NOVARTIS

Patient Safety & Pharmacovigilance

Remibrutinib

LOU064

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Remibrutinib
Product(s) concerned (brand name(s)):	Rhapsido®
Document status:	Final
Version number:	1.2
Data lock point for this RMP	04-Aug-2024
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Rationale for submitting an updated RMP: This Risk Management Plan (RMP) is updated in response to the List of Outstanding Issues (LoOI) received during the review of the remibrutinib European Union (EU) Marketing Authorization Application (MAA) procedure (EMEA/H/C/006313).

Summary of significant changes in this RMP: The following changes are made to the RMP:

- "Malignancies" is included as important potential risk
- Included "Malignancies" as a safety concern to be addressed in the Category 3 Post Authorization Safety Study CLOU064A2303B

Part	Major changes compared to RMP v 1.1
Part I	Updated the trade name of remibrutinib
Part II	
Module SI	No change
Module SII	• Updated to include "Malignancies" as an important potential risk
Module SIII	No change
Module SIV	• Updated to include "Malignancies" as an important potential risk • Included an update to the rationale for the following criteria: Major surgery and significant bleeding; History of live attenuated vaccine; Use of strong inhibitors of CYP3A4, moderate and strong inducers of CYP3A4
Module SV	No change
Module SVI	No change
Module SVII	• Included an update to the rationale for not including an identified or potential risk in the list of safety concerns in the RMP for the following risks: "Infections" (Identified risk), "Impaired immune response to vaccines" (Potential risk) • Updated to include "Malignancies" as important potential risk • Included an update to "Preventability" for the important potential risk "Serious bleeding events"
Module SVIII	• Updated to include "Malignancies" as an important potential risk
Part III	• Included "Malignancies" as a safety concern that will be addressed in Study CLOU064A2303B
Part IV	No change
Part V	• Updated routine risk minimization measures in alignment with the SmPC for "Serious bleeding events" and "Teratogenicity" • Updated to include "Malignancies" as important potential risk
Part VI	• Included the trade name, Rhapsido, for remibrutinib • Updated routine risk minimization measures in alignment with the SmPC for "Serious bleeding events" • Updated to include "Malignancies" as important potential risk
Part VII	
Annex Number	

Part	Major changes compared to RMP v 1.1
Annex 4	No change
Annex 6	No change

Other RMP versions under evaluation

No other RMP versions are currently under evaluation.

Details of the currently approved RMP

Not applicable.

QPPV name: Dr. Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization applicant´s QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse Drug Reaction
AESI	Adverse events of special interest
aHR	Adjusted hazard ratio
ALT	Alanine aminotransferase
aOR	Adjusted odds ratio
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under curve
BCR	B cell antigen receptor
BCRP	Breast cancer resistance protein
BMI	Body mass index
BSEP	Bile salt export pump
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CINDU	Chronic inducible urticaria
Cmax	Maximum serum concentration
CSR	Clinical study report
CSU	chronic spontaneous urticaria
CU	Chronic urticaria
CYP	Cytochrome
DDI	Drug-drug interactions
EAIR	Exposure-adjusted incidence rate
EAOR	Exposure-adjusted occurrence rate
ECG	Electrocardiogram
EEA	European Economic Area
EFD	Embryo-fetal development
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EXTEM	Extrinsic thromboelastometry
FCεR1	FC epsilon receptor 1
FCγR	FC gamma receptor
FMI	Final market image
FPFV	First patient first visit
GP	General practitioner
LoOI	List of Outstanding Issues
H1-AH	H1 antihistamine
HI	Hepatic impairment
HVs	Healthy volunteers
IC50	Half maximal inhibitory concentration
ICD	International classification of diseases

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgE	Immunoglobulin E
IgG	Immunoglobulin G
INN	International nonproprietary name
LD	Lactation day
LFT	Liver function test
LPLV	Last patient last visit
LVF	Left ventricular failure
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum recommended human dose
NOAEL	No observed adverse effect level
NYHA	New York heart association
OAT3	Organic anion transporter 3
OATP1B1	Organic anion transporting polypeptide 1B1
P-gp	P-glycoprotein
PPND	Pre and postnatal development
PPV-23	Pneumococcal polysaccharide vaccine 23-valent
q.d.	Once daily
QoL	Quality of life
QPPV	Qualified person responsible for pharmacovigilance
RMP	Risk Management Plan
ROTEM	Rotational thromboelastometry
SAE	Serious adverse event
SCS	Summary of clinical safety
SmPC	Summary of Product Characteristics
TDAR	T cell-dependent antibody response
UAS7	Weekly Urticaria activity Score
ULN	Upper limit normal
VAL	VårdAnalysdataLagar (the Healthcare Data Analysis Regulations in Sweden)

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Remibrutinib
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, selective immunosuppressants (L04AA60)
Marketing Authorization Applicant	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Rhapsido®
Marketing authorization procedure	Centralized procedure
Brief description of the product	**Chemical class:** Remibrutinib (LOU064) is a Bruton's tyrosine kinase (BTK) inhibitor.
	Summary of mode of action: BTK is an intracellular protein selectively expressed in mast cells, basophils, B cells, macrophages, and thrombocytes. BTK is a key node of the intracellular signalling via Fc epsilon receptor-1 (FcεR1), Fc gamma receptors (FcγR) and the B cell antigen receptor (BCR). Remibrutinib is an oral, highly selective BTK inhibitor. It inhibits mast cells and basophil degranulation mediated by pathogenic IgE or IgG directed against the FcεR1 or IgE. It blocks IgE- and IgG-mediated FcεRI activation of mast cells and basophils. In patients with CSU, remibrutinib prevents the release of histamine and other proinflammatory mediators that cause itch, hives, or angioedema.
	Important information about its composition: Remibrutinib Finished Product is formulated as 25 mg film coated tablets administered orally
Hyperlink to the Product Information	[Proposed SmPC]
Indication(s) in the EEA	**Current:** Chronic spontaneous urticaria (CSU) in adult patients with inadequate response to H1-antihistamine (H1-AH) treatment.
	Proposed: Not applicable
Dosage in the EEA	**Current:** 25 mg b.i.d., once in the morning and once in the evening
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Film-coated tablet, 25 mg
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication

The terms “remibrutinib” and “LOU064” are used interchangeably in this document.

Remibrutinib is indicated for the treatment of CSU in adult patients with inadequate response to H1-AH treatment.

Incidence:

Three population-based studies using data from Germany, Italy, and Sweden report the incidence rate of CSU in Europe.

A cross-sectional study using German statutory health insurance claims analyzed a total of 3.53 million insured individuals. The annual incidence rate of a diagnosis of CSU alone was 1.0 per 1,000 person-years, and that of CSU combined with chronic inducible urticaria (CSU+CINDU) was 0.2 per 1,000 person-years in 2017 (Weller et al 2022). Based on these estimates, the annual incidence rate of a diagnosis of either CSU or CSU+CINDU was 1.2 per 1,000 patient-years (calculated as the sum of both reported estimates).

A cohort study from Italy (2002-2013) used a national database of general practitioners (GPs) to assess the annual incidence of CSU in patients ≥15 years. In the observed period, 14,859 patients with CSU were identified, with an annual incidence rate ranging from 0.10 per 1,000 people in 2002 to 1.50 per 1,000 people in 2009 (Lapi et al 2016).

A registry-based study using data from Stockholm County Council VårdAnalysdataLagar (VAL) database, which collects anonymized data from all publicly subsidized healthcare provided in Stockholm County, included 10,642 adult patients with chronic urticaria (CU; 89% of them had CSU). A 5-year (2015-2019) mean annual incidence rate of 0.8 per 1,000 person-years was reported (Tayefi et al 2022).

Prevalence:

The point prevalence of CSU in the general population ranges from 0.5% to 1.0% according to a review by (Maurer et al 2011). The proportion of CSU patients among all CU patients (i.e., CSU and/or CINDU patients) was reported between 50% and 90% in all age groups according to reviews of the literature (Maurer et al 2011, Hon et al 2019, Schaefer 2017, Nettis et al 2020). In Table 2-1, studies assessing the prevalence of CSU in European countries are displayed.

A study using a large German health insurance claims database observed an annual prevalence of 0.40% in 2017 for the diagnosis of CSU or CSU+CINDU (Weller et al 2022). In a population-based study from Italy, the annual prevalence of CSU ranged from 0.02% to 0.38% in patients 15 years of age or older (Lapi et al 2016).

The annual prevalence of CSU in the US ranged from 0.11% to 0.19% according to two observational studies based on health care claims databases (Broder et al 2015, Geissbühler et al 2021).

Table 2-1 Prevalence of CSU in European countries

Country/ Region	Annual prevalence (%)	Age (years)	Year	Data source	Reference
Germany*	0.40	All ages	2017	Health insurance claims database	Weller et al 2022
	0.32	18-29			
	0.36	30-39			
	0.44	40-49			
	0.46	50-59			
	0.46	60-69			
	0.45	70-79			
	0.40	≥80			
Italy	0.02	≥15	2002	Electronic health record database	Lapi et al 2016
	0.38		2013		

Values refer to patients of all ages if not otherwise stated
*Annual prevalence of patients diagnosed with CSU or CSU+CINDU. The presented data were derived by summing the prevalence of patients diagnosed with CSU alone and that of patients diagnosed with CSU+CINDU as these estimates were separately reported by Weller et al 2022.
CINDU, chronic inducible urticaria; CSU, chronic spontaneous urticaria

The variation in prevalence data across studies is likely due to differences in study design, methods employed, and the geographical and cultural characteristics of the study population (as reviewed in Maurer et al 2011). Studies assessing the prevalence of CSU were generally based on large health care databases and used ICD-9 or ICD-10 codes to identify patients with CSU. Since there is no dedicated ICD code for CSU, case definitions relied on non-univocal algorithms. A commonly used one, validated by (Cherepanov et al 2015), showed a high positive predictive value of 90.4% with a lower sensitivity at 71.1%. Thus, around 30% of patients with CSU are missed in studies based on this algorithm (or adaptations thereof), and results are likely an underestimation of the true prevalence of CSU.

Other data sources such as surveys have been used to estimate prevalence. However, these studies do not specifically focus on CSU but estimate prevalence of overall CU (encompassing both CSU and CINDU). A systematic review and meta-analysis found an overall lifetime CU prevalence of 1.4% and an overall point prevalence of 0.7%. The point prevalence varied from 0.1% in North America to 0.5% in Europe, and up to 1.5% in Latin American and 1.4% in Asian countries (Fricke et al 2020).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Overall, all age groups can be affected by CSU. However, a peak incidence of disease onset is between 20 and 40 years of age, i.e., years of working age (Maurer et al 2011). In published observational studies, the mean age of included CSU patients ranged between 36.0 and 42.4 years when all ages were assessed (Zazzali et al 2012, Broder et al 2015, Kim et al 2018), and between 46.4 and 48.8 years when children were excluded (Maurer et al 2017a, Lapi et al 2016).

Reviews show that women suffer from CSU nearly twice as often as men (Maurer et al 2011, Nettis et al 2020), with a female to male ratio ranging from 2:1 to 3:1 (Zazzali et al 2012, Maurer et al 2017a). In Germany, the annual prevalence of CSU (defined as CSU or CSU+CINDU) in 2017 was 0.5% in women compared with 0.3% in men (Weller et al 2022). Broder and

colleagues reported a prevalence of CSU in the US of 0.15% in women compared with 0.07% in men (Broder et al 2015).

Racial and/or ethnic differences of patients affected by CSU have not been reported. Comparing separate studies conducted in different regions, CSU prevalence seems geographically heterogeneous. The reasons for regional differences remain largely unclear (Fricke et al 2020, Maurer et al 2020).

Risk factors for CSU

Several risk factors have been investigated and are discussed below.

Sex

Female sex is considered a risk factor for developing CSU. While this is already reflected in the female to male ratio, a large Italian-based cohort study using data from 14,859 Italian CSU patients additionally reported an adjusted hazard ratio (aHR) for CSU of 1.84 (95% CI: 1.77, 1.91) for women compared with men (Lapi et al 2016).

Medications

The same cohort study reported an increased risk of CSU diagnosis associated with prior use of immunosuppressive drugs (aHR 2.19; 95% CI: 1.67, 2.88) and with prior chronic use (≥180 days) of systemic corticosteroids (aHR 1.95; 95% CI: 1.48, 2.57) (Lapi et al 2016).

Thyroid disorders

Whether thyroid disorders are considered a risk factor for CSU or whether they are merely co-existent diseases has not been conclusively clarified. Available evidence points toward a potential autoimmune etiology in up to 50% of patients with CSU. The concept of 'overlapping autoimmune diseases' suggests that disorders which are autoimmune in nature occur at increased frequency in patients with known autoimmune disease (Bracken et al 2019). Autoimmune thyroid disorders have been associated with CSU (Missaka et al 2012) and overall CU (Confino-Cohen et al 2012). In most reports, autoimmune thyroid disorders were defined on the basis of the presence of high titers of antithyroid autoantibodies (Confino-Cohen et al 2012). A Korean cross-sectional study, which assessed differences in the prevalence of CSU-related diseases between CSU patients and the general population, reported an adjusted odds ratio (aOR) for disorders of the thyroid gland of 1.87 (95% CI: 1.80, 1.95), thereby not answering the question of temporality (Kim et al 2018). In the Italian study by Lapi et al 2016, a similar trend (yet not statistically significant) was seen. Patients with autoimmune thyroiditis before or at their first GP visit (cohort entry) were at a 39.0% increased risk of developing CSU (aHR 1.39; 95% CI: 0.99, 1.95).

Psychopathologies

Lapi et al 2016 found an aHR of 1.22 (95% CI: 1.08, 1.37) for the association between anxiety, dissociative and somatoform disorders and the diagnosis of CSU. Similarly, a large nested case-control and matched cohort study analyzing data from 12,185 Danish patients with CU (i.e., encompassing CSU and CINDU) reported that a previous or present diagnosis of depression (assessed at the date of CU diagnosis) was significantly higher in the CU population (OR 1.5; 95% CI: 1.3, 1.7) compared with controls (Ghazanfar et al 2020).

The main existing treatment options:

The first-line treatment for patients with CSU is second generation H1-antihistamines (locally label-approved standard dose or up to 4-times the standard dose). Omalizumab is licensed for the treatment of CSU as an add-on to second generation antihistamines for patients who do not show sufficient benefit from treatment with second generation antihistamines (standard dose or off-label up-dosing) (Zuberbier et al 2022). Although these therapies are often effective in reducing the symptoms of CSU, many patients fail to achieve complete therapeutic benefit. A meta-analysis showed that only 38.6% (95% CI: 34.7, 42.7) of CSU patients responded to licensed doses of H1-antihistamines, and among those who remained uncontrolled (61.4%), only 63.2% (95% CI: 57, 69.6) responded to up-dosing of H1-antihistamines (Guillén-Aguinaga et al 2016). In randomized clinical trials, the proportion of patients who achieve complete response (UAS7 = 0; hives and itch free) on omalizumab 300 mg at Week 12 ranged from 34-44%, while responder rates for UAS7 $\leq$ 6 at Week 12 ranged from 52-66% (Kaplan et al 2013, Maurer et al 2013, Saini et al 2015, Saini, Kaplan 2018). Patients who do not show sufficient benefit from omalizumab treatment may be up-dosed or change the frequency of the regimen (off-label recommendation) according to recent treatment guidelines (Zuberbier et al 2022). This need for individualized treatment with omalizumab has also been reported in a systematic review of real-world evidence (Bernstein et al 2018). Despite available global CU guidelines, and most patients are treated with AH, roughly 60% of patients remain uncontrolled. Of these, less than 20% of eligible patients receive omalizumab across major international markets, leaving a substantial number of refractory patients untreated. Reasons for this are multifaceted, e.g. the treatment with omalizumab increases patient burden due to its high cost compared to antihistamines treatment, and its administration via a subcutaneous injection with the recommendation to be initiated in a healthcare setting due to anaphylaxis warning.

Natural history of the indicated condition in the untreated population including mortality and morbidity:

CSU presents with transient wheals (hives), angioedema, or both, without any definite triggers and reoccurrence of signs and symptoms for more than 6 weeks (Maurer et al 2020). In two international observational studies that assessed patients with inadequately controlled CSU, physicians abstracted angioedema data from medical records and compared them with patient-reported data. Among patients with CSU, between 41.0% (physician-reported data) and 65.8% (patient-reported data) experienced angioedema within the past 12 months (Maurer et al 2017a, Sussman et al 2018).

In addition, CINDU often appears to co-exist with CSU. In a prospective study following 1,577 German H1-antihistamine-refractory patients with CSU for two years, concomitant CINDU was observed in 24% of the study population (Maurer et al 2017b).

Patients with CSU suffer a distinct decrease in quality of life (QoL). According to a multi-national cohort of 673 adult patients with CSU whose symptoms persisted for $\geq$ 12 months despite treatment, the most affected aspects of QoL were physical symptoms/discomfort, emotional well-being, interference with daily activities, sleep, and work performance (Maurer et al 2017a). In a prior review by (Maurer et al 2011), the authors stated that CSU patients suffer in many aspects a comparable QoL impairment as patients with severe coronary artery disease waiting for bypass surgery.

There is no specific data on mortality in CSU patients compared to the general population. In most cases, CSU is a self-limiting disorder, with duration of generally 1-5 years, although 20% of patients suffer beyond 5 years (Maurer et al 2011, Saini, Kaplan 2018). In some rare cases, CSU can last up to 50 years (Maurer et al 2011). The disease duration is likely to be longer in patients with a more severe disease, concurrent angioedema, concurrent CINDU, or autoreactivity (i.e., a positive autologous serum skin test) (Toubi et al 2004, Maurer et al 2011). According to a review of studies in patients with CU (i.e., encompassing CSU and CINDU), at least 50% of patients experience at least one recurrence after an apparent spontaneous resolution (Beltrani 2002).

Important co-morbidities:

Patients with CSU constitute a multimorbid group of patients. In terms of true co-morbidities which are conditions that cannot be described as one of the symptoms of CSU, articles retrieved focused mainly on atopic and allergic diseases, autoimmune and endocrine-related disorders, neoplasms, and psychopathologies. Prevalence estimates of important co-morbidities are listed in Table 2-2.

Atopic and allergic diseases

CSU is not an atopic disease, although atopy is frequent in CSU (Gonçalo et al 2021). A higher prevalence of allergic rhinitis or asthma, food allergies, and atopic dermatitis has been reported by various publications listed in Table 2-2.

Immune- and endocrine-related diseases

Although not CSU-specific, many studies have investigated the relationship of autoimmune disease and CU (i.e., encompassing CSU and CINDU). According to a systematic review, comorbid thyroid autoimmunity is the most frequent co-morbidity, with antithyroid autoantibodies found in 4% to 37.1% of patients with CU, often in association with autoimmune thyroid disease (Kolkhir et al 2017). In addition, patients with CU are at an increased risk of other immune- and endocrine-related co-morbidities, such as rheumatoid arthritis, systemic lupus erythematosus, and type I diabetes mellitus (Confino-Cohen et al 2012).

Depression and anxiety

A systematic review in patients with CSU found a pooled prevalence of psychosocial factors of 46.1% (95% CI: 44.0%, 48.1%). Among the psychiatric disorders reported in these studies, anxiety and depression were the most frequently co-occurring mental disorders (Ben-Shoshan et al 2013). Similarly, in CU patients, almost one out of three patients had at least one underlying psychiatric disorder according to a systematic literature review with a meta-analysis of published literature. However, none of the included studies clarified whether the psychiatric disorders pre-existed the CU onset (Konstantinou et al 2019).

Regarding European data, a large retrospective cross-sectional analysis among five countries (France, Germany, Italy, Spain, and the UK) between 2010 and 2013 found that self-reported depression was approximately twice as prevalent among CU cases (i.e., encompassing CSU and CINDU) than among the general population (32.8% vs. 14.6%; $p<0.001$). Anxiety was experienced by approximately half of cases, again about double the rate than among controls (50.9% vs. 22.6%; $p<0.001$) (Balp et al 2015).

Neoplasms

Conflicting data exists on whether CSU or CU patients overall are at an increased risk for neoplasms. In one Swedish study, 1,155 patients with CU were followed in a dermatology department for an average of 8.2 years. The incidence of cancer during the observation period was compared with the expected number of cancers from the Swedish Cancer Registry, yielding a relative risk of 0.88 (95% CI: 0.61, 1.12) (Lindelöf et al 1990). Two more recent, population-based studies showed an increased cancer risk in patients with CU overall (Chen et al 2012) and CSU specifically (Kim et al 2018). In the Korean cross-sectional study investigating co-morbidities of CSU patients by (Kim et al 2018), non-hematologic tumors were more frequently present in patients with CSU, especially thyroid, liver and prostate cancers (mean OR 1.37; 95% CI: 1.31, 1.49). In patients with CU (i.e., encompassing CSU and CINDU), a Taiwanese study showed an increased risk of neoplasms (standardized incidence ratio 2.2; 95% CI: 2.0, 2.3), especially hematologic malignant tumors. Malignant diseases were identified mostly in the first year after the diagnosis of CU (Chen et al 2012).

Prevalence estimates of important co-morbidities and respective references are listed in the following table.

Table 2-2 Co-morbidities found in the CSU population

Co-morbidity	Geographic region of study population	Prevalence among CSU patients	Source
Allergic rhinitis	Europe*	16.5%	Maurer et al 2017a
	US	43.2% to 50.4%	Broder et al 2015, Zazzali et al 2012, Eghrari-Sabet et al 2018
	Asia	18.7% to 74.1%	Kulthanan et al 2007, Kim et al 2018
	ROW (Israel)	10.4%**	Magen et al 2013
Anxiety	Europe	30.0%	Staubach et al 2011
	US	9.4%	Zazzali et al 2012
	ROW	26.7%	Rafique et al 2020
Asthma	Europe	12.0% to 15.9%	Maurer et al 2017b, Ghazanfar et al 2018
	US	18.3% to 31.8%	Broder et al 2015, Eghrari-Sabet et al 2018, Zazzali et al 2012
	Asia (Korea)	39.8%	Kim et al 2018
	ROW (Israel)	1.9%**	Magen et al 2013
Atopic dermatitis	Europe	6.8 to 22.2%	Maurer et al 2017b, Ghazanfar et al 2018
	US	7.8%	Broder et al 2015, Zazzali et al 2012
	ROW (Israel)	2.4%**	Magen et al 2013
Atopy	Europe (Turkey)	16.7%	Bulur et al 2018
CINDU	Europe	24.0%	Maurer et al 2017b
Depression	Europe	9.5% to 17.0%	Maurer et al 2017b, Staubach et al 2011
	US	9.4%	Zazzali et al 2012
	ROW (Pakistan)	26.7%	Rafique et al 2020
Diabetes mellitus	Europe*	1.0% to 1.8%	Lacour et al 2018, Maurer et al 2017a
Food allergy	US	21.2%	Eghrari-Sabet et al 2018

Co-morbidity	Geographic region of study population	Prevalence among CSU patients	Source
Hyperthyroidism	Europe	1.6%	Pedersen et al 2023
	ROW (Brazil, Israel)	7.8%	Missaka et al 2012
Hypothyroidism	Europe	6.8%	Pedersen et al 2023
	ROW (Brazil, Israel)	16.5%	Missaka et al 2012
Systemic lupus erythematosus	Europe*	0.3% to 1.0%	Lacour et al 2018, Maurer et al 2017a
Neoplasms	Asia	4.9% to 5.5%	Kim et al 2018
	ROW (Israel)	1.5%**	Magen et al 2013
Rheumatoid arthritis	Europe*	0.6% to 1.0%	Lacour et al 2018, Maurer et al 2017a

*Maurer et al 2017a also includes patients from Canada (next to the European countries Germany, France, Italy, Spain, the United Kingdom, and the Netherlands).

**As co-morbidities were separately reported for adult and elderly CSU patients by Magen et al 2013, the presented data were derived by dividing the sum of the adult and elderly CSU cases with the co-morbidity of interest by the total number of adult and elderly CSU patients.

CINDU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; ROW, rest of the world; US, United States

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

An extensive non-clinical safety program served as a basis for the safety assessment of remibrutinib in humans. The non-clinical safety evaluations consisted of safety pharmacology and repeat-dose toxicity studies in rats and dogs, as well as studies to assess genotoxicity, carcinogenicity, reproductive and developmental toxicity, and phototoxicity. The toxicology program was complemented by investigative studies related to immunosafety and hemostasis.

Based on conventional assessments of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenicity and phototoxicity, no hazard, which is considered likely to be relevant for humans, has been identified. However, the non-clinical safety data confirmed potential risks linked to effects on immune cells and platelets. Furthermore, a potential risk to the fetus has been identified in an embryo-fetal development study in rabbits.

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Infections	
Remibrutinib inhibited primary antibody responses to certain, but not all tool antigens in rodent pharmacology studies at pharmacologically relevant exposure. This observation is considered related to the role of BTK in B cells, suggesting a potentially increased infection risk and a potential impact on at least some vaccination responses. No indication towards an increased risk of *Mycobacterium tuberculosis* re-activation by remibrutinib was identified in an investigative in vitro study in a 3D human granuloma model.	In the clinical development program infections were comparable in frequency with placebo and majority were mild to moderate. Most common were upper respiratory tract infections managed with standard care. No opportunistic infections were reported in the clinical studies. No data are available on the effects of live and live-attenuated vaccines in patients receiving remibrutinib and these vaccines should not be co-administered with remibrutinib. Results suggest no significant impact on the immune response to influenza and PPV-23 vaccines 4 weeks after vaccination interrupting remibrutinib one week before vaccination and re-start after 2 weeks from vaccination in healthy participants. Concomitant remibrutinib impacts immune response to T-cell independent PPV-23 and T-cell dependent KLH vaccination and to a lesser extent to T-cell dependent influenza vaccination.
Respiratory and CNS effects	
No effects on respiratory or CNS function were identified in safety pharmacology investigations in rats up to 1,000 mg/kg [Study 1470738]. There was no relevant in vitro binding to or interference with CNS-effects related targets [RD-2014-00811]. Furthermore, remibrutinib does not have structural similarity to any known drugs of abuse [Study 2220079].	Based on the current available data, there is no concern relevant to human usage.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat dose toxicity	
Repeat-dose toxicity studies have been conducted in rats (up to 26 weeks) and dogs (up to 39 weeks). Whereas a NOAEL was established at the highest tested dose level of 300 mg/kg/day in the 39-week dog study, no NOAEL was established in the 26-week rat study due to adverse endocrine pancreas effects. However, these findings are considered unlikely to be relevant for humans since they represent spontaneously occurring changes in aging rats known to be exacerbated by BTK inhibitors with no translation to other species. Related exposure multiples of approximately 15- to 146-fold (AUC0-24h) or 7.2- to 88-fold (Cmax) were calculated relative to the dose of 25 mg b.i.d. remibrutinib. The margins are defined by maximal achievable exposures in rats and dogs.	There have been no relevant safety signals attributable to effects of remibrutinib on the pancreas in patient trials. The risk to humans is considered low.
Hemostasis	
In hemostasis assessments, remibrutinib caused a reversible increase in rat tail bleeding time (i.e. in the case of large blood vessel injury) [Study 1470733], [Study 1570157] but not dog mucosa bleeding time (i.e. in the case of small blood vessel injury) [Study 1470732] at pharmacologically relevant exposure, considered to be related to effects of remibrutinib on platelets. Remibrutinib caused an increase in the ROTEM lysis index and inhibition of collagen-induced platelet aggregation. In vitro, this was translatable across species (rat, dog, human) [Study 1570150], [Study 1520193], [Study 2120119], suggesting relevance for humans. Further investigations with human whole blood revealed that the ROTEM effects were depending on platelets (i.e., only occurring in EXTEM® containing functional platelets but not FIBTEM® in which platelets are not functional) [Study 1520193], and this is interpreted as an inhibitory effect of remibrutinib on clot retraction as seen by a different BTK inhibitor (Bye et al 2015).	“Serious bleeding events” are considered an important potential risk. In the clinical development program, majority of the bleeding events were mild and were reported with higher frequency with remibrutinib treatment compared to placebo. Overall, the bleeding events (petechiae, purpura, ecchymosis etc) were mostly localized on skin with infrequent mucosal events (epistaxis) reported and generally not associated with decrease in platelet counts or changes in coagulation parameters.
Genotoxicity	
Remibrutinib has been investigated in in vitro and in vivo tests consistent with relevant ICH Guidelines on genotoxicity [Study 1470739], [Study 1470742], [Study 1470733]. In vitro bacterial mutation and human lymphocyte micronucleus tests as well as an in vivo micronucleus assessment in rats did not show evidence of genotoxic potential of remibrutinib.	Based on the current available data, there is no concern relevant to human usage.
Reproductive and developmental toxicity	

Key Safety findings (from non-clinical studies)	Relevance to human usage
In pregnant rabbits, remibrutinib induced maternal toxicity and fetal external malformations (i.e. open/opaque eyes, small jaws, hyperflexion of forelimbs) at high exposure (300 mg/kg/day) [Study 1670382]. Fetal malformations were considered unlikely to be secondary to maternal toxicity. A NOAEL was established at 100 mg/kg/day, corresponding to steady-state safety margin of 23-fold (AUC0-24h) or 36-fold (Cmax) vs clinical 25 mg b.i.d. remibrutinib. No adverse effects were observed in an embryo-fetal development study in rats up to the highest tested dose of 1,000 mg/kg/day [Study 1670380]. Furthermore, there were no significant effects in a combined male and female fertility and early embryonic development study in rats up to 1,000 mg/kg/day [Study 1770589], indicating that remibrutinib is not associated with an increased risk of effect on fertility. In the pre and postnatal development (PPND) study, remibrutinib was administered orally to female rats at doses up to 1000 mg/kg/day from gestation day 6 to lactation day (LD) 21. Remibrutinib induced adverse effects at 1000 mg/kg/day, affected maternal animals (moribundity and clinical signs of toxicity, slightly longer gestation lengths) and offspring up to LD1 (slightly higher mean number of stillborn, dead, or missing pups, and smaller mean litter size). No adverse effects of doses up to 1000 mg/kg/day were noted for the surviving offspring developing into adulthood. NOAEL for maternal animals and offspring was established at 300 mg/kg/day, which is equivalent to approximately 67 times the MRHD of 25 mg b.i.d. based on $AUC_{0\text{-}24h}$.	"Teratogenicity" is an important potential risk (see Section 8.3). This risk is discussed in Part II Module SVII and Module SVIII. No clinically relevant cases of teratogenicity have been observed in clinical studies. Nine pregnancies have been reported (5 in completed studies and 4 in ongoing studies). In completed studies, one pregnancy (from A2201E1) was full term and resulted in normal baby with follow up at 12 months with no developmental delay; one from A2305 with full-term healthy female baby (information obtained after the cut-off date), however the pregnancy likely started after last dose of study treatment; two pregnancies ended following elective abortion and one due to spontaneous abortion in patient with risk factors (overweight and oral contraceptives). In ongoing studies, two pregnancies are still ongoing and in the remaining two, patients withdrew consent to follow-up.
In a rat juvenile toxicity study with remibrutinib dosing starting from post-natal day 19 for at least 7 weeks, supporting clinical studies across indications in pediatric patients ≥ 2 years of age, remibrutinib was associated with several cases of marked unilateral enlarged and/or protruding eyes with no dose-dependency, requiring early termination of the affected animals. No further adverse effects were observed in the study. T cell-dependent antibody response (TDAR) was inhibited and delayed during the remibrutinib dosing phase but not when initiated during a recovery period following the dosing phase, suggesting no disturbance of TDAR-related immune function development. Maximal achieved exposure multiples ranged from 21- to 105-fold in terms of steady-state AUC0-24h compared to the clinical dose of 25 mg b.i.d. remibrutinib in adults.	This finding was considered of limited relevance to human since it was regarded as primarily due to a combination of rat-specific anatomical and developmental circumstances predisposing for disrupted aqueous drainage and spontaneous intraocular bleeding in a subset of the juvenile rats in this study, with a possible contribution of the experimental procedure, exacerbated by the known hemostatic effects of remibrutinib.
Carcinogenicity	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Remibrutinib did not show evidence of carcinogenic potential in 26-week rasH2 transgenic mouse [Study 1870307] and 104-week rat [Study 1870308] carcinogenicity studies up to the highest tested dose levels of 1,500 and 300 mg/kg/day, respectively. The dose levels corresponded to exposure multiples of 7.7- to 144-fold (AUC0-24h) or 3.3- to 69-fold (Cmax) relative to the dose of 25 mg b.i.d. remibrutinib. Remibrutinib did not show any genotoxic potential in a standard battery of assays.	"Malignancies" is an important potential risk (see Section 8.3). Incidence of malignancy was low in clinical studies to date and none of the events were considered related.
Hepatotoxicity	
There were no adverse liver findings in non-clinical safety studies on remibrutinib. Non-adverse microscopic liver changes (e.g. multinucleated hepatocytes) at high dose levels in rodents were considered unlikely to be relevant for humans as they were regarded as a rodent-specific representation of increased incidences of background findings. An observed increase in liver weight is interpreted as the result of rodent-specific microsomal enzyme induction. Inhibition of BSEP (IC50 = 6.6 µM) is unlikely relevant as risk factor due to high safety margins (> 900-fold vs clinical 25 mg b.i.d.). Formation of reactive metabolites in human liver microsomes and hepatocytes in vitro was observed. Remibrutinib has been found to form covalent protein adduct via reactive metabolites [DMPK R1400730]. Covalent binding and formation of protein adducts of remibrutinib has been observed in human liver microsomes and human hepatocytes [DMPK R1400730]. The addition of glutathione reduced protein adduct formation, highlighting its role in cellular defense against reactive metabolites. Given the low anticipated exposure of remibrutinib in humans (25 mg b.i.d) it seems unlikely that protein adduct formation will translate into a clinically relevant safety signal.	Hepatotoxicity is not considered an important risk for humans based on the pre-clinical data. No concerns related to liver safety noted in A2301 and A2302 studies, other studies in CSU or other indications to date. Liver enzyme elevations were balanced, no clinical concerns for hepatotoxicity noted with remibrutinib, with newly occurring notable (ALT/AST >3xULN) liver enzyme abnormalities being isolated, asymptomatic transient/reversible liver transaminase elevations, without concurrent increase in bilirubin. No Hy's law cases reported in clinical development program to date.
Cardiovascular effects	
Remibrutinib is a mild inhibitor of the hERG channel (IC50 = 1.4 µM; unbound Cmax-based average safety margin of 192-fold based on 25 mg b.i.d. in humans), without affecting other ion channels in a relevant manner. GLP telemetry studies in dogs did not give a clear alert for QTc prolongation, arrhythmia, or other cardiovascular changes up to maximal achievable exposure. Small (maximal 3%) increases in QTc were observed in a non-GLP 3-day cardiovascular assessment study in dogs following administration of 400 mg/kg remibrutinib on Day 2 and 3 (average Cmax multiple 24-fold (total blood) or 46-fold (unbound plasma) based on the clinical dose	No risk for humans based on pre-clinical data. There were no notable findings in analysis of ECGs and no clinically relevant QTc prolongation.

Key Safety findings (from non-clinical studies)	Relevance to human usage
of 25 mg b.i.d.). These QTc increases were reversible within 6 hours. Altogether, QTc prolongation is considered unlikely to occur at pharmacological exposure.	
Phototoxicity	
Remibrutinib has no phototoxic potential in vitro [Study 1670379].	No risk for humans based on pre-clinical data.
Drug-drug interaction(s)	
In vitro, remibrutinib has been found to inhibit and induce different CYP isoenzymes as well as efflux and uptake transporters with low potency. Clinical drug-drug interaction studies in healthy volunteers (HVs) indicated that remibrutinib can be co-administered with oral contraceptives such as ethinylestradiol or levonorgestrel without any clinically relevant impact on their exposure. Moreover, remibrutinib was shown to be only a weak inhibitor of CYP3A4 and CYP2C9 (exposure to tolbutamide and midazolam probes increased less than 1.5-fold for both substrates). No inhibition of CYP1A2 was observed (no change in probe caffeine exposure). The co-administration of strong CYP3A4 inhibitor ritonavir increased remibrutinib Cmax and AUC by 3.3-fold and 4.3-fold, respectively. The co-administration of strong CYP3A4 inducer carbamazepine decreased remibrutinib Cmax and AUC by 74% and 77%, respectively. Modeling predicted an increase in remibrutinib Cmax and AUC by 1.9- and 2.1-fold when co-administered with a moderate CYP3A4 inhibitor, and a reduction by 62% and 65%, respectively, when co-administered with a moderate CYP3A4 inducer. Co-administration of remibrutinib with digoxin (P-gp substrate) increased digoxin Cmax and AUC by 108% and 40%, respectively. Co-administration of remibrutinib with rosuvastatin (BCRP, OATP1B1 and OAT3 substrate) increased rosuvastatin Cmax and AUC by 56% and 59%, respectively. The presence of remibrutinib did not change the plasma exposure to coproporphyrin I (an endogenous OATP1B1 substrate), nor the renal clearance of rosuvastatin (OAT3-mediated process), indicating that the contribution of remibrutinib to OATP1B1 and OAT3 inhibition was negligible. Consequently, the increase in rosuvastatin plasma exposure can be attributed to an inhibitory effect of remibrutinib on BCRP [DMPK R2301014].	No risks related to DDI were identified. However, caution is required when using remibrutinib with strong CYP3A4 inhibitors. Co-administration of remibrutinib with strong or moderate CYP3A4 inducers must be avoided. Caution is required when using remibrutinib with P-gp substrates with a narrow therapeutic index such as digoxin. Caution is required when using remibrutinib with breast cancer resistance protein (BCRP) substrates with a narrow therapeutic index.
Food interaction(s)	
The effect of food on the pharmacokinetics of remibrutinib has been explored as part of study CLOU064X2101 (CSF, hard gelatin capsule). Cmax	No clinically relevant impact on exposure and no risks related to food interaction.

Key Safety findings (from non-clinical studies)	Relevance to human usage
was slightly decreased (fed/fasted ratio: 0.8) while AUC was slightly increased by 1.3-fold when remibrutinib was given with food as compared to fasted. Tmax was shifted from 0.767 h (fasted) to 2.78 h (fed). The food effect has also been investigated using the FMI (film-coated tablet) in study CLOU064A02104 in healthy Chinese volunteers. Cmax decreased by 5%, Tmax increased from 1 to 2 h, while AUC increased by 33% for participants on a standard high-fat meal. The observed magnitude of the food effect on the overall bioavailability of the drug in both Study X2101 and Study A02104 is considered to have no clinical relevance.	

Source: [LOU064-Non-Clinical overview], (LOU064-SmPC)

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

This RMP contains safety information from the pivotal Phase III studies CLOU064A2301, and CLOU064A2302 (hereafter referred to as studies A2301 and A2302), supported by Phase III study CLOU064A1301 (hereafter referred to as study A1301), and Phase II studies CLOU064A2201 and CLOU064A2201E1 (hereafter referred to as study A2201 and A2201E1), all in the CSU indication.

Pooling of the studies:

Based on the clinical studies shown in Table 4-1, two safety data pools (Pool 1 and Pool 2) were created.

Also, two analysis periods were considered:

- Period 1: the placebo-controlled period (up to 24 weeks, Pool 1 only), and
- Period 2: the entire study period (up to 56 weeks in Pool 1 and up to 72 weeks in Pool 2).

Pool 1 (Pivotal Phase III studies): Period 1 and Period 2

This pool includes all available safety data from the two Phase III pivotal studies A2301 and A2302, up to 56 weeks.

In Pool 1 the dose-specific effects of remibrutinib 25 mg b.i.d. versus placebo in the 24-week placebo-controlled period are assessed, as well as safety up to Week 56 in 867 patients.

Pool 2 (Phase II/III studies): The entire study period including Period 1 and Period 2 (up to Week 72).

This data pool includes all safety data from the CSU Phase III pivotal studies (A2301 and A2302), the Phase II supportive studies, i.e., the CSU Phase II and its extension (A2201/E1), as well as the Phase III Japanese local study A1301.

In Pool 2 the long-term safety data (on varying doses including follow up) up to 72 weeks from approximately 1234 patients treated with remibrutinib are assessed.

Table 4-1 Overview of LOU064 Phase II/III studies in CSU

Phase	CLOU064 Study (Status)	Dose/Regimen	Treatment (weeks)	Enrolled / exposed	Population / Study description
Pivotal studies					
III	A2301 (completed)	LOU064 25 mg b.i.d. Placebo	52 24	Total n=470/442 (309 patients on remibrutinib up to 52 weeks) Remibrutinib n=313/309 Placebo n=157/153	Adults/ Double-blinded, randomized study; Placebo arm starts LOU064 25 mg b.i.d. treatment at Week 24; 52-week total treatment period + 4-week follow-up period

Phase	CLOU064 Study (Status)	Dose/Regimen	Treatment (weeks)	Enrolled / exposed	Population / Study description
III	A2302 (completed)	LOU064 25 mg b.i.d. Placebo	52 24	Total n=455/426 (297 patients on remibrutinib up to 52 weeks) Remibrutinib n=300/297 Placebo n=155/153	Adults/Double-blinded, randomized study; Placebo arm starts LOU064 25 mg b.i.d. treatment at Week 24; 52-week total treatment period + 4-week follow-up period
Supportive studies					
IIb	A2201 (Completed)	LOU064 10 mg q.d. LOU064 35 mg q.d LOU064 100 mg q.d LOU064 10 mg b.i.d. LOU064 25 mg b.i.d. LOU064 100 mg b.i.d. Placebo	12 12 12 12 12 12 12	Total n=311/267 Remibrutinib 10 mg q.d., n=44 Remibrutinib 35 mg q.d., n=44 Remibrutinib 100 mg q.d., n=47 Remibrutinib 10 mg b.i.d., n=44 Remibrutinib 25 mg b.i.d., n=44/43 Remibrutinib 100 mg b.i.d., n=45 Placebo n=43/42	Adults/Double-blinded, randomized study; Participants who completed treatment could roll-over into the extension A2201E1 study at Week 12 or at Week 16 (Follow up visit), following the roll-over criteria defined in the extension study protocol. Max follow-up = up to Week 16
IIb Extension	A2201E1 (Completed)	LOU064 100 mg b.i.d.	52	*Total n=194/194	Adults/Participants who completed treatment in A2201 and rolled over into the extension A2201E1 study at Week 12 or at Week 16 (Follow up visit), following the roll-over criteria defined in the protocol received LOU064 100 mg b.i.d. Open-label single arm study Max follow-up = up to Week 68
III	A1301 (completed)	LOU064 25 mg b.i.d.	52	Total n=71/71	Adults/A multicenter, open-label Phase III study of remibrutinib to investigate the safety, tolerability and efficacy for 52 weeks in adult Japanese CSU patients inadequately controlled by H1-antihistamines Open-label single arm study Max follow-up = up to Week 56

Phase	CLOU064 Study (Status)	Dose/Regimen	Treatment (weeks)	Enrolled / exposed	Population / Study description
* Includes participants who received placebo in A2201 and then received remibrutinib for the first time in A2201E1 Source: [LOU064-SCS]					

A breakdown of the duration of exposure to study drug by treatment during the placebo-controlled period of Pool 1 studies is shown in Table 4-2.

Table 4-2 SIII.1: Duration of exposure to study drug by treatment during the placebo-controlled period (Pool 1 Safety Set)

Duration of exposure	LOU064 25mg b.i.d. N = 606	Placebo N = 306	Total N = 912
Any exposure	606(100.0)	306(100.0)	912(100.0)
Exposure categories (weeks) – n (%)			
>0 - <2	6(1.0)	7(2.3)	13(1.4)
>=2 - <4	8(1.3)	5(1.6)	13(1.4)
>=4 - <8	22(3.6)	9(2.9)	31(3.4)
>=8 - <12	7(1.2)	7(2.3)	14(1.5)
>=12 - <16	14(2.3)	6(2.0)	20(2.2)
>=16 - <20	8(1.3)	0	8(0.9)
>=20 - <24	91(15.0)	54(17.6)	145(15.9)
>=24	450(74.3)	218(71.2)	668(73.2)
Exposure (weeks)			
n	606	306	912
Mean	22.52	22.09	22.38
SD	5.300	5.926	5.518
Minimum	0.1	0.3	0.1
Q1	23.86	23.86	23.86
Median	24.00	24.00	24.00
Q3	24.29	24.29	24.29
Maximum	29.4	30.3	30.3
Subject-time (subject-years)	261.57	129.55	391.12

N: Total number of subjects in the corresponding group from the analysis set.
n: Total number of subjects who satisfy the described criterion.
Duration of exposure (days) = last dose date of study treatment in placebo-controlled treatment period - first dose date of study treatment + 1.
Subject-time (subject-years) = cumulative duration of exposure in years from subjects in the corresponding treatment group, which is calculated as the sum of individual subjects durations in days divided by 365.25.
Source: Annex 7 - Table 1.2-4p1

A breakdown of the duration of exposure to study drug by treatment during the entire study period of Pool 1 studies is shown in Table 4-3.

Table 4-3 Duration of exposure to study drug by treatment during the entire study period (Pool 1 Safety Set)

Duration of exposure	LOU064 25mg b.i.d. N = 606	Transitioned to LOU064 25mg b.i.d. N = 262	Any LOU064 25mg b.i.d. N = 868
Any exposure	606(100.0)	262(100.0)	868(100.0)
Exposure categories (weeks) – n (%)			
>0 - <2	6(1.0)	1(0.4)	7(0.8)
>=2 - <4	8(1.3)	1(0.4)	9(1.0)
>=4 - <8	22(3.6)	7(2.7)	29(3.3)
>=8 - <12	7(1.2)	5(1.9)	12(1.4)
>=12 - <16	14(2.3)	4(1.5)	18(2.1)
>=16 - <20	8(1.3)	3(1.1)	11(1.3)
>=20 - <24	6(1.0)	4(1.5)	10(1.2)
>=24 - <32	14(2.3)	236(90.1)	250(28.8)
>=32 - <40	17(2.8)	1(0.4)	18(2.1)
>=40 - <52	66(10.9)	0	66(7.6)
>=52	438(72.3)	0	438(50.5)
Exposure (weeks)			
n	606	262	868
Mean	46.24	26.78	40.37
SD	14.564	5.529	15.398
Minimum	0.1	1.1	0.1
Q1	51.86	27.71	28.14
Median	52.14	28.14	52.00
Q3	52.71	28.86	52.29
Maximum	60.6	32.9	60.6
Subject-time (subject-years)	537.06	134.48	671.55

N: Total number of subjects in the corresponding group from the analysis set. For Transitioned to LOU064 25mg b.i.d. group, N refers to the number of subjects
who have transitioned to LOU064 25mg b.i.d. For Any LOU064 25mg b.i.d., N refers to number of subjects in LOU064 25mg b.i.d. group or switched to LOU064
25mg b.i.d. group from placebo from the corresponding analysis set.
n: Total number of subjects who satisfy the described criterion.
Duration of exposure (days) = last dose date of study treatment in the entire study period - first dose date of study treatment in the entire study period + 1.
Subject-time (subject-years) = cumulative duration of exposure in years from subjects in the corresponding treatment group, which is calculated as the sum of individual subjects durations in days divided by 365.25.
Source: Annex 7 - Table 1.2-5p1

A breakdown of the duration of exposure to study drug by treatment during the entire study period of Pool 2 studies is shown in Table 4-4.

Table 4-4 Duration of exposure to study drug by treatment during the entire study period Pool 2 Safety Set

Duration of exposure	LOU064 any dose N = 1234	Any LOU064 25mg b.i.d. N = 982
Any exposure	1234 (100.0)	982(100.0)
Exposure categories (weeks) – n(%)		
>0 - <2	10(0.8)	8(0.8)

Duration of exposure	LOU064 any dose N = 1234	Any LOU064 25mg b.i.d. N = 982
>=2 - <4	14(1.1)	9(0.9)
>=4 - <8	36(2.9)	30(3.1)
>=8 - <12	28(2.3)	17(1.7)
>=12 - <16	91(7.4)	54(5.5)
>=16 - <20	23(1.9)	13(1.3)
>=20 - <24	13(1.1)	10(1.0)
>=24 - <32	257(20.8)	250(25.5)
>=32 - <40	22(1.8)	18(1.8)
>=40 - <52	86(7.0)	80(8.1)
>=52	654(53.0)	493(50.2)
Exposure (weeks)		
n	1234	982
Mean	41.10	39.93
SD	17.986	16.025
Minimum	0.1	0.1
Q1	28.14	28.14
Median	52.00	52.00
Q3	52.86	52.29
Maximum	69.9	60.6
Subject-time (subject-years)	971.94	751.47

N: For LOU064 any dose group, N refers to the number of subjects in any LOU064 treatment group or switched to LOU064 from the corresponding analysis set.
For Any LOU064 25mg b.i.d., N refers to number of subjects in LOU064 25mg b.i.d. group or switched to LOU064 25mg b.i.d. group from placebo from the corresponding analysis set.
n: Total number of subjects who satisfy the described criterion.
Duration of exposure (days) = last dose date of study treatment in the entire study period - first dose date of study treatment in the entire study period + 1.
For subjects rolling over from A2201 to A2201E1, the summation of the exposures from these two studies is used (the observation period is excluded).
Subject-time (subject-years) = cumulative duration of exposure in years from subjects in the corresponding treatment group, which is calculated as the sum of individual subjects durations in days divided by 365.25.
Source: Annex 7 - Table 1.2-3p2

The overall extent of drug exposure by treatment during the placebo-controlled period of Pool-1 studies, by age and gender is presented in Table 4-5.

Table 4-5 SIII.2: Exposure to study drug by treatment during the placebo-controlled period, by age and gender-Pool 1 Safety Set

		LOU064 25mg b.i.d. N=606		Placebo N=306		Total N=912	
Age (years)	Sex	Subjects n (%)	Exposure (subject-years)	Subjects n (%)	Exposure (subject-years)	Subjects n (%)	Exposure (subject-years)
Total	Total	606 (100.0)	261.6	306 (100.0)	129.5	912 (100.0)	391.1
	Male	203 (33.5)	87.5	102 (33.3)	43.5	305 (33.4)	131.0
	Female	403 (66.5)	174.1	204 (66.7)	86.0	607 (66.6)	260.1
>=18-<65	Total	553 (91.3)	238.6	282 (92.2)	119.2	835 (91.6)	357.8

		LOU064 25mg b.i.d. N=606		Placebo N=306		Total N=912	
Age (years)	**Sex**	**Subjects n (%)**	**Exposure (subject-years)**	**Subjects n (%)**	**Exposure (subject-years)**	**Subjects n (%)**	**Exposure (subject-years)**
	Male	188 (31.0)	81.5	95 (31.0)	40.6	283 (31.0)	122.1
	Female	365 (60.2)	157.1	187 (61.1)	78.6	552 (60.5)	235.7
>=65-<85	Total	53 (8.7)	23.0	24 (7.8)	10.3	77 (8.4)	33.3
	Male	15 (2.5)	6.0	7 (2.3)	2.9	22 (2.4)	8.9
	Female	38 (6.3)	17.0	17 (5.6)	7.4	55 (6.0)	24.4
>=85	Total	0	0	0	0	0	0
	Male	0	0	0	0	0	0
	Female	0	0	0	0	0	0

N: Total number of subjects in the corresponding group from the analysis set.
n: Total number of subjects who satisfy the described criterion.
Duration of exposure (days) = last dose date of study treatment in the placebo-controlled period - first dose date of study treatment in the placebo-controlled period + 1.
Exposure (subject-years): cumulative duration of exposure in years from subjects in the corresponding subgroup category in the treatment group, which is calculated as the sum of individual subjects durations in days divided by 365.25.
Source: Annex 7 - Table 1.2-4p1_s2

The overall extent of drug exposure by treatment during the entire study period of Pool 1 studies, by age and gender is presented in Table 4-6.

Table 4-6 Exposure to study drug by treatment during the entire study period, by age and gender-Pool 1 Safety Set

		LOU064 25mg b.i.d. N=606		Transitioned to LOU064 25mg b.i.d. N=262		Any LOU064 25mg b.i.d. N=868	
Age (years)	**Sex**	**Subjects n (%)**	**Exposure (subject-years)**	**Subjects n (%)**	**Exposure (subject-years)**	**Subjects n (%)**	**Exposure (subject-years)**
Total	Total	606 (100.0)	537.1	262 (100.0)	134.5	868 (100.0)	671.5
	Male	203 (33.5)	179.9	88 (33.6)	45.8	291 (33.5)	225.7
	Female	403 (66.5)	357.1	174 (66.4)	88.7	577 (66.5)	445.9
>=18-<65	Total	553 (91.3)	489.6	242 (92.4)	124.2	795 (91.6)	613.8
	Male	188 (31.0)	168.0	82 (31.3)	42.5	270 (31.1)	210.5
	Female	365 (60.2)	321.6	160 (61.1)	81.7	525 (60.5)	403.3
>=65-<85	Total	53 (8.7)	47.4	20 (7.6)	10.3	73 (8.4)	57.8
	Male	15 (2.5)	11.9	6 (2.3)	3.3	21 (2.4)	15.2
	Female	38 (6.3)	35.6	14 (5.3)	7.0	52 (6.0)	42.6
>=85	Total	0	0	0	0	0	0
	Male	0	0	0	0	0	0
	Female	0	0	0	0	0	0

Age (years)	Sex	LOU064 25mg b.i.d. N=606		Transitioned to LOU064 25mg b.i.d. N=262		Any LOU064 25mg b.i.d. N=868	
		Subjects n (%)	Exposure (subject-years)	Subjects n (%)	Exposure (subject-years)	Subjects n (%)	Exposure (subject-years)

N: Total number of subjects in the corresponding group from the analysis set. For Transitioned to LOU064 25mg b.i.d. group, N refers to the number of subjects
who have transitioned to LOU064 25mg b.i.d. For Any LOU064 25mg b.i.d., N refers to number of subjects in LOU064 25mg b.i.d. group or switched to LOU064
25mg b.i.d. group from placebo from the corresponding analysis set.
n: Total number of subjects who satisfy the described criterion.
Duration of exposure (days) = last dose date of study treatment in the entire study period - first dose date of study treatment in the entire study period + 1.
Exposure (subject-years): cumulative duration of exposure in years from subjects in the corresponding subgroup category in the treatment group, which is calculated as the sum of individual subjects durations in days divided by 365.25.
Source: Annex 7 - Table 1.2-5p1_s2

The overall extent of drug exposure by treatment during the placebo-controlled period of Pool 1 studies by race is presented in Table 4-7.

Table 4-7 SIII.3: Exposure to study drug by treatment during the placebo-controlled period, by race-Pool 1 Safety Set

Race	LOU064 25mg b.i.d. N=606		Placebo N=306		Total N=912	
	Subjects n (%)	Exposure (subject-years)	Subjects n (%)	Exposure (subject-years)	Subjects n (%)	Exposure (subject-years)
White	341 (56.3)	148.1	163 (53.3)	67.7	504 (55.3)	215.8
Black or African American	19 (3.1)	7.0	6 (2.0)	2.1	25 (2.7)	9.0
Asian	223 (36.8)	95.8	117 (38.2)	51.1	340 (37.3)	146.9
American Indian or Alaska Native	12 (2.0)	5.6	14 (4.6)	5.9	26 (2.9)	11.5
Native Hawaiian or Pacific Islander	0	0	1 (0.3)	0.5	1 (0.1)	0.5
More than one race	9 (1.5)	4.1	3 (1.0)	1.4	12 (1.3)	5.5
Unknown	2 (0.3)	0.9	2 (0.7)	0.9	4 (0.4)	1.8

N: Total number of subjects in the corresponding group from the analysis set.
n: Total number of subjects who satisfy the described criterion.
Duration of exposure (days) = last dose date of study treatment in the placebo-controlled period - first dose date of study treatment in the placebo-controlled period + 1.
Exposure (subject-years): cumulative duration of exposure in years from subjects in the corresponding subgroup category in the treatment group, which is calculated as the sum of individual subjects durations in days divided by 365.25.
Source: Annex 7 - Table 1.2-4p1_s4

The overall exposure to study drug by treatment during the entire study period of Pool 1 studies by race is shown in Table 4-8.

Table 4-8 Exposure to study drug by treatment during the entire study period, by race-Pool 1 Safety Set

	LOU064 25mg b.i.d. N=606		Transitioned to LOU064 25mg b.i.d. N=262		Any LOU064 25mg b.i.d. N=868	
Race	**Subjects n (%)**	**Exposure (subject-years)**	**Subjects n (%)**	**Exposure (subject-years)**	**Subjects n (%)**	**Exposure (subject-years)**
White	341 (56.3)	302.4	133 (50.8)	67.1	474 (54.6)	369.5
Black or African American	19 (3.1)	14.4	4 (1.5)	2.2	23 (2.6)	16.6
Asian	223 (36.8)	198.7	108 (41.2)	56.2	331 (38.1)	254.9
American Indian or Alaska Native	12 (2.0)	11.4	11 (4.2)	5.6	23 (2.6)	17.0
Native Hawaiian or Pacific Islander	0	0	1 (0.4)	0.5	1 (0.1)	0.5
More than one race	9 (1.5)	8.6	3 (1.1)	1.7	12 (1.4)	10.3
Unknown	2 (0.3)	1.6	2 (0.8)	1.1	4 (0.5)	2.8

N: Total number of subjects in the corresponding group from the analysis set. For Transitioned to LOU064 25mg b.i.d. group, N refers to the number of subjects
who have transitioned to LOU064 25mg b.i.d. For Any LOU064 25mg b.i.d., N refers to number of subjects in LOU064 25mg b.i.d. group or switched to LOU064
25mg b.i.d. group from placebo from the corresponding analysis set.
n: Total number of subjects who satisfy the described criterion.
Duration of exposure (days) = last dose date of study treatment in the entire study period - first dose date of study treatment in the entire study period + 1.
Exposure (subject-years): cumulative duration of exposure in years from subjects in the corresponding subgroup category in the treatment group, which is calculated as the sum of individual subjects durations in days divided by 365.25.
Source: Annex 7 - Table 1.2-5p1_s4

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
History of hypersensitivity to any of the study treatments, or to its excipients or to drugs of similar chemical classes	Exclusion of patients with a history of hypersensitivity related to medications which are either remibrutinib, placebo to remibrutinib or drugs with similar chemical classes sensitivity reaction avoids inclusion of a potentially more vulnerable patient population who might be at higher risk of hypersensitivity reaction to these products.	No	Hypersensitivity is a contraindication; therefore, patients with history of hypersensitivity to remibrutinib or excipients or to drugs of similar chemical classes are not expected to receive remibrutinib.
Known or suspected ongoing, chronic or recurrent infectious diseases, including but not limited to opportunistic infections. Patients with history of Hepatitis B must remain negative for HBsAg and HBV-DNA.	BTK inhibition may increase susceptibility to infections. Consequently, this exclusion criterion was conservatively applied to ensure the safety of trial subjects.	No	Overall infections were balanced in remibrutinib studies and the majority did not lead to treatment discontinuation or treatment interruption. Hepatitis B reactivation was not reported in pivotal studies. Therefore, safety profile is not anticipated to be different in patients with ongoing infections at the time of treatment initiation as compared to patients without infections.
Pregnant women, nursing mothers, or	Fetal external malformations were	No	“Teratogenicity” is an Important potential risk (see Section 8.3).

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
women of child-bearing potential not using appropriate contraception	observed in rabbit EFD at 300 mg/kg/day. Although maternal toxicity was also observed at this dose level, the fetal findings were considered unrelated to maternal toxicity.		This risk is discussed in Part II Module SVII and Module SVIII. Sexually active women of child-bearing potential must use effective contraception (methods that result in less than 1 % pregnancy rates) during remibrutinib treatment and for at least 1 week after the last dose. Remibrutinib is not recommended during pregnancy. The patient should be advised of a potential risk to the foetus if remibrutinib is used during pregnancy or if the patient becomes pregnant while taking remibrutinib. There are no data on the effects of remibrutinib on the breast-fed newborn/infant or on milk production. Because of the potential for adverse reactions in breast-fed newborns/infants, women should be advised not to breast-feed during treatment with remibrutinib and for 1 week after the last dose.
History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), within the past 5 years, regardless of whether there is evidence of local recurrence or metastases	This exclusion was put in place to avoid inclusion of a patient population at a potential higher risk of malignant events affecting both efficacy and safety evaluations in the study.	No	"Malignancies" is an Important potential risk (see Section 8.3).
Major surgery within 8 weeks prior to treatment or planned surgery during treatment. Significant bleeding risk or coagulation disorders. History of significant	Increased bleeding risk reported with approved BTK inhibitors in patients with hematologic malignancies undergoing surgery. Recent surgery prior to initiation of	No	"Serious bleeding events" is an important potential risk (see Section 8.3). This risk is discussed in Part II Module SVII and Module SVIII. SmPC Special warnings and precautions for use include data on bleeding reported in patients receiving remibrutinib. Patients should be instructed to seek medical advice if signs and symptoms suggesting

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
gastrointestinal bleeding. Use of dual anti-platelet medications or anticoagulant medications.	treatment or while on treatment may increase risk of bleeding.		significant bleeding occur. If significant bleeding is suspected, interrupt treatment with remibrutinib. Upon resolution, resume if the benefit is expected to outweigh the risk. SmPC Dose modification section includes recommendations to interrupt remibrutinib treatment 3 to 7 days before and after surgery in case of surgery with a risk of bleeding. In addition, in the section "Interaction with other medicinal products and other forms of interaction", a benefit-risk assessment would be needed in patients requiring antithrombotic medication.
History of live attenuated vaccine within 6 weeks prior to starting treatment or requirement to receive these vaccinations.	BTK is an important signaling kinase downstream of cell surface receptors in a number of cell types of the adaptive and innate immune system, including B cells and macrophages. BTK inhibition may increase susceptibility to infections. Consequently, patients with a history of recent or planned administration of live (including live-attenuated) vaccines were excluded in remibrutinib studies.	No	SmPC Special warnings and precautions section includes the topic "Vaccinations". The safety of remibrutinib with live or live-attenuated vaccines has not been studied. Vaccination with live or live-attenuated vaccines is therefore not recommended during treatment with remibrutinib.
History of current acute or chronic hepatic disease	General exclusion criterion in protocols.	No	Safety and PK was assessed in a dedicated hepatic impairment (HI) study. Patients with mild, moderate and severe HI were included. No safety signal was observed and the study results support the recommendation for no dose adjustments.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
History of renal disease	General exclusion criterion in protocols.	No	Remibrutinib is eliminated predominantly by hepatic metabolism while excretion of unmetabolized remibrutinib into urine appears to be negligible. Therefore, the safety profile is not anticipated to be different in patients with renal disease as compared to the rest of the population.
Use of strong inhibitors of CYP3A4, moderate and strong inducers of CYP3A4	Remibrutinib is a sensitive CYP3A4 substrate.	No	SmPC Special warnings and precautions section includes the topic “Interactions”. SmPC includes the details on the impact by CYP3A4 inhibitors and inducers. Concomitant use of remibrutinib with strong CYP3A4 inhibitors must be avoided. Concomitant use of remibrutinib with strong or moderate CYP3A4 inducers must be avoided.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 SIV.2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Pediatric patients	Not included in the clinical development program
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Patients with mild, moderate and severe hepatic impairment were included in the clinical development program.
• Patients with renal impairment	Patients with severe renal impairment (creatinine level above 1.5x ULN or estimated Glomerular

• Patients with cardiovascular impairment	Filtration Rate (eGFR) <45mL/min) were not included in the clinical development program. Patients with NYHA Class III/IV LVF were excluded from clinical studies.
Immunocompromised patients	Not included in the clinical development program
Populations with relevant different ethnic origin	Populations from different race and ethnic origins were included in the clinical development program (for Race please refer to Table 4-7 and Table 4-8).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Elderly	Included in the clinical development program (for elderly patients please refer to Table 4-5 and Table 4-6).

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

Not applicable as remibrutinib has not been authorized in any country at the time of the data cut-off of this RMP, 04-Aug-2024.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Based on the nature of the drug, and the mode of action, no recreational or abuse potential has been identified for remibrutinib.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The list of risks and adverse reactions that were not considered important for inclusion in the list of safety concerns in the RMP and the reasons for non-inclusion are provided below.

Risk not considered important	Rationale for not including an identified or potential risk in the list of safety concerns in the RMP
Bleeding (Identified risk)	**Preclinical**: BTK is a signaling molecule in one of several platelet activation pathways. Remibrutinib administration was associated with an increased rat tail bleeding time (following large blood vessel injury) at pharmacologically relevant exposure. **Clinical**: In the placebo-controlled period of A2301 and A2302 studies, higher incidence of bleeding events was observed on remibrutinib versus placebo (10.6% of patients vs. 5.2%). The imbalance was seen only for mild AEs, which were the most frequently reported in both arms (mild 88.7% vs 85.0% and moderate 11.3% vs. 15.0%). There were no severe bleeding AEs. Two serious bleeding AEs, both presenting alternative etiologies (contusion due to fall and hematuria due to bladder dysplasia) were reported. Drug interruptions due to bleeding were balanced (9.6% events in remibrutinib vs. 10.0% events in placebo). Discontinuations were only observed in remibrutinib, with low incidence (2.6% of bleeding events in remibrutinib) (purpura, petechiae, contusion). Bleeding events in remibrutinib trended to occur early on treatment (primarily within first 3 months) (median time-to-onset is 29.5 days and median duration is 26 days). Majority recovered with no medical intervention. Events were primarily cutaneous bleedings (e.g., petechiae, purpura, ecchymosis, contusion). Overall, the bleeding risk observed with remibrutinib is predominately mild, well tolerated and localized on the skin with infrequent mucosal bleeding events, such as epistaxis, gingival bleeding. Mucocutaneous bleeding events are considered ADRs [LOU064-SCS]. The bleeding events observed with remibrutinib were not temporarily associated with decrease in platelet counts or change in coagulation parameters. While, in the pooled Phase 3 CSU studies, a minimal and consistent downward shift in platelet counts during the 52 weeks study duration

	was noted, no increase in Grade 3-4 low platelets counts was observed. Median levels for platelets remained in normal ranges. Therefore, no laboratory monitoring is proposed. In terms of medical management, as events have resolved spontaneously, without specific treatment or action taken with remibrutinib, no specific management is proposed. Routine minimization measures will be implemented and are aligned with the clinical study: interruption of remibrutinib 3 to 7 days before and after surgery in case of surgery with risk of bleeding. Administration of anti-thrombotic medication (except clopidogrel up to 75mg /acetyl salicylic acid up to 100 mg daily) should be done after a benefit-risk assessment [LOU064-SCS]. Based on the totality of the data, including the frequency and severity of bleeding events observed with remibrutinib, the risk is considered identified, not classified as "important" for the purpose of this RMP. Though no concern for Serious bleeding events noted in remibrutinib development to date, it is considered as an important potential risk in this RMP.
Infections (Identified risk)	**Preclinical**: Based on the mode of action (BTK inhibition), and preclinical evidence: remibrutinib can affect primary IgM and IgG responses as observed in rodent pharmacology studies. **Clinical**: In pooled pivotal studies A2301 and A2302, placebo-controlled period: Infections were observed in 33.5% of patients on remibrutinib vs. 34.3% on placebo. There was no increase with long-term treatment. Infections were mostly mild-to-moderate (severe events only 0.7%). AEs leading to interruptions were infrequent, balanced vs placebo (8.4% events vs. 7.9% events); there was only one discontinuation in remibrutinib group (due to COVID-19, not related). Most common infections were upper respiratory tract infections. SAEs remibrutinib vs placebo: 5 (0.8%) events (appendicitis, COVID-19, GI infection, wound abscess, food poisoning) vs. 2 (0.7%) events (appendicitis, pneumonia). No additional Infections SAE was reported after the placebo-controlled period. Exposure adjusted incidence rates for infections during the entire study period were not higher as compared to placebo-controlled period. No opportunistic infections were reported [LOU064-SCS]. Upper respiratory tract infections and Herpes viral infections are considered ADRs and no specific monitoring or medical management is required, as these are common in the CSU population and management is part of standard of care. Therefore, no risk minimization measures are proposed in the label.
Hepatotoxicity (Potential risk)	Cases of hepatotoxicity have been observed with other BTK inhibitors. **Preclinical:** BTK is not expressed in hepatocytes. Remibrutinib pre-clinical data showed no adverse liver findings in repeated dose toxicology studies. **Clinical**: Remibrutinib clinical data does not show a concern, with no adverse events/signs or symptoms of hepatotoxicity,

	with low frequency of LFT elevations, balanced versus placebo; single, transient higher grade LFT elevations, confounded and by negative re-challenge. No concerns related to hepatic safety emerged from the assessment of A2301 and A2302 studies, other studies in CSU or other indications. Therefore, inclusion of hepatotoxicity in the RMP as an important potential risk is not warranted. Liver enzyme elevations were balanced, no clinical concerns for hepatotoxicity with remibrutinib, with newly occurring notable (ALT/AST >3xULN) liver enzyme abnormalities being isolated, asymptomatic transient/reversible liver transaminase elevations, without concurrent increase in bilirubin (no Hy's law) [LOU064-SCS]. Based on the totality of the data to date, remibrutinib is not associated with hepatotoxicity. Therefore, hepatotoxicity is considered to be a non-important potential risk for the purpose of this RMP.
Impaired immune response to vaccines (Potential risk)	A dedicated study CLOU064F12101 in healthy volunteers assessed the impact of concomitant and interrupted remibrutinib administration on the immune response and safety with different types of non-live vaccines. Results suggest no significant impact on the immune response to influenza and PPV-23 vaccines 4 weeks after vaccination interrupting remibrutinib one week before vaccination and re-start after 2 weeks from vaccination in healthy participants. Concomitant remibrutinib impacts immune response to T-cell independent PPV-23 and T-cell dependent KLH vaccination and to a lesser extent to T-cell dependent influenza vaccination. The safety of remibrutinib with non-live vaccines has been studied; therefore, non-live vaccines can be given during remibrutinib treatment. To optimize immune response to non-live vaccines, treatment interruption of remibrutinib (from 1 week prior to the planned vaccination until 2 weeks after the vaccination) should be considered ([CSR-CLOU064F12101]). No data are available on the effects of live and live-attenuated vaccines in patients receiving remibrutinib and these vaccines should not be co-administered with remibrutinib.

Source: [LOU064-SCS], [CSR-CLOU064F12101].

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 8-1 Important identified risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
None	Not applicable

Table 8-2 Important potential risks

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Serious bleeding events	The risk of serious bleeding events may have significant impact on the benefit-risk balance. The potential mechanism (effect on platelets function based on pre-clinical evidence of bleeding) justifies the classification of serious bleeding as an important potential risk. Based on the evidence in remibrutinib clinical studies (no serious related case and only non-serious, mild to moderate and mostly skin bleeding events) (Table 8-4, Annex 7 - Table 2.6-5p1, Annex 7 - Table 2.6-2p2), causal relationship is not demonstrated at this stage.
Teratogenicity	Pre-clinical evidence showed an increased fetal external malformations (e.g. open/opaque eyes, small jaws, hyperflexion of forelimbs) and maternal toxicity (transiently reduced food consumption and adverse clinical signs), which occurred only in rabbits at 300 mg/kg/day (67 times the MRHD of 25 mg b.i.d. based on AUC0-24h) (Table 3-1). Considering the clinical significance of the risk of teratogenicity in general population, including in patients with CSU (predominantly young, female patients), the risk is classified as an important potential risk.
Malignancies	Pre-clinical data did not show evidence of carcinogenic potential in 26-week rasH2 transgenic mouse and 104-week rat carcinogenicity studies up to the highest tested dose levels of 1,500 and 300 mg/kg/day, respectively (Table 3-1). Incidence of malignancies was low in clinical studies to date and none of the events were considered related to the study drug. Though no concerns for malignancies were noted in the remibrutinib development program to date, this safety topic is considered an important potential risk in this RMP (Table 8-8).

Table 8-3 Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Long-term safety	Remibrutinib was well-tolerated and demonstrated a favorable safety profile in pivotal clinical studies with a treatment duration up to 1 year. Some patients with CSU may require prolonged treatment with remibrutinib. The safety information in clinical studies of patients who received remibrutinib for more than 1 year is limited. Unexpected adverse reactions may occur in patients requiring prolonged treatment. Long-term safety is therefore classified as missing information.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Not applicable, as this is the first version of the RMP.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important Potential Risk: Serious bleeding events

Table 8-4 Clinical trial data of Serious bleeding events during the placebo-controlled period - Pool 1 Safety Set

	LOU064 25mg b.i.d. N=606 n (%) 95% CI	Placebo N=306 n (%) 95% CI	LOU064 25mg b.i.d. vs. Placebo Risk difference 95% CI
Subjects with at least one AE	2 (0.3)	0 (0.0)	0.3
	(0.1, 1.3)	(0.0, 1.5)	(-0.7, 1.0)
EAOR	0.8	0.0	
EAIR	0.8	0.0	
Maximum severity			
Mild	1 (0.2)	0	
Moderate	1 (0.2)	0	
Severe	0	0	
AE outcome			
Recovered/resolved	2 (0.3)	0	
Recovering/resolving	0	0	
Not recovered/not resolved	0	0	
Recovered/resolved with sequelae	0	0	
Fatal	0	0	
Unknown	0	0	

N = number of subjects from the corresponding treatment groups in the analysis set.
n = counts of subjects with the event.
CI = confidence interval for the absolute risk (percentage) (Newcombe 1998) and risk difference (Agresti, Caffo 2000).
EAOR = exposure adjusted occurrence rate (number of event episodes per 100 patient-years at risk).
EAIR = exposure-adjusted incidence rate, defined as the number of subjects with the event per 100 patient-years of exposure, where the exposure time at risk is event-specific (terminated by incident events).
MedDRA version 26.1.
Case Retrieval Strategy version 22-Feb-2024.
Source: Annex 7 - Table 2.6-4p1

Table 8-5 Important potential risk Serious bleeding events: Other details

Serious bleeding events	Details
Potential mechanisms	BTK is a signaling molecule in several platelet signaling pathways involved in platelet aggregation and clot retraction, and effects of remibrutinib on platelet functions were observed in the remibrutinib preclinical toxicology program. Remibrutinib led to an increased rat tail bleeding time (following large blood vessel injury) at pharmacologically relevant exposure. The mode

Serious bleeding events	Details
	of action by which remibrutinib could potentially cause bleeding is currently not fully understood.
Evidence source(s) and strength of evidence	Clinical: In Pool 1 placebo-controlled period (24 weeks), two SAEs of Bleeding AESIs occurred in the remibrutinib group (EAIR 0.8): 1) contusion related to a fall and 2) hematuria in a patient with bladder dysplasia and bladder surgery; both events were considered not related to remibrutinib. Causality with remibrutinib is confounded in both cases. No SAEs of Bleeding AESIs occurred in the placebo group. Due to small number of cases, comparison between treatment groups is limited. During the entire study period (52 weeks), in Pool 1, no additional patient experienced a serious bleeding event in remibrutinib group (EAIR 0.4 per 100 patient-years) or in patients transitioning from placebo to remibrutinib. In Pool 2 (n=1234), which includes Phase II and Phase III studies, in Phase II extension study A2201E1 (52 weeks), one SAE (melaena) due to bariatric surgery was reported in the remibrutinib group (considered not related to remibrutinib by the investigator). Overall, the EAIR of serious bleeding events was 0.3 per 100 patient-years (Table 8-4, Annex 7 - Table 2.6-5p1, Annex 7 - Table 2.6-2p2), [LOU064-SCS]. Pre-clinical: In vitro assessments in human whole blood revealed an increased ROTEM EXTEM® but not FIBTEM® lysis index, as well as an inhibition of collagen-induced platelet aggregation, suggesting an impact of remibrutinib on platelets. The potential mechanism to affect platelet function based on pre-clinical evidence of bleeding justifies the classification of serious bleeding as an important potential risk.
Characterization of the risk:	As of the DLP of this RMP, in CSU, in pooled pivotal studies (Pool 1), the incidence of serious bleeding events was 0.3% (2 patients reporting 2 SAEs: contusion and hematuria) in the remibrutinib group (EAIR was 0.8) and 0 in the placebo group (EAIR was 0) during the 24 weeks placebo-controlled period. Both SAEs were considered not related to remibrutinib by the investigator and resolved without requirement of blood transfusion or surgical intervention; none led to discontinuation of remibrutinib. No additional SAE was reported during the entire study period in Pool 1 (52 weeks). In Pool 2 (n=1234), which includes Phase II and Phase III studies, the overall exposure adjusted incidence rate of serious bleeding events in remibrutinib was 0.3%. In Phase II extension study A2201E1, one SAE (melaena) was reported in the remibrutinib group and was considered not related to remibrutinib by the investigator, which recovered. In A2201E1, the incidence of serious bleeding events was 0.5%. None of the serious bleeding events during the placebo-controlled period and in the entire study period were associated with low platelet counts. Based on the low number of relevant cases in clinical studies conducted to date, not related to study treatment, but considering the possible clinical significance, this risk is classified as an important potential risk for remibrutinib in CSU patients (Table 8-4, Annex 7 - Table 2.6-5p1, Annex 7 - Table 2.6-2p2, [A2301-Listing 16.2.7-1], [A2302-Listing 16.2.7-1], [LOU064-SCS]).
Risk factors and risk groups	Surgery with risk of bleeding, concomitant anticoagulant treatment or anti-platelet medication, history of significant gastrointestinal bleeding or coagulation disorders, are known risk factors for serious bleeding.
Preventability	No data are available on co-administration of remibrutinib with anticoagulants. The concomitant use of remibrutinib and anticoagulants was not allowed in clinical studies. Use of acetylsalicylic acid up to 100 mg daily

Serious bleeding events	Details
	or clopidogrel up to 75 mg daily was allowed in the remibrutinib clinical studies. Routine risk minimization activities are proposed (e.g., in patients requiring anticoagulant and anti-platelet therapies, a benefit-risk assessment of concomitant administration will be considered) aiming to mitigate and minimize the risk of potential serious outcomes, e.g., interruption of remibrutinib treatment 3 to 7 days before and after surgery in patients undergoing surgical procedures with risk of bleeding. Patients are instructed to seek medical advice if signs and symptoms suggestive of significant bleeding occur. If significant bleeding is suspected, interrupt treatment with remibrutinib. Upon resolution, resume if the benefit is expected to outweigh the risk.
Impact on the benefit-risk balance of the product	The risk of serious bleeding may have a significant impact on the benefit-risk balance in CSU indication. However, considering that the bleeding events associated with the administration of remibrutinib as reported in the pivotal studies were non-serious, mild to moderate in severity, mostly skin bleeding recovering spontaneously, the impact of bleeding on the benefit-risk balance is expected to remain low.
Public health impact	The bleeding events may be serious or fatal. However, given the low prevalence of CSU in the overall population, with most of bleeding events with remibrutinib being mild to moderate in severity, the impact on public health is expected to be low.

8.3.1.2 Important Potential Risk: Teratogenicity

Table 8-6 Clinical trial data of Teratogenicity during the placebo-controlled period (Pool 1 safety set) (Females subset)

	LOU064 25mg b.i.d. N=403 n (%) 95% CI	Placebo N=204 n (%) 95% CI	LOU064 25mg b.i.d. vs. Placebo Risk difference 95% CI
Subjects with at least one AE	1 (0.2)	0 (0.0)	0.2
	(0.0, 1.6)	(0.0, 2.3)	(-1.2, 1.2)
EAOR	0.6	0.0	
EAIR	0.6	0.0	
Maximum severity			
Mild	1 (0.2)	0	
Moderate	0	0	
Severe	0	0	
SAEs	0	0	
AE outcome			
Recovered/resolved	1 (0.2)	0	
Recovering/resolving	0	0	
Not recovered/not resolved	0	0	
Recovered/resolved with sequelae	0	0	
Fatal	0	0	
Unknown	0	0	

	LOU064 25mg b.i.d. N=403 n (%) 95% CI	Placebo N=204 n (%) 95% CI	LOU064 25mg b.i.d. vs. Placebo Risk difference 95% CI

N = number of subjects from the corresponding treatment groups in the analysis set.
n = counts of subjects with the event.
CI = confidence interval for the absolute risk (percentage) (Newcombe 1998) and risk difference (Agresti, Caffo 2000).
EAOR = exposure adjusted occurrence rate (number of event episodes per 100 patient-years at risk).
EAIR = exposure-adjusted incidence rate, defined as the number of subjects with the event per 100 patient-years of exposure, where the exposure time at risk is event-specific (terminated by incident events).
MedDRA version 26.1.
Case Retrieval Strategy version 22-Feb-2024.
Source: Annex 7 - Table 2.6-2p1

Table 8-7 Important potential risk Teratogenicity: Other details

Teratogenicity	Details
Potential mechanisms	In the pregnant rabbits preclinical study, remibrutinib induced maternal toxicity and unrelated fetal external malformations (i.e., open/opaque eyes, small jaws, hyperflexion of forelimbs) at high exposure (300 mg/kg/day). The mechanism is not understood.
Evidence source(s) and strength of evidence	Teratogenicity is considered as a potential risk, based on findings in rabbits at a remibrutinib dose of 300 mg/kg/day. No effects on rat fertility and early embryonic development, or rat or rabbit embryo-fetal development, were seen at oral doses of remibrutinib up to 1,000 mg/kg/day (rats) or 100 mg/kg/day (rabbits). Adverse findings in a pre- and postnatal development study in rats affecting maternal animals and offspring (up to lactation day 1) were observed at the highest tested dose of 1,000 mg/kg/day. A NOAEL in rabbits was established at 100 mg/kg/day, corresponding to steady-state safety margin of 23-fold (AUC0-24h) or 36-fold (Cmax) vs clinical 25 mg b.i.d. remibrutinib in humans.
Characterization of the risk:	No cases of teratogenicity were reported in clinical studies. Nine pregnancies have been reported in the remibrutinib program across all indications including 5 pregnancies in the completed studies and 4 in the ongoing studies up to the cut-off of 04-Aug-2024. Five pregnancies have been reported in 4 remibrutinib completed studies. • A 32-year-old patient received remibrutinib until study Day 40 in Study A2201E1, when it was discontinued due to pregnancy. The patient delivered a full-term normal baby without any complications and with a normal 12-month follow-up. • A 33-year-old patient in Study A2301 who was on oral contraceptives became pregnant on an unspecified date while receiving remibrutinib and had spontaneous abortion at about 6 months after initiation of remibrutinib. The event was reported as not related to study treatment considering risk factors such as overweight (BMI 39. 9 kg/m^2) and use of oral contraceptives as per the investigator. • The two pregnancies in Study A2302 were reported in a 34-year-old patient and a 37-year-old patient, respectively. Both patients underwent elective abortions during the first trimester due to patient decision. • A 22-year-old patient in Study A2305 who used condoms as contraception, completed study treatment on Day 85, had her last menstrual period on Day 88 and pregnancy was communicated on Day

Teratogenicity	Details
	141. The first day of pregnancy is unknown. At time of the data cutoff date, the pregnancy was ongoing. According to the information obtained after the cut-off date, the patient gave birth to a healthy female baby who was full-term. Four pregnancies have been reported in 3 remibrutinib ongoing studies: • 2 patients withdrew informed consent (a 29-year-old patient in CLOU064A2303B study and a 34-year-old patient in CLOU064C12302 study). • 2 pregnancies are ongoing (a 30-year-old patient in Study CLOU064A2303B and a 39-year-old patient in Study CLOU064M12301). Refer to Table 8-6, Annex 7 - Table 2.6-3p1, Annex 7 - Table 2.6-1p2, [LOU064-SCS].
Risk factors and risk groups	Women of child-bearing potential not using effective contraception, breast feeding women.
Preventability	Sexually active women of child-bearing potential must use effective contraception (methods that result in less than 1 % pregnancy rates) during remibrutinib treatment and for at least 1 week after the last dose. The patient should be advised of a potential risk to the fetus if remibrutinib is used during pregnancy or if the patient becomes pregnant while taking remibrutinib. Remibrutinib is not recommended during pregnancy. There are no data on the effects of remibrutinib on the breast-fed newborn/infant or on milk production. Because of the potential for adverse reactions in breast-fed newborns/infants, women should be advised not to breast-feed during treatment with remibrutinib and for 1 week after the last dose.
Impact on the benefit-risk balance of the product	Teratogenicity can have a significant impact on the benefit-risk balance. Teratogenicity was observed in rabbits. There is no available data in patients informing the drug associated risk and the potential risk is mitigated by the appropriate preventive measures mentioned in the SmPC. The benefit-risk balance with respect to teratogenicity remains positive.
Public health impact	Public health impact is expected to be low as the prevalence of CSU is low in general population and the risk is appropriately communicated in the SmPC with advice for usage of effective contraception.

8.3.1.3 Important potential risk: Malignancies

Table 8-8 Clinical trial data of Malignancies during the placebo-controlled period – Pool 1 Safety Set

	LOU064 25mg b.i.d. N=606 n (%) 95% CI	Placebo N=306 n (%) 95% CI	LOU064 25mg b.i.d. vs. Placebo Risk difference 95% CI
Subjects with at least one AE	1 (0.2) (0.0, 1.1)	1 (0.3) (0.0, 2.1)	-0.2 (-1.3, 0.7)
EAOR	0.4	0.8	
EAIR	0.4	0.8	
Maximum severity			

	LOU064 25mg b.i.d. N=606 n (%) 95% CI	Placebo N=306 n (%) 95% CI	LOU064 25mg b.i.d. vs. Placebo Risk difference 95% CI
Mild	0	0	
Moderate	1 (0.2)	0	
Severe	0	1 (0.3)	
AE outcome			
Recovered/resolved	1 (0.2)	0	
Recovering/resolving	0	0	
Not recovered/not resolved	0	1 (0.3)	
Recovered/resolved with sequelae	0	0	
Fatal	0	0	
Unknown	0	0	

N = number of subjects from the corresponding treatment groups in the analysis set.
n: counts of subjects with the event.
CI = confidence interval for the absolute risk (percentage) based on score method with continuity correction (Newcombe 1998) and risk difference (Agresti, Caffo 2000).
EAOR = exposure adjusted occurrence rate (number of event episodes per 100 patient-year at risk).
EAIR = exposure-adjusted incidence rate, defined as the number of subjects with the event per 100 patient-years of exposure, where the exposure time at risk is event-specific (terminated by incident events).
MedDRA version 26.1.
Case Retrieval Strategy version 22-Feb-2024.
Source: Annex 7 - Table ADAR081_1.1

Table 8-9 Important potential risk Malignancies: Other details

Malignancies	Details
Potential mechanisms	No potential mechanism identified in preclinical studies (no evidence of carcinogenicity).
Evidence source(s) and strength of evidence	Current evidence is based on the pooled analysis of the A2301 and A2302 CSU studies. To further characterize the safety concern and confirm if any causal relationship exists, longer term follow-up is warranted.
Characterization of the risk	Clinical: During the double-blind placebo-controlled period in Pool 1, malignancies (MedDRA SMQ Malignant or unspecified tumours) were balanced between remibrutinib (1 patient with mucinous adenocarcinoma of appendix, 0.2%) and placebo groups (1 patient with breast cancer, 0.3%) (Table 8-8). Overall malignancies in Pool 1, both reported during the double-blind placebo-controlled period (noted above) and during the open-label treatment period (pancreatic carcinoma, small intestine adenocarcinoma, gastrointestinal stromal tumour), as well as a case of benign neoplasm of esophageal leiomyoma, had a short time to onset (LOU064-SCS), (A2301), (A2302). This observation is not compatible with the time to onset for malignancy development of several years from the exposure to the risk factor (including for instance, from the exposure to immunosuppressive treatment, such as methotrexate) described in the literature (Hicks et al 2023, Brennan et al 2025, Iizuka et al 2025). Furthermore, most cases presented confounding factors providing a more likely explanation for malignancy development.

Malignancies	Details
Risk factors and risk groups	Since this is a potential risk, no attributable risk increase due to remibrutinib has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	No apparent pattern exists to prevent/predict the event.
Impact on the benefit-risk balance of the product	Malignancies may have significant impact on the benefit-risk balance. However, considering the risk is a potential risk, the benefit-risk balance remains positive.
Public health impact	Unknown at this time; however, given the low prevalence of malignancies in the overall population, the public health impact is low.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

Table 8-10 Missing information: Long-term safety

Long-term safety	Details
Evidence source	**Anticipated risk/consequence of the missing information:** Remibrutinib was well-tolerated and demonstrated a favorable safety profile in pivotal clinical studies with a treatment duration up to 52 weeks. However, the number of patients who received remibrutinib for > 52 weeks is limited, although conforming with the ICH exposure minimum requirements. CSU may require prolonged treatment with remibrutinib and therefore it is important to determine whether there are new safety findings, or known safety findings which worsen in severity, after long-term treatment. Long-term safety data will continue to be collected in the ongoing extension study program.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	None
Important potential risks	Serious bleeding events Teratogenicity Malignancies
Missing information	Long-term safety

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

None

Other forms of routine pharmacovigilance activities

None

10.2 Part III.2. Additional pharmacovigilance activities

10.2.1 Study CLOU064A2303B

Study short name and title:

A multicenter, double-blind, placebo-controlled, randomized withdrawal and open-label extension study followed by long-term open-label treatment cycles to assess the efficacy, safety and tolerability of remibrutinib (LOU064) in adult chronic spontaneous urticaria patients who completed the preceding remibrutinib Phase III studies.

Rationale and study objectives:

The purpose of this extension study is to collect long-term efficacy, safety and tolerability data on remibrutinib 25 mg b.i.d. in a selected group of participants with CSU who previously completed the treatment phase of remibrutinib preceding Phase III studies.

This study is intended to fulfill the Novartis commitment to provide post-trial access to participants who have completed the preceding Phase III studies, where applicable.

- **Primary Objective:** To assess the efficacy of remibrutinib (25 mg b.i.d.) in participants with CSU with a UAS7 (Weekly Urticaria Activity Score) <16 at Week 52 in the prior core study with respect to time to first of the three events: relapse or study treatment discontinuation due to lack of efficacy or intake of strongly confounding prohibited medication up to Week 24 compared to placebo.
- **Secondary Objective:** To assess the long-term safety and tolerability of remibrutinib 25 mg b.i.d.

Study design:

This is a Phase IIIb multicenter, double-blind, placebo-controlled, randomized withdrawal and open-label extension study to evaluate the efficacy and safety of remibrutinib 25 mg b.i.d. in adult CSU participants who have completed one of the preceding Phase III core studies A2301, A2302, A1301 or A2304. Future Phase III remibrutinib studies (including CLOU064A2305) are also planned to be included in the second study period of the study (Epoch 2), if endorsed by the participating countries and sites as per local laws and regulations.

Study population:

The study consists of two Epochs and the total study duration is approximately 160 weeks. Approximately 1,021 adult participants with CSU are expected to be included in this extension trial.

Milestones:

Protocol submission: 30-Jun-2022

Start of data collection: 09-Dec-2022 (FPFV)

End of data collection: Aug-2027 (LPLV)

Final study report completion Nov-2027

Date of publication: Nov-2027

Final report submission: Dec-2027

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
[Study CLOU064A2303B] A multicenter, double-blind, placebo-controlled, randomized withdrawal and open-label extension study followed by long-term open-label treatment cycles to assess the efficacy, safety and tolerability of remibrutinib (LOU064) in adult chronic spontaneous urticaria patients who completed the preceding remibrutinib Phase III studies. Status: Ongoing	To collect long-term efficacy, safety and tolerability data on remibrutinib 25 mg b.i.d. in a selected group of participants with CSU who previously completed the treatment phase of remibrutinib preceding Phase III studies.	• Serious bleeding events • Malignancies • Long-term safety	Protocol submission	30-Jun-2022
			Final report submission	Dec-2027

11 Part IV: Plans for post-authorization efficacy studies

There are no plans for post-authorization efficacy studies.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Safety concern	Routine risk minimization activities
Important Identified Risks	
None	
Important Potential Risks	
Serious bleeding events	**Routine risk communication** SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) SmPC Section 4.8 (Undesirable effects) SmPC Section 5.3 (Preclinical safety data) Package leaflet (PL) Section 2 (What you need to know before you take remibrutinib) PL Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended to interrupt remibrutinib treatment for 3 to 7 days before surgery and for 3 to 7 days after surgery depending upon the type of surgery and the risk of bleeding. The risks and benefits of co-administration of antithrombotic agents with remibrutinib must be considered. **Other routine risk minimization measures beyond the Product Information:** None
Teratogenicity	**Routine risk communication** SmPC Section 4.6 (Fertility, pregnancy, and lactation) SmPC Section 5.3 (Preclinical safety data) PL Section 2 (What you need to know before you take remibrutinib) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Sexually active women of child-bearing potential must use effective contraception (methods that result in less than 1% pregnancy rates) during remibrutinib treatment and for at least 1 week after the last dose. Remibrutinib is not recommended during pregnancy. **Other routine risk minimization measures beyond the Product Information:** None
Malignancies	**Routine risk communication** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:**

Safety concern	Routine risk minimization activities
	None
Missing Information	
Long-term safety	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3. Summary of risk minimization measures

Table 12-1 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
None		
Important Potential Risks		
Serious bleeding events	Routine risk minimization measures: SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) SmPC Section 4.8 (Undesirable effects) SmPC Section 5.3 (Preclinical safety data) PL Section 2 (What you need to know before you take remibrutinib) PL Section 4 (Possible side effects) Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study CLOU064A2303B (Final study report completion date: Nov-2027)
Teratogenicity	Routine risk minimization measures: SmPC Section 4.6 (Fertility, pregnancy, and lactation) SmPC Section 5.3 (Preclinical safety data)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	PL Section 2 (What you need to know before you take remibrutinib) Additional risk minimization measures: None	None
Malignancies	Routine risk minimization measures: None Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study CLOU064A2303B (Final study report completion date: Nov-2027)
Missing information		
Long-term safety	Routine risk minimization measures: None Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study CLOU064A2303B (Final study report completion date: Nov-2027)

13 Part VI: Summary of the risk management plan for Rhapsido® (remibrutinib)

This is a summary of the RMP for Rhapsido. The RMP details important risks of Rhapsido, how these risks can be minimized, and how more information will be obtained about Rhapsido's risks and uncertainties (missing information).

Rhapsido's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Rhapsido should be used.

This summary of the RMP for Rhapsido should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rhapsido's RMP.

13.1 Part VI: I. The medicine and what it is used for

Rhapsido is authorised for treatment of CSU in adult patients with inadequate response to H1-AH. It contains remibrutinib as the active substance and it is given by oral route, b.i.d., film-coated tablet, 25 mg.

Further information about the evaluation of Rhapsido's benefits can be found in Rhapsido's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage*:* https://www.ema.europa.eu/en/medicines/human/EPAR/rhapsido

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Rhapsido, together with measures to minimize such risks and the proposed studies for learning more about Rhapsido's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Rhapsido is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI: II.A: List of important risks and missing information

Important risks of Rhapsido are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rhapsido. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	None
Important potential risks	Serious bleeding events Teratogenicity Malignancies
Missing information	Long-term safety

13.2.2 Part VI: II.B: Summary of important risks

Table 13-2 Important potential risk: Serious bleeding events

Evidence for linking the risk to the medicine	In Pool 1 placebo-controlled period (24 weeks), two SAEs of Bleeding AESIs occurred in the remibrutinib group (EAIR 0.8): 1) contusion related to a fall and 2) hematuria in a patient with bladder dysplasia and bladder surgery; both events were considered not related to remibrutinib. Causality with remibrutinib is confounded in both cases. No SAEs of Bleeding AESIs occurred in the placebo group. Due to small number of cases, comparison between treatment groups is limited. During the entire study period (52 weeks), in Pool 1, no additional patient experienced a serious bleeding event in remibrutinib group (EAIR 0.4) or in patients transitioning from placebo to remibrutinib, In Pool 2 (n=1234), which includes Phase II and Phase III studies, in Phase II extension study A2201E1 (52 weeks), one SAE (melaena) due to bariatric surgery was reported in the remibrutinib group and was considered not related to remibrutinib. Overall, the EAIR of serious bleeding events was 0.3%. In vitro assessments in human whole blood revealed an increased ROTEM EXTEM® but not FIBTEM® lysis index, as well as an inhibition of collagen-induced platelet aggregation, suggesting an impact of remibrutinib on platelets. The potential mechanism to affect platelet function based on pre-clinical evidence of bleeding justifies the classification of serious bleeding as an important potential risk.
Risk factors and risk groups	History of significant gastrointestinal bleeding or coagulation disorders, surgery, concomitant anticoagulant treatment or anti-platelet medication are known risk factors for serious bleeding.
Risk minimization measures	**Routine risk minimization measures:**

	SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) SmPC Section 4.8 (Undesirable effects) SmPC Section 5.3 (Preclinical safety data) PL Section 2 (What you need to know before you take remibrutinib) PL Section 4 (Possible side effects) **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CLOU064A2303B See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-3 Important potential risk: Teratogenicity

Evidence for linking the risk to the medicine	Teratogenicity is considered as a potential risk, based on findings in rabbits at a remibrutinib dose of 300 mg/kg/day. No effects on rat fertility and early embryonic development, or rat or rabbit embryo-fetal development, were seen at oral doses of remibrutinib up to 1,000 mg/kg/day (rats) or 100 mg/kg/day (rabbits). Adverse findings in a pre- and postnatal development study in rats affecting maternal animals and offspring (up to lactation day 1) were observed at the highest tested dose of 1,000 mg/kg/day. A NOAEL in rabbits was established at 100 mg/kg/day, corresponding to steady-state safety margin of 23-fold (AUC0-24h) or 36-fold (Cmax) vs clinical 25 mg b.i.d. remibrutinib in humans.
Risk factors and risk groups	Women of child-bearing potential not using effective contraception, breast feeding women.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.6 (Fertility, pregnancy, and lactation) SmPC Section 5.3 (Preclinical safety data) PL Section 2 (What you need to know before you take remibrutinib) **Additional risk minimization measures:** None

Table 13-4 Important potential risk: Malignancies

Evidence for linking the risk to the medicine	Current evidence is based on the pooled analysis of the A2301 and A2302 CSU studies. To further characterize the safety concern and confirm if any causal relationship, longer term follow-up is warranted.
Risk factors and risk groups	Since this is a potential risk, no attributable risk increase due to remibrutinib has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures:** None

	Additional risk minimization measures: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CLOU064A2303B See section II.C of this summary for an overview of the post-authorization development plan.

Table 13-5 Missing information: Long-term safety

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CLOU064A2303B See section II.C of this summary for an overview of the post-authorization development plan.

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Rhapsido.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 13-6 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study CLOU064A2303B	The purpose of this extension study is to collect long-term efficacy, safety and tolerability data on remibrutinib 25 mg b.i.d. in a selected group of participants with CSU who previously completed the treatment phase of remibrutinib preceding Phase III studies. This study is intended to fulfill the Novartis commitment to provide post-trial access to participants who have completed the preceding Phase III studies, where applicable. **Primary objective:** To assess the efficacy of remibrutinib (25 mg b.i.d.) in CSU participants with a UAS7 (Weekly Urticaria Activity Score) <16 at Week 52 in the prior core study with respect to time to first of the three events: relapse or study treatment discontinuation due to lack of efficacy or intake of strongly confounding prohibited medication up to Week 24 compared to placebo. **Secondary objective:** To assess the long-term safety and tolerability of remibrutinib 25 mg b.i.d.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.