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REASSERT

GMA Evidence Generation, Immunology

Non-Interventional Study Protocol (PASS)

Redacted Protocol

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Title	Remibrutinib in real-world clinical practice: a prospective, multi-country, non-interventional, effectiveness and safety study (REASSERT)
Protocol version number	V01
Content final date	22-Dec-2025
HMA-EMA Catalog of real-world data studies register number	Study not registered yet

NIS Type	Primary Data Collection
Active substance	Remibrutinib (LOU064)
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)
Authors	PPD

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List of abbreviations

1L	First-line
2L	Second-line
3L	Third-line
4L	Fourth-line
AAS	Angioedema Activity Score
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	
MARS	Medication Adherence Report Scale	
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
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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)

Protocol version and release date

V01; 22-Dec-2025

Name and affiliation of main authors

PPD

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) and sgH_1-AH treatment (cohort 1) in patients with CSU over 24 months.

2. Evaluate the early (starting week 1) real-world effectiveness of remibrutinib (cohort 2 and 3 separate and pooled) and sgH_1-AH treatment alone (cohort 1) up to week 12.
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) and in patients treated with sgH_1-AH (cohort 1).
4. Characterize the escalation pattern to remibrutinib and its effectiveness among patients with CSU who switched to remibrutinib following failure on sgH_1-AHs alone (cohort 1 and cohort 2 separate).
5. Assess QoL in CSU patients treated with remibrutinib (cohort 2 and 3 separate and pooled) and in patients with sgH_1-AH treatment (cohort 1) up to 24 months.
6. Determine healthcare resource utilization (HCRU) and work productivity in patients treated with remibrutinib (cohort 2 and 3 separate and pooled) and in patients with sgH_1-AH treatment (cohort 1).
7. 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.
8. Assess the safety profile of sgH_1-AH in CSU patients treated with sgH_1-AH treatment alone over a 24-month period.

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 either escalate current sgH_1-AHs treatment or 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. Countries will generate local study documentation (i.e., concept, protocol, statistical analysis plan (SAP)) to be applied in their country; the local study documentation will be a minimized version of the global document set, modified to align with country's evidence needs, given local disparities in treatment guidelines, access, physician type and electronic patient-reported outcomes (ePROs)/electronic diaries (eDiaries) used. To achieve the core objectives the observation needs to include either the Urticaria Control Test (UCT) or Urticaria Activity Score over 7 days (UAS7) and the Dermatology Life Quality Index (DLQI). These, and safety data must be observed across all participating countries.

Data from all countries will be pooled and analyzed globally. In certain instances, some modifications of the global protocol may be permitted. For example, in countries where prospective monitoring of off-label antihistamines (AH) is prohibited, cohort 1 will not be enrolled.

The study has 2 periods:

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

and observes 3 cohorts (also described in Section 6.1):

- **Cohort 1**: Inadequate control of CSU despite licensed dose of sgH_1-AH (no other pretreatments permitted, with the exception of first generation H_1 antihistamine (H_1-AH) at licensed dose) and decision (independent of study enrollment) to escalate sgH_1AH treatment. The baseline visit consists of the clinical assessment at licensed dose, and the follow-up visits capture clinical outcome(s) of escalated sgH_1-AH treatment. (Note: this cohort participation is dependent on local regulations). Patients can move from cohort 1 to cohort 2 at any timepoint as per physician decision and continue at baseline in cohort 2. Enrollment will be capped at a maximum of 30% of the total local and global population.
- **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 (± sgH_1-AH). For patients transitioning from cohort 1 to cohort 2, a distinct "cohort 2 baseline" will be derived using data from original cohort 1 baseline visit and the last visit in cohort 1 (pre-switch). A minimum enrollment of 40% of the total global and local population is planned, without cap (including switchers from cohort 1).

- **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 (± sgH_1-AH). Enrollment will be capped at a maximum of 30% of the total global and 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, depending on the structure of the participating country's healthcare system. The aim is to observe the real-world practice of the different participating countries 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. Of note, each country will have an enrollment target (410 patients). In specific scenarios this may be modified (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 eCRF. At enrollment, patients are required to download the study app.

Variables

The following variables will be characterized at baseline:

- Age (years, months)
- Sex (Female/Male)
- Height (cm)
- Weight (kg/lbs)
- Smoking status
- Race
- Ethnicity
- 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., 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

- CCI
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- 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 using an eCRF, 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 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 total sample size is expected is 3,277 patients (410 per country across 8 countries), based on the primary objective: estimating the proportion of patients achieving UCT7 ≥ 12 at week 12 after initiating remibrutinib treatment.

To ensure a 95% confidence interval (CI) of 52.8%–57.2% around an expected response rate of 55%, 1,879 patients are required in cohort 2 and 3 combined. For the primary objective, patients in cohort 2 (including those transitioning from cohort 1) and cohort 3 are combined, as response rates are assumed similar (as observed in the REMIX trials). Accounting for a 14% dropout rate, this increases to 2,185 patients. Addition of cohort 1 bringing the total to 3,277. Per country, 273 patients in cohort 2 and 3 are required after adjusting for 14% dropout. 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 global minimum/maximum caps for each cohort to ensure balanced representation. Enrollment for cohort 1 is capped at a maximum of 30% of the total study population, which translates to approximately 983 patients out of the total 3,277 patients. Cohort 2 has no cap on enrollment, but an enrollment of 40% of the total study population is planned, ensuring at least 1,311 patients. It is assumed that approximately 25% of the patients enrolled in cohort 1 might switch to cohort 2, thus facilitating the expected number of patients available for the analysis in cohort 2. Enrollment for cohort 3 is capped at a maximum of 30% of the total study population, which translates to approximately 983 patients out of the total 3,277 patients.

Each of the 8 participating countries aims to recruit 410 patients. However, under specific circumstances, adjustments to the local target sample size may be warranted (refer to Section 7.4 for further details).

Milestones

Table 2-1 Planned dates of study milestones*

Milestone	Planned date
Start of data collection	05-Jan-2026
End of data collection	30-Oct-2031
Final report of study results	31-Oct-2032
Others of relevance	See Table 4-1

* Dates may change based on product approval dates.

3 Amendments and updates

Table 3-1 Study protocol amendments and updates

Version date	Version number	Section of protocol	Substantial Amendment or update	Reason
CCI [redacted]				

4 Milestones

Table 4-1 Planned dates of 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 for urticaria recommend second-generation H_1 antihistamines (sgH_1-AHs) as first-line (1L) treatment, with varying doses (from licensed dose to 4x off-label dosages) across regions (Bernstein et al., 2014, Hide, 2018, Zuberbier et al., 2022, Xu J-H, 2020). Recommendations for subsequent lines vary across regions. Guidelines are summarized in Table 5-1. 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).

Table 5-1 CSU treatment guidelines (International, United States, Japan, and China)

LOT	Guideline			
	International	**United States**	**Japan**	**China**
1L	sgH_1-AH monotherapy; if needed, increase the dose up to 4 times	sgH_1-AH monotherapy	sgH_1-AH monotherapy up x2 dose	sgH_1-AH in routine/licensed dosages
2L	Addition of omalizumab; if needed, increase dose and/or shorten interval	• Increase dose sgH_1-AH • Additional sg-H_1AH • Add H_2-AH • Add leukotriene receptor agonist (LTRA) • Add first generation AH before bed	Addition of: • H_2-AH • LTRAs • Tranexamic acid • Diaphenylsulfone • Anxiolytics • Glycyrrhizin • Chinese herbal medicine	Replace/combine/increase AHs • Different AH • Increase dose x2-4 • Combine AHs
3L	Addition of ciclosporin	Increase dose of potent AH (e.g., hydroxyzine or doxepin) as tolerated	Omalizumab, oral corticosteroids, or ciclosporin	• Tripterygium • Ciclosporin • Corticosteroids • Biologics • Phototherapy
4L	None	Add an alternative agent: • Omalizumab or ciclosporin • Other anti-inflammatory agents, immunosuppressant, or biologics	Experimental trials	None

Abbreviations: 1L = first-line, 2L = second-line, 3L = third-line, 4L = fourth-line, AH = antihistamine, CSU = Chronic Spontaneous Urticaria, LOT = line of therapy, LTRA = leukotriene receptor agonist, H_2-AH = H_2 antihistamine, sgH_1-AH = second-generation H1 antihistamines.

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, where there are periods of intermittent remission and spontaneous resolution. 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, make 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 is a prospective, multi-country, non-interventional study in patients with CSU where prior to study enrollment the treatment decision has been made for either escalation of sgH_1-AHs or 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.

Moreover, the study will address the necessity of local data due to variations in national and local practice guidelines, local reimbursement requirements, healthcare system structures (e.g., non-specialist versus specialists, allergists versus dermatologists), and ethnic heterogeneity across different regions. Localized data are crucial for informed decision-making and tailoring treatment approaches to specific populations, local healthcare system environments or local access and reimbursement conditions. Given that healthcare practices can differ significantly

based on regional guidelines and the availability of resources, having robust local data enables practitioners to optimize care strategies effectively on a local level.

The inclusion of patients where the decision has been made to escalate current sgH$_1$-AH monotherapy (cohort 1) enables the establishment of a baseline for intermittent remission and remission rates in a broader CSU patient population. The investigation of this rate is essential if a treatment needs to be evaluated for disease-modifying potential, when used in an early treatment setting. In addition to establishing a baseline for intermittent remission and spontaneous remission rates, cohort 1 will also enable a greater understanding of treatment escalation patterns, real-world treatment outcomes, and safety of up-dosed sgH$_1$-AHs over the long-term.

The REASSERT global umbrella protocol describes the full study plan. 7-day recall period version of the Urticaria Control Test (UCT7), UCT, and Dermatology Life Quality Index (DLQI) are internationally validated tools that will need to be utilized across localized studies (in addition, countries may also collect UAS7). Apart from those, countries may minimize the endpoint collection of the umbrella protocol to their own local needs.

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. Next to remibrutinib, real-world sgH$_1$-AH use, including treatment patterns and effectiveness as well as long-term safety will be collected and analyzed, together with potential treatment switch patterns from sgH$_1$-AH to escalated second-line (2L) treatment options, including remibrutinib.

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. Observed intermittent remission and remission rates from the sgH$_1$-AH cohort, where no disease modification is expected, will serve as a reference for the early treated patients from cohort 2.

Note, endpoints are analyzed from globally pooled data, with potential regional or per country analysis. Local protocols will outline the research questions relevant for local evidence gaps, with the retention of UCT7/UCT and DLQI across all local studies, together with safety data.

The study includes 3 cohorts:

- **Cohort 1**[1]: Inadequate control[2] of CSU despite licensed dose of sgH_1-AH (no other pretreatments permitted, with the exception of first generation H_1-AH at licensed dose) and decision (independent of study enrollment) to esc-alate sgH_1AH treatment. The baseline visit consists of the clinical assessment at licensed dose, and the follow-up visits capture clinical outcome(s) of escalated -sgH_1-AH treatment. (Note: this cohort participation is dependent on local regulations). Patients can move from cohort 1 to cohort 2 at any timepoint as per physician decision and continue at baseline in cohort 2. Enrollment will be capped at a maximum of 30% of the total population.
- **Cohort 2**: Inadequate control[3] 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. Patients can move from cohort 1 to cohort 2 at any time, per the physician's decision. Baseline visit comprises clinical assessment while treated with sgH_1-AH (i.e., before switch to remibrutinib), and follow-up visits/data entry capture the clinical outcome of escalated treatment (i.e., remibrutinib ± sgH_1-AH). For patients transitioning from cohort 1 to cohort 2, a distinct "cohort 2 baseline" will be derived using data from original cohort 1 baseline visit and the last visit in cohort 1 (pre-switch). A minimum enrollment of 40% of the total global and local population is planned, without cap (including switchers from cohort 1).
- **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 (± sgH_1-AH). Enrollment will be capped at a maximum of 30% of the total 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.

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).

6.2 Study objectives

Primary objective

The study evaluates the following primary objective and endpoint. Collection of 7-day recall period version of the UCT (UCT7)/UCT (with or without Urticaria Activity Score (UAS)) is mandatory across all local studies.

[1] Participation in this cohort is dependent on local regulations.

[2] Treatment failure will be determined per Investigator assessment.

[3]Treatment failure will be determined per Investigator assessment.

Table 6-1 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 symptomatic despite sgH_1-AHs (cohort 2 and 3 pooled).	• Achievement of well-controlled disease (UCT7 ≥ 12 or UAS7 ≤ 6) at week 12 after initiating remibrutinib treatment.

Secondary objectives

The study evaluates the following secondary objectives and endpoints if sufficient data are available. Collection of Dermatology Life Quality Index (DLQI) (and UCT/UCT7) is mandatory across all local studies.

Table 6-2 Secondary objectives and endpoints

Secondary Objectives	Secondary Endpoints
1. Evaluate the real-world effectiveness of remibrutinib treatment (cohort 2 and 3 separate and pooled) and sgH_1-AH treatment (cohort 1) in patients with CSU over 24 months.	• Achievement of well-controlled disease (UCT ≥ 12, UAS7 ≤ 6) at months 6, 9, 12, 15, 18, 21, 24. • Achievement of complete control (UCT=16, UAS7=0) at months 6, 9, 12, 15, 18, 21, 24. • Change from baseline (CFB) in UCT score (if applicable CFB 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 and change in angioedema activity score (angioedema activity score (AAS)) from baseline at months 6, 9, 12, 15, 18, 21, 24. • Number of weeks without angioedema and/or change in Angioedema Control Test (AECT) from baseline at months 6, 9, 12, 15, 18, 21, 24. • Rescue medication requirement assessed at months 3, 6, 9, 12, 15, 18, 21, 24 by type (AH, steroids, others). • Characterize CSU relapse (and number of relapses) at 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 separate and pooled) and of sgH_1-AH treatment (cohort 1) up to week 12 in patients with CSU.	• UCT7 (and if applicable UAS7) at weeks 1, 2, 4, 8. • Change in UCT7 score (and if applicable UAS7) from baseline at weeks 1, 2, 4, 8, 12. • Achievement of well-controlled disease (UCT7 ≥ 12, UAS7 ≤ 6) at weeks 1, 2, 4, 8 and complete control (UCT7=16, UAS7=0) at weeks 1, 2, 4, 8 and 12. • Number of weeks without angioedema at weeks 4, 8, 12, and change in AAS from baseline at weeks 1, 2, 4, 8, 12. • Number of weeks without angioedema and/or 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. • 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

Secondary Objectives	Secondary Endpoints
	(yes/no), location, duration (hours/days), severity (UCT/UAS) and/or 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 treated with remibrutinib (cohort 2 and cohort 3 separate) and in patients treated with sgH_1-AH* (cohort 1).
*Note: analysis only performed in countries where cohort 1 can be documented.
	• Administration of remibrutinib as monotherapy at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 24.
	  • Monotherapy duration (days/weeks/months).
	  • UCT7/UCT/UAS7 (as appropriate) at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 24.
	• Administration of remibrutinib as monotherapy with "on demand" sgH_1-AH at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 24.
	  • Duration of monotherapy with "on demand" sgH_1-AH (days/weeks/months).
	  • UCT7/UCT/UAS7 (as appropriate) at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 24.
	• Administration of rescue medication (corticosteroids, others) (type, dose, duration) at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 24.
	• Usage of concomitant sgH_1-AHs (including combinations) and additional prescribed CSU treatments (type, dose, frequency) at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 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/international guidelines and impact on patient, disease control, treatment patterns and healthcare resource utilization (HCRU) during early and long-term follow-up.
	• Delay of treatment escalation contrary to local and/or international guidelines (recommending escalation within 2-4 weeks from up-dosed sgH_1-AH) when UCT < 12 or UAS > 6 at time points measuring UCT7 (early) / UCT (month 3 onwards) / UAS7 group.
	• Time (days/months) without escalation, with UCT < 12 or UAS7 > 6 at time points measuring UCT7 (early) / UCT (month 3 onwards) / UAS7 group.

4. Characterize the escalation pattern to remibrutinib and its effectiveness among patients with CSU who switched to remibrutinib following failure on sgH_1-AHs alone (cohort 1, cohort 2).	• Escalation to remibrutinib at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 21, 24. • Time from study enrollment to escalation to remibrutinib (days/months). • Administration of 2 times, 3 times, 4 times, > 4 times above the licensed dose of sgH_1-AH prior to remibrutinib switch assessed at weeks 1, 2, 4, 8, 12, and months 6, 9, 12, 15, 18, 21, 24. • UCT7 / UCT / UAS7 score at time of switch. • Number of sgH_1-AH treatment escalations and switches prior to remibrutinib escalation. • Demonstrate benefit of early vs late treatment escalation (from cohort 1 to cohort 2) (e.g., time to urticaria control UCT ≥ 12 and/or to UAS7 ≤ 6), angioedema, QoL, HCRU.

Secondary Objectives	**Secondary Endpoints**
	• Proportion of patients with uncontrolled angioedema escalated to remibrutinib (and number of angioedema episodes). • Proportion of patients requiring corticosteroids prior to switch and number of days prescribed corticosteroids.
5. Assess QoL in CSU patients treated with remibrutinib (cohort 2 and 3 separate and pooled) and in patients with sgH$_1$-AH treatment (cohort 1) 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, 12, 18, 24. • Change in DLQI scores from baseline at weeks 1, 2, 4, 8, 12, and months 6, 12, 18, and 24. • Change in Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) questionnaire scores from baseline to weeks 4, 8, 12, and months 6, 12, 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.

6. Determine HCRU and work productivity in patients treated with remibrutinib (cohort 2 and 3 separate and pooled) and in patients with sgH$_1$-AH treatment (cohort 1).	• Quarterly and annualized number of events related to CSU (e.g., inpatient hospitalizations, length of stay, emergency room visits, outpatient visits) assessed at 3, 6, 12, 18, 21, 24 months.
	• Work productivity and activity impairment (WPAI)-CU score at baseline, months 3, 6, and then every 6 months, 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.

7. 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).
8. Assess the safety profile of sgH$_1$-AH in CSU patients treated with sgH$_1$-AH treatment alone (cohort 1) over a 24-month period (note: only collected where permissible).	• Incidence (including exposure-adjusted) of AEs, including serious AEs.

Exploratory objectives

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

Table 6-3 Exploratory objectives and endpoints

Exploratory Objectives	Exploratory Endpoints
CCI	

Exploratory Objectives	Exploratory Endpoints
CCI	[redacted]

Exploratory Objectives	Exploratory Endpoints
CCI	[redacted]

7 Research methods

7.1 Study design

REASSERT is a global, 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. Countries will generate local study documentation (e.g., protocol) to be applied in their country. This umbrella protocol will be adapted to align with country's needs given disparities in treatment guidelines, access, physician type, and ePROs used locally. The collection of UCT and DLQI is mandatory across all participating countries, as is safety data. Countries may select further relevant objectives and associated endpoints for their local evidence needs. Data from each country will be globally pooled and analyzed as available. The global protocol may be adjusted to allow for local regulatory reasons. For e.g., in countries where prospective monitoring of off-label antihistamines is prohibited, cohort 1 will not be enrolled

The study has 2 periods:

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

The study includes 3 cohorts (also described previously in Section 6.1):

- **Cohort 1**[4]: Inadequate control of CSU despite licensed dose of sgH_1-AH (no other pre-treatments permitted, with the exception of first generation H_1-AH at licensed dose) and decision (independent of study enrollment) to escalate sgH_1-AH treatment. The baseline visit consists of the clinical assessment at licensed dose, and the follow-up visits capture clinical outcome(s) of escalated sgH_1-AH treatment. (Note: this cohort participation is dependent on local regulations). Patients can move from cohort 1 to cohort 2 at any timepoint as per physician decision and continue at baseline in cohort 2. Enrollment will be capped at a maximum of 30% of the total population.
- **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. Patients can move from cohort 1 to cohort 2 at any time, per the physician's decision. Baseline visit comprises clinical assessment while treated with sgH_1-AH (i.e., before switch to remibrutinib), and follow-up visits/data entry capture the clinical outcome of escalated treatment (i.e., remibrutinib ± sgH_1-AH). For patients transitioning from cohort 1 to cohort 2, a distinct "cohort 2 baseline" will be derived using data from original cohort 1 baseline visit and the last visit in cohort 1 (pre-switch). A minimum enrollment of 40% of the total global and local population is planned, without cap (including switchers from cohort 1).
- **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 (± sgH_1-AH). Enrollment will be capped at a maximum of 30% of the total 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.

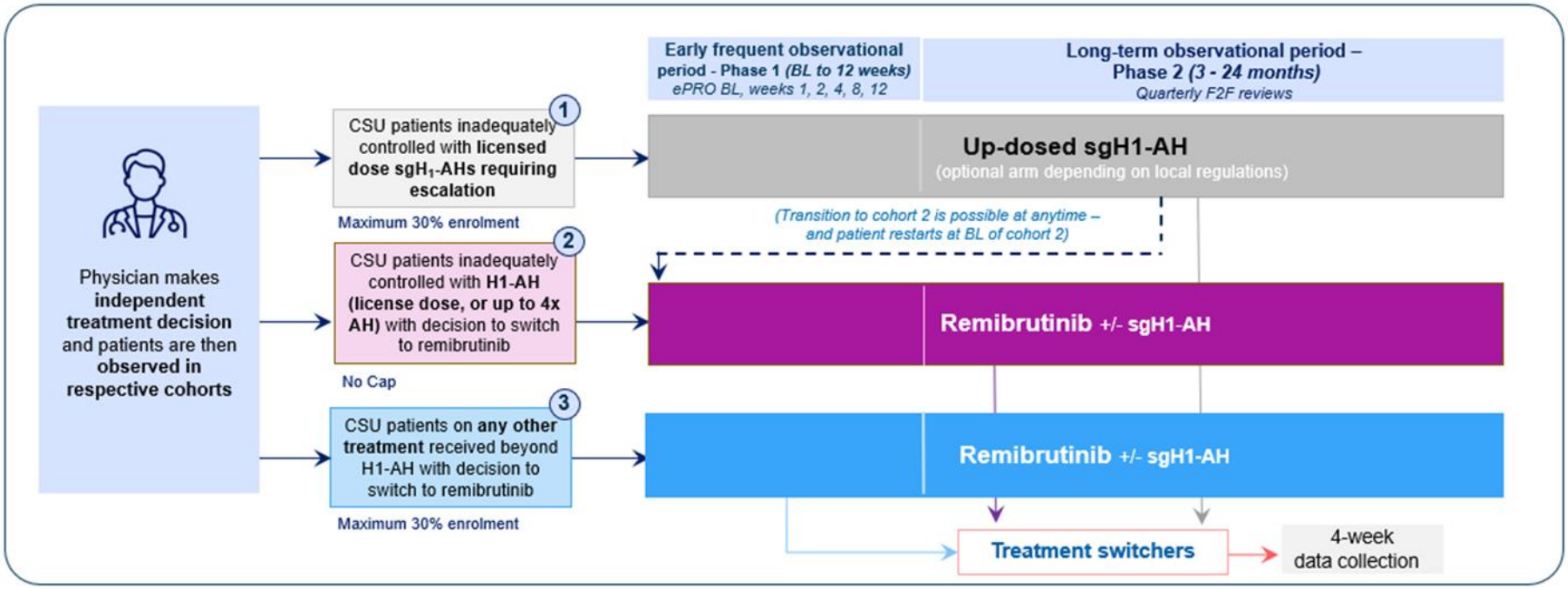
Patients being switched from remibrutinib treatment (cohort 2 and 3) to another treatment (other than H_1-AH) will be followed for another 4-weeks in the 'Switch Cohort', after treatment switch. Patient observation ends in this scenario after 4 weeks (instead of the planned 24 months).

Note: Candidate patients must not have initiated the next escalated treatment step (i.e., escalated AH for cohort 1, or remibrutinib for cohorts 2 and 3) prior to their enrollment to ensure the baseline visit captures their clinical status before treatment escalation.

The study design is shown in Figure 7-1.

[4] Participation in this cohort is dependent on local regulations.

Figure 7-1 REASSERT study design



Treatment switchers: 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, UCT = Urticaria Control Test.

7.2 Setting and study population

Study setting

The study is conducted in various healthcare system settings, office- and hospital-based, depending on the structure of the participating country's healthcare system. The aim is to observe the real-world practice of the different participating countries in the management of CSU patients. The split of 70% office-based (dermatologists, allergists, immunologists, and GPs where applicable) and 30% specialist centers is designed to allow for the inclusion of a broad variety of physician and patient types.[5] This split may not be adhered to if a given country has a specific health care system set-up/ practice that is incompatible.

The study is planned to be conducted in 8 countries: the United States (US), Germany, Japan, China, Spain, Italy, Canada, and South Korea. Of note, each country will have an enrollment target (410 patients). In specific scenarios an adjustment of the enrollment target may be permitted (see Section 7.4). At enrollment, patients are required to download the study app. 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 in the 8 participating countries. Patients under the care of office-based dermatologists (OBDs), allergists, immunologists, CSU specialists/specialist centers, or general practitioners (if permitted locally) are enrolled. The target ratio of specialists to non-specialists (OBDs/office-based allergists/GPs) will be 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 global 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 with at least licensed dose sgH_1-AH and has made a treatment decision that is compatible with one of the 3 cohorts.

[5] 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.

b. **Baseline study start date:** Date of baseline assessment (captured by treating physician via EDC), BEFORE treatment escalation/switch – i.e., before the escalation of sgH_1-AH in cohort 1 or initiation of remibrutinib in cohort 2 or cohort 3.
c. **Escalated sgH_1-AH start date:** Date of first intake of prescribed increased sgH_1-AH dose treatment (provided by patient, via study app) – cohort 1.
d. **Remibrutinib treatment start date**: Date of first intake of prescribed remibrutinib treatment (provided by patient, via study app) – cohort 2 and 3.
e. **Early observational period (Study Phase 1): First 12 weeks** and commences at date of first prescribed treatment intake; i.e., steps "c" or "d" above - patients will perform data entry via study app. One office visit is recommended during this 12-week timeframe.
f. **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 via EDC).

Note for "d" and "e" 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).

The treating physician may decide to switch a patient's treatment from sgH_1-AH (cohort 1) to remibrutinib (cohort 2), here the patient transitions from cohort 1 to cohort 2. For patients moving to cohort 2, the observation period will restart but the overall observational time of 2 years will remain. For example, a patient newly prescribed remibrutinib after contributing 6 months (day 182) of time to the sgH_1-AH cohort will have their 12-week remibrutinib evaluation at day 266, which is day 84 (12 weeks) in cohort 2.

Upon transitioning from cohort 1 to cohort 2, the baseline in cohort 2 is assessed on the incoming sgH_1-AH treatment from cohort 1 (e.g., UCT) plus existing baseline data e.g., medical history. Importantly, and in line with the process in cohort 1, the patient is asked to register date of first remibrutinib intake (via study app), and enter ePRO data at weeks 1, 2, 4, 8, 12 as per the "early observational period" requirements. Data collection timepoints should be rescheduled according to this new start of follow-up for each patient for whom this scenario applies.

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 (according to country specifications) and willingness to complete full follow-up period of 24 months.
4. Cohort-specific observational inclusion criteria:

a. **Cohort 1:** Inadequate control of CSU despite licensed dose of sgH_1-AH (no other pre-treatments permitted, with the exception of first generation H_1-AH at licensed dose) and decision (independent of study enrollment) to escalate sgH_1-AH treatment.
b. **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.
c. **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. 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 the next escalated treatment step (i.e., up-dosed AH for cohort 1, or remibrutinib for cohorts 2 and 3) 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. Currently enrolled in a clinical trial or on any experimental treatment.
2. Patients within the safety follow-up phase of a previous interventional or non-interventional study.
3. Patients who received remibrutinib as an investigational medical product during a remibrutinib interventional study or managed access program (MAP)/post study drug supply (PSDS) 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 centre's 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. 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 7-1. Countries are required to update the table to reflect any changes to the objectives and/or endpoints when designing their localized protocol.

Table 7-1 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**	**Months 6, 9, 12, 15, 18, 21**	**24 months**
Inclusion/exclusion criteria	X				
Information & informed consent	X				
Physical examination	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**	**Months 6, 9, 12, 15, 18, 21**	**24 months**
eCRF and/or ePRO/eDiary					
Baseline demographics	X				
Medical history	X				
Comorbidities	X				
Comorbidities related to CSU	X			X	X
Previous CSU medications	X				
CCI					
Non-CSU medications	X			X	X
Current CSU medications	X	X	X	X	X
CCI					
Angioedema	X		X	X	X
AAS[1]	(if specified in local protocol)		X (collected prospectively if angioedema occurs)	X (collected prospectively if angioedema occurs)	
AECT[1]	X (If angioedema present)		(if specified in local protocol)	(if specified in local protocol)	(if specified in local protocol)
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 in **addition to UCT** (if specified in local protocol)	X if ≥ 7 days since clinic/ enrollment and if selected in **addition to UCT**	X in **addition to UCT** (if specified in local protocol)	X in **addition to UCT** (if specified in local protocol)	X in **addition to UCT** (if specified in local protocol)

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**	**Months 6, 9, 12, 15, 18, 21**	**24 months**
CCI					
Sleep[1]	X		(if specified in local protocol)	(if specified in local protocol)	(if specified in local protocol)
WPAI score[1]	X		(if/as specified in local protocol)	(if/as specified in local protocol – captured 6 monthly)	(if/as specified in local protocol)
HADS	X		(if/as specified in local protocol)	(if/as specified in local protocol)	(if/as specified in local protocol)
CU-Q2oL[1]	X		(if/as specified in local protocol)	(if/as specified in local protocol)	(if/as specified in local protocol)
HCRU[1]	X		(if specified in local protocol)	(if specified in local protocol)	(if specified in local protocol)
CCI					
AEs (physician assessed at clinic only)			X (assessed retrospectively in clinic)	X (assessed retrospectively in clinic)	X (assessed retrospectively in clinic)
CCI					

"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.

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**	**Months 6, 9, 12, 15, 18, 21**	**24 months**
Abbreviations: AAS = Angioedema Activity Score, AEs = Adverse events, AECT = Angioedema Control Test, BL = baseline, CCI , 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 CCI , 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] CCI					

Note: Below is a summary of the data capture by the patient using ePROs/eDiary via mobile phone app.

- Enrollment: download study app, set-up user profile, test functionality (~10 min)
- Treatment start (intake of escalated sg-H_1AH, or remibrutinib ± sg-H_1AH): 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)
- CU symptoms 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 this study is 3,277 patients. The sample size calculation for this study is based on 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).

This calculation includes patients in cohort 2 (including those transitioning from cohort 1 to 2) and 3. 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% (pooled across cohort 2 and 3, and 8 countries), the required sample size for cohort 2 and 3 combined, across the 8 participating countries, that would ensure the 95% CI lies between 52.8% to 57.2% is **1,879 patients**.

Furthermore, assuming a dropout/missing data rate of around 14%[6] at week 12, the sample size would need to be **2,185 patients**. Given the study design, the sample size in cohort 1 across all countries is expected to be equal to that of cohort 2 and cohort 3 separately, which means approximately half of the 2,185 patients, or approximately 1,092 patients, would be needed for cohort 1. Therefore, the total sample size required for the study will be **3,277 patients, with 410 patients per country**.

For the estimation of the proportion of patients achieving UCT7 ≥ 12 at week 12 in cohort 2 and 3 combined and per country, a sample size of 235 patients (1,879 patients identified above divided by 8) 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%. Adjusting for the approximately 14% dropout rate at week 12, the sample size for cohort 2 and 3 combined per country will be 273 patients, which is approximately two-thirds of the 410 patients per country.

In the Phase 3 studies (pooled REMIX 1 and 2), the observed proportion of patients on remibrutinib achieving UCT7 ≥ 12 at week 12 ranged from 51% in China to 64% in the US. It is estimated that approximately 25% of the patients enrolled in cohort 1 might switch to cohort 2, which is roughly half of the 50% of patients with CSU that is not well-controlled. This transition is expected to increase the number of patients available for the analysis of the remibrutinib treatment experience.

For the key secondary objectives (such as sustained effectiveness), the pooled REMIX studies observed the following UCT7 response rates at week 52; UCT7 ≥ 12 at week 52 was 63.2% (95% CI: 58.8% - 67.5%), and the proportion of patients achieving complete control, i.e., UCT7 = 16, at week 52 was 30.8% (95% CI: 26.8% - 35.0%). Assuming a dropout/missing

[6] To obtain information about discontinuation at week 12 (not reported in AWARE), the availability of data for wheals in AWARE was used. At baseline, data for 89% of the 3,683 patients included in the analysis were observed. At 12 weeks, data were reported for 2,752 patients. Assuming the same data availability rate and not counting discontinuation due to remission, the estimated discontinuation rate without remission is 14% at week 12.

data rate of 30% at week 52, which is twice the dropout rate observed in REMIX, a sample size of 1,530 patients for cohorts 2 and 3 combined and across the 8 participating countries will result in an expected precision of 4.9% when the target response rate for UCT7 ≥ 12 at week 52 is 60%, and an expected precision of 4.6% when the target response rate for UCT7 = 16 at week 52 is 30%.

CCI [redacted]

The study design includes global caps for each cohort to ensure balanced representation. Enrollment for cohort 1 is capped at a maximum of 30% of the total study population, which translates to approximately 983 patients out of the total 3,277 patients. Cohort 2 has no cap on enrollment, but a minimum enrollment of 40% of the total study population is planned, ensuring at least 1,311 patients. Enrollment for cohort 3 is capped at a maximum of 30% of the total study population, which translates to approximately 983 patients out of the total 3,277 patients. These caps ensure a balanced representation of patients across different treatment pathways while allowing for sufficient data collection to meet the study objectives. Each of the 8 countries will have its own recruitment target (410 patients) and mirrored cohort caps.

In certain scenarios, adjustments to the country-level sample size may be considered, contingent upon discussion with and final endorsement by the Global team:

- Health Authority (HA) request
- UAS7 is required as primary endpoint for regulatory reasons and is local standard of practice
- Powering study based on local prevalence data due to substantial epidemiological diversity observed across the target population, providing primary endpoint can still be met.

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, 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 will complete ePRO assessments using their own device, expected to take approximately 15 minutes. 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 and 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 7-1) 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. If an assessment is not completed, site staff will send a further reminder via phone calls, or email notifications.
  - Patients, where locally possible, 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, or

UAS7 ≤ 6) 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 ≥ 12 or UAS7 ≤ 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.

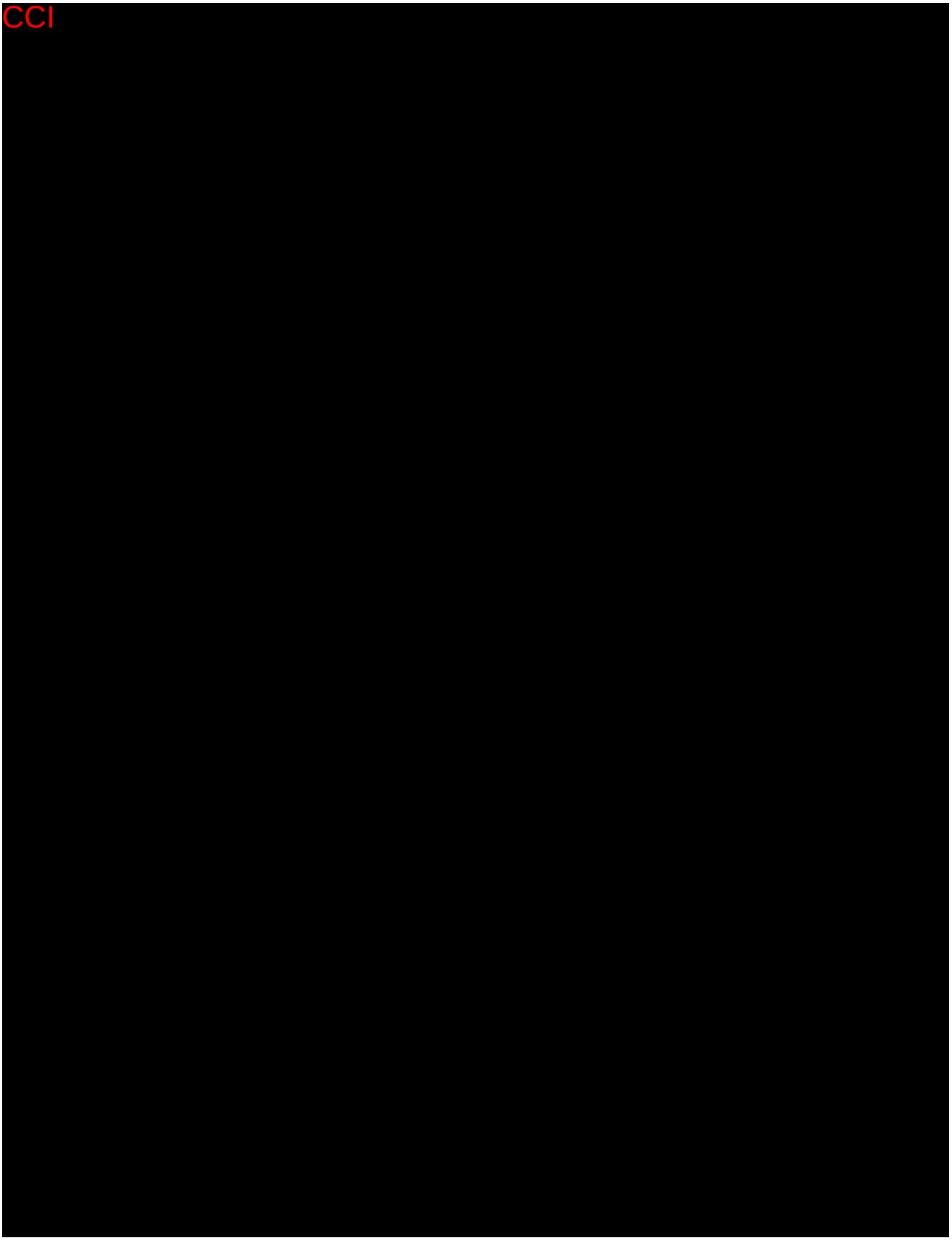
To assess the impact of remibrutinib on QoL, changes in DLQI scores from baseline to 24 months (and other continuous longitudinal measures) are analyzed using regression models, such as mixed models for repeated measures. The changes from baseline are summarized by the number of non-missing observations, 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 improvements. 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.

Exploratory endpoint analysis

All variables relevant to the exploratory endpoints can be found in the exploratory objective endpoint table in Section 6.2. Full details for the analysis of all exploratory endpoints are described in the SAP.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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. All sites are trained on the protocol, study logistics, eCRF pages, and on the use of the EDC 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 study is unblinded, meaning patients and physicians know the administered treatment. This awareness can introduce bias, as patient knowledge of their treatment regimen may influence their reporting of outcomes and adherence to the study protocol.

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 or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. 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 1 month 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.

Participating countries will ensure compliance with local safety data collection and reporting regulations and add details to their local protocols accordingly.

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

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.

11 References

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

Table 12-1 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 – Protocol signature page

GMA Evidence Generation, Immunology

LOU064

Protocol No. CLOU064A2402

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

Document type: Amended Protocol Version No. 01 Clean and Track Changes Signature Page

Referring to: Amended Protocol Version No. 01 content final date on 22-Dec-2025

Novartis approval signatures for:

Amended Protocol Version 01 Clean and Track Changes to Non-interventional Study Protocol v00

Electronic Document Identifier: provided on the separate protocol signature page

PPD	Signature	Date
PPD	Signature	Date

Investigator approval signatures for:

Amended Protocol Version 01 Clean and Track Changes to Non-interventional Study Protocol v00

Electronic Document Identifier: provided on the separate protocol signature page

Investigator signature

I have read the amended protocol version 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.

N/A – Investigators will sign signature pages of local protocols		
Investigator	Signature	Date

12.4 Annex 4 – 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 Ana Giménez-Arnau
- Professor Martin Metz
- PPD

- PPD

13 Appendices

None