Germany Evidence Generation and GMA Evidence Generation, Immunology

Non-Interventional Study Protocol (PASS)

Redacted Protocol

CLOU064ADE02

Title	Remibrutinib in real-world clinical practice: a prospective, multi-country, non-interventional, effectiveness and safety study (REASSERT) - Local adaptation in Germany from global umbrella protocol (CLOU64A2402)
Protocol version number	V00
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HMA-EMA Catalog of real-world data studies register number	Study not registered yet

NIS Type	Primary Data Collection
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Medicinal product	Not yet authorized – Remibrutinib
Product reference	EMEA/H/C/006313
Procedure number	NA
Name of marketing authorization holder(s)	Novartis Europharm Limited
Joint EU PASS	No
Research question and objectives	Investigate real-world effectiveness and safety of remibrutinib in adult patients diagnosed with CSU who remain symptomatic despite sgH_1-AHs over 24 months
Countries of study	Global (USA, Germany, Japan, China, Spain, Italy, Canada, South Korea)
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NIS Protocol Template Primary Data Collection Version 5.0 dated 30-Jun-2025

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List of abbreviations

1L	First-line
ADR	Adverse drug reaction
AE	Adverse event
AECT	Angioedema Control Test
AH	Antihistamine
BTK	Bruton's tyrosine kinase
CFB	Change from baseline
CI	Confidence interval
CIndU	Chronic inducible urticaria
CRO	Contract research organization
CSU	Chronic spontaneous urticaria
CU	Chronic urticaria
CU-Q2oL	Chronic Urticaria Quality of Life Questionnaire
CURE	Chronic Urticaria Registry
DLQI	Dermatology Life Quality Index
eCRF	Electronic case report form
eDiary	Electronic diary
EDC	Electronic data capture
EHR	Electronic health record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ePRO	electronic patient-reported outcome
EU	European Union
FcεRI	High-affinity IgE receptor
GMA	Global Medical Affairs
GP	General practitioner
GPP	Good Pharmacoepidemiology Practices
H_1-AH	H_1 antihistamine
H_2-AH	H_2 antihistamine
HA	Health Authority
HADS	Hospital Anxiety and Depression Scale
HCP	Health care practitioner/health care provider
HCRU	Healthcare resource utilization
ICF	Informed consent form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IgE	Immunoglobulin E
IRB	Institutional review board
IQR	Interquartile Range
LOT	Line of therapy
LPLV	Last Patient Last Visit
LTRA	Leukotriene receptor agonist
MAH	Marketing authorization holder
MAP	Managed access program
[redacted]	[redacted]

MedDRA	Medical Dictionary for Regulatory Activities	
MID	Minimal important difference	
NIS	Non-interventional study	
OBD	Office-based dermatologist	
PAS	Post-authorization study	
PASS	Post-authorization safety study	
PIs	Principal Investigators	
PRO	Patient-reported outcome	
PROMs	Patient-reported outcome measures	
PSDS	Post study drug supply	
QoL	Quality of life	
QPPV	Qualified Person for Pharmacovigilance	
RCT	Randomized controlled trial	
SAE	Serious adverse event	
SAP	Statistical analysis plan	
SAS	Statistical Analysis System	
SD	Standard deviation	
SIS	Sleep interference score	
sgH_1-AH	Second-generation H_1 antihistamine	
STROBE	Strengthening the Reporting of Observational Studies in	Epidemiology
TPO	Thyroid pyroxidase	
UAS	Urticaria Activity Score	
UAS7	Urticaria Activity Score over 7 days	
UCARE	Urticaria Centers of Reference and Excellence	
UCT	Urticaria Control Test	
UCT7	7-day recall period version of the Urticaria Control Test	
US	United States	
WHO	World Health Organization	
WPAI	Work Productivity and Activity Impairment	

1 Responsible parties

Table 1-1 Responsible parties

Role	Person
Main protocol author(s)	[redacted], PhD, [redacted] Novartis Nuremberg, GE, [redacted] PhD, [redacted] Novartis, GE, [redacted], PhD, Global Medical Affairs [redacted], Novartis, Basel, CH [redacted], PhD, Global Evidence Generation, [redacted], Novartis, IRE
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Principal investigators (PIs)	Chair: Prof [redacted] Spain. Co-chair: Prof [redacted] Germany
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2 Abstract/Study summary

This section contains a summary of the study information. Additional details can be found in each subsequent section of the protocol.

Title

Remibrutinib in real-world clinical practice: a prospective, multi-country, non-interventional, effectiveness and safety study (REASSERT) - Local adaptation in Germany

Protocol version and release date

V00; 04-Feb-2026

Name and affiliation of main authors

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Rationale and background

Chronic urticaria (CU) is a mast cell-driven disease marked by the presence of itchy wheals (hives), angioedema, or both for over 6 weeks. CU affects about 0.1-1.4% of the global population, predominantly occurs in women (around 70%), and disproportionately effects people of working age (20-40 years). It poses a significant health burden due to its symptoms, their impact on various aspects of quality of life (QoL) and the high rates of uncontrolled disease.

Current international (i.e., EAACI/GA²LEN/EuroGuiDerm/APAAACI) and national treatment guidelines for urticaria recommend second-generation H_1 antihistamines (sgH_1-AHs) as first-line (1L) treatment, with varying doses across regions. Recommendations for subsequent lines vary across regions. Evidence suggests that in real-world clinical practice, patients are often inadequately controlled by 1L therapies and treatment escalation to more effective therapies is only performed inconsistently. In real-world, > 90% of patients are managed by hospital or office-based dermatologists and allergists, rather than CU specialist centers, e.g., Urticaria Centers of Reference and Excellence (UCARE) (Novartis data on file). The paucity of information on patients treated in the broader office-based space, versus the specialized centers, where patients tend to have chronic spontaneous urticaria (CSU) symptoms for many years continuously, further limits our understanding of the natural history of the disease, particularly in its waxing and waning nature, where there are periods of intermittent remission and spontaneous resolution.

Remibrutinib is an oral, highly selective Bruton's Tyrosine Kinase (BTK) inhibitor that blocks BTK-mediated degranulation of mast cells and basophils downstream of high-affinity IgE receptor (FcεRI). In the two Phase 3 placebo-controlled REMIX-1 and REMIX-2 studies, remibrutinib demonstrated a fast (as early as week 1) and sustained improvement of CSU symptoms (up to week 52), with a favorable safety profile in patients with CSU inadequately controlled with H_1 antihistamine (H_1-AH).

Research question and objectives

The study is designed to investigate the real-world early (first 12 weeks) and long-term (up to 24 months) effectiveness and safety of remibrutinib in a broad clinical practice patient population.

Primary Objective:

Evaluate the 12-week real-world effectiveness of remibrutinib in adult patients diagnosed with CSU who remain inadequately controlled despite sgH_1-AHs (including all patients who initiate remibrutinib, regardless of prior treatment).

Secondary Objectives

1. Evaluate the real-world effectiveness of remibrutinib treatment (cohort 2 and 3 separate and pooled) in patients with CSU over 24 months.
2. Evaluate the early real-world effectiveness of remibrutinib (cohort 2 and 3 separate and pooled) up to week 12 in patients with CSU.
3. Characterize the short-term (up to 12 weeks) and long-term (up to 24 months) real-world treatment patterns and concomitant CSU medication(s) in patients with CSU treated with remibrutinib (cohort 2 and cohort 3 separate).
4. Assess QoL in CSU patients treated with remibrutinib (cohort 2 and 3 separate and pooled) up to 24 months.
5. Determine healthcare resource utilization (HCRU) and work productivity in patients treated with remibrutinib (cohort 2 and 3 separate and pooled).
6. Assess the safety profile of remibrutinib among all patients with CSU who initiate remibrutinib, (cohort 2 and 3, separate and pooled) over a 24-month treatment period in a real-world setting.

Study design and population

This is a prospective, multi-country, non-interventional study in patients with CSU where the treatment decision prior enrollment has been made to escalate/switch current treatment to remibrutinib. The primary aim of this study is to gather real-world effectiveness and safety data for remibrutinib, a new treatment option, covering a broader, real-world clinical practice population at a wider range of sites than in the Phase 2 and Phase 3 (REMIX) development trials. The study employs an umbrella design which brings together the evidence needs from multiple countries under the REASSERT global program.

This version of the protocol has been tailored to meet the specific requirements of Germany; the local study documentation is a minimized version of the global document set, modified to align with local evidence needs, given local disparities in treatment guidelines, access, legal requirements, physician type and electronic patient-reported outcomes (ePROs)/electronic diaries (eDiaries) used.

The major protocol adaption for Germany from the umbrella protocol is the exclusion of cohort 1:

- Cohort 1 (Inadequate control of CSU despite licensed dose of sgH_1-AH and decision to escalate sgH_1-AH treatment.) will not be addressed as this is considered off-label in Germany.
- Protocol deviations of off label use will be collected.

Data from all countries will be pooled and analyzed globally and locally.

The study has 2 periods:

- Early frequent observational period (Phase 1): Baseline to week 12
- Long-term observational period (Phase 2): From Month 3 to 24

and observes in Germany the following cohorts:

- **Cohort 2:** Inadequate control of CSU despite licensed dose or escalated sgH_1-AH(s) (no other pre-treatment with exception of first generation H_1-AH permitted) with decision (independent of study enrollment) to switch to remibrutinib treatment as per local label. Baseline visit comprises of clinical assessment while treated with sgH_1-AH (i.e., preescalation to remibrutinib) and follow-up visits capture clinical outcome of escalated treatment with remibrutinib as per local label.
- **Cohort 3**: Any other treatment received in addition to H_1-AH, any time during patients CSU treatment history, with decision (independent of study enrollment) to switch to remibrutinib treatment as per local label. Baseline visit comprises of clinical assessment before switch to remibrutinib and follow-up visits capture clinical outcome of treatment with remibrutinib as per local label. Enrollment will be capped at a maximum of 30% of the local population.

Note, occasional steroid rescue medication is out of scope for cohort definition. If a patient had been on continuous steroids for at least 3 weeks during treatment history, they will be included in cohort 3.

Setting

The study is conducted in various healthcare system settings, office- and hospital-based. The aim is to observe the real-world practice in the management of CSU patients. The split of approximately 70% office-based (dermatologists, allergists, immunologists, and general practitioners (GPs) where applicable) and 30% specialist centers is designed to ensure the inclusion of a broad variety of physicians covering the intended broad CSU patient population.

The study is planned to be conducted in 8 countries: the United States (US), Germany, Japan, China, Spain, Italy, Canada, and South Korea. Germany aims to enrol 470 patients. (see Section 7.4).

There are 2 data sources. Data collected by physicians via the electronic case report form (eCRF) within an electronic data capture (EDC) system and patient collected data via mobile phone app (ePRO/eDiary) linked to the EDC. At enrollment, patients are required to download the study app and use it throughout the entire study duration.

Variables

The following variables will be characterized at baseline:

- Age (years, months)
- Sex (Female/Male)
- Height (cm)
- Weight (kg)
- Smoking status
- Race
- Medical history, including comorbidities of special interest (e.g., allergies, food allergies (e.g., milk, egg, nut), atopic dermatitis, asthma, allergic rhinitis, other forms of eczema, type 1 diabetes mellitus, Hashimoto's, vitiligo, lupus erythematosus, obesity or severe obesity (BMI > 30), hypertriglyceridemia, hypercholesterolemia, hypertension, anemia, depression, anxiety (e.g., generalized anxiety disorder, panic disorder) insomnia, sleep disturbances)
- Previous and current CSU medications (e.g., H1-AH, H_2 antihistamines (H_2-AHs), leukotriene receptor agonist (LTRA), omalizumab, ciclosporin, anti-inflammatory agents, immunosuppressants, biologics, tranexamic acid, diaphenylsulfone, anxiolytics, glycyrrhizin, tripterygium, corticosteroids, phototherapy)
- CSU-related investigations, if available (e.g., immunoglobulin E (IgE), anti-thyroid pyroxidase (TPO) antibodies, tryptase, endotyping, etc.)
- Non-CSU medications
- Concomitant chronic inducible urticaria (CIndU)(s)
    - Symptomatic dermographism
    - Cold urticaria
    - Cholinergic urticaria
    - Heat urticaria
    - Delayed pressure urticaria
    - Solar urticaria
    - Vibration urticaria
    - Aquagenic urticaria

- Presence of angioedema
- 7-day recall period version of the UCT (UCT7) / Urticaria Activity Score (UAS) score
- DLQI score
- Previous health care resources used (e.g., hospital stays, emergency room visits, number of physicians visited before diagnosis received, average number of angioedema episodes per month/year)
- Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) score
- Work Productivity and Activity Impairment (WPAI)-CU score
- Hospital Anxiety and Depression Scale (HADS) score
- Angioedema control test score (if angioedema present)
- Sleep interference

Data sources

This study involves primary data collection. Data is captured from 2 sources: by the physician (or delegate) using an eCRF interface, including patient demographics, medical history, comorbidities, clinical characteristics at baseline, and outcomes at follow-up visits and by the patient using an eDiary. All data are collected in a routine clinical practice setting and will not include any interventional or invasive measurements. All data are pseudonymized/coded, ensuring no personal identifiers are included in the final dataset used for analyses. Patient reported data are collected using electronic diary and patient-reported outcomes (PROs) (ePROs/eDiary) via a mobile phone application at all time points and in between clinical visits to confirm disease control and medication intake. The data collected via ePRO/eDiary is linked to the EDC system.

Study size

The sample size for Germany expected is 470 patients, based on both the primary objective: estimating the proportion of patients achieving UCT7 ≥ 12 at week 12 after initiating remibrutinib treatment and the secondary objective: evaluate the real-world effectiveness of remibrutinib treatment in patients with CSU over 24 months.

To ensure a 95% confidence interval (CI) of 52.8%–57.2% around an expected response rate of 55%, 235 patients are required in cohort 2 and 3 combined. For the primary objective, patients in cohort 2 and cohort 3 are combined, as response rates are assumed similar (as observed in the REMIX trials). Accounting for a 50.4 % dropout rate after 24 months, this increases to around 470 patients. With 235 patients before adjustment, the 95% CI based on the normal approximation to the binomial distribution is 48.6%–61.4%.

The study design includes a maximum cap for cohort 3 to ensure balanced representation. Enrollment for cohort 3 is capped at a maximum of 30% of the study population, which translates to approximately 141 patients out of the 470 patients.

(refer to Section 7.4 for further details).

Milestones

Table 2-1 Planned dates of local study milestones*

Milestone	Planned date
Start of data collection	01-June-2026
End of data collection	31-May-2029
Final report of study results	31-OJan-2030
Others of relevance	See Table 3 -1

* Dates may change based on product approval dates.

3 Amendments and updates

None

4 Milestones

Table 3-1 Planned dates of global study milestones, including interim reports

Milestone	Planned date*
<Protocol approval by Institutional Review/Board/Independent Ethics Committee>	IRB and EC submissions will be performed at country level sequentially based on launch timelines from 2025 onwards
Registration in the EU PAS register	TBC
Start of data collection	05-Jan-2026
End of data collection*	30-Oct-2031
Interim report 1 – 100% of Baseline data*	30-Sep-2027
Interim report 2 – 100% of 12-week data*	30-Sep-2028
Interim report 3 – 100% of 12-month data*	30-Sep-2029
Last Patient Last Visit (LPLV)*	30-Oct-2031
Final report of study results*	30-Oct-2032

* Dependent on time of product availability in countries & recruitment.

Abbreviations: EU = European Union, IRB = Institutional Review Board, EC = Ethics Committee, PAS = Post--authorization study.

5 Rationale and background

5.1 Background

Chronic urticaria (CU) is a mast cell-driven disease marked by the presence of itchy wheals (hives), angioedema, or both for over 6 weeks. CU can be spontaneous (chronic spontaneous urticaria; CSU) or inducible (chronic inducible urticaria; CIndU), triggered by specific stimuli. There are 9 CIndU subtypes, of which symptomatic dermographism, cold, and cholinergic urticaria are the most common. It has been estimated that between 15% to 40% of CSU patients have concomitant CIndU (Kovalkova et al., 2024).

CU affects about 0.1-1.4% of the global population, predominantly occurs in women (around 70%), and disproportionately effects people of working age (20-40 years) (Maurer et al., 2011, Fricke et al., 2020). It poses a significant health burden and rates of CU patients with uncontrolled disease are high (Vestergaard et al., 2017, Göncü et al., 2024, Kolkhir et al., 2024). Uncontrolled CU negatively impacts various aspects of quality of life (QoL) and sleep (Min et al., 2023, Vestergaard et al., 2017, Balp et al., 2015). CU is associated with higher incidence of psychiatric comorbidities including depression and anxiety (Konstantinou and Konstantinou, 2019, Rani et al., 2022, Huang et al., 2021, Chu et al., 2017).

Current international (i.e., EAACI/GA²LEN/EuroGuiDerm/APAAACI) and national treatment guidelines (AWMF S3-Leitlinie, Klassifikation, Diagnostik und Therapie der Urtikaria) for urticaria recommend second-generation H_1 antihistamines (sgH_1-AHs) as first-line (1L)

treatment, with varying doses (from licensed dose up to four times (off-label) across regions (Bernstein et al., 2014, Hide, 2018, Zuberbier et al., 2022, Xu J-H, 2020). Recommendations for subsequent lines vary across regions. International Guidelines recommend measuring treatment effectiveness using validated measures of control such as the Urticaria Control Test (UCT) every 2 to 4 weeks and the Urticaria Activity Score over 7 days (UAS7).

In real-world clinical practice, patients are often inadequately controlled by 1L therapies, and treatment escalation to more effective therapies is performed inconsistently and/or with significant delays. Recently, the Urticaria Voices study reported that up to 80% of participating patients did not respond adequately to antihistamines (AH) despite switching antihistamine type and up-dosing (Bernstein et al., 2023). The AWARE study found that among uncontrolled CSU patients eligible for escalation, only 3% received up-dosing of sgH_1-AHs, and only 5% were initiated on omalizumab at one-year follow-up (Maurer et al., 2019). Data from the Chronic Urticaria Registry (CURE) show that among patients at specialist centers, 36% on licensed dose sgH_1-AH and 35% on up-dosed sgH_1-AH who were eligible for treatment escalation (UCT < 12) remained on inadequate therapies at a 6-month follow-up. Moreover, there are reports of patients being treated outside guidelines with cases of up to 8 times the licensed dose of AHs and as well as with long-term corticosteroids, both of which have shown limited clinical benefit (van den Elzen et al., 2017, Seetasith et al., 2022).

CSU is a chronic disease where symptoms wax and wane; patients may experience periods of intermittent remission. In some cases, symptoms can resolve spontaneously and patients enter remission independently of current treatment options (Beltrani, 2002). A recent systematic literature review estimated that CSU resolves spontaneously in 10% to 38% of patients within the first year and 29% to 71% within the first 5 years (Balp et al., 2022). However, remission rates remain poorly characterized due to inconsistent definitions of remission and relapse, limited data on intermittent remission, variability in follow-up duration, and a tendency for studies to focus on more severe and treatment-resistant CSU populations at specialized academic centers, where treatment patterns differ significantly, thereby potentially introducing distortion on real-world remission rates in a wider CSU population (Hsieh and Lee, 2017). In the real-world, up to 90% of patients are managed outside of specialist centers (e.g., by hospital- or office-based dermatologists/allergists, and general practitioners (GPs)) (Novartis data on file). The paucity of information on patients treated in the broader office-based space, versus the specialized center space, where patients tend to have CSU symptoms for many years continuously, further limits our understanding of the natural history of the disease, particularly in its waxing and waning nature. REASSERT aims to address this evidence gap, measuring remission and relapse in the real-world in a wider patient CSU population.

Disease modification has recently emerged as a concept in CSU and is defined as a treatment-induced change in the underlying pathophysiology and disease course (Maurer et al., 2024). Similar to concepts in rheumatologic conditions like rheumatoid arthritis, disease-modifying therapies could have the potential to slow disease progression, including the evolution of acute urticaria to CU, inhibition of autoantibody production (Zuberbier et al., 2024) and prevention of comorbidity development (e.g., anxiety, depression). However, in the context of CU, the lack of adequate data for spontaneous and intermittent remission rates, particularly in patients outside specialized centers, makes it difficult to clearly differentiate disease modification from spontaneous remission (Maurer et al., 2024). Robust, prospectively collected

data on intermittent and spontaneous remission using consistent definitions are an essential first step to enable a deeper understanding whether a treatment may have disease-modifying potential in CSU.

5.2 Remibrutinib

Remibrutinib is an oral, highly selective Bruton's Tyrosine Kinase (BTK) inhibitor that blocks BTK-mediated degranulation of mast cells and basophils downstream of the high-affinity IgE receptor (FcεRI), thereby preventing the release of histamine and other proinflammatory mediators that lead to itch, hives, and angioedema (Neys et al., 2021, Mendes-Bastos et al., 2022, Kaplan et al., 2023, Hata et al., 1998). In CSU, activation of BTK downstream of FcεRI in mast cells and basophils leads to the release of histamine and other proinflammatory mediators causing CSU/CIndU symptoms (Min and Saini, 2019, Dispenza et al., 2017, Mendes-Bastos et al., 2022, Kaplan et al., 2023, Hata et al., 1998). In addition, activation of BTK has been described to be responsible for autoantibody production by B cells in CSU (Min et al., 2023, Dispenza et al., 2017, Hata et al., 1998, Mendes-Bastos et al., 2022, Kaplan et al., 2023). Remibrutinib was assessed in Phase 2b and two Phase 3 (REMIX-1 & REMIX-2) trials. Results consistently demonstrated efficacy and symptom improvement as early as week 1 sustained until week 52 (Saini, 2023, Metz et al., 2025, Maurer et al., 2022, Giménez-Arnau et al., 2024). Adverse events (AEs) were comparable between the remibrutinib and placebo control cohorts (Giménez-Arnau et al., 2024). Remibrutinib trials in other indications are ongoing, e.g., 3 CIndU indications (symptomatic dermographism, cold urticaria, cholinergic urticaria) in a Phase 3 basket trial.

5.3 Rationale

This study protocol represents the adapted version for Germany. This is a prospective, non-interventional study in patients with CSU. Prior to study enrollment, a study independent treatment decision will have been made for initiation of remibrutinib. The primary aim is to gather real-world effectiveness and safety data for remibrutinib among a broader clinical practice population. This includes collecting data from populations underrepresented in the randomized controlled trials (RCTs), such as patients from office-based and hospital settings (e.g., dermatology, immunology/allergology, and general practice). These patient types and clinical settings can comprise up to 90% of patients with CSU in clinical practice but are not reflected in large placebo-controlled trials to the same degree given the bias for highly specialized sites participating in Phase 2 and 3 clinical trials or given certain inclusion and exclusion criteria of enrolled patients (Novartis data on file).

RCTs are designed to determine the efficacy of an intervention under rigorous conditions, including strict protocols, eligibility criteria defining a well-selected patient population, and patient randomization, which maximizes their internal validity. However, for the results to be clinically meaningful, they must also be relevant to the wider patient population (i.e., have external validity) (Kennedy-Martin et al., 2015). This study aims to generate real-world effectiveness and safety data of remibrutinib in a broader patient population, thereby confirming external validity and bridging the evidence gap between controlled research environments and everyday clinical practice.

Assessing the quality of care in CSU through metrics like time to guideline-recommended therapy escalation is vital. This is of particular importance in non-specialist centers.

Previous data from global studies such as AWARE, Urticaria Voices, and data from the CURE specialist registry confirm either a lack of or significant delay in escalation to efficacious therapies despite guideline-recommendation and clinical indication to do so (Maurer et al., 2019, Bernstein et al., 2023, Göncü et al., 2024). Timely intervention can improve patient outcomes, reduce symptom burden, enhance overall QoL, and improve health care system efficiency. REASSERT intends to assess real-world CSU patient management, such as adherence to treatment guidelines, and correlate it with treatment outcomes, such as time to and degree of urticaria symptom control.

The REASSERT protocol describes the full study plan.

6 Research question(s) and objectives

6.1 Research question(s)

The REASSERT study is conducted in a CSU population significantly broader than the one included in the Phase 2 and Phase 3 trials, with 70% observed from non-specialist centers. The study is designed to investigate the real-world early (first 12 weeks) and long-term (up to 24 months) effectiveness of remibrutinib in a broad clinical practice set-up and to establish the real-world, long-term safety profile of remibrutinib.

Of particular interest is the early onset of action (from week 1), patients reported symptom relief, and remibrutinib real-world treatment patterns in CSU.

Furthermore, the study will generate evidence on the quality of care in current real-world clinical practice, assessing the implementation of guideline recommendations and the impact of delayed treatment escalation and non-compliance with the guidelines on clinical outcomes, symptom burden of patients, and on the healthcare systems. Finally, this study will investigate whether remibrutinib may have a disease-modifying potential in certain subpopulations, such as early treated patients or patients with an autoimmune component. [redacted]

Note, endpoints are analyzed from globally pooled data, with country level subgroup analysis.

6.2 Study objectives

Primary objective

The study evaluates the following primary objective and endpoint.

Table 4-1 Primary objective and endpoints

Primary Objective	Primary Endpoint
1. Evaluate the 12-week real-world effectiveness of remibrutinib in adult patients diagnosed with CSU who remain	• Achievement of well-controlled disease (UCT7 ≥ 12) at Week 12 after initiating remibrutinib treatment.

Primary Objective	Primary Endpoint
symptomatic despite sgH_1-AHs (cohort 2 and 3 pooled).	

Secondary objectives

The study evaluates the following secondary objectives and endpoints if sufficient data are available.

Table 4-2 Secondary objectives and endpoints

Secondary Objectives	Secondary Endpoints
1. Evaluate the real-world effectiveness of remibrutinib treatment (cohort 2 and 3 separately and pooled) in patients with CSU over 24 months.	• Achievement of well-controlled disease UCT ≥ 12 at months 6, 9, 12, 15, 18, 21, 24. • Achievement of well-controlled disease UAS7 ≤ 6 at months 6, 9, 12, 15, 18, 21, 24. • Achievement of complete control (UCT=16) at months 6, 9, 12, 15, 18, 21, 24. • Achievement of complete control UAS7=0 at months 6, 9, 12, 15, 18, 21, 24. • Change from baseline (CFB) in UCT score (at months 6, 9, 12, 15, 18, 21, 24. • CFB in UAS7 score at months 6, 9, 12, 15, 18, 21, 24. • CFB UAS7 ≥ minimal important difference (MID; -10.5 points) at 6, 9, 12, 15, 18, 21, 24 months. • Number of weeks without angioedema at months 6, 9, 12, 15, 18, 21, 24. • Change in Angioedema Control Test (AECT) from baseline at months 6, 9, 12, 15, 18, 21, 24. • Rescue medication requirement assessed at months 6, 9, 12, 15, 18, 21, 24 by type (AH, steroids, others). • Characterize CSU relapse (and number of relapses) by months 6, 9, 12, 15, 18, 21, 24: angioedema (yes/no), hives (yes/no), location, duration (hours/days), severity (UCT/UCT7/UAS) and/or characterize relapse (UCT7/UAS7) via app if available).
2. Evaluate the early (starting week 1) real-world effectiveness of remibrutinib (cohort 2 and 3 separately and pooled) up to week 12 in patients with CSU.	• UCT7 at Weeks 1, 2, 4, 8. • UAS7 at Weeks 1, 2, 4, 8, 12. • Change in UCT7 score from baseline at Weeks 1, 2, 4, 8, 12. • Change in UAS7 from baseline at Weeks 1, 2, 4, 8, 12. • Achievement of well-controlled disease UCT7 ≥ 12, at Weeks 1, 2, 4, 8. • Achievement of complete control UCT7=16 at Weeks 1, 2, 4, 8 and 12. • Achievement of well-controlled disease UAS7 ≤ 6 at Weeks 1, 2, 4, 8, 12. • Achievement of complete control UAS7=0 at Weeks 1, 2, 4, 8 and 12. • Number of weeks without angioedema at Weeks 1, 2, 4, 8, 12. • Change in AECT from baseline at Weeks 1, 2, 4, 8, 12. • Requirement of rescue medications by type at Weeks 1, 2, 4, 8, 12.

Secondary Objectives	**Secondary Endpoints**
	• CFB UAS7 ≥ MID (-10.5 points) at Weeks 1, 2, 4, 8, 12. • Characterize CSU relapse (and number of relapses) at Weeks 1, 2, 4, 8, 12: angioedema (yes/no), hives (yes/no), location, duration (hours/days), severity (UCT/UAS) • Characterize relapse (UCT7/UAS7 via app, if available).

3. Characterize the short-term (up to 12 weeks) and long-term (up to 24 months) real-world treatment patterns and concomitant CSU medication(s) in patients with CSU treated with remibrutinib (cohort 2 and cohort 3 separate).	• Administration of remibrutinib according to label at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 21, 24.
	  • Therapy duration (days/weeks/months).
	  • UCT7/UCT/UAS7 (as appropriate) at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 21, 24.
	• Administration of rescue medication (corticosteroids, others) (type, dose, duration) at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 21, 24.
	• Usage of concomitant sgH_1-AHs and additional prescribed CSU treatments (type, dose, frequency) at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 21 and 24.
	• Administration of CSU-related treatment(s) outside of local and/or international guidelines at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 24, and by treatment type. Demonstrate relationship between non-adherence to local and or international guidelines and impact on patient, disease control, treatment patterns and healthcare resource utilization (HCRU) during early and long-term follow-up at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 21 and 24.
	• Delay of treatment escalation contrary to local and/or international guidelines Time (days/months) without escalation, with UCT < 12 or UAS7 > 6 at time points measuring UCT7 (early) / UCT (month 3 onwards) / UAS7 group.

4. Assess QoL in CSU patients treated with remibrutinib (cohort 2 and 3 separately and pooled) up to 24-months.	• Occurrence of DLQI scores of 0-1, 2-5, 6-10, 11-20, and 21-30 at baseline, Weeks 1, 2, 4, 8, 12, and Months 6, 9,12, 15, 18, 21, 24. • Change in DLQI scores from baseline at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 21 and 24. • Change in Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) questionnaire scores from baseline to weeks 4, 8, 12, and months 6, 9, 12, 15, 18, 21, 24. • Baseline sleep interference score and achievement of no interference (0), mild interference (1), moderate interference (2), and substantial interference with sleep (3) up to week 12. • (Question: How much did your urticaria interfere with your sleep in the past week?) • Hospital anxiety and depression scale (HADS) at baseline, week 12, months 6, 12, 18, 24 months and change from baseline at each timepoint.
5. Determine HCRU and work productivity in patients treated with remibrutinib (cohort 2 and 3 separately and pooled).	• Quarterly and annualized number of events related to CSU (e.g., inpatient hospitalizations, length of stay, emergency room visits, outpatient visits) assessed at week 12 and months 6, 9, 12, 15, 18, 21, 24.

Secondary Objectives	Secondary Endpoints

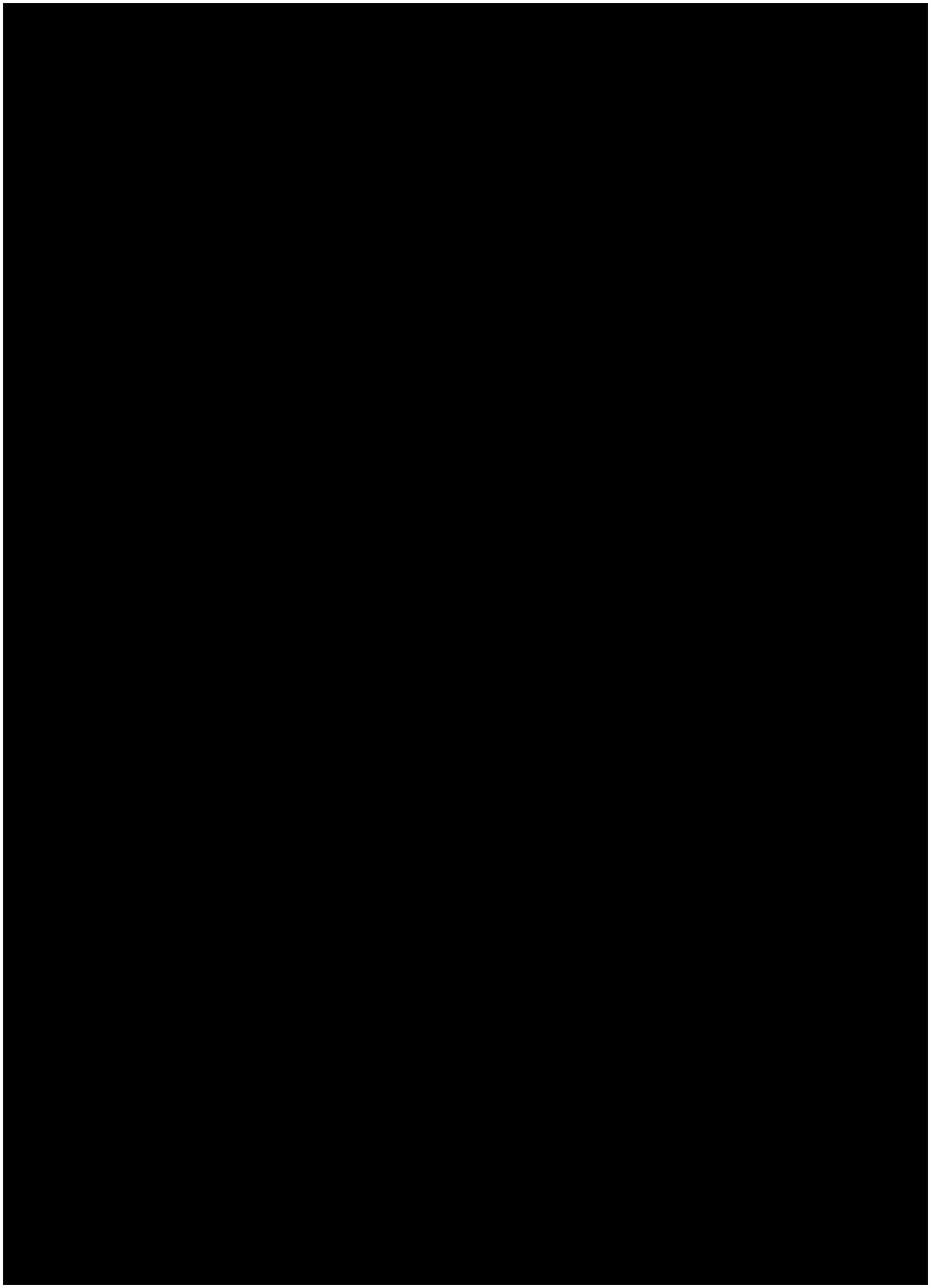
	• Work productivity and activity impairment (WPAI)CU score at baseline, week 12and months 6, 12, 18 and 24 and change from baseline.
	  • Absenteeism (work time missed).
	  • Presenteeism (impairment at work/ reduced on-the-job-effectiveness).
	  • Work productively loss (overall work impairment).
	  • Activity impairment.

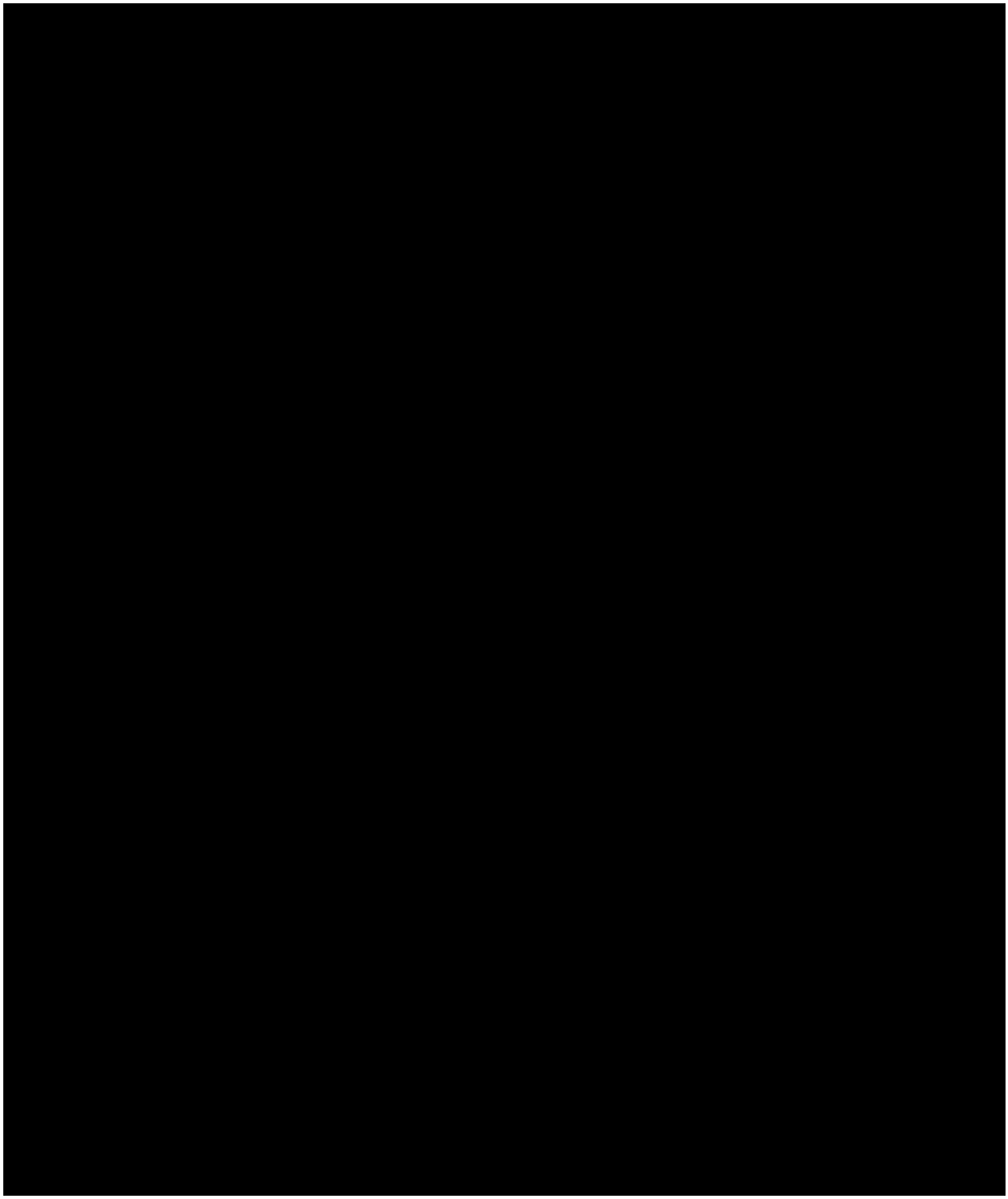
6. Assess the safety profile of remibrutinib among all patients with CSU who initiate remibrutinib (cohort 2 and 3 separate and pooled) over a 24-month treatment period in a real-world setting.	• Incidence (including exposure-adjusted) of AEs, including serious AEs (SAEs). ▪

Exploratory objectives

The study evaluates the following exploratory objectives and endpoints if sufficient data are available.

Table 4-3 Exploratory objectives and endpoints





7 Research methods

7.1 Study design

REASSERT is a multi-country, prospective, non-interventional primary data collection study in a real-world setting. The study employs an umbrella design which brings together the

evidence needs from multiple countries under the REASSERT global program. This version of the protocol has been tailored to meet the specific requirements of Germany. Data from each country will be globally pooled and analyzed as available.

The study has 2 periods:

- Early observational period (Phase 1): Baseline to week 12
- Long-term observational period (Phase 2): From months 3 to 24

and observes in Germany the following cohorts (also described previously in Section 2):

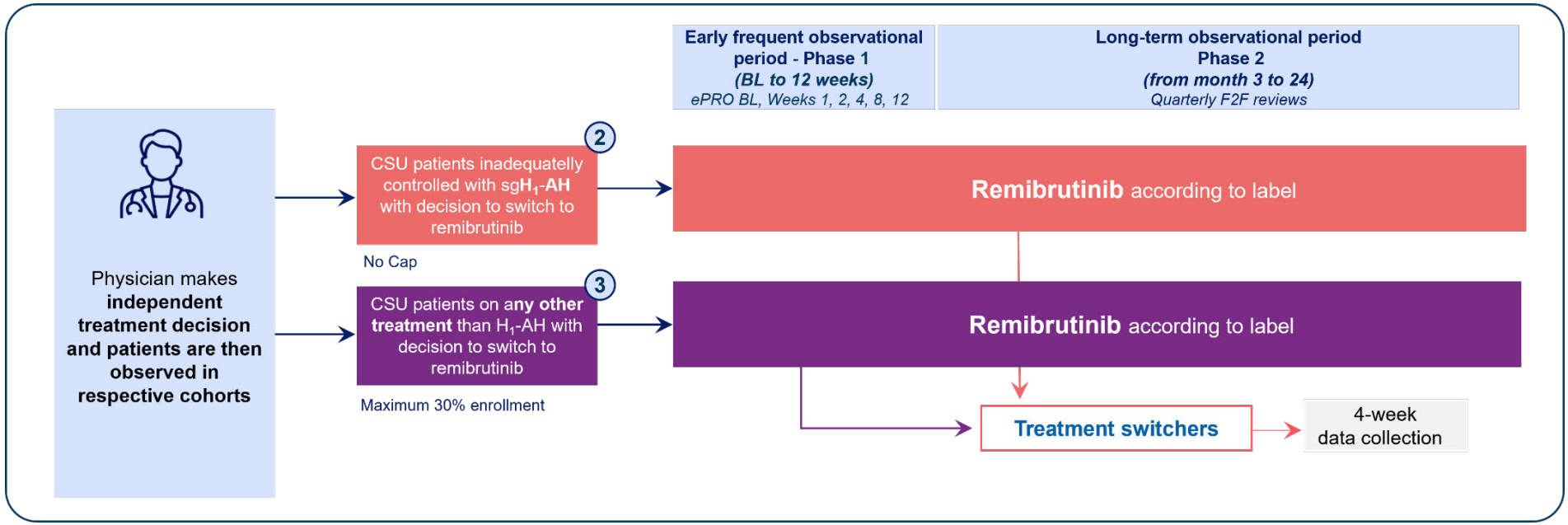
- **Cohort 2**: Inadequate control of CSU despite licensed dose or escalated sgH_1-AH(s) (no other pre-treatment with exception of first generation H_1-AH permitted) with decision (independent of study enrollment) to switch to remibrutinib treatment as per local label.

- **Cohort 3**: Any other treatment received in addition to H_1-AH, any time during patients CSU treatment history, with decision (independent of study enrollment) to switch to remibrutinib treatment as per local label. Baseline visit comprises of clinical assessment before switch to remibrutinib and follow-up visits capture clinical outcome of treatment with remibrutinib as per local label. Enrollment will be capped at a maximum of 30% of the local population. Note, occasional steroid rescue medication is out of scope for cohort definition. If a patient had been on continuous steroids for at least 3 weeks during treatment history, they will be included. Patients being switched from remibrutinib treatment (cohort 2 and 3) to another treatment (other than H_1-AH) will be followed for another 4-weeks in the 'Switch Cohort', after treatment switch. Patient observation ends in this scenario after 4 weeks (instead of the planned 24 months).

Note: Candidate patients must not have initiated remibrutinib treatment prior to their enrollment to ensure the baseline visit captures their clinical status before treatment escalation.

The study design is shown in Figure 1-1.

Figure 1-1 REASSERT study design



Treatment switchers: discontinuation of Remibrutinib treatment AND switch from Remibrutinib treatment to another CSU medication other than H1-AH e.g., Omalizumab, Dupilumab, Ciclosporin, or other medication that became commercially available during the study timeframe.

Abbreviations: AH = Antihistamines, BL = baseline, CSU = Chronic Spontaneous Urticaria, ePRO = electronic patient-reported outcome, F2F = Face to Face, H_1-AH = H_1 antihistamine, sgH_1-AH = Second-Generation H_1 Antihistamines.

7.2 Setting and study population

Study setting

The study is conducted in various healthcare system settings, office- and hospital-based. The aim is to observe the real-world practice in the management of CSU patients. The split of around 70% office-based (dermatologists, allergists, immunologists, and GPs) and around 30% specialist centers is designed to allow for the inclusion of a broad variety of physician and patient types.[1]

Only patients who are willing to download the study app and document on a regular basis in the study app should be considered for enrollment. ePROs at specified timepoints are collected outside of the hospital setting. Patients are asked to confirm medication intake daily via the app (electronic diary (eDiary)) for the first 4 weeks of escalated treatment. From month 3, patients are asked weekly to confirm medication intake and if symptoms occurred in the last week (if yes, a UCT7 is prompted via eDiary on the study app). If a treatment break and/or remission occurs during the study, patients are asked to confirm/update this status via the app. Data collection during physician visits will also be collected via electronic data capture (EDC) system. Data captured via the app is linked to the EDC.

Study population

The study includes adult CSU patients being managed for their disease. Patients under the care of office-based dermatologists (OBDs), allergists, immunologists, CSU specialists/specialist centers, or general practitioners are enrolled. The target ratio of specialists to non-specialists (OBDs/office-based allergists/GPs) will be around 30/70. All treatment decisions will be at the discretion of the healthcare practitioner/health care provider (HCP).

Study period and relevant dates

The study follows patients for 24 months (regardless of remission status), with the local study end date defined by the last patient's last visit. The relevant dates are described as follows:

a. **Enrollment phase:** No predefined enrollment phase. Patients are enrolled for observation on a rolling basis when their physician identifies a lack of disease control that is compatible with one of the 2 cohorts.
b. **Baseline study start date:** Date of baseline assessment (captured by treating physician via EDC), BEFORE treatment escalation/switch – i.e., before the initiation of remibrutinib. The baseline date may, but does not have to, coincide with the day of remibrutinib initiation.
c. **Remibrutinib treatment start date**: Date of first dose intake of prescribed remibrutinib treatment (provided by patient, via study app)
d. **Early observational period (Study Phase 1): First 12 weeks** and commences at date of first prescribed treatment intake, i.e., steps "c" above - patients will perform data entry via study app. One office visit is recommended during this 12-week timeframe.

[1] Note, this split is a suggestion and not mandate. If a country has prescriber rules which restrict office-based dermatologists from enrolling patients, they may focus more of their enrollment in the specialist centers.

e. **Long-term observational period (Study Phase 2):** from month 3-24 months (patients will perform data entry via study app and physician's perform data entry of patient visits at the medical site via EDC).

Note for "c" and "d" above: if data are not entered into the study app, then prescription date will be used as a proxy for treatment start date (and patients will be excluded from the analysis pertaining to fast onset of action of remibrutinib).

Patients are asked to confirm medication intake daily via the app (eDiary) for the first 4 weeks, and symptoms and medication intake weekly thereafter. If in treatment break or remission they will have the option to confirm absence of treatment/symptoms and re-initiation of treatment and recurrence of symptoms (if applicable).

7.2.1 Inclusion criteria

Patients must meet all the following criteria to be eligible for inclusion in this study.

1. Patients with a confirmed diagnosis of primary CSU by the treating physician.
2. Aged at least 18 years on the date of enrollment.
3. Written informed consent of the patient to participate in the study and willingness to complete full follow-up period of 24 months.
4. Cohort-specific observational inclusion criteria:

   a. **Cohort 2:** Inadequate control of CSU despite licensed dose or escalated sgH_1-AH(s) (no other pre-treatment with exception of first generation H_1-AH permitted) with decision (independent of study enrollment) to switch to remibrutinib treatment as per local label.
   b. Cohort3: Any other treatment received in addition to H_1-AH, any time during patients` CSU treatment history, with decision (independent of study enrollment) to switch to remibrutinib treatment as per local label. Note, occasional steroid rescue medication is out of scope for cohort definition. If a patient had been on continuous steroids for at least 3 weeks during treatment history, they will be included in cohort 3.

Note: Candidate patients must not have initiated remibrutinib treatment prior to their enrollment to ensure the baseline visit captures their clinical status before treatment escalation.

7.2.2 Exclusion criteria

Patients are excluded if they meet any of the following criteria:

1. Simultaneous participation in any investigational trial or simultaneous participation in another Novartis-sponsored non-interventional study with remibrutinib.
2. Patients within the safety follow-up phase of a previous interventional or non-interventional study.
3. Patients who received remibrutinib at any time in the past.
4. Patients not capable or willing to continuously provide ePRO/eDiary data via electronic means throughout the duration of the study.

5. Patients who are treated with remibrutinib outside of the local label.

7.3 Data sources

This study is based on primary data collection as currently available data sources on CSU are insufficient to address the study objectives. Existing data sources often have inconsistent endpoint definitions, lack follow-up data, sparse assessment time points, and often include biased patient phenotypes (e.g., patients within expert centers with severe and long disease duration ~5+ years).

Data for this study are collected using an electronic case report form (eCRF), including patient demographics, medical history, comorbidities, clinical characteristics at baseline, and outcomes at follow-up visits. All data are collected in a routine clinical practice setting and will not include any protocol-mandated physical assessments. All data are pseudonymized/coded, ensuring no personal identifiers are included in the final dataset used for analyses.

Additionally, ePROs are collected via mobile phone application at all time points and in between clinical visits. In addition, medication intake, disease control, treatment break and remission/intermittent remission status are captured via an eDiary available on the study app. The ePRO/eDiary data is linked to the EDC system and provides patients the ability to report symptoms and medication use outside of clinic visits (Friedman et al., 2024).

This functionality is of high importance due to the waxing and waning nature of CSU; patients may not have symptoms at the time of their clinic visit, so the ePRO/eDiary provides an additional opportunity to capture key data on CSU symptoms, treatment and control throughout the 24-month observational period. Various studies have found that patients prefer mobile health apps to paper documentation when documenting and tracking their disease activity and control (Neisinger et al., 2024, Cherrez-Ojeda et al., 2021). Additionally, recent studies of app use in chronic allergic conditions have demonstrated high patient interest, satisfaction, compliance, and subjective improvements in their disease. Standardized, validated patient-reported outcome measures (PROMs), captured in the ePRO, are a key tool for monitoring responses to treatment in patients with CSU and are recommended in the current international guidelines. Key PROMs include:

- UCT is available as either looking back retrospectively for 28 days or 7 days (UCT7) and consists of 4 questions. Each question is scored 0-4, with a total score range of 0-16. < 12 indicates poor disease control, 12-15 = well-controlled and 16 indicates complete control. The tool is available in 30+ languages and standard UCT is validated for 18+ years.
- UAS7 is based on 2 daily questions (number of wheals (hives) and intensity of pruritus (itch)). Each question is scored 0-3 per day, with a maximum daily score of 6 and weekly total score ranging from 0-42. Score of 0 suggests urticaria free, ≤ 6 = well-controlled, 7-15 = mild activity, 16-27 = moderate activity, and 28-42 = severe activity. UAS7 is validated for adults 18+ years.
- DLQI consists of 10 questions looking back retrospectively for 7 days. Each question is scored from 0 (not at all) to 3 (very much). Total score ranges from 0-30. Scores 0-1 = no effect on a person's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, 21-30 = extremely large effect The DLQI is translated to over 110 languages and validated for 16+ years.

Concomitant and prior medications entered into the database are coded using the World Health Organization (WHO) Drug Reference List. Medical history/current medical conditions and AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Safety data are transferred to Novartis at a frequency as defined in Section 9 of this protocol and/or contract research organization (CRO) contract. Clinical data are transferred to Novartis throughout and after the closure of the study.

Data collection schedule

Patients need to be initiated on remibrutinib treatment according to the local prescribing information. The treating physician is asked to complete the appropriate eCRF at every patient visit. This includes baseline, one visit in the early phase (weeks 1-12), and quarterly thereafter. A patient ePRO/eDiary data capture system (accessible on mobile phone or desktop) linked to the EDC system is developed to enable patients to enter data at earlier time points (e.g., week 1) at home and during symptom free periods, where no physician visits will be necessary. The recommended data collection schedule is one that most likely mirrors the patterns of routine clinical care of most patients being treated with remibrutinib. When the patient is returning for a routine appointment, they may complete the ePRO's prior to the clinician visit via the study app, or the physician can enter the data into the EDC system during the visit.

Upon return to clinic, ePRO data entered by the patient will be reviewed by the physician together with the patient (e.g., summary report from EDC).

It is expected that patients with CSU will enter periods of remission (intermittent or full remission) and may have treatment break(s). During these periods, they may or may not be attending with their clinician for medical review. In this instance, patients are requested to confirm the continuation (or end) of these periods (i.e., treatment break, intermittent remission, remission) via the eDiary in study app throughout the 24-month study duration.

Assessment schedule

The assessment schedule is outlined in Table 5-1.

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study. The treating physician is asked to complete the appropriate eCRF at every patient visit.

Table 5-1 Optional assessment schedule

Time of Visit	**Baseline/ study inclusion**	**Treatment start**	**At each visit (via app and minimum of one physician visit in the early observational period (Phase 1))**	**At each visit in the long-term observational period (Phase 2)**	**Final study visit**
	BL	**Day 1**	**Weeks 1, 2, 4, 8, 12**	**From Month 3, 6, 9, 12, 15, 18, 21**	**24 months**
Inclusion/exclusion criteria	X				
Information & informed consent	X				
Physical examination	X				
eCRF and/or ePRO/eDiary					
Baseline demographics	X				
Medical history	X				
Comorbidities	X				
Comorbidities related to CSU	X		X	X	X
Previous CSU medications	X				
CSU-related investigations (IgE, anti-TPO antibodies, tryptase, endotyping etc.,), if available	X		X	X	X
Non-CSU medications	X		*X (updated if needed)*	X *(updated if needed)*	X *(updated if needed)*
Current CSU medications	X	X	X	X	X
[redacted]					
Angioedema	X		X	X	X
AECT[1]	X (If angioedema present)		X	X	X
UCT[2]	X	X (if ≥ 7 days since clinic/ enrollment)	X	X	X
DLQI score	X	X (if ≥ 7 days since clinic/ enrollment)	X	X	X
UAS7[1]	X	X if ≥ 7 days since clinic/ enrollment	X	X	X

Time of Visit	**Baseline/ study inclusion**	**Treatment start**	**At each visit (via app and minimum of one physician visit in the early observational period (Phase 1))**	**At each visit in the long-term observational period (Phase 2)**	**Final study visit**
	BL	**Day 1**	**Weeks 1, 2, 4, 8, 12**	**From Month 3, 6, 9, 12, 15, 18, 21**	**24 months**
[redacted]					
Sleep[1]	X		X	X	X
WPAI score[1]	X		X	X	X
HADS	X		X	X	X
CU-Q2oL[1]	X		X	X	X
HCRU[1]	X		X	X	X
[redacted]					
AEs (physician assessed at clinic only)			X (assessed retrospectively in clinic)	X (assessed retrospectively in clinic)	X (assessed retrospectively in clinic)
Treatment break[3]			X (assessed if in clinic, and logged at home via app)	X (assessed if in clinic, and logged at home via app)	X (assessed if in clinic, and logged at home via app)
Intermittent remission[3]			X (assessed if in clinic, and logged at home via app)	X (assessed if in clinic, and logged at home via app)	X (assessed if in clinic, and logged at home via app)
Remission[3]			X (assessed if in clinic, and logged at home via app)	X (assessed if in clinic, and logged at home via app)	X (assessed if in clinic, and logged at home via app)

"X" denotes minimum assessment. Additional assessments at discretion of physician and local study adaptations possible.

Data may be gathered via an ePRO platform, or in clinic. Patients can confirm symptoms, pill intake, and remission/treatment break status, if applicable, via app.

Abbreviations: AEs = Adverse events, AECT = Angioedema Control Test, BL = baseline, [redacted], CSU = Chronic Spontaneous Urticaria, CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire, DLQI = Dermatology Life Quality Index, eCRF = Electronic Case Report Form, eDiary = electronic diary, ePRO = electronic patient-reported outcome, HADS = Hospital anxiety depression score, HCRU = healthcare resource utilization, IgE = Immunoglobulin E, [redacted] TPO = Thyroid Peroxidase Antibodies, UAS7 = Urticaria Activity Score over 7 days, UCT = Urticaria Control Test, UCT7 = 7-day recall period version of the Urticaria Control Test, WPAI = Work Productivity and Activity Impairment.

[1] Additional optional assessment, selected by countries based on local needs.

[2] UCT7 will be collected during the early observational period (Phase 1), UCT (i.e., 28-day look back) will be collected during the long-term observational period (Phase 2).

[3] If in treatment break, intermittent remission or remission: confirmation of status will also be tracked via app.

Note: Below is an overview of the data that patients are asked to record using ePROs/eDiary via a mobile app, along with an estimate of the time typically required for each task.

- Enrollment: download study app, set-up user profile, test functionality (~10 min)
- Treatment start (intake of remibrutinib according to label): confirm medication intake (and if > 7 days lapsed since enrollment visit repeat DLQI, UCT) (~5-10 min)
- Medication confirmation: daily for first 4 weeks and weekly thereafter (<2 mins)
- From week 3: weekly CU symptom check (with ePRO(s) if symptomatic): week 3, 5, 7, 9, 10, 11 and weekly thereafter (~2-8min)
- Weeks 1, 2, 4, 8, 12: ePROs (minimum UCT/UAS7 and DLQI (~15 min)
- Quarterly ePRO input from month 3 (aligned with physician visits) (~15 min)

7.3.1 Early Study termination by the Sponsor

The study can be terminated by Novartis at any time. Reason for early termination (but not limited to) includes:

- Failure to meet the required recruitment goals overall or at a particular study site.
- Emergency of any safety or efficacy information that could potentially affect the continuation of the study.
- Any administrative reasons.
- Violation of study protocol or contract by Investigator or study site.
- Withdrawal of consent.

In taking the decision to terminate, Novartis will always consider participant welfare and safety.

7.4 Study size/power calculation

The total sample size required for Germany is 470 patients. The sample size calculation for this study is based on both the primary objective: Evaluate the 12-week real-world effectiveness of remibrutinib in adult patients diagnosed with CSU who remain symptomatic despite sgH_1-AH (all patients who initiate remibrutinib, regardless of prior treatment; cohorts 2 and 3 pooled) and the secondary objective: Evaluate the real-world effectiveness of remibrutinib treatment in patients with CSU over 24 months.

Cohort 2 and 3 are assumed to have similar response rates and can be combined, as observed in the REMIX trials.

In the Phase 3 studies (pooled REMIX 1 and 2), the observed proportion of patients on remibrutinib achieving UCT7 ≥ 12 at week 12 was **58.4% (95% confidence interval (CI): 54.1 – 62.6)**. Based on these studies and an expected **response rate of 55% in this study**, assuming a precision (width of 95% CI) of 4.5%, the required sample size for cohort 2 and 3 combined, that would ensure the 95% CI lies between 52.8% to 57.2% is **235 patients**.

For the estimation of the proportion of patients achieving UCT7 ≥ 12 at week 12 in cohort 2 and 3 combined, a sample size of 235 will produce a two-sided 95% CI with a precision of 12.7%, when the expected proportion is 55% using the normal approximation of the binomial distribution. The 95% CI is estimated to range from 48.6% to 61.4%.

The key secondary objective is the collection of 24-month real world effectiveness data. To date, 24-month real world data are lacking, also existing clinical data from the REMIX studies only extend up to 52 weeks.

To achieve a 95% confidence interval estimated to range from 48.6% to 61.4%. at the end of a 24-month observation period, the patient number is adjusted to account for the known dropout rate from the AWARE[2] German study data, which was 50.4% after 24 months. Therefore, the required sample size for cohort 2 and 3 combined, at 24 months is around **470 patients**.

The study design includes caps for balanced representation. Cohort 2 has no cap on enrollment, but a minimum enrollment of 70% of the local study population is planned, ensuring at least 329 patients. Enrollment for cohort 3 is capped at a maximum of 30% of the total study population, which translates to approximately 141 patients out of the total 470 patients. These caps ensure a balanced representation of patients across different treatment pathways while allowing for sufficient data collection to meet the study objectives.

7.5 Data management

All data collected in this study will be stored in accordance with local laws and regulatory requirements. IQVIA is involved in building the database. Electronic data collection is performed using eCRFs. Sites will enter data into the EDC system. The system used for capturing patients' data complies with industry standards and regulatory expectations for software developers and service providers within the global regulatory environment (US 21 CFR Part 11, EU Commission Directive 2005/28/EC). The platform is a secure, easy to use and reliable web-based EDC platform for the collection and reporting of clinical data. Patients are identified using a study identification number assigned to them when they enroll in the study. The Investigator and site staff will receive training on recording the data on the eCRFs using the EDC system. All participating sites will have access to the data entered regarding the individual site, its own enrolled patients. Investigators and site personnel will be able to access their account with a username and password. Only authorized personnel will have access to the EDC system.

Data need to be entered into eCRFs in accordance with the study's eCRF completion guidelines. The Investigator is responsible for ensuring that accurate data are entered into the eCRFs in a timely manner. Online logic checks are built into the system, where possible, so that missing or illogical data are not submitted. If inconsistent data persist, queries may be issued electronically to the study site and answered electronically by site staff. The identifying information (assigned username, date, and time) for both the originator of the query and the originator of the data change (if applicable), as well as the Investigator's approval of any data changes in the eCRF will be recorded. The Investigator is responsible for reviewing eCRFs, resolving data queries generated by the Sponsor and/or designee via the system, providing missing or corrected data,

[2] To obtain information about discontinuation at month 24 for German study participants (not reported in AWARE), the availability of data from the disposition of patients from the German AWARE data was used. At baseline, 2260 patients were enrolled. Premature withdrawal was observed for 1114 patients. Assuming the same for the REASSERT study, the estimated discontinuation rate for Germany is 50.4% at month 24.

approving all changes performed on patient data, and a password that together will represent a traditional handwritten signature.

All submitted eCRFs are checked for missing information and queries will be generated to prevent the occurrence of missing data. In most cases, the eCRF should be reviewed, electronically signed, and dated by the Principal Investigator. All changes or corrections to eCRFs are documented in an audit trail and an adequate explanation is required. Concomitant or prior medications entered into the database are coded using the WHO Drug Reference List. Medical history/current medical conditions and AEs are coded using the MedDRA terminology. Safety data are transferred to Novartis at a frequency as defined in Section 9 and/or CRO contract. All study data will be transferred to Novartis after closure of the study.

Data collection

An EDC system is used for data collection in this study. The site personnel will review patients' electronic health records (EHRs)/medical records and manually abstract the required data directly into the eCRF within the EDC system to support acquisition of data for baseline assessment. Thereafter, data collection is prospective. All participating sites will have access to the data entered for patients enrolled at their site. All sites will be fully trained on using the EDC system, including eCRF completion guidelines and help files. The details of data management procedures to ensure the quality of the data will be described in a separate data management plan.

ePRO and data collection process

Patients are asked to complete ePRO assessments using their own device, expected to take approximately 15 minutes per visit. Patients should be reminded by clinic staff to complete the ePRO assessments prior to their appointment (e.g., research nurse or clinic administration staff). In addition, patients are asked to confirm medication intake daily during first 4 weeks of escalated/switched treatment and thereafter to provide weekly confirmation of disease status, medication intake and remission status via the eDiary.

- The research nurse or appointed site staff will train the patient to use the ePROs on their device, if necessary. A test run will need to be performed in clinic on the day of enrollment.
- All ePRO questionnaires are completed using an ePRO app on the patient's device. A key aspect of study success will be to have high ePRO compliance. Therefore, every effort will be taken to follow the assessment schedule (Table 5-1) including:
  - Patients who cannot attend the visit will receive email and phone reminders (SMS texts), if they have opted in for a reminder service.Study personnel are asked to monitor assessment compliance through a compliance dashboard.
  - Patients, will be remunerated for their time spent on data entry.

Data processing

Data entered in the eCRF is immediately saved to a central database and changes are tracked to provide an audit trail. Healthcare providers and site personnel are able to access their account with a username and password. All eCRFs must be completed by designated, trained personnel

or the study coordinator, as appropriate. When data have been entered, reviewed and edited, the eCRFs should be reviewed, electronically signed, and dated by the HCP. Data will be locked to prevent further editing during final database lock. A copy of the eCRF will be archived at the site after the final database lock.

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs include programmable edits to obtain immediate feedback if critical data are missing, out of range, illogical or potentially erroneous. Review of supplemental programmed validation checks performed on downloaded data are applied to ensure accurate, consistent, and reliable data. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. All modifications to the data will be recorded in an audit trail.

For observational research studies it is understood that some of the real-world data could be missing or incomplete in the EHR. Incomplete and missing eCRF data will be flagged and collected as part of ongoing data quality monitoring in the study.

Statistical software

All analyses are performed using Statistical Analysis System (SAS) for Microsoft Windows operating system statistical software (SAS Institute, Cary, North Carolina, USA) version 9.4 or higher, using validated implementations of each application or SAS custom programming.

Additional software such as R maybe used for data visualizations or other analyses as needed.

7.6 Data analysis

Overview

All analyses are performed by a CRO in collaboration with Novartis. Detailed information about the CRO and the collaboration is provided in the statistical analysis plan (SAP). This study is descriptive in nature, and no formal hypotheses will be tested. The non-interventional study (NIS) protocol and SAP includes detailed statistical procedures, including multivariable analysis.

Analysis overview

Data is analyzed pooled (global and regional) and locally for each of the participating countries. Pooled analyses are conducted according to the following timelines:

- Baseline data at 10%, 25%, 50%, 100% recruitment.
- 12-week data at 10%, 25%, 50%, 100% recruitment.
- 12-month data at 25%, 50%, 100% recruitment.
- 24-month data at 50% recruitment.
- Close-out report at 24 months with 100% recruitment.

Data stratified by region and country are provided at each time point where available.

As per Table 4-1, interim reports are generated at 3 timepoints: 100% baseline data is available, 100% 12-week data available, and 100% 12-month data available.

Descriptive statistics

Data are summarized using descriptive statistics. Continuous variables are summarized by the number of non-missing observations, mean, SD, median, first and third quantiles, and ranges (minimum and maximum values). Categorical variables are presented as counts and percentages. Time-to-event variables are presented using Kaplan-Meier methods with the median survival time with a 95% CI if reached, and the survival probability at specific time points with a 95% CI is reported.

All patients enrolled in the study and assessed at various time points are included in the analysis. Due to the multi-cohort design and long-term follow-up nature of the study, the sample sizes contributing to summary statistics are expected to vary. These differences will be explicitly mentioned when results are available.

Summary of baseline characteristics

Variables collected at baseline, including patient characteristics, medical history, co-morbidities, disease status, clinical characteristics, medications, and used health care resources since diagnosis, are summarized descriptively, both overall and by cohort.

Primary endpoint analysis

The primary objective is to evaluate the 12-week real-world effectiveness of remibrutinib in adult patients diagnosed with CSU who remain symptomatic on sgH_1-AHs. The primary endpoint is the proportion of patients achieving well-controlled disease (UCT7 $\geq$ 12) at week 12 after initiation of remibrutinib treatment. The proportions are summarized as frequency and proportion, with two-sided 95% CIs. Analysis is conducted in the remibrutinib cohort 2 and 3 separately and pooled.

Secondary endpoint analysis

The secondary objectives include evaluating the long-term effectiveness, QoL improvements, remission rates, safety, and treatment patterns. For the long-term effectiveness, the analysis focuses on the proportion of patients achieving well-controlled disease (UCT7 $\geq$ 12 or UAS7 $\leq$ 6) up to 24 months, and is summarized as frequency and proportion, with two-sided 95% CIs. The analysis is conducted separately for remibrutinib cohort 2 and 3 and pooled together.

To assess the impact of remibrutinib on QoL, changes in DLQI scores from baseline to 24 months (and other continuous longitudinal measures) are analyzed using regression models, such as mixed models for repeated measures. The changes from baseline are summarized by the number of non-missing observations, mean, SD, median, first and third quantiles, ranges (minimum and maximum values), and the model-estimate means with two-sided 95% CIs are reported. These models adjust for baseline QoL, disease severity, and demographic factors to estimate the effect of remibrutinib on QoL. The analysis is conducted for each cohort separately and for cohorts 2 and 3 pooled together. Other QoL measures, e.g., CU-Q2oL are optional.

Treatment patterns are summarized by examining the frequency and proportion of patients on each treatment type at each time point. This includes the use of Sankey visualizations to provide insights into treatment trajectories over time. The analysis also explores the patterns of concomitant medication use, summarizing the frequency and proportion of patients with each type of concomitant medication at each time point.

All variables relevant to the secondary endpoints can be found in the secondary objective endpoint table in Section 6.2. Full details for the analysis of all secondary endpoints are described in the SAP.

[redacted]

[redacted]

[redacted]

[redacted]

Safety analyses

Safety analyses include all enrolled patients who receive at least one dose of remibrutinib treatment. AEs are summarized by counts, percentages, exposure-adjusted rates, seriousness, and severity. To confirm that patients have received at least one dose, adherence is ascertained by clinician upon next clinical review.

7.7 Quality control

Designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative sites and ensure the collection of high-quality data for this study. At all sites site staff will be trained on the protocol, study logistics, eCRF pages, and on the use of the EDC and ePRO/eDiary system. Retraining will be conducted as needed. Investigators will be reminded of the processes and importance of reporting adverse reactions, SAEs, and other information. Monitoring is performed to ensure that informed consent forms (ICFs) have been completed for all enrolled patients. Subsequently, escalated monitoring may be performed at selected sites as needed, according to the study Monitoring Plan. At monitoring visits, the progress of the study and any procedural or data issues will be discussed with the Investigator and/or site staff. The Investigator will make patient source documents available for review and will permit the Sponsor, representatives of the Sponsor, Independent Ethics Committee (IEC), or regulatory authorities to inspect the facilities and original records relevant to this study. The Investigator will allocate adequate time to discuss findings and relevant issues and, after the visit, to complete appropriate corrective actions, as necessary. The Investigator is responsible for the completeness and accuracy of the data reported.

Data will need to be entered by the Investigator/Study Coordinator into the study database. IQVIA, the designated 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 all 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.

Data validation

To ensure data integrity, a comprehensive validation process is implemented, including:

- Consistency checks (range validation, logical inconsistencies, and missing data detection).
- Cross-referencing with source documents to verify accuracy, especially for real-world data sources such as ePROs/eDiary.
- Reconciliation of data sources to address discrepancies across clinical and ePRO and eDiary datasets.

Independent double programming

IQVIA will implement independent double programming to verify the accuracy of all statistical analyses, ensuring reproducibility. Statistical outputs, including tables, listings, and figures, will undergo independent programming by a second statistician/programmer/analyst, and any discrepancies will be reviewed and resolved before issuing results. All programming validation steps will follow established standard operating procedures, with detailed documentation of changes and resolution of inconsistencies.

7.7.1 Data quality management

IQVIA will capture, check, store and analyze the data. IQVIA will ensure database quality processes are followed including review of the data entered into the eCRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

In case of audit or inspections, IQVIA will assure that access to the required/requested study-related documents is provided.

7.7.2 Data recording and document retention

The eCRF's for individual patients are provided by the CRO with inputs from study Sponsor. In all scenarios, the physician must maintain source documents which provides evidence for the existence and substantiate the integrity of the data collected for each patient in the study, consisting of case and visit notes (e.g., hospital or clinic medical records, dermatologist or GP records, as applicable) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the eCRF must be traceable to these source documents in the patient's file. Any discrepancies between the source documents and the eCRF must be explained. The study-related records will be kept for up to 15 years depending on applicable legal and regulatory framework.

The physician must give Novartis (or designee), institutional review board (IRB)/ IEC and competent authorities access to all relevant source documents to confirm their consistency with the eCRF entries.

7.7.3 Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

IQVIA will ensure compliance monitoring.

7.8 Limitations of the research methods

This study has several limitations and potential risks that need to be considered:

The study involves a 24-month follow-up period. Patients may be lost to follow-up for various reasons, either related to or independent of their disease state, such as a change in personal circumstances, address, and HCP, among other factors. This attrition could impact the study's ability to maintain a consistent patient cohort over time.

As this is a non-randomized study, there is a risk and expectation that patients in each cohort will not be comparable on baseline characteristics.

The definition of remission is not established, which could pose challenges in accurately and consistently identifying intermittent remission. Regular contact between the HCP and patients, including telephone consultations, will be implemented to help mitigate this. Based on current literature and knowledge, an expert Steering Committee will be formed to agree on an appropriate definition of remission (this is further discussed in the "additional information" Section).

7.9 Other aspects

None.

8 Protection of human subjects

Any participant records or datasets that are transferred to Novartis will contain the participant's identifier only or will be aggregated; participant names or any information which would make the participant directly 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.

All regulatory and data protection requirements will be met in accordance with any specific local and national regulation and guidance. Data protection requirements specific to individual countries (e.g., conditions to transfer data between countries) will be described in individual country protocols.

8.1 Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki (2016, Vandenbroucke et al., 2007).

This study fulfills the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct.'((EMA). 2018).

8.2 Informed consent procedures

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/IEC/REB. The physician or his/her representative will explain the nature of the study, including the risk and benefits to the participant or their legally authorized representative and answer all questions regarding the study. Participants must be informed that their participation is voluntary, but also that they can leave the study at any time.

The physician must keep the original ICF signed by the patient (a signed copy is given to the patient).

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/Ethics Committee-approved informed consent. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to treating physicians or other involved medical professionals in a separate document a proposed ICF that complies with the Declaration of Helsinki principle and regulatory requirements and is considered appropriate for this study.

9 Management and reporting of adverse events/adverse reactions

All AEs will be collected and recorded in the study database, regardless of seriousness or causal association. All SAEs and reports of drug exposure during pregnancy in patients exposed to remibrutinib (the Novartis drug of interest), irrespective of causality, must be reported to Novartis Patient Safety within 24 hours of becoming aware of the event. All non-serious AEs must be reported to Novartis Patient Safety within 7 calendar days of awareness of the non-serious AE.

Adverse drug reactions (ADRs) occurring in patients exposed to a Novartis drug other than the Novartis drug of interest (e.g., remibrutinib) can be reported to the local HA in accordance with national regulatory requirements for individual case safety reporting or to Novartis Patient Safety as a spontaneous report.

All adverse reactions identified for non-Novartis products should be reported to the local HA in accordance with national regulatory requirements for individual case safety reporting or to the Marketing Authorization Holder, as these will not be recorded in the Novartis safety database.

For guidance on the management of certain AEs, please, refer to the local prescribing information.

1. Adverse event collection and reporting

A) Definition

An **adverse event** (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A **serious adverse event** (SAE) is defined as an AE which:

- Results in death or is life-threatening
- Results in persistent or significant disability/incapacity

- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require 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
    - Note: Transmission of infectious disease via medication is considered to be a serious adverse reaction and should be reported and assessed as medically significant in the absence of other seriousness criteria.
    -

An **adverse drug reaction** (ADR) is a response to a medicinal product which is noxious and unintended. An ADR implies at least a reasonable possibility of a causal relationship between a medicinal product and an adverse event.

The **Novartis drug(s) of interest** evaluated in this study is: *Remibrutinib*

B) AE collection

All AEs from all patients enrolled in the study must be collected and recorded in the study database, irrespective of seriousness or causal association.
The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs may also be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Medical conditions/ diseases ongoing before starting treatment with a study drug are only considered AEs if they worsen after starting the study drug.

All AEs must be recorded on the AE case report form (CRF) with the following information:

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a SAE

In addition, all reports of the following **special scenarios**, whether or not associated with AEs, are also collected and reported in the same manner as AEs:

- Drug-drug or drug-food interaction
- Drug use during lactation
- Lack of efficacy
- Overdose
- Intentional drug abuse and misuse
- Medication errors including drug maladministration
- Dispensing or prescribing errors
- Drug dependence or addiction
- Withdrawal reaction/ syndrome or rebound symptoms
- Unexpected beneficial effect
- Treatment non-compliance (with clinical symptoms)

Note: Occupational or accidental exposure, for example of study personnel or family members of the patient should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or to Novartis Patient Safety as a spontaneous report.

Any action taken with study drug or addition of treatment medication as a result of an AE should be recorded on the AE CRF. Some examples to be recorded are: no action taken (i.e., further observation only); study drug dosage adjusted/ temporarily interrupted; study drug permanently discontinued due to this AE.

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

Information about common adverse effects already known about the study drug(s) can be found in the locally available labeling document for the approved indication under evaluation in this study.

C) AE reporting

- Serious adverse events (SAE)

Information about all SAEs that occurred in patients exposed to the Novartis drug(s) of interest, irrespective of causality, must also be recorded in the Novartis safety database. The treating physician or other involved HCP must assess the relationship to the Novartis drug and complete the AE CRF page marking the event as serious within 24 hours of becoming aware of the event. In case of issues not allowing to complete the AE CRF form, complete the paper

AE Report Form and send the completed, signed form by fax/ email **within 24 hours** to the local Novartis Patient Safety department.
The email address, telephone and telefax number of the contact persons in the local Patient Safety department, specific to the site, are listed in the treating physician/ HCP folder provided to each site. The original copy of the AE Report Form and the fax confirmation sheet or the email must be kept with the CRF documentation at the study site.

- Exposure during pregnancy

Any occurrence of a pregnancy in a patient exposed to the Novartis drug(s) of interest must be reported to Novartis **within 24 hours** of learning of its occurrence. The pregnancy should be followed-up to determine the 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.

Information about the pregnancy should be recorded on the Pregnancy Form and reported by the treating physician or other involved HCP to the local Novartis Patient Safety department. In case of any congenital abnormality, birth defect or maternal and newborn complications, the possible relationship to the Novartis drug should be reported.

Additionally, any SAE/ non-serious AE experienced during pregnancy must be collected on the respective CRF and reported to Novartis following the respective reporting routes described in this section.

- Non-serious AEs and events describing a special scenario (other than drug exposure during pregnancy)

Non-serious AEs as well as events describing a special scenario (other than drug exposure during pregnancy) that occurred in patients exposed to the Novartis drug(s) of interest must also be recorded in the Novartis safety database. In general, special scenarios with no associated clinical event will be considered as non-serious event. Where considered as serious, they should be reported following the SAE reporting route.

Information on all non-serious AEs and events describing a special scenario must be collected on the individual patient eCRFs *or* on paper CRFs which must be made available *to Novartis data management group/IQVIA* **within 7 calendar days** of the site becoming aware of it. Information on all non-serious AEs that occurred in patients exposed to the Novartis drug(s) of interest is then transferred from the study database to the Novartis Patient Safety department by *Novartis data management group/IQVIA* on a periodic basis as per the terms defined in the *Safety Plan.*

- Protocol-exempt events

Fatal outcomes cannot be exempt from collection, and this includes death due to disease progression.

The following events are defined as "exempt" from collection and entry into the safety database

transient exacerbations of chronic spontaneous urticaria, as these events are considered part of the expected clinical course of the disease.

Any exempted event which is suspected to the Novartis drug(s) of interest (i.e. an Adverse Drug Reactions, ADR) may be reported by the investigator to Novartis Patient Safety as a spontaneous report or to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting.

- Safety reporting for Novartis drugs other than the Novartis drug(s) of interest and for non-Novartis drugs

Adverse Drug Reactions (ADRs) occurring in patients exposed to a Novartis drug other than the Novartis drug(s) of interest, can be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting **or** to Novartis Patient Safety as a spontaneous report.
All adverse reactions identified for non-Novartis drugs should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder as these will not be recorded in the Novartis safety database.

2. Follow-up information

Recurrent episodes, complications, or progression of the initial event must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within the same timelines as defined for initial information. Any event that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information is sent to the same contact person to whom the initial information was sent, stating, where an AE report form is used, that this is a follow-up to the previously reported event and providing the date of the original report. If known, the information missing from the initial report should be completed. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

In case an SAE is not previously documented in the labeling document for the study, a Novartis Patient Safety associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

In case an adverse event is considered to be of particular interest, a Novartis Patient Safety associate may seek additional information concerning the event. Corresponding questionnaires will then be provided by Novartis Patient Safety to the treating physician or other involved health care professional on a case-by-case basis.

3. Safety reporting period

Every SAE, exposure during pregnancy, non-serious AE and special scenario, regardless of causality assessment, that occurred in patients exposed to the Novartis drug(s) of interest must be reported to Novartis:

- after the patient has provided informed consent
- until 30 calendar days after the patient discontinued the Novartis drug of interest during the study conduct or until 30 calendar days after the last patient last visit if the patient is still receiving the Novartis drug of interest.

Any SAEs, pregnancies, non-serious AEs and special scenarios experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the Novartis drug(s) of interest.

10 Plans for disseminating and communicating study results

Planned interim analyses and reports will be used for congress and publication submissions. Upon completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

The final study report will be submitted to the competent authorities according to local regulations.

For applicable non-interventional post-authorization safety study (PASS) (in the European Union (EU) or mandated by an EU HA outside the EU), the final manuscript will be submitted to European Medicines Agency (EMA) and the competent authorities of the Member States in which the product is authorized within 2 weeks after first acceptance for publication.

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

Table 6-1 List of stand-alone documents

Number	Document name/type	Date	Title
None			

12.2 **Annex 2 – ENCePP checklist for study protocols –** Electronic Document Identifier: VV-TMF-11861912

12.3 Annex 3 – Definitions

12.3.1 Treatment switch:

Discontinuation of Remibrutinib treatment AND switch from Remibrutinib treatment to another CSU medication other than H1-AH.

12.3.2 Treatment History

Cohort 2:

- sgH_1-AH (mandatory)
- fgH_1-AH (permitted)
- Previous occasional steroid rescue medication (less than 3 weeks in a row) (permitted)
- any add on topical treatment (permitted)

Cohort 3:

- Systemic CSU treatment other than fg/sgH_1-AH any time during patients CSU treatment history (mandatory)
- Previous continuous use of systemic steroids for at least three weeks in a row (permitted)
- any add on topical treatment (permitted)

12.4 Annex 4 – Protocol signature page

Germany Evidence Generation and GMA Evidence Generation, Immunology

LOU064

Protocol No. CLOU064ADE02

Remibrutinib in real-world clinical practice: a prospective, multi-country, non-interventional, effectiveness and safety study (REASSERT) - Local adaptation in Germany

Document type:	Protocol Version No. 00 Clean and Track Changes Signature Page
Referring to:	Protocol Version No. 00 content final date on 04-Feb-2026

Novartis approval signatures for:

Non-interventional Study Protocol v00

[redacted]

Patient Safety [redacted]

[redacted]

Signature

Date

[redacted]

Non-interventional [redacted]

[redacted]

Digitally signed by [redacted]
DN: dc=com, dc=novartis, ou=people, ou=IM, serialNumber=2354061, cn=[redacted]
Date: 26.02.05 08:53:28 +01'00'

Signature

Date

Investigator approval signatures for:

Non-interventional Study Protocol v00

Electronic Document Identifier: provided on the separate protocol signature page

Investigator signature

I have read the protocol and agree to conduct this non-interventional study in accordance with all stipulations of the protocol, with applicable laws and regulations and in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct and with the ethical principles laid down in the Declaration of Helsinki.

Investigator	Signature	Date

12.5 Annex 5 – Additional information

The global concept sheet and protocol will serve as primary documents for the study. The global concept sheet reflects and summarizes the individual evaluation needs of all 8 countries. Participating countries will select the relevant objectives and end points for their local needs and will generate a fit for purpose local study concept and protocol.

The recruitment of patients will be done 70% from office-based space and 30% from specialist centers (or as close as is feasible).

Off-Label (as defined by German HAs) is also the observation of approved drugs outside the approved indication, population and posology. For Germany, prospective documentation of off-label use is not permitted, and the concept sheet and protocol will be adapted accordingly.

The signs and symptoms of CSU can either occur on a daily or an intermittent basis. Even if complete remission is assumed, CSU may recur after months or years (Zuberbier et al., 2022). Hence, while recording remission, differentiating between true and intermittent remissions will be crucial.

Where feasible (e.g., US) study tokenization will be considered and defined in local concept and protocol stage.

Where feasible, sites may investigate option of bio-banking patient samples. This would require separate consent and ethics approval and would be managed by the local team.

If a country fails to meet its recruitment target for a given cohort, another country may enroll more patients in that cohort so that the proportions planned per cohort are met. This requires endorsement by the global team.

Consideration may be given later to enroll an additional wave of countries such as UK, France, Australia, Nordics, Brazil, and Belgium. Consideration may also be given to extending the duration beyond 24 months, and recruitment target based on local need.

Additional indications may be added at a later stage (e.g., CIndU), subject to appropriate amendments being made. Note, different terms are used in the literature for remission, including: “spontaneous”, “complete”, “clinical” as well as “natural” remission. For this study, the term “remission” will be used on its own. Remission is defined as a period of ≥ 3 months and ≥ 6 months following a UCT = 16 and/or UAS7 = 0 and complete withdrawal of treatment. The terms “remission” and “spontaneous remission” are used interchangeably in this document.

This is also separate from the term “intermittent remission”, which is defined as a period when a patient is asymptomatic (UCT = 16 and/or UAS7 = 0) in the absence of (oral) treatment(s) for at least 2 weeks.

Steering Committee

An international Steering Committee includes the following experts:

- Professor [redacted]
- Professor [redacted]
- Professor [redacted]
- Professor [redacted]

- Professor [redacted]
- Japan representative TBC

13 Appendices

None