- High frequency of adverse event
- Recommendations from DMCafter review of safety data
- Discontinuation of further study treatment 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 the 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 Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in Section 1.3. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in Section 1.3, is essential and required for study conduct.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Screening

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 8.4.4 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. ABPM, if assessment failed, may be repeated between Day -4 day and Baseline visit.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. 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.

8.2 Participant demographics/other baseline characteristics

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

Baseline CSU activity will be assessed using the eDiary from Day -7 to Day -1. Participant demographic and baseline characteristic data to be collected on all participants include age, sex, race and ethnicity. Participant race and ethnicity, as required by some Health Authorities, are collected to assess the diversity of the study population and to evaluate their impact on the safety and efficacy parameters in the study. Relevant medical history (including evaluation of inclusion/exclusion criteria, CSU history and cardiovascular history) and current medical condition present before signing the informed consent will be captured. 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.

8.3 Efficacy assessments

Planned time points for all efficacy assessments are provided in Section 1.3 SoA.

8.3.1 Ambulatory blood pressure monitoring (ABPM)

ABPM over a 24-hour period will be conducted at two time points during the study in all participants:

- The first 24-hour ABPM evaluation will commence and complete within 4 days prior to Baseline visit. After a successful completion of ABPM, the participant will start the treatment phase.
- The second 24-hour ABPM evaluation will begin after approximately 4 weeks of study medication treatment at visit "Week 4 -1 day" and will be completed the following day at visit Week 4. All remaining Week 4 assessments will be performed after successful completion of ABPM or after repeated measurement, if the previous measurement is failed, to get a valid recording.

The procedure below will be followed for each 24-hour ABPM period (see [ABPM Study Training/Reference Manual] for more details):

- The ABPM device will be attached to the NON-DOMINANT arm (i.e., left arm for right-handed and right arm for left-handed) of the participant.
- A correlation will be made between the ABPM device readings and the measurements taken with a sphygmomanometer.

Following the successful correlation procedure, BP [redacted] will be measured using the ABPM device at study specified intervals.

Further details on the ABPM assessment will be provided in the [ABPM Study Training/Reference Manual].

8.3.1.1 ABPM procedures

Start of first ABMP evaluation/"Day -1": Application of ABPM device

If the participant has met inclusion and none of the exclusion criteria (see Section 5.1 for details), he/she will present at the site between Day -4 and Day -1 before 11:00 AM local time. The ABPM will be placed on the non-dominant arm after sphygmomanometer readings. Correlation readings will be obtained as described in the ABPM Study Training/Reference Manual and recorded in the source documentation. When the correlation procedure is successful, the investigator/study coordinator will initiate the “Beginning of Test” reading. The participant will then be instructed regarding ABPM procedures and will be required to return to the site after 24 hours for removal of the device.

Baseline/Day 1: Removal of ABPM device

The ABPM is removed only after it has been worn for a minimum of 24 hours from the "Beginning of Test" reading. The ABPM data will be downloaded and quality control evaluated on site, using the study specific ABPM software. The quality control criteria for the specific monitoring will be immediately displayed on the ABPM laptop.

If the criteria for successful readings are not met, ABPM procedures may be repeated twice within 24 to 48 hours. In this case, the participant will be re-instructed regarding ABPM procedures.

Following completion of the ABPM session, if the ABPM quality control criteria are met, all Baseline (Day 1) procedures will then be performed, and the participant will be dispensed the first dose of study medication.

The time of study drug (morning dose) intake will be recorded in the eCRF.

Start of second ABPM evaluation/"Week 4-1 day": Application of ABPM device

At "Week 4 -1 day", the participant will present at the site at approximately the same time of the day as he/she did for initial ABPM completed at Baseline (Day 1) in order to ensure that the second ABPM will cover the same period of time as the first ABPM.

The ABPM will be placed on the non-dominant arm after sphygmomanometer readings.

Correlation readings will be obtained as described in ABPM Study Training/Reference Manual and recorded in the source documentation. When the correlation procedure is successful, the investigator/study coordinator will initiate the "Beginning of Test" reading and the participant will take the morning dose of study drug.

The time of study drug (morning dose) intake will be recorded in the eCRF. If the participant has taken the morning dose at home/ before the visit, the investigator will ask the participant at what time he/she had taken the morning dose and will enter the corresponding time onto the eCRF. The participant will then be re-instructed regarding ABPM procedures and will be required to return to the site after 24 hours for removal of the device.

[redacted]

Week 4: Removal of ABPM device

The ABPM is removed only after it has been worn for a minimum of 24 hours from the "Beginning of Test" reading. The ABPM data will be downloaded and quality control evaluated on site, using the study specific ABPM software. The quality control criteria for the specific monitoring will be immediately displayed on the ABPM laptop. BP results will remain blinded.

If the criteria for successful readings are not met at Week 4, ABPM procedures may be repeated twice within 24 to 48 hours. In this case, the participant will continue to take study drug and will be re-instructed regarding ABPM procedures. The investigator/site coordinator will have to ensure the participant has sufficient study drug to last until the ABPM can be re-scheduled.

If three unsuccessful attempts are made, not further ABPM measurements should be completed and participant may continue to participate in the trial.

The time of study drug (morning dose) intake will be recorded in the eCRF. If the participant has taken the morning dose at home/before the visit, the investigator will ask the participant at what time he/she had taken the morning dose and will enter the corresponding time onto the eCRF.

Table 1-1 includes all assessments associated with ABPM and indicates with an "X" the visits when they are performed.

8.3.2 Patient Reported Outcomes

All participants will be provided with an electronic device (eDiary) that contains the following Patient Reported Outcomes (PRO) assessments: Urticaria Patient Daily Diary (UPDD) and Angioedema Activity Score (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.

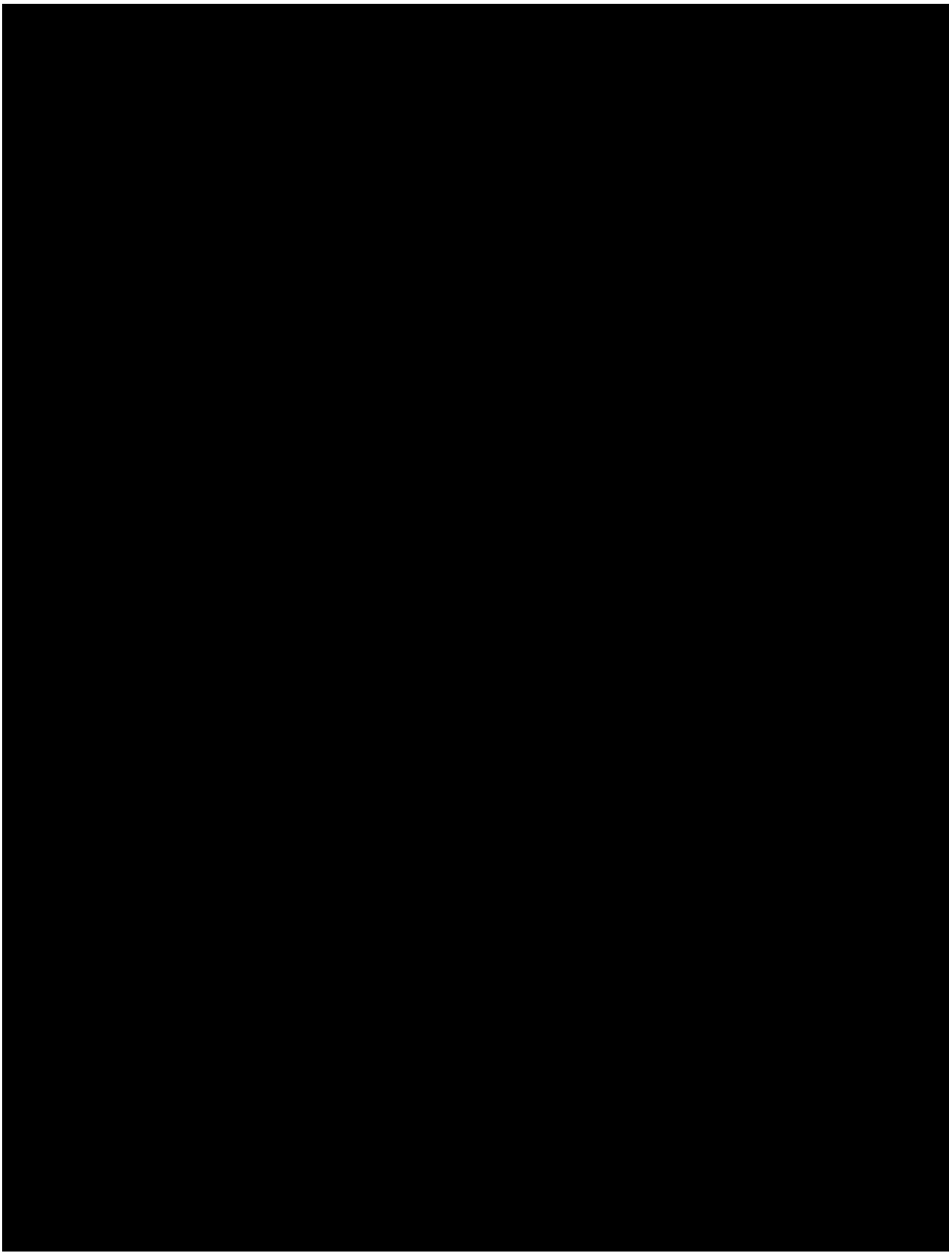
Assessments will be completed twice daily (UPDD), once daily (AAS, if triggered by opening question within the UPDD) or as detailed in the assessment schedule.

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.

[redacted]

8.3.2.1 [redacted]

[redacted]



8.3.2.1.6 H1-AH rescue medication use

The number of tablets of rescue medication used over the past 24 hours to control conditions such as itch or hives is recorded once daily in the evening in the eDiary by the participant.

8.3.2.1.8 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.

[redacted]

[redacted]

8.4 Safety assessments

Safety assessments are specified below within Section 1.3 SoA detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 8.6.

As per Section 4.5, 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.

8.4.1 Physical examinations

A complete physical examination (performed at screening visit of the respective core study) includes the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance, assessment of the skin for signs of urticaria and other skin lesions and vital signs (Blood Pressure [SBP and DBP], pulse and body temperature measurement as per local practice). A short physical examination will be at all visits starting from Visit 1 except where a complete physical examination is required (see above).

Body temperature (Celsius degree) will be measured as per local practice (the same method to be used consistently for all participants at each site), will be included in both complete and short physical examinations.

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 1-1.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

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.

8.4.2 Vital signs

Vital signs include BP and pulse measurements. After the participant has been sitting for five minutes, with the back supported and both feet placed on the floor, SBP and DBP 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. Vital signs will be measured at all visits, except at the time of extension study entry where it will be transferred from the preceding core study.

Clinical notable vital signs are defined in Section 10.3.

8.4.3 Electrocardiograms

Figure 8-1 Timing of study procedures

Electrocardiograms (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 with ECG machines supplied by the core laboratory. The mean QTcF value for each visit 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 (i.e., severe arrhythmia, conduction abnormality of QTcF > 500 msec, 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. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

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

8.4.4 Clinical safety laboratory tests

A central laboratory will be used for analysis of all specimens detailed in this Table 1-1 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.

As per Section 4.5, 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, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

Clinically notable laboratory and instrumental findings, liver and renal laboratory findings are defined in Appendices Section 10.3, Section 10.5 and Section 10.6.

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

Table 8-7 Laboratory assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, [in the case of clinically significant anemia the following parameters will be assessed: Ery. 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 participants at Week 12/EOT and when deemed necessary by the investigator at later visits Fasting glucose assessed at screening visit
Urinalysis	Done on site (unless prohibited by local guidelines, then sample to be sent to central laboratory): Macroscopic Panel (Dipstick (Occult Blood, Macroscopic Blood))
Coagulation	Prothrombin time (PT), International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Hepatitis markers	Hepatitis B screening: Antibodies against Hepatitis B virus core antigen (HBcAb or anti-HBc); antibodies against Hepatitis B virus surface antigen -HBsAg antibodies (HBsAb); Hepatitis B surface antigen (HBsAg, only in participants who are positive

	for HBcAb/anti-HBc), and Hepatitis B-Deoxyribonucleic acid (HBV-DNA, only in participants who are positive for HBcAb/anti-HBc). 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 HBc-Ab (anti-HBc positive) and negative for anti-HBsAg and HBV-DNA at screening: HBsAg, HBV- DNA
HIV testing	HIV test performed at screening, only when required by local regulations
Liver Event Testing and Liver Follow-Up Testing	Refer to Section 10.5.1Section 10.5 and Table 10-1 for complete definitions of liver laboratory triggers, and Table 10-2 and Table 10-3 for actions required in case of liver events
Renal follow-up	Refer to Section 10.6, Section 10.6.1 and Table 10-4 for renal laboratory alerts or renal safety events, and Table 10-4 and Table 10-5 for actions required for renal events follow-up
[redacted]	[redacted]
Pregnancy Test and Assessments of Fertility	Serum / Urine pregnancy test for WoCBP (refer to Section 8.4.5)

8.4.5 Pregnancy testing

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

A woman is considered of childbearing potential from menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.6 Appropriateness of safety measurements

The selected safety monitoring assessments (including laboratory assessments covering clinical chemistry, hematology, coagulation status and immunoglobulins, 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

No additional tests will be performed on participants entered into this study.

8.5.1 Clinical Outcome Assessments (COAs)

Trial feedback

This study includes an optional anonymized questionnaire, the ‘Trial Feedback Questionnaire’ (TFQ) for trial participants to provide feedback on their clinical trial experience at the end of the trial about the trial experience, as appropriate and in adherence to local regulations and guidelines. TFQ will be made available in eDiary device. Individual trial participant responses will not be reviewed by investigators. Responses may be used by Novartis to understand where improvements can be made in the clinical trial process. This feedback asks questions about trial experience. It does not ask questions about the trial participant's disease, symptoms, treatment effect, or adverse events, and, therefore is not considered as trial data.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 8.6.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs or AEs that are serious, considered related to the study treatment or the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

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

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 8.6.2):

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 8.6.2 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 (i.e., recovery status or whether it was fatal)

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 28 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (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 appendices Section 10.5 and Section 10.6 for alert ranges for laboratory and other test abnormalities.

8.6.2 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, fetal death or a congenital abnormality or 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

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.

All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.

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

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 28 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, 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) 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 or included in the trial): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis within 24 hours of learning of it's occurrence.
2. Enrolled OR 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, 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 (new occurrence) and is thought to be related to the study treatment, a 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 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 28-day period following the last administration of the 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.

8.6.4 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 1 year after the last study drug intake.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post study pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to Novartis as described in Section 8.6.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous 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 same 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.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable

8.6.6 Adverse events of special interest

Analysis of Adverse events of special interest (AESI) will be according to Statistical Analysis Plan (SAP) and AESIs will be specified in SAP.

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Residual Samples

If the participant agrees, the samples that remain after analysis is completed (blood, plasma, serum, etc.) may be kept for up to 15 years to be used for additional studies related to remibrutinib, or CSU, including research to help develop ways to detect, monitor, or treat related diseases. [redacted]

The list may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the trial. Sample(s) will be collected at the time point(s) defined in the SoA Table 1-1.

Optional Additional Research

If the participant agrees, by signing the optional consent for Additional Research, biological samples and data that remain after analysis is completed may be used for additional research to help better understand how the study treatment works, learn more about the disease, improve the way clinical studies are conducted, or to help develop ways to detect, monitor or treat human diseases. A decision to perform such exploratory research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability.

8.9 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10 Health economics OR Medical resource utilization and health economics

Health economics OR Medical resource utilization and health economics parameters are not evaluated in this study.

9 Statistical considerations

The analysis will be conducted on all participants' data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

The following analysis sets will be used in this study.

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

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

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

9.2 Statistical analyses

9.2.1 General considerations

For all efficacy analyses, the FAS will be used whereas for all safety analyses, the SAF will be used.

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

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

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

[redacted] For other assessments, baseline is the assessment on or before Day 1.

9.2.2 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 by SOC and preferred term for the Safety Set.

9.2.3 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 by means of descriptive statistics using the safety set.

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

9.3 Primary endpoint(s)/estimand(s) analysis

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

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

9.3.1 Definition of primary endpoint(s)

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

9.3.2 Statistical model, hypothesis, and method of analysis

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

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

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

9.3.3 Handling of intercurrent events of primary estimand (if applicable)

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

- Discontinuation of study treatment due to any reason prior to Week 4: participants will be excluded from the analysis as there is no data at Week 4.
- Intake of prohibited antihypertensive treatment prior to Week 4 (see Section 6.8.2): Composite strategy (irrespective of potential occurrence of other intercurrent events). Measurements after this event will be excluded from the analysis and will be imputed using an increase by 3mmHg in 24-hour SBP from baseline at Week 4.

9.3.4 Handling of missing values not related to intercurrent event

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

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

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

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

Participants with a missing 24-hour SBP baseline value will be excluded from the analysis. For missing 24-hour SBP values at Week 4 for participants who did not discontinue study treatment, the missing at random (MAR) assumption will be applied.

9.3.5 Multiplicity adjustment (if applicable)

Not applicable.

9.3.6 Sensitivity analyses

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

9.3.7 Supplementary analysis

The supplementary analysis is planned for the primary endpoint.

In addition to the intercurrent events (IE)s described in Section 3.1, the following IE will be considered in the analysis of the primary endpoint:

- Intake of prohibited BP-modifying treatment (see Section 6.8.2) prior to Week 4: Composite strategy (irrespective of potential occurrence of other IEs). Measurements after this event will be excluded from the analysis and will be imputed using an increase by 3mmHg in 24-hour SBP from baseline at Week 4.

9.4 Secondary endpoint(s)/estimand(s) analysis

This section will detail the statistical analysis of the secondary (efficacy) estimands (see Section 3.2).

9.4.1 Efficacy and/or pharmacodynamic endpoint(s)

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

The secondary clinical question of interest is: What is the effect of remibrutinib treatment on the change from baseline in 24-hour average SBP after 4 weeks treatment in adult participants

without past or ongoing history of hypertension and with 90< SBP <140mmHg, 60< DBP<90 mmHg at screening, with CSU who are inadequately controlled by H1-AH and receiving a stable local label-approved standard dose of a second generation H1-AH, excluding participants who discontinue from study treatment for any reason before Week 4 and considering intake of prohibited antihypertensive treatment as an unfavorable outcome?

Other secondary endpoints are listed below:

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

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

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

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

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

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

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

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

The analyses will be performed based on the data after the missing data imputation for the intercurrent events have been performed. Same intercurrent events defined for the primary estimand will be used for the secondary estimands and will be handled in the same way.

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

9.4.2 Safety endpoints

For all safety analyses (i.e., AEs, laboratory data, vital signs, and ECG), the SAF will be used. All listings and tables will be presented by treatment.

Adverse events

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

The number (and percentage) of participants with 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) will be summarized in the following ways:

- by treatment, primary SOC and preferred term.
- by treatment, primary SOC, preferred term and maximum severity.

- by treatment, 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.

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

A participant with multiple adverse events within a primary SOC is only counted once towards the total of the primary SOC.

If a participant reported more than 1 AE with the same preferred term, the AE with the greatest severity will be presented. If a participant reported more than 1 AE within the same primary SOC, the participant will be counted only once with the greatest severity at the SOC level, where applicable.

All AEs with onset in the follow-up period will be considered as treatment emergent.

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign. Change from baseline will only be summarized for participant with both baseline and post-baseline values. Participants with notable vital signs will be listed.

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. Change from baseline will only be summarized for subjects with both baseline and post baseline values. 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]

[redacted]

9.6 (Other) Safety analyses

Not applicable.

9.7 Other analyses

Not applicable.

9.8 Interim analysis

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

[redacted]

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

Signing 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

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

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.

10.1.2 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

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.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant’s agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/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.

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 upon obtaining consent and also 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 IN 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:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- Pregnancy Outcomes Reporting Consent for female participants

[redacted]

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

As per Section 4.5, 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.).

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

10.1.4.1 Data Monitoring Committee

This study will be included in the program level 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 Novartis 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 Novartis and the DMC.

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan, contracts.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (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 (recorded on CRFs) (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.

10.1.5.2 Database management and quality control

Novartis personnel (or designated clinical research organisation (CRO)) 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 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, screen failures and study completion, and 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 a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) 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. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in, e.g., source data acknowledgment or monitoring guidelines.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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 / delegated CRO / 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.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT public website. In addition, after study completion *(*defined as last participant 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.

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

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

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.

10.1.8.1 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.

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.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

AAS	Angioedema Activity Score
AAS7	Weekly Angioedema Activity Score
ABPM	Ambulatory Blood Pressure Monitoring
ACEi	Angiotensin Converting Enzyme inhibitor
ACR	albumin-creatinine ratio
AD	Atopic Dermatitis
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
APTT	Activated Partial Thromboplastin Time
ARBs	Angiotensin II Receptor Blockers
ASMA	Anti-smooth muscle antibody
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
b.i.d.	bis in die/twice a day
BCRP	breast cancer resistance protein
BP	Blood pressure
BTK	Bruton's Tyrosine Kinase
BUN	Blood Urea Nitrogen
CCBs	Calcium Channel Blockers
CIU	Chronic Idiopathic Urticaria
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CO	Country Organization
COA	Clinical Outcome Assessment
CQA	Clinical Quality Assurance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive Protein
CSR	Clinical study report
CSU	Chronic Spontaneous Urticaria
CU	Chronic Urticaria
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DILI	Drug-Induced Liver Injury
DIN	Drug Inducted Nephrotoxicity
DLQI	Dermatology Life Quality Index
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee

DNA	Deoxyribonucleric Acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
ERCP	Endoscopic retrograde cholangiopancreatography
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
h	Hour
H1-AH	H1-antihistimines
HBcAb	Hepatitis B virus core antigen
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCP	Healthcare Professional
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HIV	Human immunodeficiency virus
HR	Heart Rate
HSS7	Weekly Hives Severity Score
HSV	Herpes Simplex Virus
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
IE	Intercurrent Event
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISS7	Weekly Itch Severity Score
IUD	Intrauterine Device
IUS	Intrauterine System
LC-MS	Liquid Chromatography–Mass Spectrometry
LDH	lactate dehydrogenase
LDL	Low-Density Lipoprotein

LFT	Liver function test
LLOQ	lower limit of quantification
MAO	Monoamine Oxidase
MAOIs	Monoamine Oxidase Inhibitors
MAR	Missing at Random
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic resonance imaging
NOAC	Novel Oral Anti-Coagulants
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
OHP	Off-site Healthcare Professional
OTC	Over the Counter
PCR	protein-creatinine ratio
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PT	prothrombin time
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RMS	Relapsing Multiple Sclerosis
RNA	Ribonucleic Acid
s.c.	subcutaneous
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation
SjS	Sjoegren's Syndrome
SMQ	Standardized MedDRA Query
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SoA	Schedule of Activities
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCAs	Tricyclic Antidepressants
TFQ	Trial Feedback Questionnaire
TPO IgGs	Anti-Thyroid Peroxidase Antibodies
TSH	Thyroid Stimulating Hormone
UAS	Urticaria Activity Score
UAS7	Weekly Urticaria Activity Score
ULN	upper limit of normal
UPDD	Urticaria Patient Daily Diary

UV	Ultraviolet
WHO	World Health Organization
WoCBP	Women of child-bearing potential

10.2.2 Definitions

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
Auxiliary medicinal product	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess end-points in the clinical trial). Concomitant therapy is not considered as AMP.
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
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 intervention 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.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
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

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.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
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 participant about the status of a participant's health condition without amendment or interpretation of the participant'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.
Remote	Describes any trial activities performed at a location that is not the investigative site.
Rescreening	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
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 electronic source (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
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 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 consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or 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. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 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/mm^3
- Leukocytes: < 3 000/mm^3
- Neutrophils: < 1 500/mm^3

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 Table 10-5 for clinically notable laboratory values for hepatotoxicity.

Refer to Section 10.6 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 msec for males or greater than 460 msec for females or QTcF increase ≥60 msec from baseline value – all such ECGs will be flagged by the central CRO's cardiologist and require assessment for clinical relevance by the investigator.

10.4 Appendix 4: 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 time points 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
- Trial Feedback Questionnaires (TFQ) - end of trial

10.5 Appendix 5: 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 10-1 in Section 10.5 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 10-1 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 10-2, Table 10-3.

- 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 the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
  - These investigations can 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.

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-1 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

Definition/ threshold
● Any adverse event potentially indicative of a liver toxicity

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

Table 10-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	● **No change to study treatment** ● Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms.
	If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline AND > 5 x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	● **Interrupt study treatment** ● Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms. ● Initiate close monitoring and workup for competing etiologies. ● Study treatment can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline AND > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline AND > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 10-3 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 or to baseline
> 3 - 10 × 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 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

10.6 Appendix 6: Renal safety monitoring

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trail staff as summarized in Table 10-4.

Every renal laboratory trigger or renal event should be followed up by the investigator or designated personnel at the trial site as summarized in Table 10-5.

10.6.1 Specific Renal Alert Criteria and Actions and Event Follow-up

Table 10-4 Specific Renal Alert Criteria and Actions and Event Follow-up

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 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] When urine proteins are measured as a follow-up of positive urine dipstick measurements: Protein-creatinine ratio (PCR) ≥1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • 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, e.g., dehydration due to delirium, tumor lysis.	

Table 10-5 Renal Events Follow-up

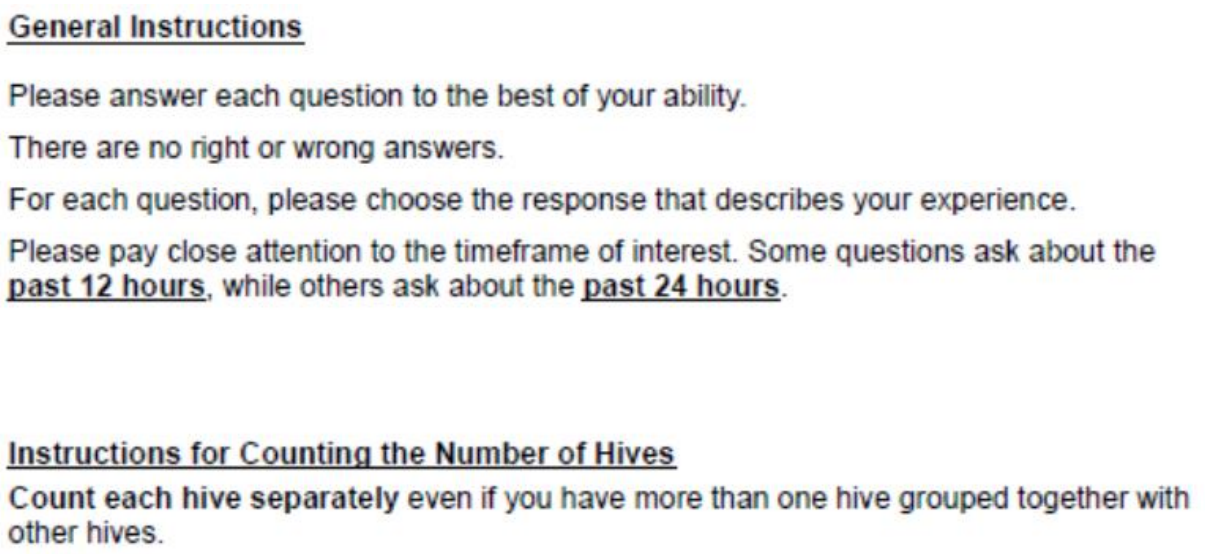
Follow-up of Renal Events
Assess, document and record in the CRF: ● Urine dipstick and sediment microscopy evidence of Drug-Induced Nephrotoxicity (DIN): crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells ● Blood pressure and body weight ● Serum creatinine, blood urea nitrogen (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 albumin-creatinine ratio (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

10.7 PRO tools

Samples of questionnaires provided here are for illustrative purpose only. The text format and wording might slightly vary.

Patient Diary: Urticaria Patient Daily Diary (UPDD)

Figure 10-1 Patient Diary: Urticaria Patient Daily Diary (UPDD)



General Instructions

Please answer each question to the best of your ability.

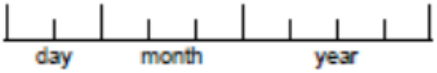
There are no right or wrong answers.

For each question, please choose the response that describes your experience.

Please pay close attention to the timeframe of interest. Some questions ask about the past 12 hours, while others ask about the past 24 hours.

Instructions for Counting the Number of Hives

Count each hive separately even if you have more than one hive grouped together with other hives.

Today's Date 

Please complete this section <u>every morning</u> throughout the duration of the study.
(Please circle only one response.)

1. Thinking about the **<u>past 12 hours</u>**, please record the severity of itch and the number of hives you may have had associated with your skin condition. **<u>Please count each hive separately</u>** even if you have more than one hive grouped together with other hives.

Itch (severity)

0 = none

1 = mild

2 = moderate

3 = severe

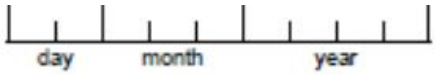
Hives (number)

0 = none

1 = between 1 and 6 hives

2 = between 7 and 12 hives

3 = greater than 12 hives

Today's Date 

Please complete this section every evening throughout the duration of the study.
(Please circle only one response.)

2. Thinking about the **past 12 hours**, please record the severity of itch and the number of hives you may have had associated with your skin condition. **Please count each hive separately** even if you have more than one hive grouped together with other hives.

Itch (severity)

0 = none

1 = mild

2 = moderate

3 = severe

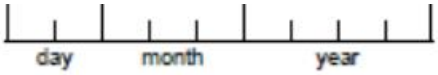
Hives (number)

0 = none

1 = between 1 and 6 hives

2 = between 7 and 12 hives

3 = greater than 12 hives

Today's Date 

Please complete this section once each day throughout the duration of the study (preferably at the same time each day).

(Please circle only one response.)

3. Please rate how much your hives or itch interfered with your sleep during the **past 24 hours**.

   0 = No interference

   1 = Mild, little interference with sleep

   2 = Moderate, awoke occasionally, some interference with sleep

   3 = Substantial, woke up often, severe interference with sleep

4. Please rate how much your hives or itch interfered with your daily activities during **the past 24 hours**. This could include work, school, sports, hobbies, and activities with friends and family.

   0 = No interference

   1 = Mild, little interference with daily activities

   2 = Moderate, some interference with daily activities

   3 = Substantial, severe interference with daily activities

These next questions are about your symptoms and how you managed them during the past 24 hours.

5. During the **past 24 hours**, how many tablets of rescue medication did you use in order to control symptoms of your skin condition such as itch or hives?

   ☐

   The maximum number of tablets per day should be according to your doctor's recommendation.

6a. During the **past 24 hours**, did you have any rapid swelling on your face, (especially your eyelids or lips), inside your mouth (including your throat or tongue), or elsewhere on your body? This rapid swelling, also called angioedema, is at a deeper level under your skin than hives.

   0 = No **(GO TO Question 7)**

   1 = Yes

6b. If Yes, how did you treat this rapid swelling? **(Circle all that apply.)**

   0 = Did nothing **(GO TO Question 7)**

   1 = Took some prescription or non-prescription medication

   2 = Called my doctor, nurse or nurse practitioner

   3 = Went to see my doctor, nurse or nurse practitioner

   4 = Went to the emergency room at the hospital

   5 = Was hospitalized

7. During the **past 24 hours**, did you or someone else call your doctor, nurse or nurse practitioner because of your skin condition?

   0 = No

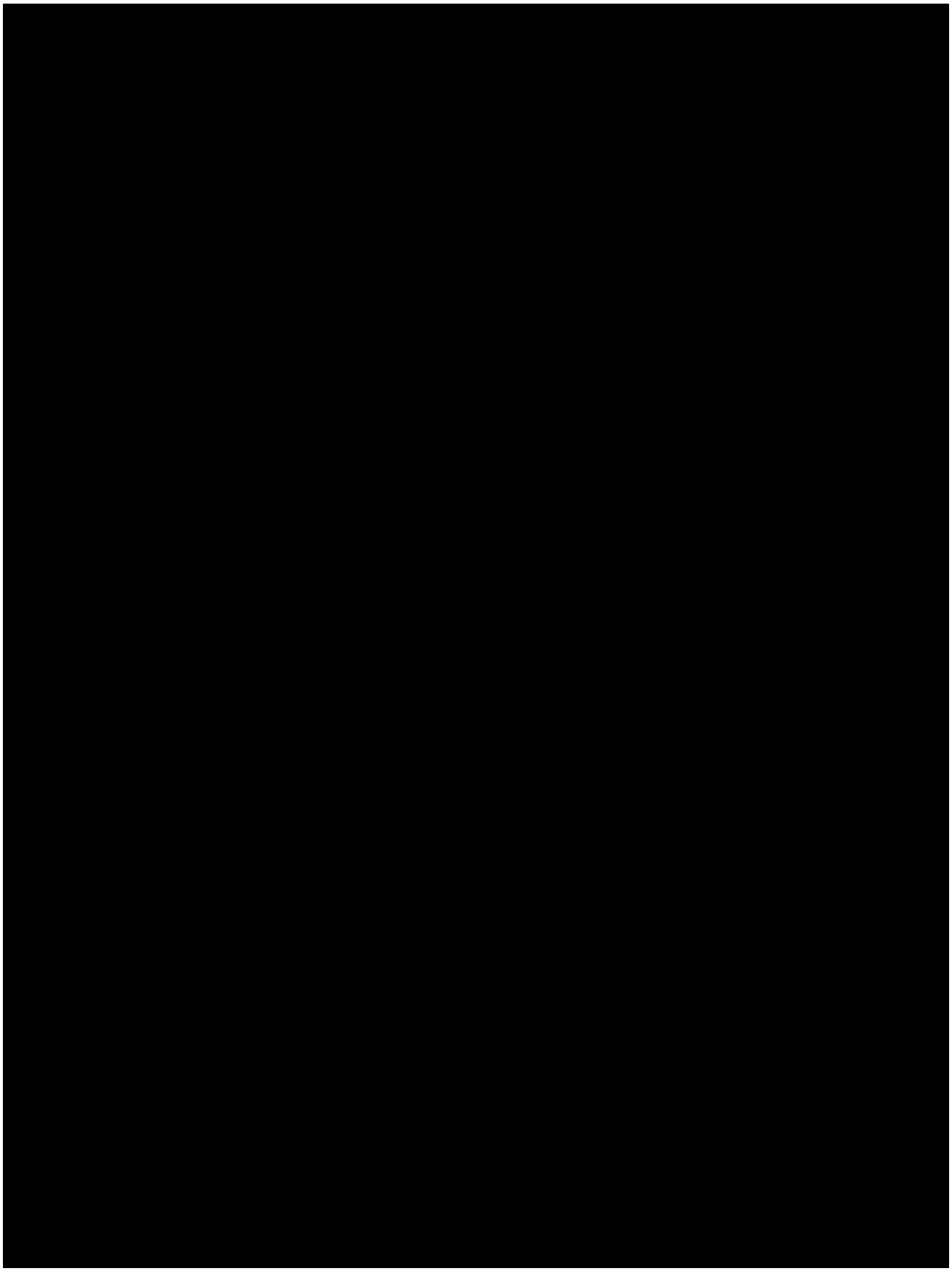
   1 = Yes

Participant Diary: Angioedema Activity Score (AAS)

Figure 10-2 Angioedema Activity Score

Instructions: Please document your symptoms retrospectively once a day. Refer to the last 24 hours in each case. Please answer all questions as fully as possible

		Day						
		1	2	3	4	5	6	7
Have you had a swelling episode in the last 24 hours?	no							
	yes							
⇩ **Please answer the questions below about this swelling episode during the last 24 hours. If you did not have a swelling episode, leave them blank.**								
At what time(s) of day was this swelling episode(s) present? (please select all applicable times)	midnight – 8 a.m.							
	8 a.m. – 4 p.m.							
	4 p.m. - midnight							
How severe is / was the physical discomfort caused by this swelling episode(s) (e.g., pain, burning, itching?)	no discomfort							
	slight discomfort							
	moderate discomfort							
	severe discomfort							
Are / were you able to perform your daily activities during this swelling episode(s)?	no restriction							
	slight restriction							
	severe restriction							
	no activities possible							
Do / did you feel your appearance is / was adversely affected by this swelling episode(s)?	no							
	slightly							
	moderately							
	severely							
How would you rate the overall severity of this swelling episode?	negligible							
	mild							
	moderate							
	severe							



11 References

References are available upon request

Angst D, Gessier F, Janser P, et al (2020) Discovery of LOU064 (Remibrutinib), a Potent and Highly Selective Covalent Inhibitor of Bruton's Tyrosine Kinase. J Med Chem; 63(10):5102-18.

Biagtan MJ, Viswanathan RK, Evans MD, et al (2011) Clinical utility of the Chronic Urticaria Index. J Allergy Clin Immunol; 127(6):1626-7.

Estupiñán HY, Berglöf A, Zain R, et al (2021) Comparative Analysis of BTK Inhibitors and Mechanisms Underlying Adverse Effects. Front Cell Dev Biol; 9:630942.

Finlay AY (2005) Current severe psoriasis and the rule of tens. Br J Dermatol; 152(5):861-7.

[redacted]

Food and Drug Administration (2022) Guidance for Industry. Assessment of Pressor Effects of Drugs. US Department of Health and Human Services. Center for Drug Evaluation and Research (CDER). February 2022. Clinical/Medical

Gabizon R, London N (2020) A Fast and Clean BTK Inhibitor. J Med Chem; 63(10):5100-01.

Greaves MW (2003) Chronic idiopathic urticaria. Curr Opin Allergy Clin Immunol; 3(5):363-8.

Hawro T, Ohanyan T, Schoepke N, et al (2018) The Urticaria Activity Score-Validity, Reliability, and Responsiveness. J Allergy Clin Immunol Pract: 6(4);1185-1190.

Hendriks RW, Yuvaraj S, Kil LP (2014) Targeting Bruton's tyrosine kinase in B cell malignancies. Nat Rev Cancer; 14(4):219-32.

Hongbo Y, Thomas CL, Harrison MA, et al (2005) Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol; 125(4):659-64.

[redacted].

Powell RJ, Du Toit GL, Siddique N, et al (2007) BSACI guidelines for the management of chronic urticaria and angio-oedema. Clin Exp Allergy; 37(5):631-50.

Rip J, Van Der Ploeg EK, Hendriks RW, et al (2018) The Role of Bruton's Tyrosine Kinase in Immune Cell Signaling and Systemic Autoimmunity. Crit Rev Immunol; 38(1):17-62.

Saini SS, Kaplan (2018) AP Chronic Spontaneous Urticaria: The Devil's Itch. J Allergy Clin Immunol Pract:1097-106.

[redacted]

[redacted]

Zauli D, Grassi A, Ballardini G, et al (2002) Thyroid autoimmunity in chronic urticaria: Implications for Therapy. Am J Clin Dermatol; 3(8):525-8.

Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al (2021) The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy; 77(3):734-766.

Zuberbier T, Aberer W, Asero R, et al (2014) The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy; 69(7):868-87.