26 February 2026
EMADOC-1829012207-46485
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rhapsido

International non-proprietary name: remibrutinib

Procedure No. EMEA/H/C/006313/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AAS	Angioedema activity score
AAS7	Weekly angioedema activity score
ADR	Adverse drug reaction
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
AESI	Adverse event of special interest
AI	Acceptable intake
Al	Aluminium
API	Active pharmaceutical ingredient
AR	Assessment report
AUC	Area under the blood concentration-time curve
AUC0-t	AUC from time zero to time 't' where t is a defined time point after administration
AUCinf	AUC from time zero to infinity
AUClast	AUC from time zero to the time of the last quantifiable concentration
AUC0-t	AUC from time zero to the end of the dosing interval tau
BCS	Biopharmaceutical classification system
b.i.d.	Bis in die (twice a day)
BTK	Bruton's tyrosine kinase
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	The observed maximum blood concentration following drug administration
CMA	Critical material attribute
CoA	Certificate of analysis
CPCA	Carcinogenic potency categorization approach
CPP	Critical process parameter
CQA	Critical quality attribute
CSU	Chronic spontaneous urticaria
CTCAE	Common terminology criteria for adverse events
CU	Content uniformity
DLQI	Dermatology life quality index
DS	Design space
EAACI	European Academy of Allergy and Clinical Immunology
EAT	Enhanced ames test
ECG	Electrocardiogram
EI	Elemental impurity
EMA	European medicines agency
FAS	Full analysis set
FCT	Film-coated tablet
FNH	Focal nodular hyperplasia
GC	Gas chromatography
GIST	Gastrointestinal stromal tumour
GMP	Good manufacturing practice
H1-AH	H1-antihistamine

HGC	Hard gelatin capsule
HSS7	Weekly hives severity score
HPLC	High pressure liquid chromatography
HR-MS	High-resolution mass spectrometry
IPC	In-process control
IR	Infrared
KF	Karl Fischer
LC	Liquid chromatography
LOA	Letter of access
LOD	Limit of detection
LOD	Loss on drying
LOQ	Limit of quantification
MAA	Marketing authorisation application
MAD	Multiple ascending dose
MAH	Marketing Authorisation holder
MDD	Maximal daily dose
MedDRA	Medical dictionary for regulatory activities
MO	Major objection
MS	Mass spectrometry
ND	Not detected
NIRS	Near infrared spectroscopy
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
OOS	Out of specification
PA	Polyamide
PACMP	Post approval change management protocol
PAR	Proven acceptable range
PCS	Photon correlation spectroscopy
PD	Pharmacodynamics
PDE	Permitted daily exposure
Ph. Eur.	European pharmacopoeia
PK	Pharmacokinetics
PI	Polydispersity index
PL	Patient leaflet
PRAC	Pharmacovigilance risk assessment committee
PRO	Patient reported outcome
PROM	Patient reported outcome measure
PVC	Polyvinyl chloride
PS	Particle size
PSD	Particle size distribution
QC	Quality control
QOS	Quality overall summary
QP	Qualified person
QTc	Corrected QT interval
QTcF	QT corrected for heart rate by Fridericia's cube root formula
QTPP	Quality target product profile
rBA	Relative bioavailability
RH	Relative humidity
RMP	Risk management plan

RRT	Relative retention time
RTRT	Real time release testing
SAE	Serious adverse event
SM	Starting material
SmPC	Summary of product characteristics
SOC	System organ class
TEAE	Treatment-emergent adverse event
TGA	Thermal gravimetric analysis
TK	Toxicokinetic
TLC	Thin liquid chromatography
Tmax	Time to reach maximal drug concentration
TTC	Threshold of toxicological concern
UAS7	Weekly urticaria activity score
UPDD	Urticaria patient daily diary
UV	Ultraviolet
USP/NF	United states pharmacopoeia/national formulary
XRPD	X-ray powder diffraction

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Rhapsido
Active substance	Remibrutinib
INN or common name	Remibrutinib
Applicant	Novartis Europharm Limited Vista Building Merrion Road Elm Park Dublin 4 D04 A9N6 IRELAND
EMA product number	EMEA/H/C/006313
ATC code and pharmacotherapeutic group	L04AA60, Immunosuppressants, selective immunosuppressants,
Pharmaceutical form(s) and strength (s)	Film-coated tablet 25 mg
Packaging	blister (PA/alu/PVC//alu)
Package size(s)	180 tablets, 30 tablets and 60 tablets
Route of administration	Oral use
Device or diagnostic	Not applicable
Orphan designation	No
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	Rhapsido is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients with inadequate response to H1 antihistamine treatment
New active substance status	Granted

1.2. Scientific advice

Table 1: Scientific advice

Date	Topic (quality/ non-clinical/ clinical)	Reference number(s))	Coordinator(s)
29 January 2021	NC/C	EMA/SA/0000045805	Brigitte Schwarzer-Daum, Minne Casteels
14 October 2021	Q	EMA/SA/0000065974	Stephan Lehr, Dina Apele-Freimane
22 April 2022	NC/C	EMA/SA/0000077727	Ewa Balkowiec Iskra, Carin Bergquist
26 January 2023	C	EMA/SA/0000112282	Sheila Killalea, Johanna Lähteenvuo
20 July 2023	Q/NC	EMA/SA/0000138208	Martin Walter, Audrey Sultana

The previous Scientific Advices addressed the following issues on the development of Remibrutinib for treatment of chronic spontaneous urticaria in patients who have an inadequate response to H1-antihistamine treatment:

- Adequacy of the non-clinical and clinical pharmacology programmes to support the Phase 3 clinical programme and a MAA; the design of the Phase 3 studies including the inclusion/exclusion criteria, primary and key secondary endpoints, estimand strategy, statistical analysis methods, comparator, and dose/regimen; adequacy of the proposed Phase 3 clinical programme to support the MAA of remibrutinib for the treatment of subjects with CSU.
- The designation of starting materials for the commercial manufacture of drug substance (EMA/SA/0000065974)
- Adequacy of the clinical pharmacology study design including waiver for renal impairment and QT study for marketing authorization application (EMA/SA/0000077727)
- Waiving the need for a renal impairment study based on results from modelling predictions, previous patient data on renal impairment, as well as human ADME results (EMA/SA/0000112282)
- The approach for a Nitrosamine Drug Substance Related Impurity; The method to control the drug substance particle size in drug product (EMA/SA/0000138208)

1.3. Eligibility to the centralised procedure

The applicant Novartis Europharm Limited submitted on 26 February 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Rhapsido (Remibrutinib), through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 March 2023.

The applicant applied for the following indication: Rhapsido is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies.

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision(s) P/0453/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0453/2023 had not yet been completed as some measures had been deferred.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Applicant's request for consideration

1.7.1. New active substance status

The applicant requested the active substance Remibrutinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.7.1.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance remibrutinib, it is considered that remibrutinib is to be qualified as a new active substance in itself, as it is not a constituent of a medicinal product previously authorised within the European Union.

1.8. Patient experience data

Table 2: Patient experience data relevant to the application

Patient experience data submitted with this application				Section where discussed (if applicable)
☐	Patient experience data submitted by the applicant:			
	☐	Clinical outcome assessments (COAs) such as		
		x	Patient-reported outcomes (PRO)	5.3.2.1.2.4 Study assessments
		☐	Other	
	☐	Patient preference studies		
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		
☐	Other patient experience data not submitted by the applicant but considered in this evaluation:			
	☐	Input informed from participation in meetings or public hearings with patient stakeholders		
	x	CHMP early dialogue with patient organisations		5.3.6 Patient experience data
	☐	Third party interventions from patients and patient groups		
	☐	Other (e.g. medical literature, summaries/analysis from patient engagement activities - please specify)		

1.9. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

rapporteur:	Margareta Bego
Co-rapporteur:	Elita Poplavska

The application was received by the EMA on	26 February 2025
The procedure started on	27 March 2025
The CHMP rapporteur's first assessment report was received on	16 June 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	19 June 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	26 June 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	09 October 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	14 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	04 December 2025
The applicant submitted the responses to the CHMP list of outstanding issues on	27 January 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	11 February 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint updated assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	19 February 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rhapsido on	26 February 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see appendix on NAS)	26 February 2026

1.10. CHMP outcome

1.10.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

1.10.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.10.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus

that the benefit-risk balance of Rhapsido is favourable in the following indication:

Rhapsido is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients with inadequate response to H1 antihistamine treatment.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.10.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.10.5. Other conditions and requirements of the marketing authorisation

1.10.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

1.10.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.10.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.10.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

2.1. Therapeutic context

Disease or condition

Chronic spontaneous urticaria (CSU) is an unpredictable disease of the skin characterised by the spontaneous and recurrent appearance of itchy wheals (hives), angioedema, or both lasting for at least 6 weeks. In contrast to chronic inducible urticaria, CSU is not triggered by specific triggers. This means that the presence of the triggers does not always cause signs and symptoms, but that they also occur without them, i.e. spontaneously. However, some patients may have more than one subtype of urticaria. CSU is a self-limited disorder in most patients with an average disease duration of two to five years. The data show that the rate of spontaneous remission at one year is approximately 30 to 50%. In up to 30% of patients, however, symptoms persist beyond five years (UpToDate). The burden of the disease is substantial and affects both objective functioning and subjective well-being (Zuberbier et al 2022).

Aetiology and pathogenesis

The aetiology of CSU is still not well understood but believed to be partially dependent on production of autoantibodies that activate and recruit inflammatory cells (Yosipovitch et al 2023). As such, CSU is considered as an autoimmune disease, with the detection of autoantibodies of IgE or IgG type (Xiang et al 2023). Wheals and angioedema are induced by the degranulation of skin mast cells. Proinflammatory mediators such as histamine, proteases, and cytokines are released by mast cells which subsequently induce vasodilation, increase vascular permeability, and stimulate sensory nerve endings leading to the characteristic redness, itch, and swelling of urticaria (Kaplan et al 1978, Saini, Kaplan 2018).

Epidemiology

CSU affects approximately 1% of the global population, and many patients suffer detrimental effects on their health-related QoL (Maurer et al 2022). Both children and adults can develop CSU, although it is more common in adults. The mean age of patients with CSU has been reported to be between 34 and 67 years, and women constitute roughly 61-80% of the population with CSU (Balp et al 2022b).

Diagnosis

CSU should be differentiated from other diseases and syndromes that may manifest with wheals and/or angioedema. The diagnosis of CSU is based on a detailed history and physical examination (signs and symptoms associated with the lesions, duration of the lesions and accompanying angioedema, elimination of a possible underlying cause). Basic diagnostic tests include a differential blood count, ESR and/or CRP for all patients, IgG anti-TPO and total IgE for patients in specialist care (Zuberbier et al 2022).

Management

Disease activity is assessed using the weekly Urticaria Activity Score (UAS7), a validated patient reported outcome measure (PROM) that measures the main urticaria symptoms and signs (wheals and itching). The treatment goal is complete disease control (UAS7=0) and normalisation of quality of life until the urticaria resolves spontaneously. Treatment approach is to treat the disease until it is gone.

According to the international guidelines (Zuberbier et al. 2022), the treatment strategy for CSU includes second-generation H1-Antihistiamine (H1-AH) at the approved dose as first-line therapy, an up-dosing to four times the approved H1-AH dose as second-line therapy (off-label), then the addition

of omalizumab as third-line therapy and the addition of ciclosporin as last-line therapy (off-label), as well as short-term treatment with corticosteroids.

Other available treatments include dupilumab, authorised in the EU and indicated for the treatment of moderate to severe chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamines and who are naive to anti-IgE therapy for CSU.

Unmet medical need

The experience from clinical studies showed that less than 50% of patients treated with omalizumab reach complete control of signs and symptoms by Week 24 (Kaplan et al 2016, Zuberbier et al 2022) and ciclosporin has potentially serious adverse effects. Considering the high impact and chronicity of CSU and the paucity of effective treatments, an unmet medical need exists for new therapies with novel mechanisms of action, enhanced efficacy, and favorable safety profiles.

2.2. Aspects of development

The clinical development program for remibrutinib in patients with CSU comprises two identical pivotal Phase III studies A2301 and A2302. Additional efficacy and safety data come from four supportive studies (Phase IIb dose-finding study A2201, Phase IIb extension study A2201E1, Phase III study A1301) and study A2305.

2.3. Description of the product

Remibrutinib (LOU064) is a selective oral inhibitor of Bruton's tyrosine kinase (BTK) that forms a covalent bond with a cysteine residue in the BTK active site, leading to durable inactivation of BTK. The therapeutic effect of remibrutinib in CSU is achieved through inhibition of mast cell and basophil degranulation, including release of histamine and other proinflammatory mediators, mediated by pathogenic IgE or IgG directed against the FcεR1 or IgE.

The initially claimed indication was:

Rhapsido is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment.

The proposed recommended dose is 25 mg taken orally twice daily.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

2.4.3. Good clinical practice (GCP) inspection(s)

No inspection required.

3. Quality aspects

3.1. Introduction

3.1.1. Introduction

The finished product is presented as film-coated tablets containing 25 mg of remibrutinib as active substance.

Other ingredients are: mannitol, microcrystalline cellulose, copovidone, croscarmellose sodium, sodium stearyl fumarate, sodium lauryl sulfate for the tablet core and polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172) for the film coating.

The product is available in PA/Al/PVC (polyamide/aluminium/polyvinylchloride) blisters with aluminium foil backing, containing 30, 60 or 180 film-coated tablets.

3.1.2. Active substance

General information

The chemical name of remibrutinib is N-(3-{6-Amino-5-[2-(N-methylprop-2-enamido)ethoxy]pyrimidin-4-yl}-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide corresponding to the molecular formula $C_{27}H_{27}F_2N_5O_3$. It has a relative molecular mass of 507.54 and the following structure, as depicted in Figure 1.

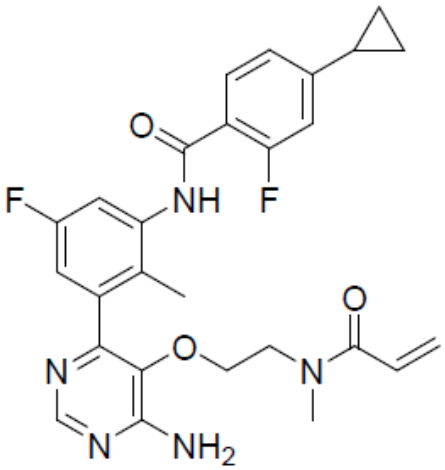


Figure 1: active substance structure

The chemical structure of remibrutinib was elucidated by a combination of high-resolution mass spectrometry (HR-MS), ultraviolet absorption (UV), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (^{1}H-, ^{13}C-, ^{15}N-, ^{19}F-NMR). The solid state properties of the active substance were measured by DSC, TGA and XRPD.

Remibrutinib is white to pale yellow powder. It has low solubility across the physiological pH range and is a highly permeable and highly lipophilic compound, therefore is classified as BCS Class II compound. Based on the hygroscopicity and water sorption study, remibrutinib is classified as non-hygroscopic compound. The active substance does not exhibit stereoisomerism and does not contain a disubstituted double bond, therefore no E/Z-isomers are possible.

Polymorphism has been observed for remibrutinib. The applied manufacturing process consistently reveals anhydrous modification A. Polymorphic form is stable during the active substance storage. Polymorph form A is controlled at the level of the active substance specification by XRPD.

Manufacture, characterisation and process controls

The active substance manufacturing site has been stated in the dossier and satisfactory GMP documentation has been provided. Remibrutinib is synthesized in 10 chemical steps followed by a milling step, using well defined starting materials with acceptable specifications. Designation of the starting materials is in line with the received scientific advice.

During the synthesis, four intermediates are isolated, for which the specifications and analytical procedures with summary of validation data are provided.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

During the procedure, a major objection (MO1) was raised in relation to the control of impurities originating from the starting materials and intermediates, including mutagenicity assessment. The MO was resolved by providing a clarification on the impurities present in the starting materials and intermediates, a justification of the control strategy of the impurities based on the purge of the impurities themselves and by further substantiating the mutagenicity assessment and control strategy of all detected impurities.

For each of the starting materials, manufacturers, the synthesis routes, description of analytical methods, methods validation summary, batch analyses results and justification of specifications are presented. The proposed specifications for the starting materials include relevant testing parameters. Proposed acceptance criteria are acceptable.

One of the intermediate is secondary amine from which nitrosamine impurity could be formed. In order to minimize its formation, reaction conditions of steps are optimised, and an acceptable nitrite control is introduced in the relevant raw material of that manufacturing step. In addition, nitrosamine impurity is controlled in intermediate which corresponds to AI of less than 18 ng/day, and therefore acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The mutagenic potential and other toxicities of actual and potential impurities as well as reagents used in the active substance have been assessed in line with the requirements of ICH M7 (additionally see non-clinical AR).

Identified mutagenic impurities formed or used as reagents in the later phase of the synthesis are found below 30% of TTC limit. For an impurity, potentially formed in the last step, its purging by spiking study was demonstrated. A specific degradation product is controlled in the active substance specification, in view of its genotoxic potential.

Solvents used in the late process steps of active substance synthesis are included in the active substance specification with ICH limits. Other class 2 and 3 solvents used in the upper steps of the synthesis are

demonstrated to be below 10% of ICH limits and therefore, it is acceptable not to include them in the active substance specification. The absence of potential impurities (class 1 solvents) in active substance batches is demonstrated (less than 30% of ICH limits), therefore no additional control is needed.

The commercial manufacturing process for the active substance has been briefly described. The active substance manufactured using the proposed commercial process has been used for setting specification, re-test period and during the development of the finished product.

Proven acceptable ranges have been defined for the following steps of the manufacturing process of the active substance. During the procedure, upon request from the CHMP, summary of the experimental data for each PAR has been provided. The development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. No design space is claimed.

The active substance is packaged in low-density polyethylene (LDPE) bag which complies with Commission Regulation (EU) 10/2011, as amended. The bag is placed into triple laminated foil bag and sealed. The bags may be stored in drums for handling and transportation.

Specification

The active substance specification includes tests for properties (appearance by visual examination, particle size by laser light diffraction(Ph. Eur.)), identity (IR spectroscopy, XRPD both (Ph. Eur.)), purity (related substances by HPLC, residual solvents by GC-HS, residual solvents by GC, water by KF (Ph. Eur.), sulphated ash (Ph. Eur.), content of P by ICP-OES2, specific impurity by GC, specific impurity by HPLC-MS), assay (on anhydrous and solvent free basis) by HPLC, microbiology (Ph. Eur.).

The proposed tests and related limits are considered acceptable.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Residual solvents are controlled according to ICH Q3C option 1 limits, which is sufficient.

Microbiological quality is tested in line with Ph. Eur. requirements. Skip testing is acceptable taking into account the presented batch data and solid state of the active substance.

The elements intentionally added to the process. Since results for all tested elements were below 30% of the ICH Q3D limit, no additional control is needed.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (4 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer, stored in a container closure system representative of the commercial package for up to 24 months under different storage conditions (-20 °C, 5 °C, 25 °C/60% RH and 30 °C/75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches were manufactured using a previous version of the manufacturing process, which is acceptable as this is considered as worst case scenario. Additionally, three batches

manufactured with the current commercial process called as re-validation batches, were placed for stability study and results are available for 9 months at -20 °C, 5 °C, 25 °C/60% RH and 30 °C/75% RH and as well as for 6 months at 40 °C/75% RH. Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The following parameters were tested: appearance, identity by IR and XRPD, related substances, water content, assay and microbial enumeration test.

The analytical methods used were the same as for release and were stability indicating.

For all batches and at all tested conditions, all tested parameters were within specification limits without any significant trend of any of the tested parameters.

Photostability testing following the ICH guideline Q1B was performed on one batch. The results indicate that the active substance is stable when exposed to light at ⩾ 1200 kLuxh with ⩾ 200 Wh/m2 integrated near ultraviolet energy (option 1 Xenon lamp) but unstable when exposed to stress light at ⩾ 2400 kLuxh with ⩾ 400 Wh/m2 integrated near ultraviolet energy (option 1 Xenon lamp) due to increase of the degradation product impurity.

Results on stress conditions demonstrates stability of the active substance in solid state (at 50 °C and 60 °C, each at <30% RH and 75% RH, at 80 °C in nitrogen, oxygen and nitrogen with 2% of water m/m) and instability of the active substance in solution when exposed to acidic, basic and oxidative conditions. The active substance is non-hygroscopic (no water uptake when stored without packaging at 25 °C/60% RH and 25 °C/92% RH) and stable for 4 freeze-thaw cycles each consisting of 6 days at -20 °C/ambient RH and 1 day at 25 °C/60% RH.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored in the proposed container in a freezer between -15 °C and -25 °C, protected from light. Storage in a freezer between -15 °C and -25 °C has been justified as precautionary measure, particularly regarding the level of the degradation product impurity identified late in development. This is accepted. The storage conditions will be revised when additional stability data will be available from the stability batches from the current manufacturing process.

3.1.3. Finished medicinal product

Description of the product and Pharmaceutical development

Remibrutinib 25 mg film-coated tablet is an immediate release dosage form for oral administration. The finished product is presented as a light yellow, round, curved film-coated tablet with a diameter of 6.7 to 7.6 mm, debossed with "LV" on one side and with the company logo on the other side. Remibrutinib 25 mg film-coated tablets are packaged in PA/Al/PVC (polyamide/aluminium/polyvinylchloride) blisters with aluminium foil backing.

Remibrutinib is a low soluble active substance with a pH dependent solubility profile (the solubility decreases with increasing pH) with a high passive permeability; it is classified as BCS class 2.

The active substance shows polymorphism. Stability of the polymorphic form (crystalline form modification A) in the active substance and in the finished product has been adequately demonstrated.

The input active substance PSD is controlled routinely according to active substance specification.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur.

standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 3.1.1. of this report.

The choice and function of the selected excipients have been adequately described. Compatibility of the selected excipients with the active substance has been adequately demonstrated by compatibility studies.

Pharmaceutical development of the finished product contains QbD elements.

The quality target product profile (QTPP) is summarised in **Table** 3 below.

Table 3: Quality target product profile (QTPP) for Remibrutinib 25 mg film-coated tablets

Quality attributes	Product profile
Indication	Chronic spontaneous urticaria
Route of administration	Oral
Dosage form	Film coated tablet
Dosage strength	25 mg
Container closure system	Blister packs or bottles (depending on the country and/or region)
Drug release profile	Immediate release
Stability	Minimum shelf life of 24 months, Store below 25°C

The critical quality attributes were identified and clearly stated in the dossier.

A hard gelatin capsules formulation (HGC formulation) was used in early clinical trials (phase 1 and 2). Subsequently, film-coated tablet (FCT formulation) was developed for phase 2 and phase 3 clinical studies and later commercialisation. The FCT and HGC formulations differ in their qualitative and quantitative composition. The optimised HGC formulation (50 mg) and the FCT formulation (50 mg) have been compared in a relative bioavailability study CLOU064X2105 (for more information reference is made to clinical AR).

The composition of the 25 mg film-coated tablet formulations used in phase 3 clinical studies and the one developed for commercialisation differ only in the non-functional film coating. This difference is not expected to have a significant effect on the bioavailability of the active substance. Equivalence between the phase 3 clinical formulation and the proposed commercial formulation of Remibrutinib film-coated tablets 25 mg has additionally been substantiated by comparative dissolution profiles.

Remibrutinib FCTs are manufactured by using a wet media milling step for reduction of the substance particle size (resulting in a nanosuspension to enhance the bioavailability), followed by a spray granulation step. The obtained granules and outer phase excipients are screened, followed by a blending step. The final blend is compressed using a rotary tableting machine and the resulting tablet cores are coated in a perforated coating pan with a non-functional coating using standard aqueous coating suspension.

The formulation and manufacturing development have been evaluated through the use of risk assessment, design of experiments and other modelling techniques to identify the impact of the formulation components and process steps on the finished product quality attributes. The risk identification was based on the experience from formulation development, process design and scale-up studies. Reduction of active substance particle size by wet milling (to obtain a nanosuspension) is performed to enhance the bioavailability. The finished product manufacturing process was optimised to reduce the formation of the active substance degradation product.

Critical process parameters have been adequately identified.

The proposed QC dissolution method selection of dissolution medium, volume, apparatus and rotation speed has been adequately justified. The method has shown discriminatory power towards relevant formulation changes. However, discriminatory power of the dissolution method has not been demonstrated towards the active substance particle size.

In order to offset the lack of discriminatory power of the dissolution method toward different particle sizes of the active substance in the nano-size range and in order to ensure adequate bioavailability of the finished product, particle size testing (by PCS) has been introduced in the finished product specification. The proposed complementary approach to overall control strategy is considered acceptable.

The primary packaging is PA/alu/PVC/alu (polyamide/aluminium/polyvinylchloride/aluminium) blisters with aluminium foil backing. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

For all sites involved in the manufacture, control and batch release of the finished product are clearly stated in the dossier and sufficient evidence of GMP compliance has been provided.

The manufacturing process consists of 15 steps that can be grouped in the following main stages: wet media milling, spray granulation, screening, blending, tableting, film coating and packaging. The process is considered to be a non-standard manufacturing process.

The critical process steps and critical process parameters have been defined. The in-process controls are adequate for this type of manufacturing process.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs and CPPs. No design space is claimed.

Process validation has been performed on three production scale batches of the finished product, manufactured according to the proposed manufacturing process. The homogeneity of the final blend has been adequately demonstrated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf-life specifications shown include appropriate tests for this kind of dosage form: appearance (visual examination), identity (NIRS, HPLC and UV), water (KF (Ph. Eur.)), specific impurities (HPLC-MS), particle size (average PCS diameter and polydispersity index), dissolution (UV, Ph. Eur.), uniformity of dosage units by content uniformity (NIRS and HPLC), identity, assay and degradation products (HPLC), microbiology (Ph. Eur.).

The finished product is released on the market based on the release specifications, through a combination of traditional final product release testing and real time release. Real time release testing (RTRT) is proposed for two specification parameters and that has been supported by comparative data at commercial scale (parallel testing). A contingency plan, specifying the use of alternative testing is also proposed. The proposed RTRT approach is adequately justified and is considered acceptable.

Control of impurities is in line with guidance. The proposed limit for a specified impurity is above ICH Q3B qualification threshold, considering that this impurity is a metabolite of the active substance, this is acceptable. The proposed limit for unspecified impurities is in line with ICH Q3B.

The proposed limit for mutagenic degradation product impurity is based on the TTC approach and is acceptable.

Suitability of the dissolution method, supplemented by particle size testing (by PCS), has been discussed in the pharmaceutical development section.

During the procedure a MO (MO2) was raised requesting tightening the proposed limit for particle size as it was considered too wide based on the presented results of particle size for the pivotal clinical batches. To address MO2, a two-sided limit (upper and lower) for average particle size have been included in the finished product specifications. The proposed range for average particle size is acceptable. In a follow up MO to MO2, the proposed limit for polydispersity index was considered too wide as not in line with batch data. To address the follow up MO to MO2, the finished product specification was tightened in line with batch and stability and is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on six batches were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch and toxicological data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). A nitrosamine impurity can be formed during the finished product manufacturing process and from AS degradation. Routine testing of this nitrosamine impurity is included in the finished product specification. The specification limit for this impurity was not acceptable and MO3 was raised in this regard. During the procedure the limit was confirmed by NS OEG (for additional information please refer to the non-clinical assessment report). Thus, the proposed specification limit for this nitrosamine impurity is considered acceptable.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for four full scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Registration stability data from three pilot scale batches of finished product stored for up to 12 months at of -20 °C/ambient RH, up to 24 months at 5 °C/ambient RH, 25 ºC/60% RH, 30 ºC/75% RH and up to 6 months under accelerated conditions at 40 ºC/75% RH were provided. The batches of medicinal product were packed in the primary packaging proposed for marketing. Batches were tested for the following specification parameters: appearance, water, specific impurities, dissolution (UV, Ph. Eur.), assay and degradation products (HPLC), microbiology (Ph. Eur.). The proposed tests are acceptable as they are stability indicating. Additionally, the samples were tested for water activity, thickness, crushing strength, acrylic acid by headspace GC and identity by XRPD. The analytical procedures used are stability indicating. No significant change was observed in any of the tested parameters, except for

one impurity, for which two of the three registration batches demonstrated OOS results at all tested stability time points. The manufacturing process was then optimised in order to reduce the levels of this mutagenic impurity in the finished product but only 3 months data stability data from optimised process was available initially. Because of the OOS results in the registration stability batches and the limited stability data from the optimised process, the acceptability of the proposed shelf-life (2 years) was raised as MO4. The MO was resolved with the provision of further stability data (up to 6 months at 40 °C/75% RH and up to 12 months at 25 °C/60% RH and 30 °C/75% RH) of batches manufactured by the optimised process packaged in PA/Al/PVC/Al blisters. The provided stability data is in line with the proposed specification limits. No significant trends were observed.

An open dish study was performed on samples of the finished product; an increase in water content, as well as slight changes in particle size and crushing strength, were observed. It is therefore concluded that the product should be stored in its original packaging.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products, in parallel with a control sample stored in the proposed container. Samples of the finished product were stored for four complete freeze and thaw cycles (–20 °C/ambient RH for 6 days, followed by 1 day at 25 °C/60% RH). Sample was taken after 28 days and analysed. No significant change in quality is observed during the photostability and freeze/thaw studies. The finished product is not sensitive to light and does not require any restriction concerning freezing.

Based on available stability data, the proposed shelf-life of 2 years and "Store in the original package in order to protect from moisture", as stated in the SmPC (section 6.3), are acceptable.

Post approval change management protocol(s)

The applicant proposes a post approval change management protocol (PACMP) for potential changes of NIRS procedures. The PACMP includes a detailed description of the potential changes, a risk assessment, description of the studies to be performed and an overview of the proposed reporting categories for the listed changes. The proposed PACMP is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

3.1.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure a MO (MO1) raised in relation to the control of impurities originating from the starting materials and intermediates of the active substance was resolved by providing additional data, including mutagenicity assessment, and confirming the suitability of the control strategy. A second MO (MO2) was raised in relation to the control of the active substance particle size in the finished product specification; MO2 was addressed by tightening the proposed limits for particle size (average PCS diameter and PI) in the finished product specification, in line with batch data. A MO (MO3) was raised in relation to the finished product specification limit of a nitrosamine impurity. During the procedure the acceptability of the limit was confirmed by NS OEG and the MO was considered as resolved. Lastly, additional data was requested as a MO (MO4) to support the proposed shelf life was raised as MO4, as only 3 months data of batches of the finished product manufactured by the optimised process were provided. The MO was resolved with the provision of further relevant stability data. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

3.1.6. Recommendations for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

The non-clinical development programme of remibrutinib includes pharmacology, pharmacokinetics and toxicity studies in line with ICH M3(R2). Overall, it supports the proposed molecular mechanism of action at a cellular level and safety for the treatment of CSU at the recommended posology in the intended patient population.

In the context of CSU, the relevant primary pharmacodynamic activity of remibrutinib was established in vitro in biochemical assays to determine BTK inhibitory properties and in cellular assays to determine the inhibitory effect on cellular signalling in mast cells, basophils, B cells and macrophages as well as in vivo in non-clinical mouse models of skin mast cell degranulation.

PK assessment included standard studies to evaluate the ADME of remibrutinib in non-clinical species. A comprehensive assessment of comparative metabolism across species was performed in vitro, as well. Additionally, potential for formation of reactive intermediates and, as a consequence, covalent drug-protein adducts was investigated.

The toxicological assessment was performed in pharmacologically relevant species (mouse, rat, rabbit and dog) that were sufficiently exposed to remibrutinib following the intended clinical route of administration (i.e. oral). Non-clinical safety package included secondary and safety pharmacology studies as well as toxicology studies. The toxicology program comprised GLP-compliant repeat-dose toxicity studies (including immunophenotyping and also providing insights into acute toxicity and local tolerance) with daily dosing up to 26 weeks in rats and 39 weeks in dogs as well as GLP-compliant studies of genotoxicity, carcinogenicity, reproductive and developmental toxicity, and phototoxicity. Additionally, the programme included several non-GLP studies, which were investigative (related to immunosafety, hemostasis, and the mutagenic potential of some aniline moiety-containing metabolites as well as of relevant impurities) or dose-range finding.

4.2. Analytical methods

Radiolabelled [^{3}H]- and [^{14}C]-remibrutinib were synthesized for in vitro and in vivo studies. [^{14}C]-remibrutinib was labelled between the two nitrogen atoms in the pyrimidine ring, while the [^{3}H]-remibrutinib was labelled in the 5-fluoro-2-methyl phenyl ring. Radioactivity was measured by liquid scintillation counting (LSC) or Accelerator Mass Spectrometry while concentrations of radioactivity in organs and tissues were determined by quantitative whole-body autoradiography (QWBA) or LSC.

The Applicant has submitted 10 validation reports of analytical methods which used liquid chromatography tandem mass spectrometry (LC-MS/MS) to determine concentrations of remibrutinib in blood and plasma samples of mouse, rat, rabbit and dog in toxicology studies (within a range of 10.0 to 10000 ng/mL). Some validation studies were performed according to standard operating procedures (SOPs) at US-based facilities (Covance Laboratories or Labcorp Early Development Laboratories) and SGS France facility, following the Principles of GLP.

4.3. Pharmacology

4.3.1. Pharmacodynamics

The primary non-clinical pharmacodynamics (PD) of remibrutinib were investigated through in vitro studies to assess its biochemical and cellular potency and selectivity, and through in vivo rodent models including mechanistic models of sheep red blood cell immunisation, passive cutaneous anaphylaxis, and reverse passive Arthus model to evaluate its pharmacokinetics (PK), pharmacodynamic effects, and relevance to disease-related mechanisms.

4.3.1.1. Primary pharmacodynamics

In-vitro

Remibrutinib was investigated across a range of assays for its pharmacological properties. It forms an irreversible covalent bond with the conserved cysteine residue (Cys481) in ATP binding site of BTK, which is predominantly expressed in immune cells such as B cells, mast cells, basophils, macrophages, and microglia (Angst et al, 2020). In this regard, the cellular potency of remibrutinib was assessed in cellular systems in vitro that are relevant for its primary pharmacology in basophils, mast cells, B cells and macrophages.

<u>In vitro activity on relevant biological targets and selectivity</u>

The *in vitro* inhibition of BTK enzyme activity was tested with recombinant full-length human BTK protein with or without 15-minute preincubation in a Caliper format assay. The compound demonstrated potent inhibitory activity, with low nanomolar IC_{50} values confirmed by two experiments (IC_{50} = 1.3 ± 0.9 nM; n = 5 and IC_{50} = 0.6 nM; n = 1). Under a 15-minute controlled pre-incubation, remibrutinib showed selectivity against the closely related kinases TEC (IC_{50} = 124 nM), BMX (IC_{50} = 141 nM), ITK and TXK (both IC_{50} > 10 µM). In direct comparisons with rac-ibrutinib and spebrutinib, remibrutinib demonstrated similar potency but improved specificity. Kinases with a conserved cysteine at the binding site (Cys481), such as EGFR, JAK3, and HER2, were not inhibited (IC_{50} > 10 µM).

<u>B cell receptor signalling</u>

Remibrutinib selectively inhibits BTK phosphorylation at Y551, triggered by BCR activation via LYN and SYK, without affecting these upstream kinases, as shown in Ramos B cells (IC_{50} = 11.0 nM) with no impact on LYN/SYK-dependent VAV phosphorylation. In primary rat B cells, it potently inhibited BCR-induced activation (IC_{50} = 1.8 ± 0.3 nM), while in human B cells, remibrutinib suppressed CD69 and CD86 expression (IC_{50} = 18.3 nM and 7.0 nM, respectively) without affecting SEB-stimulated T cell activation (IC50 > 20,000 nM), confirming its selectivity. In splenic B cells from MD4 transgenic mice, it inhibited HEL-induced IL-6 secretion (IC_{50} = 1.2 ± 0.1 nM) and reduced CD69 and CD86 expression (IC_{50} = 1.4 ± 1.1 and 0.8 ± 0.4 nM), further demonstrating potent and selective BTK-dependent B cell inhibition across species.

Fc-receptor signalling

Remibrutinib potently inhibited FcγR-mediated IL-8 secretion in vitamin D3-differentiated human THP1 monocytic cells (IC_{50} = 2.5 ± 0.7 nM), confirming BTK-dependent pathway suppression. In human basophils, it blocked FcεRI-mediated degranulation (IC_{50} = 71.8 ± 59.1 nM), and in skin-derived mast cells, it inhibited histamine release (IC_{50} = 17.2 ± 2.7 nM), demonstrating strong activity in FcεRI-driven responses. However, regarding the basophile degranulation, the high data variability (standard deviation was about 82% of the mean) and low statistical power (only 2 to 5 replicates or donors) were noted. In contrast, remibrutinib showed only weak inhibition of FcγR-induced ROS production in polymorphonuclear leukocytes (IC_{50} = 21.2 ± 3.3 µM), likely due to the expression of BMX rather than BTK in these cells, since BMX was approximately 108-fold less sensitive to remibrutinib, as discussed above.

In-vivo

Remibrutinib was characterised across a series of rodent PK/PD mechanistic models and complex disease models (rat SRBC model, mouse PCA model, mouse RPA model) to establish its *in vivo* pharmacologic profile.

BTK occupancy and preclinical PK/PD relationship

Study RD-2014-00816 investigated the experimental and *in silico* PK/PD analysis of remibrutinib. The levels of BTK occupancy were determined in separate ELISAs for total BTK protein and for unoccupied BTK (= free BTK) according to study RD-2014-00810.

BTK target occupancy by remibrutinib was evaluated in various rat studies using different strains (Lewis, OFA-1, Wistar) with no notable differences in pharmacokinetics or pharmacodynamics. Following single oral doses of 1, 3, or 10 mg/kg, dose-dependent BTK occupancy was observed, with maximal spleen occupancy at 3 mg/kg and corresponding blood levels of 2.4, 13.1, and 71.7 nM, respectively, at 5 hours post-dose. Despite a short systemic exposure, full BTK occupancy was achieved, consistent with the covalent binding profile of remibrutinib. The pharmacodynamic effects persisted beyond drug clearance due to irreversible binding, and recovery of free BTK was faster in spleen than in blood, indicating tissue-specific differences. Analysis showed a BTK occupancy half-life of ~87 hours in blood versus ~5 hours in spleen, likely due to varying turnover rates of BTK-expressing cells. In this regard, the longer persistence of BTK occupancy in blood has been reported before (Evans et al 2013, Haselmayer et al 2019, Watterson et al 2019).

Mechanistic model systems

The correlation between remibrutinib pharmacokinetics, BTK occupancy, and pharmacodynamic efficacy was demonstrated in a rat model of immune response to sheep red blood cell (SRBC) immunisation. Female albino OFA rats (n=5/group) were immunised on day 0 and treated once daily with remibrutinib (0.3, 1, or 3 mg/kg) or reference compound - cyclosporine A (6 mg/kg) from day 0 to 3. On day 4, splenic SRBC-specific IgM-secreting B cells were quantified, showing a dose-dependent reduction: 66% (0.3 mg/kg), 73% (1 mg/kg), and 96% (3 mg/kg). Peak blood concentrations occurred at 0.5 h post-dose, with <10% remaining at 5 h. Corresponding spleen BTK occupancy levels 24 h after the last dose were 31.0%, 47.1%, and 71.6%, reflecting dose-dependent inhibition and recovery due to new BTK synthesis, which is in line with other internal and published studies.

Relevant disease model systems

The effects of remibrutinib on non-clinical models of skin mast cell degranulation induced by FcγR and FcεR mediated hypersensitivity were assessed in the mouse passive cutaneous anaphylaxis (PCA) and in the mouse reverse passive Arthus (RPA) reaction.

The effect of remibrutinib on FcεR-mediated mast cell activation was evaluated in a mouse PCA model using low and high doses of hapten-specific IgE for sensitisation. BALB/c mice received oral remibrutinib (3, 10, 30, or 100 mg/kg) 14 and 2 hours prior to challenge, with blood exposure and BTK occupancy assessed 2.5 hours after the final dose. In the low-IgE model, remibrutinib inhibited skin oedema in a dose-dependent manner, with 60.7% to 87.4% inhibition and peak spleen BTK occupancy ranging from 89.1% to 99.7%. However, in the high-IgE model, remibrutinib showed no significant inhibition of skin edema and only a trend to efficacy at the highest dose. The relative spleen BTK occupancy in the high IgE study was 93.6 % ± 1.2 for the 3 mg/kg dose and ranged from 97.1 to 98.5 % in the doses of 10 to 100 mg/kg. These levels of BTK occupancy were comparable to other studies performed in mice.

In another in vivo model, the acute mouse RPA model, the effect of remibrutinib on IgG-mediated dermal anaphylaxis was evaluated, where C57Bl6 mice received a single oral dose (3–100 mg/kg) 2 hours before antigen challenge. Skin swelling, measured 3 hours post-induction, showed dose-dependent inhibition: minimal at 3 and 10 mg/kg (22.9% and 29.2%) and significant at 30 and 100 mg/kg (73.0% and 61.2%). These levels of inhibition are comparable to published data with the genetically BTK deficient mice, as well as BTK inhibitors (Chang et al 2011, Fiedler et al 2011). Corresponding spleen BTK occupancy at 5 hours' post-dose increased with dose, ranging from 68.1% (3 mg/kg) to 99.3% (100 mg/kg). Furthermore, the Applicant assessed the duration of the pharmacological effect of remibrutinib in the skin. In this study, the Arthus reaction was induced at different timepoints after a single 30 mg/kg oral dose of remibrutinib. The inhibitory effect of remibrutinib was maximal for a challenge at 2 hours post dosing and returned to background levels for a challenge at 45 hours post dosing.

4.3.1.2. Secondary pharmacodynamics

Receptor, ion-channel and protease profiling in vitro

Remibrutinib was tested across a broad range of targets to assess selectivity and showed inhibition of only one kinase, PI4Kb (IC_{50} = 3.1 μM), among 64 tested, with no other off-targets identified in a KinomeScan panel of 456 kinases. It fully displaced probe binding to BTK and partially to TEC, showing 175-fold higher affinity for BTK. In screens against 85 non-kinase targets, including cardiac ion channels, remibrutinib showed low activity (IC_{50s} > 48 μM for Nav1.5, Cav1.2, and KCNQ1). Off-target effects were limited to BSEP (IC_{50} = 6.4 μM), VMAT2 (IC_{50} = 13 μM), and cathepsin S (IC_{50} = 21 μM).

To further assess potential off-target effects, remibrutinib was tested for inhibition of EGFR signalling in EGFR-overexpressing A431 cells, since EGFR is among the kinases that have a conserved cysteine corresponding to Cys481 in BTK. Despite extended preincubation, remibrutinib did not inhibit EGFR phosphorylation (IC_{50} > 60 μM).

In vitro effects on platelets

Remibrutinib was tested for its effects on platelet function due to BTK's role in ITAM-mediated signalling via the GpVI collagen receptor. In platelet-rich plasma from healthy donors, it strongly inhibited collagen-induced aggregation at low collagen levels (IC_{50} < 1 μM at 1 μg/ml), with reduced effects at higher concentrations. These results support that BTK inhibition blocks platelet aggregation at low agonist levels but can be overcome with higher collagen concentrations.

Cytotoxicity in vitro

Remibrutinib demonstrated low non-specific cytotoxicity, showing minimal inhibition of serum-induced proliferation in human THP1 cells (IC_{50} = 35 ± 21.2 μM). It did not affect the proliferation of parental

IL-3-dependent BaF3 cells or 41 kinase-transformed BaF3 sublines (IC_{50} > 11 µM), including those expressing JAK3 and BLK. A weak inhibitory effect was observed only in the BMX-transformed BaF3 line (IC_{50} = 5.5 µM), consistent with BMX being a known off-target. In primary murine bone marrow cells stimulated with IL-3, remibrutinib caused only minor inhibition of proliferation (IC_{50} = 1.97 ± 0.2 µM).

Assessment of effects on *Mycobacterium tuberculosis* re-activation and dormancy

Remibrutinib was evaluated in a 3D in vitro human granuloma model to assess its impact on *M. tuberculosis* dormancy and reactivation (Study 1920027). Treatment with remibrutinib (1–300 nM) promoted bacterial dormancy in a dose-dependent manner, unlike positive controls adalimumab and tofacitinib, which triggered reactivation. This effect was not due to a direct action on bacterial metabolism.

In vivo effects in a model of T-dependent (TD) humoral responses

Effects of remibrutinib on the primary B cell response induced in the mouse (Female C57BL/6 mice) by the T-dependent antigen, DNP-KLH (Dinitro-Phenol-Keyhole Limpet Hemocyanin), was investigated in study RD-2020-00385. Oral dosing at 30 mg/kg b.i.d. achieved ~300 nM blood levels and 100% BTK occupancy for up to 12 hours. Remibrutinib treatment reduced serum anti-DNP-KLH IgM and IgG levels by 76 ± 8% and 70 ± 14%, respectively, indicating inhibition of BTK-dependent antibody responses. Although results did not reach statistical significance due to sample loss and variability in the control group (n=3), could still be considered valid as within the range of the mean IgM and IgG measured in other control groups of parallel studies.

Inhibition of human and rat MOG-specific antibody response in the EAE model

Two distinct EAE (experimental autoimmune encephalomyelitis) models in C57BL/6 mice were used to assess remibrutinib's effects: a B cell–dependent model induced by human MOG (myelin oligodendrocyte glycoprotein) and a B cell–independent model induced by rat MOG. In the human MOG model, remibrutinib (3 and 30 mg/kg) caused a small but statistically significant reduction in serum IgM and IgG levels, measured by ELISA. However, the modest antibody changes contrast with the observed clinical efficacy, suggesting B cell antigen presentation, rather than antibody production, drives pathology. In the rat MOG model, remibrutinib had no impact on serum IgM or IgG levels.

4.3.1.3. Safety pharmacology

A complete battery of standard safety pharmacology studies was conducted for remibrutinib. A summary of the studies performed, and the results obtained are displayed in the table below. All studies were conducted in accordance with GLP regulations except for an exploratory hERG channel study (Study 1314548) and in vivo 3-day cardiovascular assessment study in dogs treated with combination of remibrutinib and another potential development compound (Study 2070138).

Table 4: Summary of safety pharmacology studies conducted for remibrutinib

Study ID/ GLP	Study type	Test system	Concentration/ dose/ route	Major results
Study 1314548 Non-GLP	Cardiovascular hERG channel	In vitro HEK293 cells	0, 1, 3, 10, 30 µM	Remibrutinib inhibited dose-dependently hERG channel activity (IC_{50} = 11.7 µM).
Study 1470740 GLP	Cardiovascular hERG channel	In vitro HEK293 cells	0, 0.3, 1, 3, 10 µM	Remibrutinib inhibited dose-dependently hERG channel activity (IC_{50} = 1.4 µM (equivalent to 711 ng/mL)).
Study 1470741 GLP	Cardiovascular	Dog (Beagle) M, n=4	0, 50, 200, 450 mg/kg Oral (gavage)	**No effect** on arterial blood pressure, heart rate, core body temperature or ECG parameters
Study 2070138 Non-GLP	Cardiovascular	Dog (Beagle) M, n=4	400 mg/kg Oral (gavage) combination of remibrutinib with another potential development compound	Small (≤ 3%) increases in QTc interval on Study Days 2 and 3, reversible within 6 hours; no effect on heart rate, arterial blood pressure and body temperature
Study 1470738 GLP	CNS and respiratory	Crl:WI(Han) rats 10 F (CNS); 8 F (respiratory)	0, 100, 1000 mg/kg	**No effect** on central nervous system or respiratory function
Study 2220079	Similarity assessment between remibrutinib and known drugs of abuse	In silico	/	Remibrutinib not similar to known drugs of abuse defined under the US Controlled Substance Act (CSA)

4.3.1.4. Pharmacodynamic drug interactions

No dedicated non-clinical pharmacodynamic interaction studies were performed which is acceptable. As stated by the Applicant, remibrutinib acts at an intracellular level before degranulation of mast cells or basophils and release of inflammatory mediators. Therefore, no pharmacodynamic interaction is expected. In addition, H1-antihistamines do not affect B cell or platelet function.

4.3.2. Pharmacokinetics

The pharmacokinetic and toxicokinetic (TK) studies were performed in mouse, rat, rabbit and dog. ADME studies were conducted in the same animal strains as those used in toxicity studies using [^{3}H]- or [^{14}C]-radiolabelled drug. PK and TK studies were performed using non-radiolabelled remibrutinib. In vitro studies assessed plasma protein binding, blood-to-plasma distribution, protein adduct formation, and metabolism in both animal and human samples. These results were compared to human data to support species selection for toxicity studies and safety extrapolation to humans.

4.3.2.1. Absorption

Single dose studies

A total of 10 non-GLP single-dose studies were conducted to assess remibrutinib's absorption, bioavailability, and pharmacokinetics across mouse, rat, dog, and pregnant rabbit. Radiolabelled compound stability was confirmed with >95% radiochemical purity pre- and post-dosing. Oral absorption was rapid in all species (Tmax 0.25–2 h), while terminal half-life after i.v. dosing was short (0.2–1 h in rodents, up to 7 h in dogs), though possibly underestimated due to limited sampling. Absorption (based on total radioactivity) ranged from 37–78%, yet oral bioavailability remained low: 16% in mice, 7–29% in rats, and 2–5% in dogs, indicating significant first-pass metabolism. Blood clearance exceeded hepatic blood flow in rodents, suggesting extra-hepatic elimination, while volume of distribution was moderate (1–2.7 L/kg), implying tissue distribution. Inter-animal PK variability was moderate to high, but acceptable given oral administration. In rabbits, only oral data were available, preventing bioavailability calculation. Improved formulations (e.g., wet-media milled nanosuspensions) later achieved bioavailability up to 50% in dogs, highlighting formulation as a key factor influencing systemic exposure.

Repeated-dose studies – Toxicokinetics

Toxicokinetics measurements were performed as part of toxicity studies in mouse, rat, rabbit and dog using mainly a nanosuspension formulation. All TK studies used a single daily dose regimen.

In rats, absorption was rapid, with Tmax ranging from 0.5 to 4 hours. Females consistently showed higher exposure than males, ranging from 2- to 14-fold depending on the study and dose. Across 2-, 13-, and 26-week GLP studies (doses 30 to 1000 mg/kg/day), remibrutinib exposure generally increased with dose but often in an under-proportional manner. No significant accumulation was observed after repeated dosing, except in one combination study where up to 5-fold accumulation occurred. In carcinogenicity studies, females showed 4- to 16-fold higher exposure than males. Juvenile rats also demonstrated higher female exposure (4.3- to 9.6-fold), with proportional exposure increases between 30 and 300 mg/kg/day but decreased exposure at 1000 mg/kg/day in some males.

In Beagle dogs, remibrutinib was rapidly absorbed with Tmax between 0.5 and 2 hours across 10-day to 39-week studies (doses 10 to 450 mg/kg/day). Exposure increased dose-proportionally at lower doses but under-proportionally at higher doses, with no accumulation observed after repeated dosing. Female dogs showed 1.9- to 5.4-fold higher exposure than males in a 2-week study, but gender differences were less marked or absent in longer studies. In telemetry-instrumented dogs dosed at 400 mg/kg/day, Tmax was 1.5 hours, and exposure parameters were consistent with earlier studies.

Embryo-foetal development studies in rats (100 to 1000 mg/kg/day) and rabbits (100 to 450 mg/kg/day) showed rapid absorption with Tmax between 1 and 3 hours. In rats, exposure increased under-proportionally across doses, with AUC0-24 increasing approximately 2-fold from 100 to 1000 mg/kg/day. In rabbits, exposure increased dose-proportionally from 100 to 300 mg/kg/day but over-proportionally from 300 to 450 mg/kg/day, where mortality limited further analysis. Inter-animal variability was observed in rabbits, but individual AUC values were not available due to study design. The clear separation between the NOAEL (100 mg/kg/day) and LOAEL (300 mg/kg/day) and the non-overlapping mean AUCs indicate that this does not significantly affect the embryo–foetal risk assessment. Placental transfer was only studied in pregnant rabbits with unclear foetal tissue radioactivity, and the rat study lacked toxicokinetic data on remibrutinib transfer to offspring or maternal milk. Juvenile rat studies showed dose-proportional increases in exposure up to 300 mg/kg/day, with females exhibiting 4.9- to 7.2-fold higher exposure than males, and no accumulation was noted after repeated dosing.

4.3.2.2. Distribution

Blood/plasma distribution and plasma protein binding

In vitro blood distribution (concentration, temperature and time dependency), plasma protein binding (concentration dependency) as well as stability in blood and plasma of rat, dog and human were compared for remibrutinib and LTG751, an analogue of remibrutinib where the acrylamide moiety has been deactivated, to investigate the impact of the arylamide moiety which could lead to the covalent protein binding (study DMPK R1400850).

Remibrutinib and analogue LTG751 were stable in rat, dog, and human blood/plasma at 37 °C up to 2 h, with minimal covalent protein binding (<10%), supporting the reliability of blood distribution and plasma protein binding data.

Both remibrutinib and LTG751 were preferentially located in plasma of all species. Fractions in plasma (fp % – mean ± SD; range 100-10000 ng/mL) were as follows: Human (76.3 ± 3.02%) ≈ Dog (78.3 ± 2.71%) > Rat (66.7 ± 1.47%). The corresponding blood to plasma ratios were as follows (mean ± SD): Rat (0.915 ± 0.0202) > Human (0.813 ± 0.0321) > Dog 0.668 ± 0.0235).

Remibrutinib and LTG751 were highly bound to plasma proteins of all tested species. Plasma protein binding was concentration independent over the whole range of 10-10000 ng/mL and mean *fu* (fraction unbound) showed up to 2-fold differences between species for both compounds. No clear differences between both compounds were observed. Unbound fractions in plasma (fu,p) were as follows (mean ± SD): 10.2 ± 1.01% (Rat), 7.19 ± 0.597% (Dog) and 4.65 ± 0.583% (Human).

Tissue distribution in rat

Tissue distribution of remibrutinib-derived radioactivity was assessed in rats using QWBA with [^{3}H]-remibrutinib (3 mg/kg i.v. or 10 mg/kg p.o., up to 168 h; Study DMPK R1400753) and with [^{14}C]-remibrutinib (10 mg/kg p.o., up to 336 h; Study DMPK R1701246a).

After oral dosing of [^{3}H]-remibrutinib (10 mg/kg) in male albino rats, Tmax occurred between 0.5 and 2 hours in most tissues, indicating rapid distribution. The highest Cmax was in the small intestine wall, followed by the kidney, liver, and stomach, with tissue concentrations several-fold higher than blood. The greatest overall exposure (AUClast) was seen in kidney and liver tissues, while no radiolabel was detected in the brain, suggesting no blood-brain barrier penetration. Most tissues reached last measurable concentrations by 24 hours post-dose, with only liver and kidney retaining detectable levels at 168 hours, where the liver half-life was 70.5 hours. In pigmented rats, notable radiolabel accumulation was observed in the eye's choroid and ciliary body, which was significantly lower in albino rats.

Following a single oral 10 mg/kg dose of [^{14}C]-remibrutinib in partially pigmented rats (Study DMPK R1701246-a), radiolabelled components were widely distributed except in the brain, spinal cord, eye lens, and white fat, with Tmax at 0.5 h in females and 2 h in males. Highest Cmax values were seen in adrenal cortex, uveal tract/retina, GI mucosa, kidney cortex, and liver; AUClast was greatest in kidney medulla, pigmented skin, and small intestine mucosa, with tissue-to-blood AUC ratios ranging from 1.13–7.02 (males) and 2.02–11.3 (females). Radioactivity persisted in blood, kidney cortex, pigmented skin, and uveal tract up to 336 h, with longest half-lives in harderian gland (94.5 h, males) and adrenal medulla (96.9 h, females). Melanin-rich tissues retained radioactivity, suggesting partly reversible melanin binding. Overall, tissue distribution patterns were similar between sexes, though females showed ~2.6-fold higher Cmax and AUClast than males.

Study in Pregnant or Nursing Animals

The transfer of remibrutinib-related radioactivity was investigated by LSC in pregnant rabbits following a single p.o. dose of 10 mg/kg [^{14}C]-remibrutinib on gestation day 17 (study DMPK R2100372). At 168 h post-dose, remibrutinib-related radioactivity in liver (0.816 µM) and kidney (0.278 µM) was 13- and 4-fold higher, respectively, than in blood (0.0643 µM). While foetal tissue levels were below the limit of detection in two rabbits, a low detectable concentration (0.0325 µM) in one rabbit suggests potential foetal exposure, though the chemical nature of the radioactivity could not be determined due to low levels and poor recovery.

Other distribution studies

The melanin binding study (DMPK R1400849) showed that remibrutinib and its analogue LTG751 exhibit medium to high affinity for synthetic melanin. The CR values (ratio of the maximum binding capacity (Bmax) to the dissociation constant (Kd) of a binding site), ranged from 1.82–5.30, while chloroquine, as a positive control, showed much stronger binding (CR = 138).

In brain distribution studies (RD-2022-00247), Pgp-KO mice had significantly higher remibrutinib exposure in brain and CSF compared to wild-type mice, confirming that remibrutinib is a Pgp substrate with limited brain penetration (brain:blood ratio 0.01–0.06). Despite detectable levels in wild-type brain tissue, values were close to vascular contamination thresholds, suggesting minimal true brain penetration.

In a skin distribution study (DMPK R1500395), i.v. dosing of 3 mg/kg in mice showed rapid clearance of remibrutinib from blood (Tlast 2 h) and skin (Tlast 1 h), with skin:blood ratios of 0.697–1.29, indicating relevant distribution into skin.

4.3.2.3. Metabolism

Metabolism in vitro

In vitro metabolism of [^{3}H]-remibrutinib was studied using mouse, rat, dog, and human hepatocytes, and human liver microsomes. Profiles were analysed via UPLC with radioactivity detection and LC-MS for metabolite characterization (study DMPK R1400836).

In human liver microsomes, major oxidative metabolism involved N-demethylation and acrylamide moiety oxidation (M23, M24 [DWC499], M28, M31 [LQT456]). Minor pathways included O-dealkylation (M22 [LTP763]), N-oxidation (M29), C-hydroxylation (M15), and trace amide hydrolysis (M2 [LSX574]).

In hepatocytes, extensive metabolism yielded 31 metabolites, with remibrutinib recovery ranging from 0.15% (mouse) to 10.2% (human) after 6 h. Major pathways included glutathione conjugation at the acrylamide moiety, plus glucuronidation, sulfation, and N-acetylation alongside oxidative metabolism.

Assessment of reactive intermediate formation and covalent protein binding

The potential of remibrutinib to form reactive intermediates capable of binding covalently to proteins was tested in vitro by incubating remibrutinib and the analogue LTG751 with human liver microsomes, human hepatocytes, recombinant enzymes and rat, dog and human blood and plasma. Significant drug-protein adduct formation occurred in human microsomes and hepatocytes, primarily due to CYP3A4-mediated metabolic activation, with the acrylamide double bond identified as the key reactive site. However, the toxicological assessment did not identify any safety concerns. In plasma, time-dependent protein binding was observed even without metabolic activation, particularly in rats and dogs, while binding in blood was generally lower. SDS-PAGE and autoradiography confirmed covalent binding to a broad range of proteins, especially albumin in plasma, though specific targets remained unidentified.

Metabolism in vivo

The in vivo metabolism of remibrutinib was assessed in ADME or exploratory cold (no radiolabel) metabolism studies in mouse (DMPK R1870307-metid), rat (DMPK R1400753), DMPK R1701246-metid), rabbit (DMPK R2100372-metid), dog (DMPK R2000056-metid) and human (Study X2104).

While metabolic pathways were qualitatively similar across species, the quantitative contributions of remibrutinib and its metabolites to overall drug exposure varied. In humans and dogs, remibrutinib remained the most abundant circulating component, whereas in rats and rabbits it was a minor one. The main circulating human metabolite was a pair of diastereomers, M68a and M68b (EHT330), formed through a combination of amide hydrolysis, N-acetyl cysteine conjugation, and sulfoxidation, but each remained below 10% of total exposure. Across species, key metabolic pathways included: (i) inactivation via modification of the N-methyl acrylamide group, including glutathione conjugation and epoxide formation; (ii) O-dealkylation yielding metabolites like M22 (LTP763); (iii) amide hydrolysis forming M2 (LSX574) and its derivatives; and (iv) combinations of these with further phase I and II reactions such as sulfation and glucuronidation.

In mice, 24 metabolites were identified with M24, M19, and M65 as prominent, all previously seen in other species. In rats, M22 and M2 were dominant in blood and excreta, with significant metabolite formation via O-dealkylation, glutathione conjugation, and amide hydrolysis. The main metabolites in dog blood were M24 (Dihydrodiol), M22 (O-dealkylation) and M15 (C-hydroxylation), with relatively higher systemic exposure to some metabolites compared to humans. In rabbits the main circulating metabolites in blood were M2, M1, co-eluting M33 and M72, M15 and M68a,b. Notably, the amide hydrolysis pathway observed in other species (M2 (LSX574)) was absent in dogs. In pregnant rabbits, repeated dosing showed that unchanged remibrutinib constituted a small fraction of systemic exposure, with predominant metabolites including the amide hydrolysis product M2 and glutathione conjugates. Metabolite profiles in fetal and organ tissues were limited due to low radioactivity.

4.3.2.4. Excretion

Following single oral or intravenous doses of [^{3}H]- or [^{14}C]-remibrutinib, excretion studies in rats, rabbits, dogs, and humans showed that the primary route of elimination was via feces, with urine playing a secondary role. In rats, over 90% of the dose was recovered in feces within 168 hours, regardless of administration route, and biliary excretion was confirmed as the major pathway. Rabbits also excreted most of the dose fecally (77.2%) with 17% via urine, achieving nearly complete recovery. In dogs, fecal excretion dominated (73–76%), though total recovery was slightly incomplete (~89%), indicating slow or partial retention of radioactivity and prolonged excretion.

4.3.2.5. Pharmacokinetic drug interactions

No animal dedicated drug-drug interaction studies were conducted. Human in vitro and in vivo pharmacokinetic drug-interaction studies are presented in the clinical pharmacology section.

4.4. Toxicology

4.4.1. Single-dose toxicity

No dedicated single-dose toxicity studies were conducted. Acute toxicity information was obtained from repeat-dose toxicity studies in rats and dogs. In these studies, remibrutinib was well tolerated after

single administration up to the highest tested dose levels, i.e., up to 1,000 mg/kg in rats and 450 mg/kg in dogs.

4.4.2. Repeat-dose toxicity

GLP repeat-dose toxicity studies were conducted in rats (up to 26-week daily dosing; dose levels in 26-week rat study were 30, 300, and 1000 mg/kg/day) and dogs (up to 39-week daily dosing; dose levels in 39-week dog study were 10, 50, and 300 mg/kg/day). Non-GLP dose-range finding studies in rats and dogs were performed to guide the dose selection. TK was included in all repeat-dose toxicity studies, in addition to the following standard parameters: clinical signs, body weight, food consumption, ophthalmology, clinical pathology (haematology, blood clinical chemistry, urinalysis), macroscopic examinations, organ weight measurements as well as microscopic examinations on a standard list of organs and tissues. Micronucleus test was included in rat 2-week GLP study (see section 4.4.3.). Most of the repeat-dose toxicity studies included some specific assessments, such as immunophenotyping due to the role of BTK in immune cells, liver glutathione concentrations and a detailed haemostasis assessment due to the involvement of BTK in specific platelet functions (tail or buccal mucosa bleeding time, whole blood platelet aggregometry (collagen- and/or ADP-induced) and rotational thromboelastometry). Recovery was assessed only in rats, in the 2- and 26-week studies.

Generally, remibrutinib was well tolerated up to maximal achievable exposure in both species. Noteworthy alterations in both species, not considered adverse due to minor change or spontaneous findings without associated functional changes, were related to lymphoid tissues (low-grade decrease in germinal centre development and increase in sinusoidal red blood cells in mesenteric and mandibular lymph nodes) and liver (cytoplasmic brown pigment consistent with lipofuscin in hepatocytes and Kupffer cells). Alterations in standard (T/B/NK cells in rats; T/B cells in dogs) immunophenotyping were very variable across the studies of different duration, but were minor and reversible. No significant change in mature class-switched B cells was observed.

Assessments of effects of remibrutinib on bleeding time in rats (involving tail tip incision affecting large blood vessels) and dogs (involving buccal mucosa incision affecting small blood vessels) were included in the 2-week GLP repeat-dose toxicity studies only. Remibrutinib prolonged the rat tail bleeding time at all tested dose levels (doses ≥ 30 mg/kg/day). This alteration was considered adverse. No adverse or consistent effect of remibrutinib on bleeding time was observed in the dog mucosa bleeding assay up to the highest tested dose of 450 mg/kg/day. The prolongation of rat tail bleeding time was fully reversible within 2 weeks up to the highest tested dose of 1,000 mg/kg/day. The prolongation of rat tail bleeding time was associated with inhibited collagen-induced platelet aggregation and an increase in the ROTEM lysis index in blood samples. Nevertheless, platelets, red blood cell and coagulation parameters were not affected in both species. The effects of remibrutinib on bleeding time, platelet aggregation and ROTEM lysis index were followed-up in a series of four mechanistic studies (section 4.4.8.).

The effects observed only in rats included non-adverse (i) multinucleated hepatocytes (26-week study), (ii) hepatocellular hypertrophy and thyroid hypertrophy/hyperplasia accompanied by increased liver and thyroid weight (2-week, 13-week and 26-week study) and (iii) adrenal mononuclear inflammatory cell infiltrates (26-week study), and iv) adverse effects on endocrine pancreas (26-week study). Multinucleated hepatocytes are an adaptive response occasionally seen in toxicological studies with no consequences as known from aging rats in which such changes can be spontaneously observed; hepatocellular hypertrophy and thyroid hypertrophy/-plasia are adaptive changes of liver and thyroids to hepatic microsomal enzyme induction and increased hepatic clearance of thyroid hormones, while adrenal mononuclear inflammatory cell infiltrates are exacerbation of a specific

background change.

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 an increased incidence and severity of endocrine pancreas fibrosis, haemorrhage and pigment at all tested dose levels (i.e., 30, 300, and 1000 mg/kg/day). However, these changes were considered unlikely to translate to humans since they represented spontaneously occurring changes in aging rats, known to be exacerbated by BTK inhibitors with no translation to other species (Erickson et al 2017, Bhaskaran et al 2018). Exposure multiples were limited by maximal achievable exposure, i.e., in terms of steady-state AUC_{0-24h}, 15- to 79-fold (male/female) in rats and 77- to 146-fold (male/female) in dogs, and in terms of steady-state C_{max}, 7.2- to 46-fold (male/female) in rats and 58- to 88-fold (male/female) in dogs, compared to human exposure at the clinical dose of 25 mg b.i.d. remibrutinib.

4.4.3. Genotoxicity

Remibrutinib showed no evidence of genotoxicity in GLP *in vitro* (reverse mutation assay *in Salmonella typhimurium* strains TA98, TA100, TA1535, TA97a, and TA102; micronucleus tests in human peripheral blood lymphocytes) or *in vivo* (reticulocyte micronucleus test in rat blood) studies. *In vivo*, remibrutinib did not induce a statistically significant increase of micronuclei in rat peripheral blood reticulocytes up to the highest tested dose of 1,000 mg/kg/day, which translates into a 33- to 82- fold (male/female) and 65- to 84-fold (male/female) safety margin based on AUC_{0-24h} and C_{max}, respectively.

Based on hypothesis of B cell genomic instability associated with BTK pathways via enhanced expression of activation-induced cytidine desaminase (AID) (Compagno et al., 2017), a series of five non-GLP investigative *in vitro* micronucleus, chromosome aberration and gene mutation tests with BTK inhibitor ibrutinib and with the extended incubation time (up to 3 days vs. standard 1 day) revealed no evidence of genome instability despite enhanced AID expression.

4.4.4. Carcinogenicity

The carcinogenicity of remibrutinib was assessed in GLP studies in RasH2 transgenic mice (dose levels: 150, 500 and 1500 mg/kg/day) and in rats (dose levels: 30, 100 and 300 mg/kg/day). The following parameters were evaluated: clinical observations, body weight, food consumption, ophthalmology, macroscopic and microscopic pathology examinations. TK assessment was included in both studies. Doses for the 26-week Tg RasH2 mouse study were selected based on 5-day and 4-week dose-range finding studies. The selection of the maximum dose level in rat study was based on the observation from repeat-dose toxicity studies that a maximal feasible exposure in rats is reached with exposure saturation at doses above 300 mg/kg/day.

Remibrutinib was well tolerated up to the highest tested dose in the 26-week RasH2 transgenic mouse carcinogenicity study. No remibrutinib-related neoplastic changes were noted up to the highest tested dose of 1,500 mg/kg/day. Non-neoplastic low-grade alterations related to lymphoid tissues (decrease in germinal centre cellularity in spleen (in males at all tested dose levels; in females at the dose of 1500 mg/kg/day) and mesenteric lymph nodes (only in females at the dose of 1,500 mg/kg) and liver (hepatocyte cytoplasmic eosinophilic inclusions, karyocytomegaly, and/or multinucleated hepatocytes at doses ≥ 500 mg/kg/day with no morphologic evidence of infiltrates, degeneration or necrosis) were observed.

Remibrutinib was well tolerated up to the highest tested dose of 300 mg/kg/day in the 104-week rat carcinogenicity study. No remibrutinib-related neoplastic changes were noted up to the highest tested

dose of 300 mg/kg/day. Non-neoplastic remibrutinib-related alterations were observed in lymphoid tissues (increase in sinusoidal red blood cells, sinusoidal dilatation, focal angiomatous hyperplasia, diffuse reticuloendothelial hypertrophy/-plasia, and/or pigmented macrophages at all dose levels, i.e., doses ≥ 30 mg/kg/day, in mesenteric, mandibular, axillary, popliteal, and/or inguinal lymph nodes, correlating with a higher incidence of dark, red, and/or large lymph nodes), thyroid (marginal increase in severity of follicular cell hyperplasia at the 300 mg/kg/day dose), and pancreas (increase in fibrosis in pancreatic islets at all tested dose levels, i.e., doses ≥ 30 mg/kg/day).

Since no remibrutinib-related neoplastic changes were noted up the highest tested dose levels (1500 mg/kg/day in Tg RasH2 transgenic mice and 300 mg/kg/day in rats), the exposure multiples at these dose levels in terms of steady-state $AUC_{0\text{-}24h}$ were 58- to 144-fold (male/female) in RasH2 transgenic mice and 7.7- to 98-fold (male/female) in rats, and 53- to 68-fold (male/female) in RasH2 transgenic mice and 3.3- to 69-fold (male/female) in rats in terms of steady-state C_{max}, compared to human exposure at the clinical dose of 25 mg b.i.d. remibrutinib.

4.4.5. Developmental and reproductive toxicity

The reproductive and developmental toxicity of remibrutinib was assessed in a series of GLP studies: (i) a combined male and female fertility and early embryonic development (FEED) study in rats, (ii) embryo-foetal development (EFD) studies in rats and rabbits, and (iii) a pre- and postnatal development (PPND) study in rats. The highest tested dose was 1,000 mg/kg/day in the rat studies and 450 mg/kg/day in the rabbit study (doses > 450 mg/kg/day were generally not tolerated by pregnant rabbits). Additionally, juvenile toxicity was assessed in rats in a non-GLP DRF study from post-natal day (PND) 21 to PND 42 and in a GLP study from PND 19 to PND 68. Erroneously, dosing started two days earlier than planned in GLP juvenile toxicity study. Animals were planned to commence dosing on PND 21; however, after the in-life phase of the study was completed, a deviation was noted between the expected and actual age of the animals. Animals were confirmed to be 2 days younger than expected.

Fertility

In the combined FEED study, remibrutinib was administered at dose levels 100, 300 and 1000 mg/kg/day 4 weeks prior mating for at least 9 weeks to male rats and 14 days prior mating until gestation day (GD) 6. The following parameters were investigated: clinical signs, body weight, food consumption, mating, fertility indices and gross necropsy observations. Furthermore, oestrus cycles and pregnancies on GD 13 were assessed in females. TK assessment was not included.

Remibrutinib was generally well tolerated up to the highest tested dose of 1,000 mg/kg/day. Low incidence of transient clinical signs and slightly lower body weight gain in males at the dose of 1,000 mg/kg/day were not considered adverse. No remibrutinib-related changes in FEED parameters were noted up to the highest tested dose of 1,000 mg/kg/day, which translates to safety margins presented in section 4.4.2., since the study did not include TK assessment.

Embryo-foetal development

Pregnant rats and rabbits were dosed with remibrutinib (rats: 100, 300 and 1000 mg/kg day; rabbits: 100, 300 and 450 mg/kg/day) during the period of organogenesis. Clinical observations, body weight, food consumption were examined and gross necropsy was performed. Examinations of pregnancies and embryo-foetal development (gravid uterine weight, maternal performance, ovarian and uterine findings, foetal body weights, external/visceral/skeletal/fixed head examination of foetuses and foetal skeletal ossification) was assessed. The ovaries and uterus were examined for number and distribution of: corpora lutea, implantation sites, placentae (size, colour or shape), live and dead foetuses as well

as early and late resorptions. TK was included in all EFD studies. In rat, the selection of dose levels was guided by repeat-dose toxicity studies, while preliminary EFD study was performed to inform the dose level for pivotal rabbit study.

No remibrutinib-related maternal toxicity or effects on EFD were noted in rats up to the highest tested dose of 1,000 mg/kg/day, and in rabbits at a dose of 100 mg/kg/day in the GLP EFD studies, which represents NOAELs. The dose of 450 mg/kg/day was not tolerated by pregnant rabbits, and all pregnant rabbits of this dose group were terminated early (with no assessment of embryo-foetal development). At the dose level of 300 mg/kg/day, one pregnant rabbit was terminated early due to clinical signs of toxicity whereas maternal effects in the other pregnant rabbits in this dose group were only limited to lower food consumption during the dosing period. Furthermore, foetal external malformations (open/opaque eyes, small jaws and/or hyperflexion of the forelimbs) were observed in this study at 300 mg/kg/day. The foetal malformations were considered unlikely to be secondary to maternal toxicity, suggesting a teratogenic potential of remibrutinib in pregnant rabbits.

NOAEL-based safety margins for maternal toxicity and embryo-foetal development in the GLP embryo-foetal development studies were 126-fold in rats and 23-fold in rabbits in terms of steady-state AUC_{0-24h} and 67-fold in rats and 36-fold in rabbits in terms of steady-state C_{max}, compared to human exposure at the clinical dose of 25 mg b.i.d. remibrutinib.

Prenatal and postnatal development

The effects of remibrutinib (dose levels: 100, 300 and 1000 mg/kg/day) on the pregnant rat [clinical signs, body weight, food consumption, pregnancy indices, parturition and macroscopic examination on postnatal day (PND) 22] and the pre- and postnatal development of the F1 generation were evaluated following remibrutinib (dose levels: 100, 300 and 1000 mg/kg/day) administration to female maternal animals from implantation of the embryo (GD 6) to lactation day (LD) 21. The assessment of offspring (F1) development included three dedicated offspring (F1) cohorts with monitoring of clinical signs, body weight and food consumption until necropsy: (i) 20 animals/sex/group for post-natal development assessment (sexual maturity, pupillary reflex, acoustic startle response, locomotor activity, learning and memory), with subsequent reproductive performance assessment and macroscopic examinations at necropsy (males on PND 101-102; females on PND 88-102); (ii) 10 animals/sex/group for assessment of T cell-dependent antibody response (TDAR), followed by macroscopic examinations at necropsy on PND 84; (iii) 10 animals/sex/group for haematology, blood and spleen T/B/NK cell immunophenotyping and assessments of spleen weight and histopathology on PND 70. This study did not include TK neither in maternal animals nor in offspring. Milk excretion was not investigated.

No adverse effects were observed up to the dose level of 300 mg/kg/day. Remibrutinib induced adverse effects at the highest tested dose of 1,000 mg/kg/day, affecting maternal animals (moribundity and clinical signs of toxicity in two animals, slightly longer gestation lengths: mean 23.3 vs control mean of 23.0 and historical control mean 23.1) and offspring up to LD 1 (slightly higher mean number of stillborn, dead, or missing pups on LD 0/1, confined to three litters, and smaller mean litter size).

No adverse effects were noted for the surviving offspring developing into adulthood (including neurobehavior, sexual maturation/reproductive performance, and immune function). TDAR was normal, and immunophenotyping and spleen histopathology did not reveal an immunotoxic response. Minimally lower red blood cell mass as well as lymphocyte and white blood cell counts were observed within the haematology assessment, but were not considered toxicologically relevant.

If using TK data from the embryo-foetal development study in pregnant rats, the NOAEL dose of 300 mg/kg/day with steady-state exposure of 26,200 h.ng/mL (AUC_{0-24h}) and 4,410 ng/mL (C_{max}) in

maternal rats corresponds to safety margins of 67-fold (AUC_{0-24h}) and 68-fold (C_{max}) compared to human exposure at the clinical dose of remibrutinib 25 mg b.i.d.

Juvenile toxicity

In the non-GLP rat DRF juvenile toxicity study with dosing from PND 21 for 3 weeks, remibrutinib was well tolerated with no remibrutinib-related adverse findings up to 1000 mg/kg/day.

In the GLP rat juvenile toxicity study with dosing (100, 300 and 1000 mg/kg/day) from PND 19 for at least 7 weeks, remibrutinib was associated with marked unilateral enlarged and/or protruding eyes, requiring early termination of affected rats, in altogether 12 animals across all tested dose levels with no dose-dependency (5 at 100 mg/kg/day, 3 at 300 mg/kg/day, 4 at 1000 mg/kg/day). Therefore, a NOAEL was not established. This finding was considered primarily related to rat-specific anatomical and developmental circumstances such as anterior segment dysgenesis (persistent pupillary membranes, anterior synechia, abnormal pupil shape) and ocular immaturity (persistent hyaloid vessels) observed in a fraction of animals in this juvenile toxicity study. Anterior segment dysgenesis is a risk factor for disrupted aqueous humour drainage, and foetal remnants such as persistent hyaloid vessels increase the risk of spontaneous intraocular haemorrhages, eventually increasing intraocular pressure by mechanical obstruction of the trabecular meshwork and ultimately resulting in large/protruding eyes. Any spontaneous bleeding may be further favoured by experimental procedures (e.g. spontaneous haemorrhage during handling) and become uncontrolled in the presence of remibrutinib considering its inhibitory effect on certain platelet functions at pharmacologically relevant exposure. The predisposing factors for enlarged/protruding eyes in this study were considered further enhanced by the erroneously earlier than planned dosing start on PND 19 instead of PND 21 due to increased stress (and possibly higher blood pressure) as well as more immature ocular structures at dosing start. The terminal and recovery animals did not exhibit any remibrutinib-related change in the eyes.

With the exception of the eye-related observations in a subset of rats, remibrutinib was well tolerated up to the 1000 mg/kg/day, and no further adverse effects were observed (including clinical signs, body weight, food consumption, clinical pathology, developmental landmarks, oestrous cyclicity, femur length/density, sperm analysis, macroscopic and microscopic assessment). Additionally, no remibrutinib-related effects on neurobehavior were determined at the end of the 4-week recovery phase. Remibrutinib induced increased liver weights at all tested dose levels (i.e., ≥ 100 mg/kg/day) in females without any histopathological correlation. This change was reversible and not considered adverse. TDAR to KLH was inhibited and delayed when initiated during the dosing phase at all tested dose levels (i.e., ≥ 100 mg/kg/day) but not when initiated during the recovery period following the dosing phase. This in line with pharmacological effect of remibrutinib in B cells (i.e. BTK inhibition). In parallel, a mild increase in T cell subsets (total T cells, helper CD4+ T cells, and cytotoxic CD8+ T cells) and a mild decrease in B cell counts were noted in blood and spleen in animals from all dose groups. Since the effects on immune cell subsets and the TDAR were almost fully resolved by the recovery phase and were subject to a high degree of inter-animal variability also in the control groups, these findings were considered non-adverse and not toxicologically relevant. Exposures of 8,320 to 40,900 h.ng/mL (AUC_{0-24h}, males – females) and 642 to 8,980 ng/mL (C_{max}, males – females) at the highest tested dose of 1000 mg/kg/day correspond to exposure multiples of 21- to 105-fold (AUC_{0-24h}) and 9.9- to 138-fold (C_{max}) compared to the clinical dose of 25 mg b.i.d. in adults.

4.4.6. Toxicokinetics and exposure margins

Toxicokinetics measurements were performed as part of toxicity studies in mouse (Tg RasH2), rat, rabbit and dog. All TK studies used a single daily dose regimen. Remibrutinib was administered orally (gavage). Remibrutinib was rapidly absorbed in all species, with Tmax values ranging from 0.5 to 2 h

(dog), 3 h (mouse) or 4 h (rat). Generally, exposure to remibrutinib increased with the dose, but the relationship between dose and exposure was not strictly dose-proportional, especially at higher doses. In most studies, remibrutinib demonstrated an under-proportional increase in exposure with increasing dose. Across all studies, there was no indication of accumulation of remibrutinib after multiple administrations. Female animals consistently exhibited higher exposure levels than males (up to 16-fold difference for $AUC_{0\text{-}24h}$ in 104-week rat GLP carcinogenicity study).

The human-relevant safety margins based on total remibrutinib concentrations in blood are summarised in the table below. They are limited by maximal achievable exposure, which was the lowest in male rats. Average clinical steady-state exposure to remibrutinib at 25 mg b.i.d. in blood is 390 ng.h/mL ($AUC_{0\text{-}24h}$) and 64.9 ng/mL (C_{max}).

Table 5: Animal-to-human exposure multiples of 25 mg twice daily dose in humans

Species	NOAEL[b] (mg/kg/day)	Animal $AUC_{0\text{-}24}$ (ng.h/ml)		C_{max} (ng/ml)		Exposure Multiple[a]			
						Based on AUC		Based on Cmax	
		♂	♀	♂	♀	♂	♀	♂	♀
Repeat-dose toxicity									
Rat (26 week)	1,000[c] (300[d])	5,970	30,900	470	2,960	**15**	**79**	**7.2**	**46**
Dog (39 week)	300	30,000	57,100	3,790	5,680	**77**	**146**	**58**	**88**
Carcinogenicity									
Tg mouse	1,500[e]	22,600	56,200	3,410	4,410	**58**	**144**	**53**	**68**
Rat	300[e]	2,990	38,200	211	4,470	**7.7**	**98**	**3.3**	**69**
Embryo-foetal development									
Rat	1,000	-	49,200	-	4,370	-	**126**	**-**	**67**
Rabbit	100	-	8,990	-	2,360	-	**23**	**-**	**36**

[a] Based on mean steady-state exposure: human AUC0-24h = 390 ng.h/mL; human Cmax = 64.9 ng/mL (Source: Study A2201]. Note $AUC_{0\text{-}24h}$ value was derived by multiplying the AUC_{tau} (0-12h) value of 195 ng.h/mL by 2).
[b] NOAEL = no-observed-adverse-effect-level.
[c] this does not represent the NOAEL dose in rats due to adverse pancreas findings (at all tested dose levels) which are considered unlikely to translate to human; this dose is used for calculation of exposure multiples based on the 26-week rat study; similar exposure and related exposure multiples may also be assumed for the rat fertility and early embryonic development study with no adverse finding at any dose level up to 1,000 mg/kg/day.
[d] $AUC_{0\text{-}24h}$ at steady state (26 weeks) was higher at 300 mg/kg/day than at 1,000 mg/kg/day; therefore, the mid-dose TK data at 300 mg/kg/day is included in animal-to-human exposure multiples;
[e] Based on absence of remibrutinib-related neoplastic changes at highest tested dose levels.

No remibrutinib-related adverse effects were observed in the 39-week dog toxicity study (doses up to 300 mg/kg/day), and adverse effects on the endocrine pancreas observed at all tested dose levels in the 26-week rat toxicity study (doses up to 1,000 mg/kg/day) were considered unlikely to translate to human. Exposure multiples ranged from 15- to 146-fold in terms of steady-state $AUC_{0\text{-}24h}$.

Remibrutinib did not show evidence of carcinogenic potential in 26-week RasH2 transgenic mouse and 104-week rat carcinogenicity studies up to the highest tested doses of 1500 and 300 mg/kg/day, respectively, corresponding to exposure multiples ranging from 7.7- to 144-fold in terms of steady-state $AUC_{0\text{-}24h}$.

TK was not included in the rat combined male and female fertility and early embryonic development study with no adverse findings up to 1000 mg/kg/day. Similar exposure margins as those obtained in repeat-dose toxicity studies in rats may be assumed.

Remibrutinib induced maternal toxicity and/or foetal external malformations in pregnant rabbits at doses ≥ 300 mg/kg/day. The foetal malformations were considered unlikely to be secondary to maternal toxicity, suggesting a teratogenic potential of remibrutinib in pregnant rabbits and, thus, a potential risk to the foetus in pregnant patients. A NOAEL was established at the dose level of 100 mg/kg/day, resulting in a safety margin of 23-fold in terms of steady-state $AUC_{0\text{-}24h}$. No maternal toxicity or adverse effects on EFD were observed in the rat EFD study up to the highest tested dose of 1000 mg/kg/day, corresponding to a safety margin of 126-fold in terms of steady-state $AUC_{0\text{-}24h}$.

In the rat PPND study, remibrutinib induced adverse effects at the dose of 1000 mg/kg/day, affecting maternal animals and offspring up to LD 1. No adverse effects were noted at doses up to 1000 mg/kg/day for the surviving offspring developing into adulthood (including neurobehavior, sexual maturation/ reproductive performance, and immune function). A NOAEL was established at the dose level of 300 mg/kg/day, resulting in a safety margin of 67-fold in terms of steady-state $AUC_{0\text{-}24h}$ (when using TK data in pregnant rats from the rat EFD study since no TK was included in the PPND study).

Important potential risks at pharmacologically relevant exposure are related to effects of remibrutinib on primary antibody responses (potential risks of infection, impact on at least some antibody responses) as well as on specific platelet functions (potential risk of bleeding).

4.4.7. Local tolerance

No dedicated studies to evaluate local tolerance by the intended therapeutic route (oral) were conducted. Remibrutinib did not show any sign of local tolerance issues upon oral administration, i.e., no gastrointestinal irritation in any non-clinical toxicity study up to maximal achievable exposure, including repeat-dose toxicity studies up to 26 weeks in rats and 39 weeks in dogs.

Furthermore, in the context of occupational health hazard assessment, remibrutinib did not show any skin irritating or sensitizing potential *in vitro* (human skin model based on OECD Guideline 439) or *in vivo* (murine local lymph node assay based on OECD Guideline 429).

4.4.8. Other toxicity studies

Antigenicity

No dedicated studies to evaluate antigenicity were conducted. Standard assessment, as well as immunophenotyping, in various toxicity studies did not point towards antigenicity of remibrutinib.

Immunotoxicity

No dedicated immunotoxicity studies have been conducted for remibrutinib. Remibrutinib inhibited primary antibody responses to certain, but not all, tool antigens in rodent pharmacology studies at pharmacologically relevant exposure, considered related to the role of BTK in B cells. Remibrutinib did not cause re-activation of Mycobacterium tuberculosis in a 3D in vitro human granuloma model. Alterations in blood immunophenotyping in repeat-dose toxicity studies were limited to minor decreases in B cell subsets at all dose levels, with no significant changes in mature class-switched B cells, and minor increase in T cell subsets. No effects on blood standard (T/B/NK cells) immunophenotyping or antibody responses were observed in the offspring (F1 generation) in the rat PPND study in which maternal animals received up to 1000 mg/kg/day remibrutinib from GD 6 to LD 21.

Dependence

No dedicated studies to evaluate abuse liability/dependence were conducted. Remibrutinib showed no

distribution to the brain in a rat QWBA study (section 4.3.2.2.). In a mouse PK study that measured remibrutinib in brain homogenate and CSF, no clear evidence for brain penetration was observed (section 4.3.2.2.). Even in a scenario, where the blood-brain barrier may be compromised and remibrutinib may exert pharmacodynamic effects (i.e., BTK inhibition) in the CNS as demonstrated in a mouse EAE model (section 4.3.1.2.), it is not expected that remibrutinib has liability for drug abuse or dependence. In vitro investigations indicated an inhibitory potential on the CNS off-target VMAT-2 at high concentrations (IC50 = 13 µM) (section 4.3.1.2.). Any relevant activity of remibrutinib on VMAT-2 under pharmacological conditions is considered unlikely. No other CNS off-target was identified. An *in silico* assessment demonstrated that remibrutinib is not similar to any known drugs of abuse (defined under the US Controlled Substances Act (CSA)) (section 4.3.1.3.).

No effects of remibrutinib on CNS function were observed in a dedicated GLP single-dose CNS safety pharmacology assessment in rats at doses up to 1000 mg/kg (section 4.3.1.3.). Furthermore, no CNS-related effects of remibrutinib were noted in repeat-dose toxicity studies up to 26 weeks in rats and up to 39 weeks in dogs up to maximal achievable exposures (section 4.4.2.). In summary, no relevant potential for abuse/dependence was identified.

Studies on metabolites

No metabolite had an exposure of > 10% of the overall AUC in human blood, i.e., no major metabolites were produced. Although metabolism is extensive, the main metabolic pathways observed were similar across species. Therefore, human metabolites have been assessed in the toxicology studies with remibrutinib and no toxicology studies with metabolites were required.

Nevertheless, the aniline moiety-containing metabolite M2 was assessed in an early non-GLP in vitro mutagenicity screen based on Salmonella typhimurium strains TA98 and TA100 and did not show evidence of a mutagenic potential. Furthermore, metabolite M68 (= diastereomers M68a and M68b), quaternary metabolites containing the identical aniline moiety as M2, was evaluated *in silico* for potential mutagenic properties in comparison to M2. Based on the *in silico* assessment, M68 was considered as non-mutagenic, in line with M2.

Studies on impurities

Actual and potential impurities were assessed by applying computational (Q)SAR methodologies following the ICH M7(R2) recommendations. The *in silico* analysis was performed using knowledge-based (Derek Nexus) and statistical-based (Sarah Nexus) systems. A second statistical system (Case Ultra) was used when support to the expert review of results obtained from Derek Nexus and Sarah Nexus was needed. Impurities with a structural alert for mutagenicity were either assessed based on available literature data or tested in a bacterial mutagenicity (Ames) test. All mutagenic impurities are controlled below the TTC of 1.5 µg/day.

There are 5 potential N-nitrosamines potentially present in remibrutinib. Of these, there are 3 nitrosamine impurities with acceptable intakes provided by regulatory authorities (EMA, FDA). Carcinogenic Potency Categorisation Approach (CPCA) was used to derive an AI for the forth nitrosamine impurity, which fell into the category 2, with an AI of 100 ng/day. For an active substance related nitrosamine impurity, the proposed AI of 100 ng/day was established based on read-across to an appropriate surrogate molecule, with regulatory established limit of 100 ng/day, based on the most sensitive TD50 derived from the most robust TD50 dataset from carcinogenic potency database (CPDB) or Lhasa Carcinogenicity Database (LCD).

Phototoxicity studies

Within sunlight range, remibrutinib shows relevant light absorption in the UVB and UVA range (maximum molar extinction coefficient of 18,087 M-1 cm-1 at 290 nm, measured in methanol).

Therefore, the phototoxic potential of remibrutinib was further assessed. Remibrutinib did not show any phototoxic potential in the GLP in vitro 3T3 Neutral Red Uptake (NRU) phototoxicity test.

Mechanistic studies on haemostasis

A serie of 4 non-GLP mechanistic studies was conducted as a follow-up to the effects of remibrutinib on bleeding time, platelet aggregation, and ROTEM lysis index observed in the GLP 2-week rat repeat-dose toxicity study. They included a 3-day in vivo evaluation of haemostatic effects in rats, an in vitro evaluation of haemostatic effects in rat and dog whole blood, and two in vitro studies evaluating and characterising haemostatic effects in human whole blood.

Remibrutinib prolonged the rat tail bleeding time at pharmacologically relevant exposure. A full effect was observed even at the lowest tested dose of 0.15 mg/kg/day within 3 days with mean blood BTK occupancy of 73%. Reversibility within 3 days was limited, correlating with blood BTK occupancy (improvement at mean blood occupancy of 33%).

Consistent with the role of BTK in specific platelet functions, remibrutinib inhibited collagen-induced platelet aggregation and caused an increase in the ROTEM lysis index at pharmacologically relevant exposure in blood samples from rats dosed with remibrutinib in vivo. Similarly, remibrutinib inhibited collagen-induced platelet aggregation and caused an increase in the ROTEM lysis index in rat, dog, and human whole blood (in vitro), suggesting translatability across species. The inhibition of collagen-induced platelet aggregation has previously been described in humans treated with ibrutinib, which can be explained by the central role of BTK in glycoprotein VI signalling. Although in the 3-day rat study a trend towards correlation between mean BTK occupancy and mean whole blood aggregation and tail bleeding time appeared possible on group basis, at an individual animal basis, the relationship of these changes and exposure to remibrutinib in blood or with BTK receptor occupancy in blood or spleen was not obvious, suggesting that other factors than inhibition of collagen−induced platelet aggregation might be involved in prolongations in tail bleeding time. The increase in LI45 and LI60 in thrombelastometry may indicate either decreased fibrinolysis or impaired clot retraction. Further mechanistic investigations in human whole blood indicated that the effects of remibrutinib on the ROTEM lysis index were due to disturbances in platelet function, since remibrutinib increased lysis index parameters in the ROTEM EXTEM test in which functional platelets were present, but not in the ROTEM FIBTEM test, in which platelet function was inactivated. Hence, remibrutinib most likely inhibits clot retraction. These platelet effects (inhibition of collagen-induced platelet aggregation and increase of the ROTEM lysis index) correlated with blood BTK occupancy and B cell inhibition based on IC50/EC50 comparisons.

Combination toxicity studies

Three 13-week GLP rat repeat-dose combination toxicity studies of remibrutinib with other compounds were submitted because they included groups of animals which received remibrutinib alone, either at a dose of 200 mg/kg/day or at 300 mg/kg/day.

Remibrutinib was well tolerated at dose levels of 200 or 300 mg/kg/day in the 13-week rat oral (gavage) combination toxicity studies. Besides few inconsistent alterations, i.e., reversible minimal-to-moderate haemorrhage in sublingual salivary gland or low-grade presence of pigment in adrenal cortex or macrophages in pancreatic islets and lymph nodes, unique to single studies and not considered adverse, alterations related to endocrine pancreas, lymphoid tissues, thyroids, liver, and adrenals were consistent with changes in the 13- and/or 26-week repeat-dose toxicity studies in rats.

4.4.9. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) for remibrutinib was prepared in accordance with the principles of the EMA "Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr 1, February 2024).

The PECsw for remibrutinib is 0.25 µg/L. Since this value exceeded the threshold for further investigations, the assessment proceeded to Phase II- Tier A.

Remibrutinib remains predominantly non-ionized at environmental pH (5 - 9), with an estimated pKa of 4.1. It has low water solubility and moderate lipophilicity (log D: 3.1–3.2). While the basic pKa was determined experimentally, the acidic pKa (~12) could not be confirmed due to limitations of the experimental range.

The n-octanol/water partitioning behaviour of remibrutinib was investigated through the performance of a partition coefficient study using the shake-flask method (OECD 107). The log KOW was determined at environmentally relevant pH-range (at 3 pH values ranging from pH 5 to 9). Given the log Kow values of 3.1 to 3.2 were <4.5, it was concluded that no further screening for persistence, bioaccumulation, and toxicity was necessary. As these log Kow values were >3, a bioconcentration study in Tier B was triggered.

With 1% degradation within 28 days, remibrutinib is considered as not readily biodegradable compound.

In an OECD 308 aerobic water–sediment study (Study 20220285), remibrutinib dissipated rapidly from the water phase (DT_{50}: 3.0–3.7 days at 20 °C; 6.5–7.9 days at 12 °C). It progressively partitioned to sediment, where non-extractable (bound) residues increased up to ~47–51% by Day 100, mainly associated with humic substances. Total system DT_{50} values were 56.9 days (Calwich Abbey Lake) and 16.1 days (Golden Lake), corresponding to 121.5 and 34.4 days at 12 °C, indicating persistence under these conditions. Mineralisation and volatilisation were low. No metabolite exceeded 10% AR; only metabolite M6 (N-[2-[4-amino-6-(3-amino-5-fluoro-2-methyl-phenyl)pyrimidin-5-yl]oxyethyl]-N-methyl-prop-2-enamide) exceeded 5% AR and declined toward the end of the study. In an OECD 106 study (Study 20220284), the adsorption and desorption behavior of ^{14}C-remibrutinib was assessed in three soils and two sludges. Adsorption equilibrium was reached within 24 hours (48 h for one soil), with 78.7–89.2% AR adsorbed in soils and 72.2–79.1% AR in sludges. Mean Koc values ranged from 1900 to 7919 mL/g in soils and 352 to 660 mL/g in sludges, indicating low to very low mobility. Desorption was limited (5.8–14.7% AR in soils; 16.6–21.9% AR in sludges), and Koc,des values ranged from 3323 to 15013 mL/g in soils and 401 to 741 mL/g in sludges. The highest Kd value in soil (166 mL/g) was used for PECsed calculation.

Although Freundlich adsorption isotherms (KF and KFoc) were not determined, the study relied on Kd and Koc values. Remibrutinib is not expected to be mobile in terrestrial compartments, and a terrestrial risk assessment is not triggered.

In an OECD 305 study (Study 20220290), the bioconcentration potential of ^{14}C-remibrutinib was assessed in Rainbow Trout (Oncorhynchus mykiss) under flow-through conditions at nominal concentrations of 0.5 and 5 µg/L. Measured concentrations averaged 0.509 µg/L (low dose) and 4.435 µg/L (high dose), with >91% of the radioactivity corresponding to parent remibrutinib. No mortality occurred during the exposure phase. Radioactivity was below the limit of quantification (LOQ) in all low-dose fish, and detectable in only 3 of 24 fish from the high-dose group. Resulting steady-state BCFs were <2 L/kg (LD) and <1 L/kg (HD), indicating very low bioaccumulation potential.

In an OECD 210 study (Study 20220286), the early life stage toxicity of remibrutinib was evaluated in fathead minnow (Pimephales promelas) over a 32-day exposure period under flow-through conditions.

No treatment-related effects on hatching success, growth, or development were observed up to the solubility limit of the substance (2.0 mg/L). A statistically significant but minor increase in mortality (3.8%) was observed at the highest concentration compared to 0% in pooled controls. Based on these results, the NOEC for juvenile survival and overall effects was determined to be 0.68 mg/L (mean measured concentration), with a LOEC of 2.0 mg/L.

In a 21-day OECD Test Guideline 211 reproduction study (Study 20220287), Daphnia magna was exposed to remibrutinib at time-weighted mean concentrations of 0.021–2.1 mg/L. Survival was ≥90% at all concentrations, with no treatment-related mortality (NOEC for survival ≥2.1 mg/L). Reproduction was reduced by 22% at 2.1 mg/L (solubility limit), establishing a NOEC of 0.64 mg/L and a LOEC of 2.1 mg/L. The EC_{10} for reproduction was 0.91 mg/L; the EC_{50} was above the highest concentration tested. Effects on reproduction below 0.64 mg/L and on body length were not considered biologically relevant due to the lack of a dose–response relationship.

In a 72-hour algal growth inhibition study conducted according to OECD Test Guideline 201 (Study 20274608), Raphidocelis subcapitata was exposed to remibrutinib at measured concentrations up to 2.5 mg/L (saturated solution). Test concentrations were generally stable, except for a decline at the highest level. No statistically significant effects on growth rate or yield were observed at any concentration, and cell morphology remained normal. The 72-hour NOEC for both growth rate and yield was 1.7 mg/L, corresponding to the maximum solubility in the test medium.

In a study 20274610 (OECD 209 – Activated Sludge, Respiration Inhibition), remibrutinib caused no inhibition of respiration in activated sludge at 10 and 100 mg/L, and only 6% inhibition at 1000 mg/L. The NOEC was determined to be 1000 mg/L, and the EC_{50} was >1000 mg/L, indicating no toxicity to wastewater microorganisms under the test conditions.

In a 28-day sediment toxicity study conducted according to OECD Test Guideline 218 (Study 20220288), Chironomus riparius larvae were exposed to remibrutinib at 62.5–1000 mg/kg dry weight sediment. No statistically significant effects on emergence or development were observed at any concentration. The NOEC for both endpoints was 1000 mg/kg dw, with a LOEC >1000 mg/kg, indicating no toxicity at the highest concentration tested.

In the PNEC calculation the applicant did not normalize the NOEC results from the sediment toxicity tests to the standard sediment with an organic carbon (OC) content of 10%, as specified by the guideline. The organic carbon content in the sediment used in the study was 3.05 ± 0.25%. According to the guideline, toxicity results from sediment tests should be recalculated to account for this difference in organic carbon content, ensuring consistency in risk assessment. The applicant confirmed that remibrutinib's adsorption to soil does not correlate with organic carbon, presenting the Kd values of remibrutinib for the different substrates and using the Excel tool *Input_Decision* recommended in the guideline.

All calculated PEC:PNEC ratios were below trigger values for each compartment, so further evaluation (Tier B) is not required.

The applicant performed a targeted literature review on endpoints of significance to the ERA. Details of the review are provided in the ERA. No relevant study was identified.

Table 6: Summary of main study results: Phase I

Substance (INN/Invented Name):	remibrutinib		
CAS-number (if available):	1787294-07-8		
PBT/vPvB screening			
Study type	***Test protocol***	***Result***	***Conclusion***
Bioaccumulation potential-log Dow	OECD107	3.1 at pH 5 3.1 at pH 7 3.2 at pH 9	Potential PBT: N
PBT/vPvB assessment			
Property	***Parameter***	***Result***	***Conclusion***
Bioaccumulation	log Kow	3.1 at pH 7	
	BCF	<2 L/kg_{ww}	Not B
Persistence	Ready biodegradability	N	potentially P
	$DT_{50,total}$ at 12°C	121.5 d	P
Toxicity	$NOEC_{aquatic}$	0.64 mg/L	not T
PBT/vPvB statement:	Remibrutinib is considered to be not PBT, nor vPvB.		

Phase I			
Parameter	***Value***	***Unit***	***Conclusion***
PECsw, *default*	0.25	µg/L	≥ 0.01 threshold: *Y*
Other concerns (e.g. chemical class)			N

Table 7: Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	***Test protocol***	***Result***	***Remarks***
Water solubility	OECD 105	2.19 mg/L at 20ºC	Column elution method
Dissociation in Water		pK_a = 4.03*	Non-ionized across pH range 5-9 *determined for the basic site of the pyrimidine ring, the acid pKa of the secondary amine was out of the experimentally accessible range
Adsorption-Desorption Soil 1 = sandy clay	OECD 106	$K_{OC,\ soil\ 1}$ = 1900 L/kg	

Soil 2 = loam		$K_{OC, soil\ 2}$ = 7919 L/kg	
Soil 3 = sandy loam		$K_{OC, soil\ 3}$ = 5211 L/kg	
Sludge 1 = municipal		$K_{OC, sludge\ 1}$ = 660 L/kg	
Sludge 2 = municipal		$K_{OC, sludge\ 2}$ = 352 L/kg	
Ready Biodegradability Test	OECD 301B	1 % (28 d) not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = silt	OECD 308	$DT_{50, water\ 1}$ = 6.5 d $DT_{50, whole\ system\ 1}$ = 121.5 d CO_2 = 1.2 % NER_{total} = 46.7 %	12°C CO_2 and NER values at test end
Sediment 2 = sand		$DT_{50, water\ 2}$ = 7.9 d $DT_{50, whole\ system\ 2}$ = 34.4 d CO_2 = 1.5 % NER_{total} = 50.8 %	12°C CO_2 and NER values at test end
Transformation products		>10% = N *TP1 (max) = 6.2 %	TP1 reached ≥5% AR at two or more consecutive sampling intervals at day 70, sed 1 identity: N-[2-[4-amino-6-(3-amino-5-fluoro-2-methyl-phenyl)pyrimidin-5-yl]oxyethyl]-N-methyl-prop-2-enamide

Phase II Aquatic effect studies

Study type	***Test protocol***	***Endpoint***	***Value***	***Unit***	***Remarks***
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	NOEC	1.7	mg/L	growth rate
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	NOEC / EC10	0.64 / 0.91	mg/L	reproduction
Fish, ELS/ *Pimephales promelas*	OECD *210*	NOEC / EC 10	0.68 / 2.0	mg/L	Reproduction, survival, growth rate
Activated Sludge, Respiration	OECD 209	NOEC	1000	mg/L	total respiration

Inhibition Test					
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD 218	NOEC	*1000**	*mg*/kg_{dw}	development, emergence, *not normalised to 10% o.c.
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	2.5 µg/L	100000 µg/L	0.000025		No risk
Surface water	0.25 µg/L	91 µg/L	0.0027		No risk
Groundwater	0.0625 µg/L	9.1 µg/L	0.0069		No risk
Sediment	42.4 µg/kg_{dw}	10000 µg/kg_{dw}	0.00424		No risk / Risk

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Pharmacology

Remibrutinib (LOU064) is a selective, covalent BTK inhibitor under development for CSU and other immunological diseases. It forms an irreversible covalent bond with the conserved cysteine residue (Cys481) in ATP binding site of BTK, which is predominantly expressed in immune cells such as B cells, mast cells, basophils, macrophages, and microglia (Angst et al, 2020). By targeting BTK, remibrutinib disrupts key intracellular signalling pathways activated downstream of immunoglobulin receptors, particularly the B cell receptor (BCR), FcεRI, and FcγR, which are implicated in inflammatory and autoimmune processes. The clinical relevance of mast cell and basophil degranulation via IgE and FcεRI as a key pathophysiological mechanism in CSU has been substantiated in the literature, supporting the biological plausibility and therapeutic rationale for targeting BTK inhibition in the treatment of CSU.

Primary pharmacodynamics – in vitro

The primary in vitro pharmacodynamic profile of remibrutinib was characterised using biochemical and cellular assays for BTK inhibition. In enzymatic kinase assays, remibrutinib showed potent BTK inhibition with IC_{50} values of 1.3 nM (no pre-incubation) and 0.6 nM (15-min pre-incubation), indicating higher affinity for unphosphorylated BTK. Interpretation of pre-incubation effects was limited by unreliable data from one laboratory. Rapid covalent binding limited kinetic analyses, while near-complete BTK occupancy in blood after 24 hours supported durable target inhibition. The irreversibility of binding was not further confirmed by confirmatory methods, but was not considered critical given the observed occupancy.

Remibrutinib demonstrated high in vitro selectivity (>200-fold) over related kinases (TEC, BMX, ITK, TXK). Cellular BaF3 assays showed minimal off-target activity on BMX. Considering the low free drug concentrations (6 nM), clinically relevant inhibition of TEC or BMX (IC_{50} = 124 nM and 141 nM,

respectively) is unlikely. Only human BTK was tested in vitro, which was considered acceptable due to the high conservation of the ATP-binding domain across species. Compared with other BTK inhibitors, remibrutinib showed comparable potency with improved selectivity, including sparing of EGFR, JAK3 and HER2. Functional cellular assays demonstrated inhibition of BTK-dependent Fc receptor signalling, including suppression of FcγR-induced IL-8 secretion in THP-1 monocytes and FcεRI-mediated basophil degranulation, with variability mainly attributed to donor-related factors. Remibrutinib inhibited BTK phosphorylation and downstream signalling in B cells across species, with no effect on T-cell activation. Overall, the in vitro data support remibrutinib as a potent and selective covalent BTK inhibitor with pharmacological relevance for CSU.

Primary pharmacodynamics – in vivo

Remibrutinib was profiled across a series of rodent PK/PD mechanistic models and complex disease models (rat SRBC model, mouse PCA model, mouse RPA model) to establish its in vivo pharmacologic profile.

BTK target occupancy

The PD effects of remibrutinib were measured by BTK target occupancy, initially driven by systemic drug exposure, with duration dependent on the turnover of the BTK-drug complex and synthesis of new BTK. In rats, sustained BTK occupancy was observed in the spleen following dosing, while lower occupancy was noted in peripheral blood, consistent with differences in BTK turnover, cellular composition, and metabolic activity between compartments. However, no data were provided on BTK occupancy in hematologic target cells, despite the spleen containing multiple BTK-expressing cell types. Thus, contributions from these cells and platelets to remibrutinib's on-target effects cannot be excluded. Although remibrutinib inhibits BTK in B cells without affecting T cell activation (in vitro study), haemorrhage and infections remain identified risks, in line with the class effects of BTK inhibitors. In the context of CSU, Section 5.1 was updated to identify mast cells and basophils as key mediators of the therapeutic effect, while not excluding potential involvement of other BTK-expressing cell types such as platelets, B cells, or macrophages.

In vivo models

A relationship between remibrutinib PK, tissue BTK occupancy, and PD efficacy was demonstrated in a rat model of antibody response to sheep red blood cell immunisation, where oral dosing reduced IgM-secreting B cells in the spleen. The drug's PD was also evaluated in mouse skin anaphylaxis models, including passive cutaneous anaphylaxis (PCA) and reverse passive Arthus (RPA). In the PCA model, high BTK occupancy in the spleen was observed across doses, but dose-dependently reduced skin edema only under low IgE conditions, with no significant effect under high IgE doses likely due to FcεR-independent pathways. In the RPA model, remibrutinib produced dose-dependent inhibition of skin swelling, consistent with BTK occupancy and systemic exposure, with a transient duration of effect in skin. For the in vivo PCA and RPA studies, the lack of a sensitive method to measure skin BTK occupancy was noted, but the Applicant claimed that skin BTK occupancy kinetics are expected to be similar to spleen. The Applicant further suggested that the observed differences in efficacy between spleen and skin at lower doses may be explained by lower perfusion in the skin. Despite this, the discrepancy is not considered critical to the overall PD model and was not pursued by the CHMP. The findings support remibrutinib's anti-inflammatory activity in relevant tissues. These results align with the drug's mechanism as a BTK inhibitor modulating immune and inflammatory responses. Overall, the data validate remibrutinib's in vivo pharmacodynamics in CSU.

Secondary pharmacodynamics

In vitro

Secondary PD studies showed that remibrutinib is selective for its primary target, BTK, with minimal off-target effects, including negligible effects on PI4Kβ and BSEP at concentrations well above therapeutic levels. No inhibition of EGFR phosphorylation was observed, indicating a low risk of off-target kinase interactions. At the intended clinical dose of 25 mg b.i.d., the average unbound plasma Cmax of remibrutinib (Study DMPK R2301014) is more than 20-fold lower than the IC_{50} of the identified off-targets, providing an adequate safety margin and indicating minimal risk of off-target effects.

Remibrutinib inhibited collagen-induced platelet aggregation at low concentrations, consistent with BTK's role in platelet activation. The drug exhibited low cytotoxicity in monocytic and bone marrow cells, suggesting minimal hematopoietic toxicity at relevant doses. In a *Mycobacterium tuberculosis* 3D granuloma model, remibrutinib promoted bacterial dormancy without reactivation.

In vivo

In vivo studies demonstrated that remibrutinib effectively inhibits BTK-dependent B-cell antibody responses, significantly reducing IgM and IgG production by about 70% in a T-dependent antigen model (DNP-KLH) at 30 mg/kg b.i.d. However, antibody responses to myelin oligodendrocyte glycoprotein (MOG) in an autoimmune encephalomyelitis model were only marginally affected at the same dose, likely due to differences in antigens and adjuvants used. These findings highlight remibrutinib's clear immunomodulatory effects in B cell–dependent settings, with variability depending on the immune context. The results support and complement earlier in vitro data on remibrutinib's impact on humoral immunity. Despite some variability, the overall data confirm its ability to suppress primary antibody responses in vivo.

Overall, remibrutinib is considered a selective BTK inhibitor. Its off-target effects are mainly associated with inhibition of platelet function and B cell humoral response.

Safety pharmacology

A core battery of safety pharmacology studies in accordance with ICH S7A and ICH S7B requirements was performed to evaluate in vitro and in vivo effect of remibrutinib on the CNS, CV, and respiratory systems.

Cardiovascular

Cardiovascular safety studies of remibrutinib included two in vitro assessments on ion channels (hERG, Nav1.5, Cav1.2, KCNQ1) and two in vivo studies in male Beagle dogs evaluating ECG, heart rate, blood pressure, and temperature. The GLP study indicated hERG inhibition at concentration which was over 230-fold higher than the unbound clinical Cmax, providing a wide safety margin. In a GLP single-dose dog study, remibrutinib was well tolerated at high doses with no adverse cardiovascular effects or mortality. A non-GLP 3-day study also demonstrated good tolerability, with only minor, sporadic, and reversible QTc changes considered unrelated to treatment. Chronic toxicity studies and clinical data did not reveal cardiovascular safety concerns or clinically relevant QTc effects.

Central nervous and respiratory systems

No CNS effects were observed in GLP in vivo safety or repeat-dose toxicity studies in rats and dogs at exposures well above clinical levels. In a GLP single-dose study in female rats, remibrutinib at high doses had no significant impact on CNS or respiratory function, with only minor, biologically insignificant changes in respiratory parameters at the highest dose. Additionally, *in silico* assessments indicated no structural similarities between remibrutinib and known drugs of abuse.

Pharmacodynamic drug interactions

No dedicated non-clinical pharmacodynamic interaction studies were performed which is acceptable. As stated by the Applicant, remibrutinib acts at an intracellular level before degranulation of mast cells or basophils and release of inflammatory mediators. Therefore, no pharmacodynamic interaction is expected. In addition, H1-antihistamines do not affect B cell or platelet function.

Pharmacokinetics

Absorption

Single dose studies

After oral dosing, remibrutinib was rapidly absorbed across species (mouse, rat, dog, and rabbit). Terminal half-life was short to moderate, and oral bioavailability was low in preclinical species due to high first-pass metabolism, whereas absorption in humans was high. Clearance was generally high, with moderate volume of distribution and moderate to high pharmacokinetic variability after oral dosing, which is expected. Intra-colonic administration or improved formulations increased systemic exposure, with nanosuspension formulations raising bioavailability up to approximately 50% in dogs and supporting use in pivotal GLP toxicology studies.

Repeated-dose studies – Toxicokinetics

TK of remibrutinib after oral dosing were primarily evaluated within repeat-dose toxicity, carcinogenicity, and DART studies in mice, rats, rabbits, and dogs. Across species, oral absorption was generally rapid, with Tmax typically occurring within a few hours. Exposure increased with dose but was frequently nonlinear, with under- or over-proportional increases observed in mice, rats, and rabbits, suggesting nonlinear pharmacokinetics and potential saturation at higher doses. No significant accumulation of remibrutinib was observed after repeated dosing in any species. Inter- and intra-animal variability was moderate to high, and sex-related differences in exposure were occasionally observed, most notably in rats (up to 16-fold higher in females) and in some mouse studies. These sex differences may reflect physiological variations in metabolism or drug elimination, which is common and well described in rats (Czerniak 2001). Finally, the Applicant noted that the absence of human-relevant toxicity in non-clinical species at exposures above clinical levels reassures that TK variability does not affect the toxicological assessment.

Embryo–foetal development studies in rats and rabbits provided maternal exposure data, but foetal exposure was largely uncharacterised. Placental transfer was only investigated in rabbits, without clear results on foetal tissue radioactivity (see Distribution part). Nevertheless, high-dose maternal and developmental effects indicate likely placental transfer of remibrutinib and/or its metabolites in rats. As rat PPND study did not investigate exposure during lactation, excretion into maternal milk remains unclear. However, as ICH S5(R3) does not mandate TK or milk transfer data in PPND studies, the approach is considered acceptable. Accordingly, a precautionary wording is included in Section 4.6 of the SmPC, recommending discontinuation of remibrutinib during pregnancy and breastfeeding.

Distribution

Remibrutinib and its structural analogue LTG751 (which lacks acrylamide moiety) were stable in blood and plasma across species, with minimal degradation. Blood-to-plasma ratios were below 1 in all species, indicating preferential distribution to plasma, and plasma protein binding was consistently high, leaving only a small unbound fraction available for pharmacological activity. Covalent binding in blood was low in humans and dogs (3–10%) and higher in rats (up to 11%), while covalent binding in plasma was time-dependent in rats and dogs, increasing to 60–70% after 2 hours.

Tissue distribution was similar between male and female rats, with females showing higher overall exposure. Remibrutinib distributed widely, notably to the liver, kidney, gastrointestinal tract, and melanin-rich tissues such as eye and skin, with partial reversibility. Brain penetration was negligible

under normal conditions, consistent with P-glycoprotein substrate activity, but increased under inflammatory conditions with blood-brain barrier disruption, suggesting BBB disruption can enhance CNS distribution. In pregnant rabbits, remibrutinib primarily accumulated in maternal tissues, with minimal foetal exposure detected. Although direct placental transfer data are limited, foetal exposure cannot be excluded, consistent with observed teratogenicity in rabbit EFD study and in line with ICH S5 recommendations.

Metabolism

In vivo metabolism of remibrutinib was broadly similar across mice, rats, rabbits, dogs, and humans, mainly involving acrylamide metabolism, O-dealkylation, and amide hydrolysis. Blood exposure was low in rats and rabbits, higher in dogs and humans, with no single human metabolite exceeding 10% of circulating drug-related material. Key human metabolites M68a,b (total exposure 11.2%, ratio 3:1), were not detected in the blood of non-clinical toxicology species. M68a,b is a downstream mercapturic acid metabolite of M2 and it is generally considered to be non-toxic, more polar and more soluble as the parent compound. Since M68a,b and M2 were not mutagenic, the absence of M68a,b in the non-clinical species did not raise safety concerns. The relevance of non-clinical species was assessed by comparing systemic exposure to human circulating metabolites in rats and dogs, with most metabolites showing exposure ratios >2. Despite a few exceptions (e.g., M15, M23, M32), the overall metabolite coverage is considered sufficient, raising no concern for the safety assessment of remibrutinib.

Excretion

Excretion of radiolabelled remibrutinib occurred primarily via faeces in rats, pregnant rabbits, and dogs, with minimal urinary elimination, consistent with other BTK inhibitors. The drug is mainly cleared through metabolism, with only a minor fraction excreted unchanged (<1% in humans, lower in non-clinical species). Total recovery was high in rats and rabbits (>97%), reflecting efficient hepatobiliary elimination, while dogs showed slightly lower recovery (89%), suggesting slower or prolonged elimination.

Toxicology

Single- and repeat-dose toxicity

No single-dose toxicity studies were conducted, and the lack of standalone studies is supported in accordance with ICH M3(R2) and from a 3R perspective.

Repeat-dose toxicity studies were conducted for up to 26 weeks in rats and 39 weeks in dogs, in line with ICH M3(R2) recommendations. Reversibility of changes was assessed only in rats at the highest tested dose level of 1000 mg/kg/day in 2- and 26-week studies, which is acceptable from 3R perspective since no new toxicities were observed in dog studies in addition to ones already observed in rats. Generally, remibrutinib was well tolerated up to maximal achievable exposure. The toxicological profile of remibrutinib by large reflects its selectivity over off-targets, which was demonstrated in pharmacology studies. The main findings in repeat-dose toxicity studies can be grouped into: i) pharmacological effects in immune cells, lymphoid tissue and platelets, which were mostly consistent across the studies in rats and dogs and, ii) species-specific effects observed only in rats, such as pancreas toxicity (BTK inhibitor class-effect in rats), liver/thyroid hypertrophy (due to extensive metabolism) and adrenal mononuclear inflammatory cell infiltrates (exacerbation of a specific background change).

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 an increased incidence and severity of endocrine pancreas fibrosis, haemorrhage and pigment at all tested dose levels (i.e., doses of 30, 300, and 1000 mg/kg/day). However, these changes are considered unlikely to translate to

humans since they represent spontaneously occurring changes in aging rats, known to be exacerbated by BTK inhibitors with no translation to other species (Erickson et al 2017, Bhaskaran et al 2018). Therefore, it is considered justified to exempt this finding in the purpose of determination of safety margins for humans.

BTK is expressed in platelets, and BTK is involved in specific platelet functions, i.e., in (i) platelet activation through GPVI activation by collagen and GPIb activation by von Willebrand factor but not through G protein coupled receptors, (ii) GPIIb/IIIa activation by fibrinogen which is involved in clot retraction. Consistent with the role of BTK in these specific platelet functions, remibrutinib inhibited collagen-induced platelet aggregation and increased the ROTEM lysis index in blood samples, which was observed in all rat repeat-dose toxicity studies. Mechanistic investigations in human whole blood indicated that the effects of remibrutinib on the ROTEM lysis index were due to disturbances in platelet function, since remibrutinib increased lysis index parameters only in conditions with functional platelets present, but not when platelet function was inactivated. Hence, it is considered that remibrutinib most likely inhibits clot retraction. In dogs, there were variable effects on platelet aggregation and f ROTEM lysis index reported; from inhibition of collagen- and ADP-induced platelet aggregation and no effect on ROTEM parameters in 2-week study to no effects observed in 39-week study. On the other hand, remibrutinib inhibited collagen-induced platelet aggregation and caused an increase in the ROTEM lysis index in rat, dog, and human whole blood in *in vitro* non-GLP mechanistic study, suggesting translatability across species.

To note, there were no adverse histological findings and no effects on coagulation parameters observed in any repeat-dose toxicity study. As well, there was no evidence of spontaneous haemorrhages during physical examinations. However, the assessments of effects of remibrutinib on bleeding time in rats (involving tail tip incision affecting large blood vessels) and dogs (involving buccal mucosa incision affecting small blood vessels), which were included in 2-week studies, revealed the increase in rat tail bleeding time at all tested dose levels (≥30 mg/kg/day), which was considered adverse. One female in the 100 mg/kg/day group was found dead on Day 12 with marked acute centrilobular hepatocellular degeneration/necrosis suggestive of ischemia which was considered consecutive to prolonged bleeding during the tail bleeding test on the same day. The prolongation of rat tail bleeding time was fully reversible within 2 weeks up to the highest tested dose of 1000 mg/kg/day. In vivo 3-day mechanistic study in rats further characterised the bleeding time in relation to BTK occupancy. A full effect was observed even at the lowest tested dose of 0.15 mg/kg/day within 3 days with mean blood BTK occupancy of 73%. Reversibility within 3 days was limited, correlating with blood BTK occupancy (improvement at mean blood occupancy of 33%). In contrast to rats, the Applicant concludes that no adverse or consistent effect of remibrutinib on bleeding time was observed in the dog mucosa bleeding assay, which was performed in 2-week repeat-dose toxicity study, up to the highest tested dose of 450 mg/kg/day, since it occurred only in two dogs at only one of two bleeding time points in each dog, and the bleeding stopped by itself.

Remibrutinib unwanted pharmacological effects in platelets are already identified for other BTK inhibitors as well as anticipated clinically. Therefore, non-clinical data on these effects are considered superseded by the available clinical data and a warning regarding the risk of bleeding is included in section 4.4 (see section 5 clinical).

Due to the role of BTK in immune cells, blood immunophenotyping was included in all GLP repeat-dose toxicity studies. Alterations were limited to minor decreases in B cell subsets at all dose levels with no significant changes in mature class-switched B cells. Although the Applicant reports no effects on blood standard (T/B/NK cells in rats; T/B cells in dogs) immunophenotyping in some studies, e.g. the 26- and 39- week studies, respectively, minor, non-dose related and reversible changes in blood immunophenotyping observed in males and females at ≥ 300 mg/kg/day, consisting of mild increases in relative and/or absolute T cell, helper T cell and NK T cells as well as the mild decreases in relative

and/or absolute B cell and NK cell counts were reported in the study report of the 26-week rat study. In dogs, no effects are reported, but the same decrease in relative and absolute B cell count and increase in T-cell subsets is evident at least in females form the study data. Nevertheless, since no infections occurred during in-life phases of the studies, the CHMP concluded that these minor degree alterations in immunophenotyping are not adverse. Additionally, potential risks of infection and impact on at least some antibody responses are already anticipated at pharmacologically relevant exposure.

Genotoxicity

The genotoxic potential of remibrutinib was studied *in vitro* (gene mutation in bacteria, mammalian chromosome aberrations (micronucleus tests in human peripheral blood lymphocytes)) and *in vivo* (reticulocyte micronucleus test in rat blood) in line with ICH S2(R1) guidance and GLP requirements. Remibrutinib showed no evidence of genotoxicity.

Carcinogenicity

26-week RasH2 transgenic mouse and 104-week rat carcinogenicity studies were designed based on the principles of the ICH M3(R2), ICH S1A, S1B and S1C(R2). Toxicokinetics was evaluated in line with ICH S3A. For the transgenic mouse study, the dose selection was sufficiently justified. High dose of 1500 mg/kg per day was below the maximum tolerated dose (MTD) in 28-day mouse study and is limit dose per ICH S1C. Mid and low doses provide adequate exposure spacing. The selection of the maximum dose level in the rat study was based on the observation that a maximal feasible exposure in rats is reached with exposure saturation at doses above 300 mg/kg/day, most likely due to metabolism induction and solubility limiting absorption. In addition, the exposure in female rats after 26-weeks of dosing at 300 mg/kg/day was >25-fold over the predicted maximum clinical efficacious exposure. Remibrutinib metabolite exposure in the rat at 300 mg/kg/day represents ≥1-fold coverage of human metabolites at a clinical dose. At a higher dose level (1000 mg/kg/day), exposure and metabolite coverage were slightly reduced after 26-weeks dosing in the rat, suggesting stronger induction was negatively affecting maximum feasible exposure.

Non-neoplastic toxic findings were similar as in repeat-dose toxicity studies, i.e. no new findings arose. No remibrutinib-related neoplastic changes were noted up to the highest tested dose of 1500 mg/kg/day in transgenic mice. In male rats given 300 mg/kg/day of remibrutinib, a slight increase in benign haemangiomas in the mesenteric lymph node was observed, but this was not statistically significant compared with controls and was not seen in females. Although the incidence exceeded historical control ranges and a combined increase in haemangioma and haemangiosarcoma reached statistical significance in a pairwise test, no increase in malignant haemangiosarcoma alone was observed. Additionally, non-neoplastic proliferative vascular changes (focal and diffuse angiomatous hyperplasia as well as increased incidence and/or severity of pigmented macrophages, intrasinusoidal erythrocytes, and/or sinusoidal dilatation secondary to angiomatous hyperplasia) were observed in the lymph nodes. However, a detailed re-assessment of histology data and a weight-of-evidence review that was based on the comparisons of incidence of vascular neoplasms in humans vs. animals, the distribution among the sexes and the data from Tg RasH model (which is more susceptible to vascular tumours) as well as remibrutinib genotoxicity data, concluded that remibrutinib was not carcinogenic in rat mesenteric lymph nodes and that the vascular findings are unlikely to be relevant to human risk. Overall, the conclusion that no remibrutinib-related neoplastic changes were identified in rats up to the highest dose tested (300 mg/kg/day) was supported.

Developmental and reproductive toxicity

DART studies were performed in line with ICH M3(R2) and ICH S5 (R2). Pivotal studies were GLP compliant.

For assessment of fertility and early embryonic development, a combined FEED study was performed. Dose levels were selected based on TK of remibrutinib in repeat-dose toxicity studies in rats. No remibrutinib-related changes in FEED parameters were noted up to the highest tested dose of 1000 mg/kg/day. Exposure was not measured in the study. The reported exposure margins in the section 5.3 of the SmPC are obtained from 26-week repeat-dose toxicity study, although the duration of dosing in the FEED study was shorter than the 26-week repeat-dose toxicity study (4 weeks prior mating for at least 9 weeks for males and 14 days prior mating until GD 6). However, this was accepted by the CHMP due to stable steady-state exposure achieved very rapidly due to the short t1/2 and the absence of accumulation of remibrutinib with the longer administration.

Remibrutinib showed teratogenic effect only in pregnant rabbits. Foetal external malformations (open/opaque eyes, small jaws and/or hyperflexion of the forelimbs) were observed at 300 mg/kg/day, while in all pregnant rabbits receiving 450 mg/kg/day remibrutinib was not tolerated and the assessment of EFD was not possible due to early euthanasia. There was no clear maternal toxicity or any significant effect on foetal development at 100 mg/kg/day, which translates to 23-fold NOAEL-based safety margin in terms of steady-state $AUC_{0\text{-}24h}$ and 36-fold in terms of steady-state C_{max}, compared to human exposure at the clinical dose of 25 mg b.i.d. remibrutinib. Approved BTK inhibitors are teratogenic as well, however, the teratogenic effects occur at much lower exposure (near clinical exposure) and are observed in rats, as well. In contrast, no remibrutinib-related maternal toxicity or effects on EFD were noted in rats up to the highest tested dose of 1000 mg/kg/day. The potential risk for use in pregnancy is appropriately communicated in the section 4.6 of the SmPC.

In the rat PPND study, adverse remibrutinib-related effects were observed in the highest dose group (1000 mg/kg/day). Two animals administered 1000 mg/kg/day were euthanized on LD 1. A third female had two stillborn, one dead and three missing/cannibalized pups. Two pups from this litter survived and were noted as small and thin up to LD 14, with normal development thereafter. This resulted in a higher incidence of females with one or more stillborn pups, and a smaller litter size with increased decedents in the group administered 1000 mg/kg/day, compared with controls. A higher incidence of longer gestation length (mean 23.3 days) was noted for the group administered 1000 mg/kg/day, compared with control mean of 23.0 days and historical control mean of 23.1, which included litters with increased pup losses. In addition to all required PPND observations, neurobehavioral assessment and immunological evaluation (TDAR to keyhole limpet hemocyanin, immunophenotyping and spleen histopathology) was conducted and no adverse effect were observed in pre-weaning F1 or F1 mature animal. No effect was seen in developmental landmarks, anti-KLH IgM or anti-KLH IgG levels or neurobehavioral endpoints in F1 animals.

Juvenile toxicity studies were designed to evaluate toxicity of remibrutinib following administration from PND 21 (~2-year old child) to PND 42 (~ 12-year old child; DRF juvenile toxicity study) or PND 19 to PND 70 (~14-year old adolescent; pivotal juvenile toxicity study). The submission of the juvenile toxicity studies is acknowledged, but they are not relevant for the current indication which concerns an adult population. A waiver was granted for the treatment of CSU which applies to the paediatric population from birth to less than 6 years of age on the grounds that the specific medicinal product is likely to be unsafe.

Local tolerance

In the context of occupational health hazard assessment, remibrutinib skin irritating or sensitizing potential was evaluated *in vitro* (human skin model) or *in vivo* (murine local lymph node assay), according to relevant guidelines. Remibrutinib did not show skin irritating or sensitizing potential *in vitro* or *in vivo*.

Antigenicity

No antigenicity studies have been conducted with remibrutinib since no concerning findings were observed in the toxicology study, which is acknowledged.

Immunotoxicity

No dedicated immunotoxicity studies have been conducted for remibrutinib. The immunotoxicity potential of remibrutinib was adequately addressed through pharmacology and toxicology studies. The inhibition of primary antibody responses at pharmacologically relevant exposure as well as minor decreases in B cell subsets at all dose levels with no significant changes in mature class-switched B cells which were seen in several repeat-dose toxicity studies, are not surprising based on the role of BTK in B cells and were considered non-adverse. These effects of remibrutinib on primary antibody response are identified as an important potential risk at pharmacologically relevant exposure and have clinical implications (potential risks of infection), with infections (affecting upper respiratory tract) being confirmed ADRs (section 4.8 of the SmPC). Other more severe infections known for BTK inhibitors are not so far reported with remibrutinib (e.g. hepatitis B, aspergillus infections, sepsis, cryptococcal infections, pneumocystis infections, progressive multifocal leukoencephalopathy).

Studies on impurities

An overview and assessment of the impurities in remibrutinib starting materials, intermediates or the drug substance as well as in drug product is presented in the Quality section.

Impurities are adequately assessed for mutagenic potential based on ICH M7(R2). Supporting data included (Q)SAR analysis with an expert review, the internal Ames test study reports and the literature references for substances with established PDE or publicly available genotoxicity information.

The assessment of nitrosamine impurities was conducted in line with current EMA guidance (EMA/409815/2020 Rev.22). The nitrosamine drug substance related impurity were additionally evaluated in line with the suggestions provided by the CHMP in the scientific advice procedure *EMA/SA/0000138208*. Carcinogenic Potency Categorisation Approach (CPCA) was used to derive an AI for the fourth nitrosamine impurity, which fell into the category 2, with an AI of 100 ng/day. For an active substance related nitrosamine impurity, the proposed AI of 100 ng/day was established based on read-across to an appropriate surrogate molecule, with regulatory established limit of 100 ng/day, based on the most sensitive TD50 derived from the most robust TD50 dataset from carcinogenic potency database (CPDB) or Lhasa Carcinogenicity Database (LCD).

Phototoxicity

Phototoxic potential of remibrutinib is assessed in line with OECD Guideline 432 and ICH S10. Within sunlight range, remibrutinib shows relevant light absorption in the ultraviolet B (UVB) and ultraviolet A (UVA) range. Therefore, the phototoxic potential of remibrutinib was further assessed in GLP-compliant 3T3 Neutral Red Uptake (NRU) phototoxicity test, which was negative.

Environmental risk assessment

Given the log Kow values of 3.1 to 3.2 were <4.5, it was concluded that no further screening for persistence, bioaccumulation, and toxicity was necessary. As these log Kow values were >3, a bioconcentration study in Tier B was triggered. Resulting steady-state BCFs were <2 L/kg (LD) and <1 L/kg (HD), indicating very low bioaccumulation potential. With 1% degradation within 28 days, remibrutinib is considered as not readily biodegradable compound. Remibrutinib is not expected to be mobile in terrestrial compartments, and a terrestrial risk assessment is not triggered. All calculated PEC:PNEC ratios were below trigger values for each compartment, so further evaluation (Tier B) is not required.

4.5.2. Conclusions

Remibrutinib is a selective BTK inhibitor that inhibits mast cells and basophils preventing the release of inflammatory mediators when triggered by autoreactive IgE or IgG. These effects are supported by results from in vitro and in vivo models. The non-clinical pharmacokinetic profile of remibrutinib is well characterised, demonstrating rapid absorption, extensive metabolism, and predominant faecal excretion across species, with no major interspecies differences impacting the human risk assessment.

The toxicological evaluation of remibrutinib is extensive and complies with relevant non-clinical ICH guidelines in most aspects. Pivotal studies were GLP compliant. The observed toxicities developed either at pharmacologically relevant exposure and are anticipated clinically or with sufficient safety margins towards the human exposure at the MRHD.

Remibrutinib is not PBT substance, although it is considered persistent in water/sediment systems. Based on calculated risk ratios for surface water, STP, groundwater and sediment, it is not expected to pose a risk to the environment.

Overall, the non-clinical program supports the MAA of remibrutinib in the proposed indication.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC and/or Regulation (EU) No. 536/2014.

5.1.2. Tabular overview of clinical trials

Table 8: Tabular overview of main clinical studies

Study no.	Study design Population	Treatment duration	Treatment(s) No. of randomized or enrolled patients	Study status
Dose-finding (supportive) study				
A2201	Phase IIb randomized, double-blind, placebo-controlled, parallel group Adults aged 18 years and older with CSU inadequately controlled by second generation H1-AHs	12 weeks Maximum study duration*: 18 weeks	LOU064 10 mg q.d. (n = 44) LOU064 35 mg q.d. (n = 44) LOU064 100 mg q.d. (n = 47) LOU064 10 mg b.i.d. (n = 44) LOU064 25 mg b.i.d. (n = 44) LOU064 100 mg b.i.d. (n = 45) Placebo (n = 43)	Completed
Pivotal studies				
A2301	Phase III randomized, double-blind, placebo-controlled, parallel group Adults aged 18 years and older with CSU inadequately controlled by second generation H1-AHs	A total of 52 weeks: - Double-blind treatment period: 24 weeks (either LOU064 25 mg b.i.d. or placebo) - Open-label treatment period: 28 weeks (all patients on LOU064 25 mg b.i.d.) Maximum study duration*: 60 weeks	LOU064 25 mg b.i.d. (n = 313) Placebo (n = 157)	Completed
A2302			LOU064 25 mg b.i.d. (n = 300) Placebo (n = 155)	Completed
Other supportive studies				
A2201E1	Phase IIb extension, open-label, single arm Adults aged 18 years and older with CSU who completed treatment in Study A2201 and rolled-over into this study	52 weeks Maximum study duration*: 80 weeks	LOU064 100 mg b.i.d. (n = 194)	Completed
A1301	Phase III, open-label, single arm, local Japanese study Adult Japanese patients aged 18 years and older with CSU inadequately controlled by second generation H1-AHs	52 weeks Maximum study duration*: 60 weeks	LOU064 25 mg b.i.d. (n = 71)	Completed
Additional efficacy data from ABPM study				
A2305	Phase III, open-label, ABPM study in adult patients with CSU inadequately controlled by H1-AH treated with remibrutinib up to 12 weeks	12 weeks Maximum study duration*: 20 weeks	LOU064 25 mg b.i.d. (n = 144)	Completed

* Maximum study duration includes screening and treatment-free follow-up period.
Source: [Tabular Listing of All Clinical Studies]

5.2. Clinical pharmacology

5.2.1. Methods

Results from the human ADME study (Study X2104) showed that remibrutinib has no major metabolites (*i.e.*, none exceeding 10% of total radioactivity with relevant pharmacological activity). Therefore, only bioanalytical methods for quantification of remibrutinib in human matrices were developed and validated.

Quantification of remibrutinib in clinical samples was performed using LC-MS/MS methods following protein precipitation (blood) or dilution (urine). All methods were validated and, where applicable, cross-validated between two bioanalytical sites: LabCorp (Shanghai, China) and SGS (Saint-Benoît, France). A summary of the methods and validation results is provided in **Table 9**.

Key methods used in the main clinical studies (Table 9) included:

- Method 1600407: Fully validated blood method (1.00–1000 ng/mL); used in studies X2101, X2102, X1101, A1301, A2201, A2301, A2302, A02103, and F12101.
- Method 1800081: Fully validated blood method with adjusted calibration range (0.100–100 ng/mL); used in studies X2103, X2104, X2105, A2101, and A2201E1; cross-validated with 1600407 and 1900112a.
- Method 1900112a: Fully validated and cross-validated with 1800081; used in studies A02104 and A2302.

Additional methods supported specific needs, such as:

- Method 1600408: Partially validated urine method; used in X2101, X2104, and X1101.
- Method 1800080: Fully validated method for [$^{13}C_3$,^{15}N]-remibrutinib; used in X2103.
- Method 1900112: Fully validated but not used in clinical studies.

Cross-validation results confirmed comparability of methods across sites and calibration ranges.

Table 9: Summary of important validation results to support the main clinical studies, for remibrutinib quantification in human blood

Method ID	DMPK R1600407	DMPK R1800081	DMPK R1900112a
BA sites	SGS	SGS	LabCorp
Linearity (by linear regression)	1.00 to 1000 ng/mL	0.100 to 100 ng/mL	0.100 to 100 ng/mL
Weighting factor	$1/X^2$	$1/X^2$	$1/X^2$
Inter-day accuracy (Bias %) (from 3 analytical runs on 3 validation days) at LLOQ	-5.10%	-6.60%	-1.00%
Inter-day accuracy (Bias %) (from 3 analytical runs on 3 validation days) at above LLOQ	-4.00 to -0.33%	2.00 to 4.13%	-5.40 to 0.30%
Inter-day precision (CV %) (from 3 analytical runs on 3 validation days) at LLOQ	10.16%	12.74%	5.60%
Inter-day precision (CV %) (from 3 analytical runs on 3 validation days) at above LLOQ	6.32 to 7.14%	3.22 to 6.70%	2.60 to 3.10%
Post-preparative stability in extracts (Auto sampler)	192 h (at 10°C)	89 h (at 10°C)	98 h (at 2 to 8°C)
Short-term stability in spiked human blood	2 h on ice	4 h on ice	6 h on ice 2 h at RT
Freeze-thaw stability of spiked blood at ≤-15°C	3 freeze thaw cycles (at -24 ± 6°C)	1 freeze thaw cycle (at -24 ± 6°C)	5 freeze thaw cycles (at -10 to -30°C)
Freeze-thaw stability of spiked blood at ≤-70°C	3 freeze thaw cycles (at -75 ± 10°C)	2 freeze thaw cycles (at -75 ± 10°C)	5 freeze thaw cycles (at -60°C to -80°C)
Long-term stability in spiked human blood at ≤-15°C	34 days (at -24 ± 6°C)	0* days (at -24 ± 6°C)	43 days (at -10 to -30°C)
Long-term stability in spiked human blood at ≤-70°C	743 days (at -75 ± 10°C)	586 days (at -75 ± 10°C)	512 days (at -60 to -80°C)

* SGS was not able to validate this stability assessment, whereas LabCorp was able to demonstrate stability for at least 43 days when samples were stored between -10°C and -30°C. Noteworthy, this observed difference between both laboratories, does not impact the integrity of the study samples as they were kept deep frozen (ranging from -60°C to -80°C) before and after analysis.

Source: [DMPK R1600407], [DMPK R1800424], [DMPK R1600407-01], [DMPK R1800081], [DMPK R1800081-01], [DMPK R1900112a-01]

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The PK profile of remibrutinib has been extensively investigated through *in vitro* studies, series of early (Phase I/II) clinical studies and modelling and simulation analyses (PopPK, PBPK, E/R).

Table 10: Phase I/II studies

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
CLOU064X2101	FIH, SAD, MAD, food effect, formulation effect, PK, PD A 6-part FIH study of remibrutinib consisting of a 4-part randomised, double-blind, placebo-controlled SAD and MAD study to investigate the safety and tolerability in healthy volunteers (Parts 1, 3, and 5), healthy volunteers with asymptomatic atopic diathesis (Parts 2 and 4) and patients with atopic dermatitis (Part 6), an open-label food effect study, and a double-blind formulation effect study in healthy volunteers	Total (Parts 1-6): 145 remibrutinib; 40 placebo Part 1 (healthy volunteers): 60 remibrutinib; 20 placebo (21 female) Parts 2 and 4 (healthy volunteers with asymptomatic atopic diathesis): 48 remibrutinib; 16 placebo (5 female) Part 3 (healthy volunteers): 12 remibrutinib (3 female) Part 5 (healthy volunteers): 13 remibrutinib (3 female) Part 6 (patients with atopic dermatitis): 12 remibrutinib (7 female); 4 placebo (1 female)	Part 1: Single doses of 0.5; 1.5; 5; 15; 30; 60; 100; 200; 400 or 600 mg remibrutinib (HGC) Part 2: 10; 25; 50; 100; 400 or 600 mg remibrutinib q.d. for 12 days (HGC) Part 3: Two single administrations of 60 mg remibrutinib (fasted or fed) separated by 18 days (HGC) Part 4: 100 or 200 mg remibrutinib b.i.d. for 12 days (HGC) Part 5: Two single administrations of 50 mg remibrutinib separated by 18	SAD (Part 1): Cmax, Tmax, MRT, AUClast, AUCinf, T1/2, Vz/F and CL/F from the concentration-time data. MAD (Part 2 q.d. regimen): Blood (Day 1): Cmax, Tmax, MRT, AUC0-24h, and AUClast. Blood (Day 12): Cmax,ss, Tmax, AUC0-24h, AUClast, AUCinf, CLss/F, Vss/F, T1/2, and T1/2,acc. Exploratory urine: Ae0-24h on Day 1 and Day 12. The renal clearance (CLr) was determined based on AUC and Ae available for the same time period. Effect of food (Part 3): Cmax, Tmax, AUClast, AUCinf, T1/2, and MRT from the concentration-time data.

			days (wet-media milled or micronized formulation in HGC) Part 6: 100 mg remibrutinib (HGC) or Placebo b.i.d. over 4 weeks	MAD (Part 4 b.i.d. regimen): Blood (Day 1): Cmax, Tmax, MRT, AUC0-12h, and AUClast. Blood (Day 12): Cmax,ss, Tmax, AUC0-12h, AUClast, AUCinf, CLss/F, Vss/F, T1/2, and T1/2,acc. Exploratory urine PK: Ae0-12h on Day 1 and Day 12. The renal clearance (CLr) was determined based on AUC and Ae available for the same time period. Effect of formulation (Part 5): Cmax, Tmax, AUClast, AUCinf, T1/2, and MRT from the concentration-time data. Atopic dermatitis (Part 6): Blood (Day 1): Cmax, Tmax, AUClast, AUC0-12h and T1/2. Blood (Day 29, steady state): Cmax, Tmax, AUCtau, AUClast and T1/2.
CLOU064X2102	DDI An open-label, three- period, single sequence cross-over study to evaluate the effects of multiple oral doses of remibrutinib on the PK of a	30 remibrutinib (healthy volunteers, 30 female)	100 mg remibrutinib b.i.d. over 18 days (HGC)	Cmax, Tmax, AUC0-24h, AUC0-48h, AUClast, AUCinf, CL/F, Vz/F, T1/2

	monophasic combined oral contraceptive and a sensitive CYP3A, CYP1A and CYP2C9 substrate in healthy female volunteers			
CLOU064X2103	DDI A single-center, open-label, single sequence, cross-over study to investigate the effect of ritonavir and grapefruit juice on the PK of intravenous and oral remibrutinib in healthy volunteers	17 remibrutinib (healthy volunteers, 2 female)	50 mg (HGC)	Cmax, Tmax, AUC0-24h, AUClast, AUCinf, Lambda z, T1/2, MRT, CL/F, Vz/F
CLOU064X2104	Human ADME A single-center, open-label study to evaluate the ADME and PK of remibrutinib following a single dose of [^{14}C]-remibrutinib administered orally or intravenously in healthy male and female volunteers at steady-state	7 remibrutinib (healthy volunteers, 1 female)	100 mg b.i.d. (HGC) given for 5 days. On Day 2 the morning dose was replaced by a 100 mg dose of [^{14}C]-labelled remibrutinib (5 HV). In addition, 2 HV received a single dose of 0.1 mg [^{14}C]-labelled remibrutinib on top of a daily oral dose of 100 mg, b.i.d. (HGC)	Cmax, Tmax, AUClast, AUCinf, T1/2
CLOU064X2105	Relative bioavailability A randomised, open-label, cross-over study to evaluate the	32 remibrutinib (healthy volunteers, 6 female)	100 mg (FCT or HGC)	Cmax, Tmax, AUClast, AUCinf, T1/2, Lambda z, CL/F, Vz/F

	relative bioavailability of two oral remibrutinib formulations in healthy volunteers, a FCT and a HGC			
CLOU064X1101	Ethnic sensitivity A randomised, participant-blinded, placebo-controlled study to assess safety, tolerability, PK and PD of single ascending doses and a multiple dose of remibrutinib in Japanese healthy volunteers.	Total (Parts A and B): 36 remibrutinib, 10 placebo (healthy volunteers) Part A: 30 remibrutinib; 10 placebo (0 female) Part B: 6 remibrutinib; 2 placebo (0 female)	Part A: Single doses of 5; 30; 100; 200 and 400 mg remibrutinib (HGC) Part B: 100 mg remibrutinib twice daily for 5 days (HGC)	Cmax, Tmax, AUClast, AUCinf, T1/2, CL/F, Vz/F, Racc (AUC0-12h), Racc (Cmax), Ae0-72h, CLr
CLOU064A02103	DDI A Phase I, open-label, two-part study to investigate the impact of carbamazepine (a strong CYP3A4 inducer) on remibrutinib exposure and the impact of remibrutinib on the exposure of digoxin (P-gp substrate) and rosuvastatin (BCRP, OATP1B1, and OAT3 substrate) in a cocktail approach in healthy volunteers	Total (Parts 1 and 2): 46 remibrutinib (healthy volunteers) Part 1: 24 remibrutinib (1 female) Part 2: 22 remibrutinib (4 female)	100 mg b.i.d. (HGC)	Cmax,ss, Tmax,ss, AUCtau, AUClast,ss, T1/2,ss, CLss/F, Vss/F, AUC0-t, λz, CL/F, Vz/F, Ae0-t, CLr
CLOU064A02104	Ethnic sensitivity, food effect study	Total (Parts 1 and 2): 40 remibrutinib	Multiple oral doses at 25 mg	Cmax, AUC0-12h, Tmax, AUC0-4h, and CL/F

	A randomised, open- label, two-cohort, two-period, two-sequence, cross-over study to evaluate the effect of food on the steady-state PK of remibrutinib FCT in Chinese healthy volunteers	(healthy volunteers) Cohort A: 20 remibrutinib (0 female) Cohort B: 20 remibrutinib (0 female)	b.i.d. and 100 mg b.i.d. (FCT)	
CLOU064A2101	Hepatic impairment A Phase I, open-label, study to investigate the PK and safety of remibrutinib in participants with HI compared to matched healthy volunteers with normal hepatic function	38 remibrutinib (healthy volunteers, 15 female)	25 mg b.i.d. (FCT)	Cmax,ss, Tmax,ss, AUCtau, AUClast,ss, T1/2, CLss/F, Vz/F
CLOU064F12101	Vaccination immune response study A randomised, double-blind, placebo-controlled, parallel-group study to evaluate the modulation of immune response to three different types of vaccines by concomitant and interrupted administration of remibrutinib in healthy volunteers	Total: 73 remibrutinib, 34 placebo (healthy volunteers, 12 female) (38 concomitant remibrutinib, 35 interrupted remibrutinib)	100 mg b.i.d. (FCT)	AUCtau,ss (Day 15 only), AUClast, Cmax,ss, Tmax,ss
CLOU064A2201	A multicenter, randomised, double-blind, placebo-controlled Phase 2b dose	A total of 309 participants (267 remibrutinib, 42 placebo)	Patients were given 10 mg q.d., 35 mg q.d., 100 mg q.d.,	AUClast, AUCtau,ss Cmax,ss, Tmax,ss

	finding study to investigate the efficacy, safety and tolerability of LOU064 in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines	10 mg b.i.d., 25 mg b.i.d., or 100 mg b.i.d. (as HGC), or placebo.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

The following studies were pooled for the PopPK analysis and were selected to comprehensively describe a broad range of remibrutinib concentrations across multiple studies in healthy volunteers (Studies X1101, X2101, and A02104) and patients with CSU (Studies A2201/A2201E1, A1301, A2301, A2302). To mitigate the non-linearity and covalent target binding effect on exposure and to ensure robust characterisation of remibrutinib exposure at steady state for doses tested in the studies, only steady state data under fasted status for total daily doses between 10 mg and 200 mg from the pooled dataset were used to build the population PK model. A total of 7088 PK measurements from 1152 HV/CSU adult patients were used for model development. The covariates distributions with respect to demographic variables were the following: age (median: 43 years, range: 18 to 80 years, 8.2% $\geqslant$ 65 years), body weight (median: 71.3 kg, range: 39 to 162 kg), sex (63.5% females, 36.5% males) and race (59.3% non-Asian, 8.8% Mainland Chinese, 12.2% Japanese and 19.7% Other Asian).

The final PopPK model of remibrutinib was a two-compartment model with first order oral absorption rate with fixed lag time and constant clearance. Between-patient variability was included on all parameters as well as 3 correlations between random effects on CL/F, Q/F and V2/F. The residual variability was described with a proportional error model. FFM (fat free mass) and FM (fat mass) effects on CL/F, race effect on CL/F, and FM effect on V1/F were retained in the final model (**Table 11**).Diagnostic plots were used to assess the model goodness-of-fit and model assumptions (**Figure 2**).

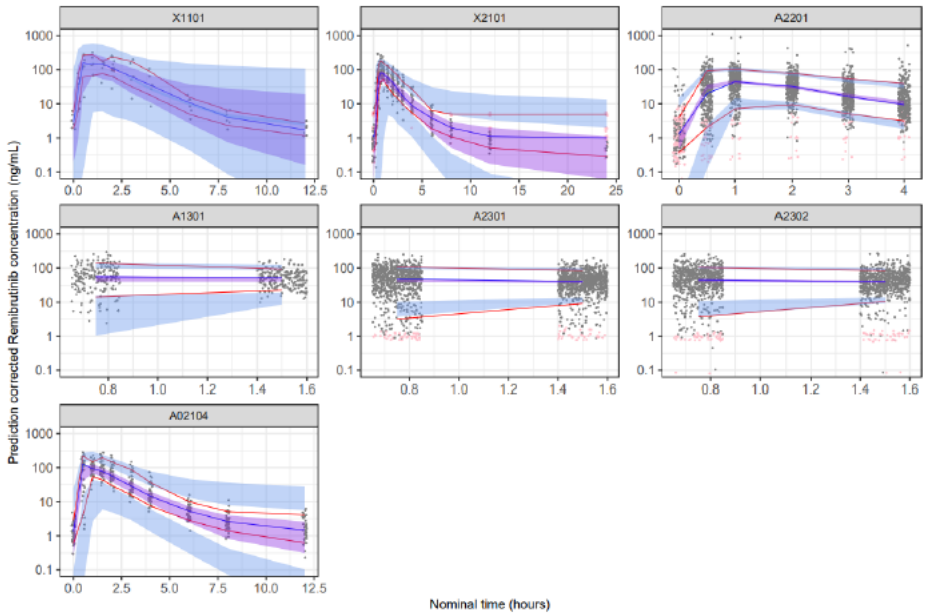
Table 11: Parameter estimates of the final Pop PK model

Parameter (unit)	Estimate (RSE in %)	Shrinkage	CV%
Structural Parameters			
Tlag (h)	0.26 (FIX)	55.5%	
k_a (1/h)	0.86 (1.7)	-	
CL/F (L/h)	160 (3.4)	31.5%	
FFM on CL/F	0.79 (12.2)		
FM on CL/F	-0.28 (18.9)		
Mainland Chinese on CL/F	-0.19 (38.7)		
Japanese on CL/F	-0.18 (35)		
Other Asian on CL/F	-0.26 (22.5)		
V_1/F (L)	58 (6.83)	65.7%	
FFM on V_1/F	1.3		
FM on V_1/F	0.48 (22.5)		
Q/F (L/h)	43 (12)	54.5%	
V_2/F (L)	1180 (20.8)	73.2%	
Inter-individual variability, standard deviations			
IIV Tlag	0.71 (FIX)		81%
IIV CL	0.65 (3.8)		73%
IIV V_1	0.98 (5.4)		127%
IIV Q	1.94 (5.3)		649%
IIV V_2	2.75 (4.8)		4386%
Correlation			
corr_CL_Q	-0.66 (6.7)		
corr_V_2_CL	-0.31 (21)		
corr_V_2_Q	0.57 (11.2)		
Residual Variability			
Proportional error (b)	0.47 (1.2)		
Objective Function			
OFV=-2LL	58313.91		
cBIC	58458.75		

Estimates of structural PK parameters are for a typical non-Asian CSU patient with FFM of 47 kg and FM of 23 kg.

Source: /MODELS/LOU064_model_final/summary.txt

Program: /MODELS/LOU064_model_final.mlxtran



The lines represent the 10th, 50th and 90th percentiles of observed data. Shaded areas are 95th prediction intervals for the 10th, 50th and 90th percentiles. Pink dots are simulated BLOQ values.
Source: /OUTPUTS/LOU064_07_vpc_final_w52.pdf
Program: /SCRIPTS/LOU064_07_vpc_final.R

Figure *2*: Prediction corrected visual predictive check (Final model)

5.2.2.2.2. Physiology based pharmacokinetic model

The PBPK model for remibrutinib was developed and refined by applying a stepwise "middle out" modelling approach by leveraging *in vitro*, *in silico* and *in vivo* data.

Values for CL, Vss and fm were input from the i.v. data from study X2103. Due to non-linear PK behaviour of remibrutinib, the PBPK model also implemented solubility-limited absorption, as well as target-mediated drug disposition. The oral absorption of remibrutinib was implemented mechanistically into the model to better describe in vivo behaviour of the formulation (nanogranules) which is associated with higher apparent solubility compared to the solubility associated with biopharmaceutic properties of the drug substance itself. The interaction part of the model includes reversible inhibition, time-dependent inhibition and induction of CYP3A4, reversible inhibition and induction of CYP1A2, CYP2B6 and CYP2C9, as well as inhibition of several transporters. Some of the model parameters were optimised to better match the observed data, i.e. KI for CYP3A4 based on midazolam clinical DDI data and Ki for CYP2C9 based on tolbutamide clinical DDI data.

Sensitivity analyses were used at critical steps of model development, e.g. to select parameters for optimisation or to test sensitivity of DDI magnitude on varying in vitro interaction parameter.

The modeling and simulation analyses were performed using the Simcyp Population-based Simulator (V21R1). (**Figure 3)**

The developed model was applied to predict the DDI potential of remibrutinib co-administered with different CYP3A4 inducers or inhibitors, CYP sensitive substrates, and P-gp and BCRP substrates. The PBPK model was also used to predict effect of acid-reducing agents and effect of renal impairment on remibrutinib PK.

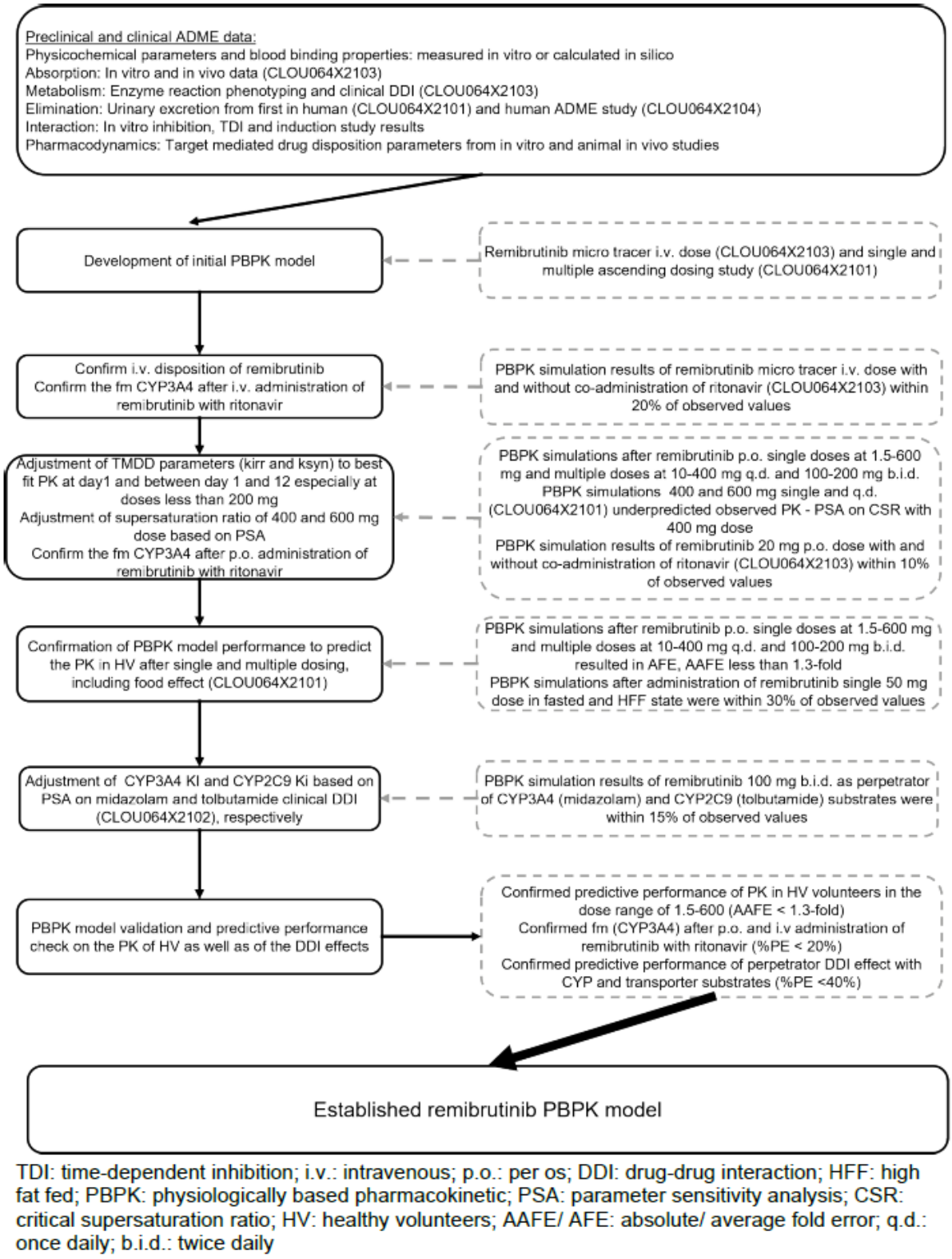


Figure *3*: Remibrutinib PBPK model development and validation workflow

5.2.2.3. Absorption

In vitro

Remibrutinib is classified as a Biopharmaceutics Classification System (BCS) class 2 drug with low solubility and high permeability.

Solubility of remibrutinib in aqueous media was pH dependent, with higher solubility at lower pH. Based on the lowest solubility results in the pH range of 1.2 - 6.8, remibrutinib drug substance was assessed as "Not highly soluble".

The predicted absorption of remibrutinib was high (>90%) based on passive permeability (Pm) at remibrutinib concentrations ≥ 50 µM (>> Km,app), where active efflux was saturated. However, at concentrations where efflux activity was not saturated (< Km,app), the predicted absorption was only low to moderate (DMPK R1500096).

In vivo

Remibrutinib was quickly absorbed with Tmax of about 1 h across all doses (0.5 mg to 600 mg). The absorption phase was characterised by a single distinct absorption peak in most participants.

Table 12: PK parameters in blood after oral dose of remibrutinib across studies

Parameter	**X2104** [1)]	**X2101** [2)]		**X2103** [3)]
	ADME	**FIH**		**DDI**
N	**5**	**12**	**12**	**11**
Remibrutinib dose	**100 mg**	**100 mg**	**100 mg**	**50 mg**
	Steady state (Day 2)	Single dose (Day 1)	Steady state (Day 29)	Steady state (Day 3)
C_{max} (ng/ml) - mean (SD)	745 (116)	249 (152)	396 (196)	139 (68.9)
T_{max} (h) - median	0.50	0.75	1.00	1.00
AUC_{last} - mean (SD)		552 (372)	877 (316)	237 (118)
AUC_{0-12} - mean (SD)	901 (258)	552 (372)	880 (313)	
$t_{1/2}$ (h)- mean	3.29	1.87	2.89	6.58
CL_{ss}/F (L/h) - mean (SD)	118 (33.9)			221 (81.0)
Vz/F (L) - mean (SD)	576 (264)			2060 (874)

1) Oral solution containing 100 mg of remivrutinib and 0.074 MBq (2 µCi) of [14C]-LOU064
2) Oral administration of two hard gelatin remibrutinib capsules at 100 mg (2 x 50 mg) b.i.d.
3) Oral administration of a hard gelatin remibrutinib capsule at 50 mg b.i.d.

Influence of food

The overall exposure (AUC) increased and peak concentrations (Cmax) decreased when remibrutinib was administered under fed condition in both Study X2101 and Study A02104. Study A02104 was conducted with the final formulation proposed for the market (film-coated tablet, FCT) at 25 mg and 100 mg b.i.d. Following administration of 25 mg FCT b.i.d., Cmax decreased by approximately 5% compared with the fasted state, while AUC0-12h increased by approximately 33%. Following administration of 100 mg FCT b.i.d., Cmax decreased by approximately 15% compared with the fasted state, while AUC0-12h increased by approximately 43%.

The observed magnitude of the food effect does not call for adaptation of doses or dosing regimen in case remibrutinib is given with food.

Acid-reducing agents

The solubility of remibrutinib is pH-dependent, with higher solubility at lower pH, which may affect the absorption. A phase I, open-label, 3-group study (A02105) assessing the effect of rabeprazole and omeprazole on the pharmacokinetics of remibrutinib 100 mg b.i.d. was conducted in healthy volunteers. The results show that AUCtau was similar (approximately 1.6% to 7.7% lower geometric mean) and 90% CIs of geometric mean ratios (GMRs) were within the bioequivalence (BE) range of 80% to 125% when remibrutinib was co-administered with rabeprazole (fasted), omeprazole (fasted) or omeprazole (fed) compared to remibrutinib alone. Remibrutinib peak (Cmax,ss) exposure was approximately 19-41% lower when remibrutinib was co-administered with rabeprazole (fasted), omeprazole (fasted) or omeprazole with standard breakfast compared to remibrutinib alone. Based on these results, there is no clinically relevant effect of acid reducing agents on the PK of remibrutinib.

Bioavailability

The absolute oral bioavailability of remibrutinib (F) is 33.8% and 80.9% when administered alone and in the presence of ritonavir (strong hepatic CYP3A4 and P-gp inhibitor), respectively (Study X2103). The average fraction metabolized (Fm) by hepatic CYP3A and P-gp transport was 0.400 (40%) indicating that the clearance of remibrutinib is driven by a strong first pass effect, in line with the observed large increase in bioavailability when co-administered with ritonavir.

In a relative bioavailability study (X2105), the FCT formulation which was planned to be used in Phase III trials and beyond, was assessed against the HGC formulation, which had been used in all remibrutinib Phase I and Phase II clinical studies conducted up to that point. Cmax, AUClast, and AUCinf were approximately 28%, 16%, and 20% lower, following the remibrutinib FCT formulation compared to the remibrutinib HGC formulation, which led to conclusion that no clinically relevant differences are expected.

5.2.2.4. Bioequivalence

Three batches of clinical remibrutinib 25 mg film-coated tablets) were compared against the biobatch and a representative batch of the proposed commercial remibrutinib 25 mg film-coated tablets) following the Guidance for Industry 'Dissolution testing of immediate Release Solid Oral Dosage Forms' (August 1997), at three different pH The dissolution conditions were USP apparatus, , and the dissolution media was prepared according to USP.

The similarity factor (f2) was between 50 to 100 in, and hence met similarity factor requirements.

In-vitro comparative dissolution testing at three different pH successfully demonstrated the bioequivalence between the remibrutinib 25 mg clinical FCTs and the commercial remibrutinib 25 mg FCTs with similar particle size.

Identical granules and final blend composition were used to manufacture phase 3 and proposed commercial remibrutinib 25 mg film-coated tablets. The composition of both formulations of remibrutinib 25 mg film-coated tablets differs only by the quantity of the colour components in the non-functional film-coating.

5.2.2.5. Distribution

Remibrutinib is a highly permeable compound and is readily distributed into blood cells with a concentration ratio between blood and plasma (Cb/Cp) of 0.813. Plasma protein binding of remibrutinib was characterised by fraction unbound in plasma of 0.0465 in humans (i.e., protein binding = 95.4%) with no significant concentration dependence observed. For [^{3}H]-LOU064, blood

distribution was concentration independent over a range of 100-10000 ng/mL for human. (DMPK R1400850).

In the oral arm of the human ADME Study X2104, the total radioactivity exposure (AUCinf) in whole blood was 85% of the AUCinf for the total radioactivity found in plasma. The geometric mean apparent elimination T1/2 of total radioactivity in plasma and whole blood were 272 h and 257 h, respectively. In the i.v. arm, the total radioactivity exposure (AUCinf) in whole blood was more than 90% of the AUCinf for the total radioactivity found in plasma. The elimination T1/2 of total radioactivity in plasma and whole blood were comparable within each arm (ranging between 291 h and 435 h). For both oral and i.v. arms, the exposure and elimination T1/2 data indicates no specific distribution or retention of drug-related components in erythrocytes.

5.2.2.6. Metabolism

After oral dosing in humans, the parent compound was the most abundant compound in blood, representing 16.7% of the blood [^{14}C]-AUC0-24h. Eighteen metabolites were characterised in blood. The most abundant ones were M68a and M68b (amide hydrolysis, hydrogenation combined with an N-acetyl cysteine conjugation combined with oxidation to sulfoxide) representing a mixture of two diastereomers which co-eluted and together accounted for 11.2% of the blood [^{14}C]-AUC0-24h with individual contributions estimated to be 8.5% and 2.7% based on ratio in urine.

Following i.v. administration of [^{14}C]-LOU064, the parent compound was the most abundant compound in blood, representing 21.7% of the blood [^{14}C]-AUC0-12h. Thirteen metabolites were characterised. The most abundant ones were M68a/M68b and M15 (6.79% and 5.70% of the blood [^{14}C]-AUC0-12h, respectively). Blood profiles after oral and i.v. administration were qualitatively similar.

Since no metabolite of remibrutinib reached an exposure of >10% of the total AUC in blood, no separate safety evaluation was deemed necessary for any of the metabolites detected in human. In addition, metabolites M68a and M68b, which showed the highest exposure in human blood were characterised as polar, low permeable (Papp=0.5 x 10-6 cm/s), quaternary Phase II metabolites, which were readily excreted in urine, and therefore considered to be of no concern based on their molecular properties. Noteworthy, M68a and M68b are also not considered to be reactive as the acrylamide moiety has been metabolised and inactivated.

After p.o. administration, a total of 31 metabolites were characterised in urine, the most abundant of which was M24 (DWC499), representing 3.49% of the dose. Other notable metabolites included M68 a,b, co-eluted M15/M65, M2 (LSX574) and co-eluted M23/M19, which represented 2.99, 2.71, 2.62 and 1.50% of the dose, respectively. All other components represented .0.903% of the dose each. LOU064 represented 0.65% of the dose, indicating that direct renal excretion of LOU064 is negligible.

After i.v. administration 27 metabolites were characterised in urine. Co-eluted M15, M22 (LTP763) and M65 was the largest peak in the radiochromatogram, representing 4.48% of the dose. M2 (LSX574), co-eluted M23/M19 and co-eluded M24 (DWC499)/M21 represented 3.74, 2.93 and 2.75% of the dose, respectively. All other metabolites were of minor abundance. LOU064 amounted to 2.93% of dose in urine.

After p.o. administration, a total of 21 metabolites were characterised in feces. The most abundant was metabolite M24 (DWC499), which represented 7.22% of the dose. All other metabolites represented. 2.29% of the dose. Unchanged LOU064 in feces amounted to 1.21% of the dose, indicating that LOU064 was almost completely absorbed (Fa >98% assuming the compound is stable in the intestine) and extensively metabolised. After i.v. administration, a total of 21 metabolites were characterised in feces, with the largest being M24 (DWC499, 16.9% of dose). Other abundant metabolites included

M57, M19, M23, M2 (LSX574), co-eluted M15/M22 (LTP73), M31 (LQT456) and M67 and represented 5.51%, 5.14%, 4.84%, 3.84%, 3.81%, 3.43% and 2.99% of the dose, respectively. All other metabolites represented 2% of the dose each. LOU064 was not detected in feces after i.v. administration, indicating that, together with the low amount eliminated in urine, that LOU064 is almost completely eliminated by metabolism.

Table 13: Contributions of the various metabolic pathways to elimination of LOU064

Route of administration	p.o.	i.v.
% of administered dose analyzed in the combined urine and feces samples	53.1	95.8
Metabolic pathway	**Fraction of the % of dose analyzed (%)**	
Oxidative pathways	65.7	64.2
GSH pathway	15.6	12.7
Unchanged LOU064	3.50	3.06
Unknown [1)]	15.3	20.2

1) Includes unidentified components and losses due to sample preparation, extraction and reconstitution

5.2.2.7. Elimination

A mass balance study (Study X2104) has been performed, indicating that the main elimination pathway for remibrutinib is metabolism since after i.v. administration remibrutinib represented only 2.93% of the dose in excreta (urine).

Overall, the arithmetic mean recovery of total radioactivity after oral dosing was incomplete (56.2%, SD: 7.95% of the administered dose of [^{14}C]-LOU064). The total radioactivity excreted after i.v. dosing was 96.8% of the administered dose of [^{14}C]-LOU064 in i.v. arm-A and 97.2% in i.v.arm-B. For both routes of administration, the excretion of radioactivity was relatively fast. In the oral arm, the route of excretion was mainly via feces, with 31.8% of the administered dose of [^{14}C] excreted in this matrix, compared to the excretion via urine of 24.4%. In feces, most of the radioactivity was recovered within 72 h. In urine, most of the radioactivity was recovered within 24 h. Only 1.21% of the 100 mg administered remibrutinib dose was excreted as unchanged remibrutinib in feces and 0.65% was excreted as unchanged in urine (DMPK RCLOU064X2104-metid-03). In the two i.v. arms A and B (one participant per arm), radioactivity was excreted predominately via feces (67.1% and 71.7%) and the excretion via urine was 29.7% and 25.5% (Study X2104). Excretion of radioactivity via feces was relatively fast: for i.v. arm-A, 57.4% (of the total 67.1% recovered via feces) was recovered within 72 h post-dose, and for i.v. arm-B, 65.7% (of the total 71.7% recovered via feces) was recovered within 48 h post-dose [Study X2104]. Recovery of radioactivity from urine was within 24 h (i.v. arm-A) and 12 h (i.v. arm-B) post-dose. After i.v. administration, 2.9% was excreted as unchanged remibrutinib in urine and the amount in feces was undetectable (DMPK RCLOU064X2104-metid-03).

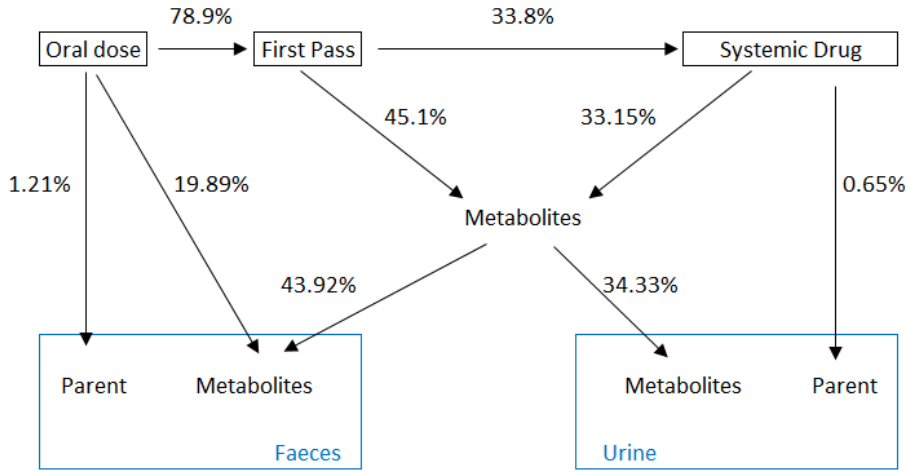


Figure 4: Elimination pathways (oral administration)

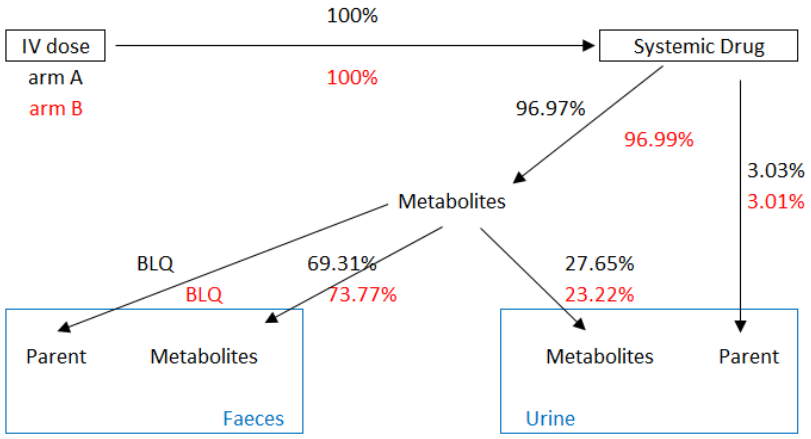


Figure 5: Elimination pathways (i.v. administration)

The cumulative recovery of total radioactivity following the oral dose was low (56.2% of the administered dose of [^{14}C]-LOU064) while it was 96.8% and 97.2% following the i.v. dose. Despite extensive investigation, the reason for the low recovery after oral administration is unknown and was attributed to a technical issue.

This is further supported by the following points:

• the metabolic profiles obtained after oral and i.v. administration in blood, urine and feces were comparable (DMPK RCLOU064X2104-metid-03-Table 2-1)

• the relative contribution of clearance pathways was also comparable between oral and i.v. administration

• no long-lasting radioactivity was detected in blood or excreta

• no volatile radioactivity was detected after oral administration from exhaled air that would suggest formation of volatile metabolites or CO2.

Following a single oral dose of 100 mg [^{14}C]-LOU064, total radioactivity exposure in whole blood was 85% of the exposure in plasma. The geometric mean apparent elimination T1/2 of total radioactivity in plasma and whole blood was comparable at 272 h and 257 h, respectively. Following the single i.v. dose of 100 µg [^{14}C]-LOU064, a near equilibrium of total radioactivity between plasma and blood was

observed, with total radioactivity exposure in whole blood being about 91% (i.v. arm-A) and 103% (i.v. arm-B) of the exposure in plasma. Additionally, the mean apparent elimination T1/2 of total radioactivity was comparable between plasma (i.v. arm-A: 291 h, i.v. arm-B: 363 h) and whole blood (i.v. arm-A: 374 h, i.v. arm-B 435 h). The mean T1/2 of total radioactivity in blood was 366 h, which was substantially longer than that of remibrutinib (3.29 h).

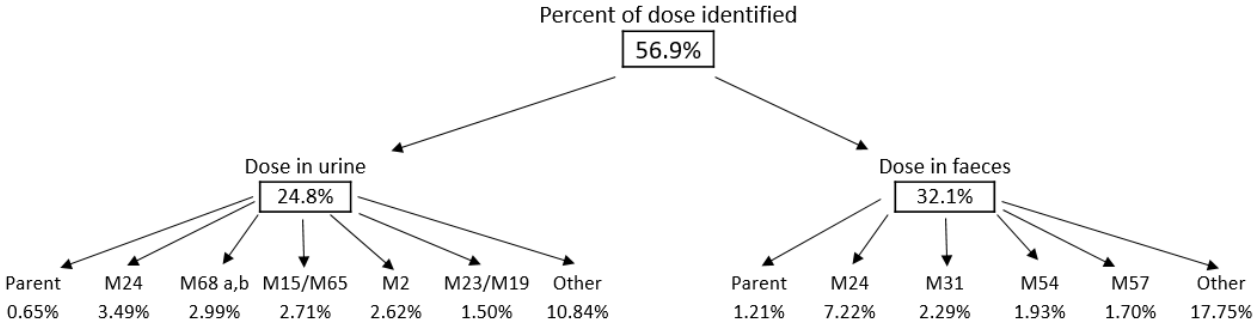


Figure 6: Mass balance study

5.2.2.8. Dose proportionality and time dependency

In both the SAD and MAD cohorts of Study X2101, Cmax and AUC increased with increasing doses across the entire range tested (0.5 mg to 600 mg in the SAD cohort and 10 mg to 600 mg in the MAD cohort). However, dose proportionality was not observed over the full range, indicating a less than proportional increase in exposure with higher doses.

PopPK analysis demonstrated approximate dose linearity within the range of 10 mg to 200 mg. At doses above 100 mg b.i.d., absorption likely becomes the exposure-limiting factor, probably due to the low solubility of remibrutinib.

The PK of remibrutinib is time-dependent due to the influence of covalent target binding on its clearance. The time-dependent change in CL/F was found to occur rapidly in between Day 1 and Day 2, resulting in an apparent stable CL/F as of Day 2 onwards. In line with that hypothesis, the difference in AUC is higher at the lower doses and the effect of target binding on the PK of remibrutinib becomes minimal at doses of 100 mg and above.

5.2.2.9. Pharmacokinetics in the target population

Dose-normalised remibrutinib concentration-time profiles at steady-state were shown to be consistent between healthy volunteers from Study X2101 and CSU patients from Study A2201. No differences are expected in PK of remibrutinib between healthy volunteers and CSU patients.

In study A2201, PK of remibrutinib was characterised at 6 different dose levels (10 mg q.d, 35 mg q.d., 100 mg q.d., 10 mg b.i.d., 25 mg b.i.d and 100 mg b.i.d). The following table presents summary of PK parameters at dose levels of 25 mg b.i.d. (proposed therapeutic dose) and 100 mg b.i.d. (exposures that could be reached in high clinical exposure scenarios).

Table 14: Summary of PK parameters from study A2201 (extracted from Table 11-9, Study A2201 CSR)

Parameter (unit)	Visit	Summary statistics	25 mg b.i.d. (n=43)	100 mg b.i.d. (n=45)
AUCtau (hr*ng/mL)	Week 4	N	19	17
		Mean (SD)	183 (97.5)	685 (368)
		CV(%) mean	53.3	53.7
		Geo-mean	164	611
		CV(%) geo-mean	49.2	51.2
		Median	145	585
		Min-Max	80.2-482	239-1730
AUCtau (hr*ng/mL)	Week 12	N	14	17
		Mean (SD)	195 (126)	761 (357)
		CV(%) mean	64.4	46.9
		Geo-mean	162	677
		CV(%) geo-mean	71.8	56.6
		Median	157	709
		Min-Max	46.4-488	189-1580
Cmax (ng/mL)	Week 4	N	32	28
		Mean (SD)	55.5 (34.7)	196 (144)
		CV(%) mean	62.5	73.4
		Geo-mean	49.0	152
		CV(%) geo-mean	89.2	94.4
		Median	51.9	166
		Min-Max	0-159	12.1-718
Cmax (ng/mL)	Week 12	N	29	25
		Mean (SD)	64.9 (42.3)	219 (125)
		CV(%) mean	65.2	57.0
		Geo-mean	56.6	188
		CV(%) geo-mean	65.9	90.6
		Median	55.3	213
		Min-Max	0-175	0-510

5.2.2.10. Special populations

Impaired renal function

No dedicated renal impairment study was conducted.

From the PopPK analysis, the creatinine clearance did not significantly affect the clearance of remibrutinib. The range of creatinine clearance was 23-275 mL/min, which includes patients with severe (1), mild-to-moderate (25), and mild renal impairment (222) and normal renal function (904). Based on the negligible renal clearance of unchanged remibrutinib corroborated by the PopPK analysis, no dose adjustment is necessary for patients with renal impairment.

Impaired hepatic function

Study A2101 evaluated the PK, safety, and tolerability of multiple-dose remibrutinib (25 mg b.i.d.) in participants with varying degrees of impaired hepatic function covering the three Child-Pugh categories of mild (N=8), moderate (N=7), and severe (N=7) HI compared to matched healthy volunteers.

Based on total remibrutinib concentrations, the exposure ratios for mild, moderate, and severe HI vs. healthy controls were, respectively, 1.85, 1.65, and 1.99 for Cmax, and 2.15, 2.07, and 3.12 for AUCtau.

Protein binding was unchanged in patients with HI, which means that any conclusions can be based on total remibrutinib concentrations.

Overall, there were several statistically significant relationships between remibrutinib blood PK parameters and measures of hepatic function: Cmax,ss increased with increasing PT and INR; AUCtau increased with increasing total bilirubin, PT, and INR, and decreased with increasing albumin level; and AUClast,ss increased with increasing total bilirubin, PT, INR, and AST, and decreased with increasing albumin level.

The exposure increases for patients with mild and moderate HI, as compared to healthy controls, were not considered to be clinically relevant. Use of remibrutinib is not recommended in patients with severe hepatic impairment.

Gender, ethnic factors, weight, age

Based on the population PK analysis, sex (63.5% females and 36.5% males) was not found as statistically significant covariate after accounting for FFM and FM.

The PopPK analyses investigating the effects of Non-Asian, Mainland Chinese, Japanese, and Other Asian as ethnicity covariates indicated that the simulated AUC increased by 21% in Mainland Chinese, 20% in Japanese, and 30% in Other Asian compared to a 70 kg Non-Asian adult patient with CSU. The proportions of the Japanese population (12.2%) and Mainland Chinese population (8.8%) were relatively small in the dataset, indicating that this finding should be interpreted with caution. These effects were not considered clinically relevant.

Based on the population PK analysis, body weight (range 39 to 162 kg) did not have a clinically meaningful impact on remibrutinib exposure.

Based on the population PK analysis, age (range 18 to 80 years) did not have a clinically meaningful impact on remibrutinib exposure. Limited data is available in elderly subjects ($\geqslant$65 years).

Remibrutinib has not yet been studied in paediatric population.

5.2.2.11. Pharmacokinetic interaction studies

In vitro

Remibrutinib as object of drug-drug interactions

The results of investigations of the metabolism of remibrutinib in human liver microsomes and with 19 recombinant human CYPs are reported (DMPK R1600559 and DMPK R1500124). These studies indicated that oxidative metabolism primarily by CYP3A4 is the major clearance pathway for remibrutinib, with a minor contribution of other enzymes of the P450 family (mainly CYP2C19). Non-oxidative pathways (amide cleavage) are anticipated to contribute to a minor extent to the overall hepatic metabolism.

Remibrutinib as precipitant of drug-drug interactions

Table 15: Summary of in vitro enzyme inhibition (pooled human liver microsomes, Study 1400510, Study 1500083, Study 1900718)

Enzyme	Substrate	Competitive inhibition[a)]	TDI[b)]		Positive signal to evaluate further
		Ki* (µM)	KI (µM)	Kinact (min-1)	Yes/No
CYP1A2	Phenacetin	70.6 ± 5.6*	Not observed	Not observed	No
CYP2A6	Coumarin	> 88.3*	/	/	No
CYP2B6	Bupropion	23.7 ± 2.4 (partially competitive)	Not observed	Not observed	No
CYP2C8	Amodiaquine	5.0 ± 0.7 (partially mixed)	Not observed	Not observed	No
CYP2C9	Diclofenac	7.7 ± 0.5 (full mixed)	Not observed	Not observed	No
CYP2C19	*S*-mephenytoin	7.7 ± 0.4 (full competitive)	Not observed	Not observed	No
CYP2D6	Bufuralol	68.5 ± 5.5*	Not observed	Not observed	No
CYP2E1	Chlorzoxazone	> 78.9*	/	/	No
CYP3A4	Midazolam	14.1 ± 1.4	6.9 ± 2.0	0.0102 ± 0.0010	Yes
CYP3A4	Testosterone	26.1 ± 2.0*	/	/	No

*IC50 value

Remibrutinib final concentration - 0, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, 100 µM

Table 16: In vitro transporter inhibition (studies 1500199, 1500200, 1500824, and 1700782)

Transporter	Substrate	In vitro system	Ki* (µM)	Positive signal (Y/N)
P-gp	1 µM digoxin	Transfected LLC-PK1 cells	29.4 ± 13.5	No
BCRP	2 µM PhIP	Transfected MDCKII cells	4.3 ± 0.3*	Yes
OATP1B1	0.1 µM E217βG	Recombinant HEK293 cells	2.8 ± 0.2	No
OATP1B3	0.1 µM E217βG	Recombinant HEK293 cells	8.8 ± 1.4	No
OAT1	1 µM [^{3}H]-cidofovir	Recombinant HEK293 cells	38.56 ± 65.87	No
OAT3	1 µM [^{3}H]-estrone-3-sulfate	Recombinant HEK293 cells	10.62 ± 5.08	No
OCT2	10 µM metformin	Recombinant HEK293 cells	68.7	No
OCT1	5 µM metformin	Recombinant HEK293 cells	7.19	No
MATE1	10 µM metformin	Recombinant HEK293 cells	13.6	No
MATE2-K	10 µM metformin	Recombinant HEK293 cells	68.3	No
BSEP	0.2 µM taurocholate	Recombinant HEK293 cells	7.80	No
MRP2	100 µM E217βG	Recombinant HEK293 cells	> 100	No

*IC50 is used instead of Ki (Ki determination not applicable since Km of PhIP is unknown)

Table 17: In vitro transporter inhibition (studies 2000485, 2200876, and 2301196)

Transporter	Substrate	In vitro system	Ki* (µM)	Positive signal (Y/N)
P-gp	1 µM NMQ	HEK293-Mock-CTRL	0.382	Yes
BCRP	1 µM E3S	HEK293-Mock-CTRL	0.467	Yes
BCRP (for HZB150)	1 µM prazosin	MDCKII	> 20	No
BCRP (for MTR479)	1 µM prazosin	MDCKII	> 20.5	No
OATP1B1	1 µM E217βG	Mock-transfected HEK293	2.36	No
OATP1B3	1 µM E217βG	Mock-transfected HEK293	7.55#	No
OAT1	5 µM tenofovir	Mock-B-transfected HEK293	9.87#	No
OAT3	1 µM E3S	Mock-transfected HEK293	1.09	No
OCT2	10 µM metformin	Mock-transfected HEK293	9.41#	No

OCT1	10 µM metformin	Mock-B-transfected HEK293	1.09	No
MATE1	10 µM metformin	MDCKII-CAT	1.70	No
MATE2-K	10 µM metformin	MDCKII-CAT	> 7.40	No
NTCP (for remi)	2 µM taurocholate	HEK293-Mock-LV	> 58.7	No
NTCP (for HZB150)	2 µM taurocholate	HEK293-Mock-LV	> 5.03	No
NTCP (for MTR479)	2 µM taurocholate	HEK293-Mock-LV	> 28.1	No

#Estimated values only as maximum inhibition did not achieve 50%.

In vivo

Clinical interaction studies have been performed to evaluate the effects of multiple daily oral doses of remibrutinib on the PK of the following:

- monophasic combined oral contraceptives
- sensitive CYP3A, CYP1A2, and CYP2C9 substrates
- sensitive P-gp and BCRP/OATP1B/OAT3 substrates

Additionally, the impact of a strong CYP3A inhibitor and a strong CYP3A4 inducer on remibrutinib exposure has been assessed.

Table 18: Summary of clinical DDI studies

Comparison	Substance Ratio, as Percent (90% CI)		Dosing Recommendation
	C_{max}	AUC_{0-24h}	
Object			
Effect of co-administration with carbamazepine (strong CYP3A4 inducer)	26 (21, 33)	22 (18, 27)*	Avoid co-administration of a strong CYP3A4 inductor
Effect of co-administration with ritonavir (strong CYP3A and P-gp inhibitor)	332 (281, 393)	431 (376, 494)+	Caution is required. No adjustment
Effect of co-administration with grapefruit juice (moderate-strong CYP3A inhibitor in gut)	124 (105, 146)	128 (109, 151)+	No adjustment
Precipitant (100 mg b.i.d.)			
Effect on ethinylestradiol	128 (119, 139)	116 (110, 122)	No adjustment
Effect on levonorgestrel	136 (124, 150)	139 (130, 149)	No adjustment
Effect on midazolam (sensitive CYP3A4 substrate)	136 (126, 147)	143 (135, 151)	No adjustment
Effect on tolbutamide (sensitive CYP2C9 substrate)	130 (121, 139)	/	No adjustment

Effect on caffeine (sensitive CYP1A2 substrate)	88.1 (84, 93)[#]	/	No adjustment
Effect on digoxin (P-gp substrate)	208 (181, 240)	145 (136, 154)[*]	No recommendation
Effect on rosuvastatin (BCRP, OATP1B1, OAT3 substrate)	156 (135, 181)	165 (147, 184)[*]	No recommendation

[*]AUC_{last}

[+]AUC_{inf}

[#]paraxanthine/caffeine concentration ratio

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Remibrutinib is a selective BTK inhibitor that has been designed to bind covalently and specifically to cysteine 481 of the BTK protein and inhibit its enzymatic activity. Based on the expression of BTK in mast cells and basophils the primary PD of remibrutinib in the context of CSU is focused on the role of BTK in mediating FcεRI intracellular signals that lead to degranulation of human basophils and mast cells from blood and skin.

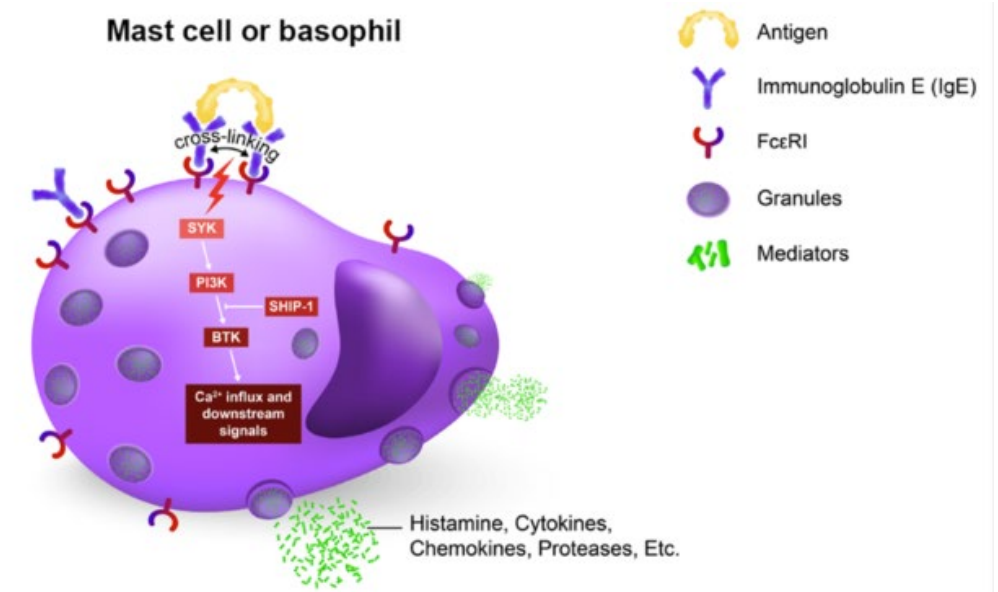


Figure adapted from Kaplan et al (2023). BTK is a central node in intracellular FcεRI signaling leading to degranulation of mast cells and basophils.

Figure 7: Role of BTK in mast cells and basophils

5.2.3.2. Primary and secondary pharmacology

Primary pharmacology

Pharmacodynamics were characterised by assessing target occupancy (i.e., BTK occupancy) and distal pathway inhibition in basophils and B cells. Phase I results for BTK occupancy in blood and inhibition of basophil activation are available from Study X2101 (FIH study with healthy volunteers with and

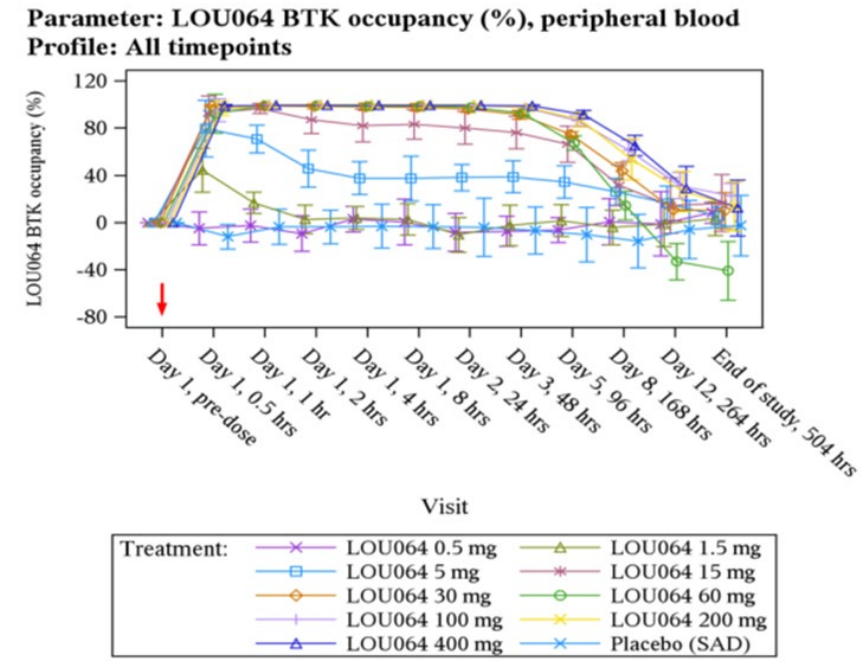
without asymptomatic atopic diathesis, including skin prick test) and Study X1101 (in Japanese healthy volunteers).

BTK occupancy in peripheral blood (Study X2101)

In the SAD cohort, starting at 30 mg and higher of remibrutinib, complete BTK occupancy (>95%) was observed and sustained beyond 4 hours. After 48 hours, BTK occupancy started to decrease and did not return to pre-dose occupancy levels until around 2 weeks post treatment.

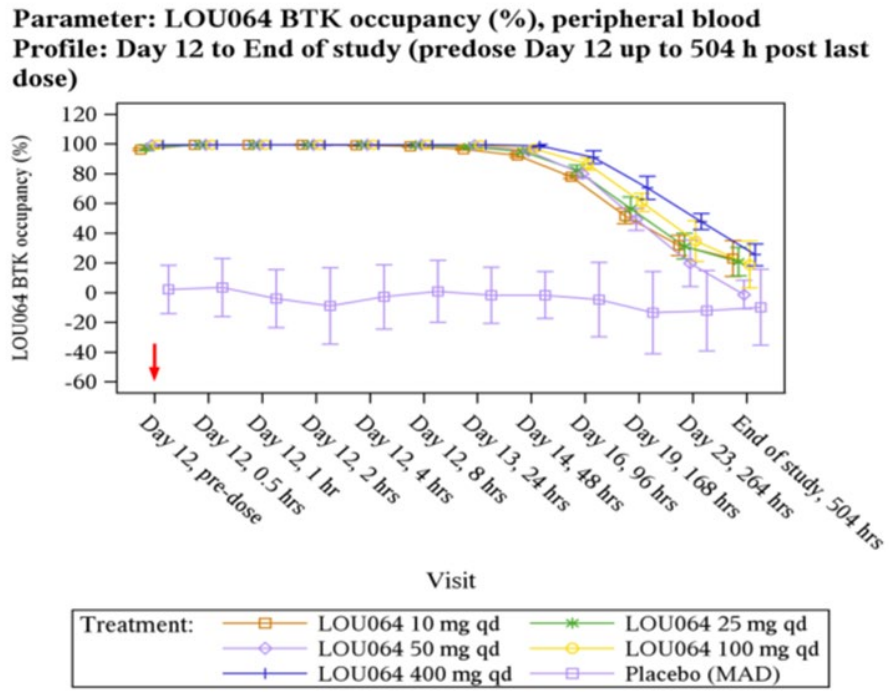
While the proposed dose of 25 mg b.i.d. was not investigated in the MAD cohort, the corresponding total daily dose of 50 mg (given as q.d.) showed almost complete BTK occupancy on Day 1. This was sustained up to 48 hours post-dose (last dose given at Day 12). BTK occupancy started to decrease 48 hours after the last dose (at Day 12) and returned to occupancy levels that were similar to pre-dose levels at approximately 3 weeks post-treatment (**Figure 8)**.

A.) SAD (Part 1) (PD analysis set)



Baseline is defined as the Day 1 pre-dose (Visit 101 pre-dose) value.
Arrow indicates time of dosing.
Source: [Study X2101 Interim-Figure 11-7]

B.) MAD q.d. (Part 2) (PD analysis set)



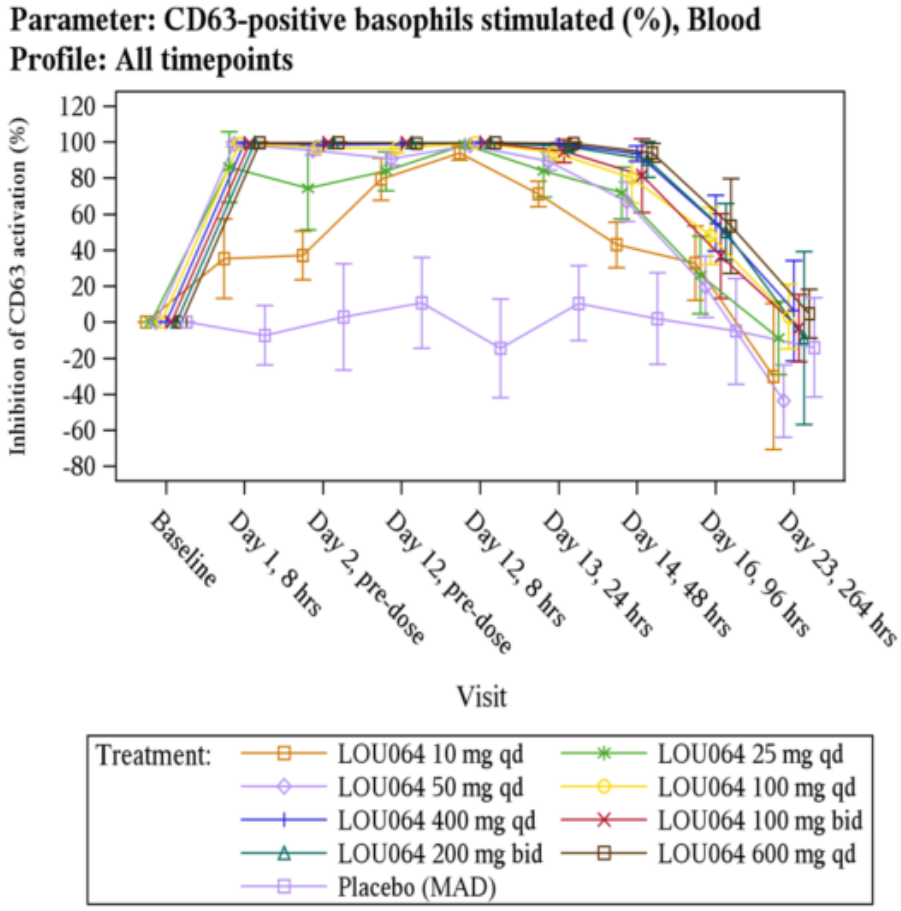
Baseline is defined as the Day 1 pre-dose (Visit 101 pre-dose) value.
Arrow indicates time of dosing.
Source: [Study X2101 Interim-Figure 11-8]

Figure *8*: Arithmetic mean (SD) percent remibrutinib BTK occupancy in peripheral blood-time profiles for SAD (A) and MAD (B) cohorts in Study X2101

Inhibition of basophil activation (Study X2101)

Dose and time-dependent decrease in anti-IgE stimulated activation of blood basophils after single and multiple doses was observed with activation marker-dependent kinetics and magnitude. In the SAD cohort, starting from 60 mg remibrutinib, the percent inhibition of stimulated basophils (as measured by CD63) was > 98% at 8 h post dose and lasted at 89% until 24 h post-treatment; with doses of 100 mg and higher, ⩾ 88% inhibition was observed up to 48 h post-treatment and returned to baseline approximately 11 days after the last dose.

In the MAD cohort, the inhibitory effect of remibrutinib was more pronounced. Starting from 50 mg q.d. dose, the percent inhibition of stimulated basophils (as measured by CD63) was > 95% at Day 2, 24 hours after the first dose; for 25 mg q.d., the inhibition was approximately 80% at Day 2. Consistent with the SAD cohort, inhibition started to decrease 48 hours after the last dose and returned to baseline approximately 11 days after the last dose. (**Figure 9**)



Source: [Study X2101 Interim-Figure 11-12]

Figure *9*: Arithmetic mean (SD) percent inhibition of basophil activation assessment-time profiles - MAD (Parts 2 and 4, Study X2101)

Inhibition of defined allergen response (skin prick test) (Study X2101)

There was a decrease in the wheal diameter in all the cohorts with a trend for dose dependency up to 100 mg q.d. (-2.85 mm) as measured by undiluted allergen skin prick test. Beyond this dose, this dose-dependent trend was much less clear, although the highest decrease was with the highest dose (-3.81 mm in the 600 mg q.d. group). There was little difference in wheal diameter decrease for b.i.d. dosing compared to q.d. dosing.

Inhibition of B cells activation (Study X1101)

Dose and time-dependent inhibition of B cells activation was observed starting at 30 mg single dose of remibrutinib. An inhibitory effect ⩾ 56% was observed for ⩾ 30 mg single dose 24 h post-treatment.

Inhibition of B cells activation with the remibrutinib 100 mg b.i.d. was similar to that with remibrutinib 100 mg single dose. With multiple doses of 100 mg b.i.d., a maximum inhibitory effect (65.3%) of remibrutinib was observed at 24 h post-first dose. The inhibitory effect was sustained over 24 h after the last dose (on Day 5).

Secondary pharmacology

Effect on blood pressure (Study A2305)

Study A2305 evaluated the effect of remibrutinib 25 mg b.i.d. open-label on systolic blood pressure measured as a change in 24-hour weighted average systolic blood pressure (assessed by ABPM) from

baseline to Week 4.

The study met its primary objective, which was to rule out an increase of > 3 mmHg in 24-hour average systolic blood pressure at steady state (Week 4) compared to baseline, measured by ABPM. The mean change from baseline to Week 4 in 24-hour average systolic blood pressure as measured by ABPM was -1.3 mmHg (95% CI: -2.3, -0.3). The upper limit of the 95% CI was -0.3 mmHg, which was less than the pre-specified upper limit of an increase of 3 mmHg, as based on FDA guidance (FDA 2022).

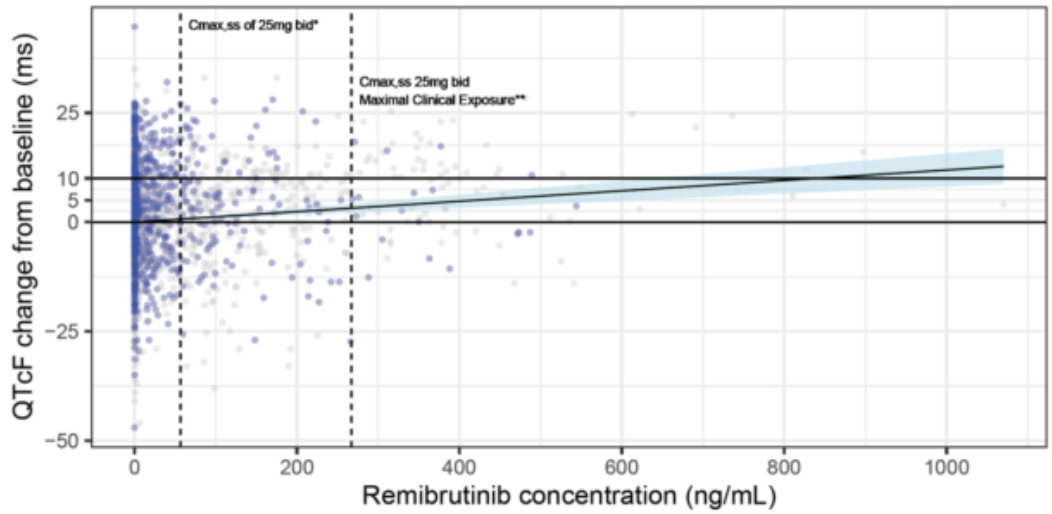
ABPM-related secondary objective analyses of 24-hour weighted average systolic and diastolic blood pressure and daytime and nighttime systolic and diastolic blood pressure demonstrated similar results as the primary analysis with no change or a slight decrease in blood pressure at Week 4 as compared to baseline.

Effect on QTc interval (Concentration-QTc analysis)

Considering the limited QTcF effect, as well as the lack of any significant electrocardiographic effects at any dose in non-clinical and clinical studies, a waiver was requested for a dedicated TQT study in the scientific advice procedure with EMA.

Concentration-QTc analysis was performed based on data from subjects who had QTcF measurement at baseline visit and matched PK and QTcF measurements at subsequent visits from studies X1101, X2101 and A2201. A linear mixed effects model was used to quantify the relationship between remibrutinib PK concentrations and change from baseline in QTcF (ΔQTcF) in the pooled analysis dataset.

The analysis showed that there was a shallow concentration-response effect with a slope of 0.012 ms/ng/mL yielding an estimated mean placebo-corrected QTcF increase from baseline (ΔΔQTcF) of 0.67 ms (upper bound of the 90% CI is 0.89 ms) at the geometric mean Cmax at steady state (56.6 ng/mL) when remibrutinib 25 mg b.i.d. is administered (**Figure 10**).



Model: Change from baseline in QTcF parameter data was analyzed using a linear mixed effects model with remibrutinib blood concentration as a continuous covariate, population (patients with CSU versus healthy volunteers) as a categorical covariate, timepoint as a categorical variable to represent diurnal variations and thus derive the placebo-corrected change from baseline in ΔQTcF, and a random participant effect on intercept.
Blue dots are QTcF data from Study A2201. Grey dots are QTcF data from Studies X1101 and X2101.
The shaded area is the corresponding two-sided lower and upper 90% confidence band of the solid linear regression line for the placebo-corrected QTcF (ΔΔQTcF). A horizontal reference line for QTcF is drawn at 10 msec (regulatory threshold of concern for upper 90% confidence limit).
Vertical Dashed Line:
* geometric mean Cmax,ss at 25 mg b.i.d. (56.6 ng/mL)
** geometric mean Cmax,ss at 25 mg b.i.d. with strong CYP3A inhibition (267 ng/mL)
Source: [ER Report-Figure 7-40]

Figure 10: Scatter plot for remibrutinib blood concentrations and corresponding placebo-corrected change from baseline in QTcF (ΔΔQTcF)

The major driver of the maximal clinical exposure is the inhibition of the predominant clearance pathway which is oxidative metabolism by CYP3A4. Results indicated that co-medication of remibrutinib with ritonavir (a strong CYP3A inhibitor) increased blood Cmax of remibrutinib by approximately 3-fold.

In the high clinical exposure scenario (administration with strong CYP3A4 inhibitor), as well as at supratherapeutic exposure (2-fold high clinical exposure), the upper bound of the 90% CI for the predicted mean ΔΔQTcF was estimated to be below the regulatory threshold of 10 ms, and a relevant QT-effect could be ruled out (**Table 19**).

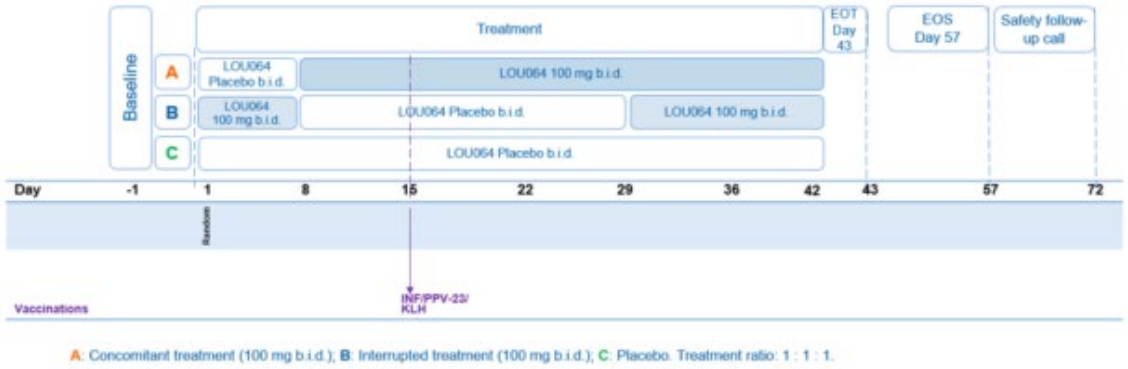
Table 19: Mean (90%CI) placebo-corrected QTcF increase from baseline for selected PK metrics of interest

	Concentration (ng/mL)	QTcF increase (msec/ng/mL) Mean (90% CI)
Cmax (geometric mean) of remibrutinib 25mg b.i.d	56.6	0.67 (0.46-0.89)
Cmax (geometric mean) of remibrutinib 25mg b.i.d administered with strong CYP3A4	267	3.18 (2.18-4.18)
Supra-therapeutic Cmax	534	6.35 (4.35-8.35)
Note: based on estimated slope of 0.012 msec/ng/mL (90% CI 0.008-0.016)		
Source: TASK_02_ER_SAFETYY/OUTPUTS/T03_S05_QTCF_Table.html		
Program: TASK_03_ER_SAFETY/SCRIPTS/ T03_S05_QTCF.R		

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Co-administration with vaccines

Study F12101 evaluated the impact of concomitant and interrupted remibrutinib administration on the immune response following administration of three different vaccines: T cell-dependent vaccines (quadrivalent seasonal Influenza and KLH) and a T cell-independent pneumococcal vaccine (PPV-23).



EOS: End of study
EOT: End of treatment
Source: [Study F12101-Figure 9-1]

Figure *11*: Vaccination immune response study design

Response to PPV-23 and influenza vaccine with interrupted remibrutinib dosing was the primary objective.

Responder rates were non-inferior with interrupted remibrutinib compared to placebo for the PPV-23 vaccine. The IgG response to PPV-23 vaccination for at least 50% of serotypes (≥ 12 of 23 serotypes) was observed in 65.6% of healthy volunteers in the interrupted remibrutinib arm compared with 70.0% in the placebo arm, with a proportion difference of −4% (95% CI: −0.28, 0.19), p=0.0155, demonstrating non-inferiority as the lower limit of the 95% CI did not meet the criteria of at least -0.30.

The antibody response to influenza B Austria antigen was non-inferior for the interrupted remibrutinib arm (40.6%) compared with the placebo arm (36.7%), with a proportion difference of 4% (95% CI: −0.20, 0.28; p=0.0030).

Non-inferiority was not demonstrated for the other three influenza antigens. Responder rates for the influenza A Darwin antigen were comparable between the interrupted remibrutinib and placebo arms (37.5% and 43.3%, respectively), with a proportion difference of −6% (95% CI: −0.30, 0.19, p=0.0263) that did not meet non-inferiority definitions as the lower limit of the 95% CI was −0.30 and the one-side p-value was marginally above the significance level of 0.025.

Responder rates were lower for the interrupted remibrutinib arm relative to the placebo arm with respect to influenza A Victoria antigen (56.3% vs. 73.3%) and Influenza B Phuket antigen (25.0% vs. 36.7%), with a difference of −17% (p=0.1441) and −12% (p=0.0588), respectively; non-inferiority was not met, as the lower limit of the 95% CI did not meet the criteria of at least -0.30.

Response to PPV-23 and influenza vaccine with concomitant remibrutinib dosing was the secondary objective.

The antibody response to influenza A Darwin antigen was comparable for concomitant remibrutinib and placebo arms (difference of -0.01%, 95% CI: -0.26, 0.23). For all other responses to influenza antigens (A Victoria, B Austria, B Phuket) and PPV-23 vaccine, the responder rates were lower for the

concomitant remibrutinib 100 mg b.i.d. arm compared to the placebo arm.

Table 20: Proportion of responders to influenza vaccine in the concomitant remibrutinib group compared with the placebo group (PD analysis set)

Parameter	Treatment group	N	Response n (%)	Proportion difference (95% CI)
Anti hemagglutinin antibody titer (Influenza A Darwin)	Concomitant LOU064	31	13 (41.9)	−0.01 (−0.26, 0.23)
	Placebo	30	13 (43.3)	
Anti hemagglutinin antibody titer (Influenza A Victoria)	Concomitant LOU064	31	19 (61.3)	−0.12 (−0.36, 0.12)
	Placebo	30	22 (73.3)	
Anti hemagglutinin antibody titer (Influenza B Austria)	Concomitant LOU064	31	3 (9.7)	−0.27 (−0.48, −0.06)
	Placebo	30	11 (36.7)	
Anti hemagglutinin antibody titer (Influenza B Phuket)	Concomitant LOU064	31	7 (22.6)	−0.14 (−0.37, 0.09)
	Placebo	30	11 (36.7)	

n= number of responders, N=number of subjects in PD analysis set with non-missing/valid titers at both baseline (Day 15) and 28 days after vaccination (Day 43).
Proportion differences (95% CI) are calculated based on normal approximation.
Source: [Study F12101-Table 11-6]

Table 21: Proportion of responders to PPV-23 in the concomitant remibrutinib group compared with the placebo group (PD analysis set)

Parameter	Treatment group	N	Response n (%)	Proportion difference (95% CI)
PPV-23 responder (≥12 of 23 serotypes)	Concomitant LOU064	31	3 (9.7)	−0.60 (−0.85, −0.36)
	Placebo	30	21 (70.0)	

n= number of responders, N=number of subjects in PD analysis set with non-missing/valid concentrations at both baseline (Day 15) and 28 days after vaccination (Day 43).
Proportion differences (95% CI) are calculated based on normal approximation.
Source: [Study F12101-Table 11-8]

The anti-KLH IgG response was non-inferior for the interrupted remibrutinib arm compared with the placebo arm. The adjusted geometric mean IgG titer was 130.22 U/mL for the interrupted remibrutinib arm vs. 119.72 U/mL for the placebo arm, with a geometric mean ratio comparing the two treatment arms of 1.09 (95% CI: 0.74, 1.60) that met the criteria for non-inferiority at a margin of 0.70.

The anti-KLH IgM response did not demonstrate non-inferiority for the interrupted remibrutinib arm compared with the placebo arm. The adjusted geometric mean IgM titer was lower for the interrupted remibrutinib arm vs. the placebo arm (62.61 vs. 81.68 U/mL), with a geometric mean ratio of 0.77 (95% CI: 0.56, 1.05).

The IgG and IgM titers in response to the KLH vaccine were lower for the concomitant remibrutinib arm compared with the placebo arm.

Table 22: Geometric mean ratio (concomitant remibrutinib treatment group to placebo group) and 95% confidence intervals for KLH antibody response (PD analysis set)

Parameter	Treatment	N*	Adjusted Geo-mean	Comparison	Treatment Comparison# Geo-Mean ratio	95%CI
Anti-KLH IgG antibody (U/mL)	Concomitant LOU064	31	94.58	Concomitant LOU064 vs Placebo	0.79	(0.54, 1.15)
	Placebo	30	119.72			
Anti-KLH IgM antibody (U/mL)	Concomitant LOU064	31	61.55	Concomitant LOU064 vs Placebo	0.75	(0.53, 1.08)
	Placebo	30	81.68			

Model: Log-transformed anti-KLH titer data analyzed by a linear model with treatment as fixed effect.
N* = Number of participants included in the analysis with non-missing/valid concentrations at both baseline (Day 15) and 28 days after vaccination (Day 43). KLH = Keyhole Limpet Hemocyanin.
Geometric mean ratio and 95% CI are back transformed from log scale to test non-inferiority at a margin of 0.70. Non-inferiority was concluded if the lower limit of the confidence interval was > 0.70.
Source: [Study F12101-Table 11-9]

Results of the post-hoc supplementary analyses of antibody levels characterised as protective against influenza (≥1:40) or pneumococcal (≥1300 µg/L for 70% of 23 serotypes) infection provide additional supportive evidence that interrupted remibrutinib treatment does not impair the ability to generate protective antibody levels (from non-protective levels at baseline) 4 weeks after vaccination with influenza and PPV-23 vaccines.

No data are available on the effects of live and live-attenuated vaccines in patients receiving remibrutinib and these should not be given concurrently with remibrutinib.

Co-administration with antithrombotic agents

In the Phase III studies patients were allowed to take acetylsalicylic acid up to 100 mg/d or clopidogrel up to 75 mg/d. Participants taking all other anti-platelet medications, dual anti-platelet therapy (e.g. acetylsalicylic acid + clopidogrel) or anti-coagulant medications were excluded from the Phase III studies.

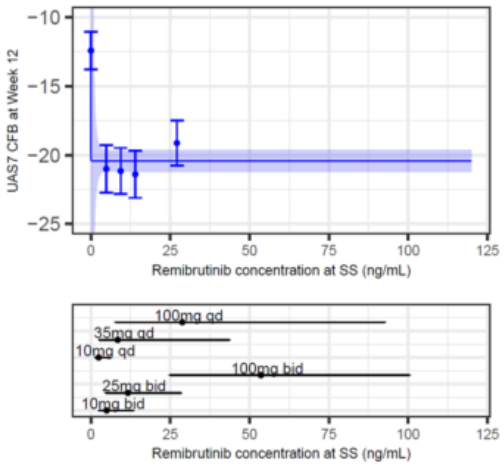
5.2.3.4. Genetic differences in PD response

Genetic differences in PD response were not discussed.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

The relationship between remibrutinib exposures and response to treatment was explored through cross-sectional analysis at Week 12 and was based on data from Studies A2201, A2301 and A2302. The primary exposure metric was Cavg,ss. The efficacy metrics included continuous efficacy endpoints (change from baseline in ISS7, HSS7 and UAS7) and binomial efficacy endpoints (UAS7 = 0, UAS7 ⩽ 6).

The exposure-efficacy analyses consistently suggested that the remibrutinib dose regimen studied in Phase III studies, 25 mg b.i.d., provided PK exposures in the plateau range of the exposure-response relationship for all explored endpoints.



Top panel: Blue line is the model predicted response with 95% CI (shaded area). Blue dots with error bars represent mean with 95% CI of the observed response by quartile of positive Cavg,ss distribution, and a separate bin for placebo response (plotted at Cavg,ss=0).
Bottom panel: Summary of individual Cavg,ss by dosing regimen: median and the 5th and 95th percentiles of distribution for each dosing regimen are represented with the dot and the horizontal bar.
Source: [ER Report-Figure 7-14]

Figure *12*: Exposure-response relationship for UAS7 change from baseline at Week 12 vs. remibrutinib Cavg,ss based on pooled data from studies A2201, A2301 and A2302

Several analyses were conducted to explore the relationship between remibrutinib Cavg,ss and rates of AEs for occurrence of any AE, SAEs, and AESIs (Bleeding, Cytopenia, and Infection) in the three data pools.

All conducted analyses suggested consistently that there is no evidence of increased risk of developing AEs across all the explored categories with increasing PK concentrations within the exposure range for remibrutinib 25 mg b.i.d. The proportion of patients developing AEs was comparable between placebo and remibrutinib exposure subgroups (based on quartiles of Cavg,ss distribution) for occurrence of any AE, SAEs, Cytopenia AESIs, and Infection AESIs. A small numerical imbalance was observed between placebo and remibrutinib exposure subgroups for occurrence of Bleeding AESIs. However, 95% CIs for the proportion of patients with occurrence of Bleeding AESIs were overlapping between remibrutinib Cavg,ss quartiles and fitted logistic regression indicated no statistically significant relationship in all analysed data pools. The observed differences are consistent with that from the pooled safety analysis from both pivotal studies. Furthermore, distribution of Cavg,ss overlapped between patients with and without occurrence of AEs from all assessed categories (no statistically significant difference) in all analysed data pools. Lastly, the fitted logistic regression did not show a statistically significant relationship for occurrence of AEs from all assessed categories with increasing remibrutinib Cavg,ss in all of the analysed data pools.

5.2.5. Dose selection and therapeutic window

The dose levels investigated in the dose range finding Phase IIb (Study A2201) were selected based on analyses from Study X2101 including: BTK occupancy, inhibition of basophil activation (monitored by CD63 and CD203c up-regulation) in healthy volunteers, and impact on skin prick test in healthy volunteers with asymptomatic atopic diathesis – a proxy for mast cell and basophil inhibition within the skin.

In Study X2101, administration of remibrutinib 10 mg q.d. resulted in nearly complete BTK occupancy in blood, > 90% reduction of CD63 up-regulation (8 h after administration of remibrutinib in steady state), and minimal inhibition of wheal size in skin prick test. It was therefore expected that remibrutinib 10 mg q.d. would correspond to the onset of biological activity. At the remibrutinib dose

of 100 mg q.d., the mean reduction of wheal size in skin prick test started to plateau in (Study X2101). Therefore, remibrutinib 100 mg q.d. was expected to correspond to the maximal effect of remibrutinib.

Remibrutinib inhibits BTK by covalent binding and, consequently, the duration of the inhibition is no longer dependent on the exposure of remibrutinib but the turnover of the target. While BTK occupancy in blood is > 24 h, fast BTK turnover in tissue (example: a half life of approximately 5 h in the spleen of rodents) indicated that it potentially required a b.i.d. dose of remibrutinib to reach maximal efficacy and achieve full target occupancy over the whole dosing interval in target tissues. Therefore, doses of remibrutinib 10 mg, 25 mg, and 100 mg, respectively, were expected to accurately describe the dose-response curves of remibrutinib when given b.i.d.

Based on data from Study A2201, remibrutinib 25 mg b.i.d. was selected as the optimal dose and dose regimen for the Phase III studies.

Scenarios of high clinical exposure include co-administration with strong CYP3A4 inhibitors (4.3-fold increase in AUC) or use in patients with severe hepatic impairment (3.12-fold increase in AUC).

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

The PK profile of remibrutinib has been extensively investigated in ten Phase 1/2 studies conducted in healthy volunteers and one Phase 2b dose finding study in CSU patients. The bioanalytical methods used for PK and PD were considered acceptable. Standard statistical methodologies were applied in the analysis of the PK and PD data. Moreover, in addition to PK evaluation by non-compartmental methods (NCA), modeling and simulation analyses using PopPK, PBPK, and E/R were carried out. The clinical program, together with the in vitro studies, is considered appropriate to investigate and provide evidence for the PK characterisation in the target population.

Remibrutinib (LOU064) is a selective oral inhibitor of Bruton's tyrosine kinase BTK, and exhibits target mediated drug disposition (TMDD), which is more pronounced on the lower end of the clinically tested dose range (up to ~50 mg total daily dose). Since no metabolite of remibrutinib reached an exposure of >10% of the total AUC in blood, no separate safety evaluation was deemed necessary for any of the metabolites detected in human.

Absorption

Remibrutinib exhibits rapid absorption across a wide dose range (0.5–600 mg), with a Tmax between 0.5 and 1.25 hours, consistent across studies

In vitro permeability and solubility

Remibrutinib is characterised as a compound with low solubility and high permeability (BCS class 2), which is supported by available data.

Permeability was evaluated in vitro using Caco-2 cell assays, which confirmed that remibrutinib exhibits passive permeability and is a substrate of P-glycoprotein (P-gp). At the proposed clinical dose of 25 mg b.i.d., P-gp–mediated efflux is expected to be saturated, as the estimated luminal concentration of remibrutinib exceeds its apparent Km (Km,app). Therefore, co-administration with P-gp inhibitors is unlikely to further increase the absorption of remibrutinib.

Low solubility is supported by in vitro data confirming that remibrutinib is either slightly soluble or practically insoluble within the whole physiological pH range (1.2 – 7.5). Consequently, co-

administration with drugs that increase gastric pH may significantly affect the solubility and bioavailability of remibrutinib. Therefore, the Applicant performed an additional Phase I study investigating the effect of PPIs rabeprazole and omeprazole on the PK of remibrutinib. The preliminary results suggest that co-administration with acid-reducing agents does not affect PK of remibrutinib in a clinically meaningful way. The applicant commited to submit the final CSR of study CLOU064A02105 as a post-authorisation measure.

Bioavailability

Remibrutinib was administered both orally and IV, alone and in combination with ritonavir (a potent CYP3A4/P-gp inhibitor) and grapefruit juice (moderate intestinal CYP3A4 inhibitor). The absolute oral bioavailability (F) of remibrutinib was 33.8% when administered alone, increasing to 80.9% when co-administered with ritonavir, reflecting substantial inhibition of first-pass metabolism. The estimated fraction metabolized (Fm) via hepatic CYP3A and P-gp was 40%, consistent with the observed increase in bioavailability when ritonavir was used. Co-administration with grapefruit juice resulted in a modest 29% increase in AUC, with an estimated fraction escaping intestinal metabolism (Fgut) of 0.789.

Influence of food

The effect of food was investigated in two Phase I studies (X2101 and A02104) which indicated a modest food effect, hence remibrutinib may be taken regardless of food intake. This is adequately reflected in section 4.2 and 5.2 of the SmPC.

Distribution

Remibrutinib blood-to-plasma ratio (Cb/Cp) is 0.813. Plasma protein binding was evaluated by ultrafiltration in two *in vitro* studies which revealed extensive binding to plasma proteins of 95.4% with no concentration dependence. These values are reported in section 5.2 of the SmPC.

Elimination

In the ADME study, the Applicant reported an arithmetic mean recovery of total radioactivity of 56.2% following oral administration of [^{14}C]-remibrutinib, with 31.8% of the dose recovered in faeces and 24.4% in urine. Following i.v. administration of [^{14}C]-remibrutinib, a total of 97% of the administered dose was recovered, with the majority of radioactivity excreted via faeces (72.9%) and a smaller portion via urine (27.1%). Faecal excretion related to hepatic metabolism represents the predominant pathway for the elimination of drug-related radioactivity. The low fraction of total radioactivity recovered in faeces after oral dosing was most likely due to the lower overall recovery observed in the oral arm, which is considered to result from inadequate homogenisation of faecal samples resulting in an under-measurement of radioactivity.

Metabolism

Metabolism of remibrutinib, investigated in both in vitro and in vivo studies, is primarily driven by CYP3A4-mediated oxidative pathways, with a total of 39 metabolites identified in human blood and excreta. After oral administration in humans, the parent compound was the main component detected in the blood, representing 16.7% of the total [^{14}C]-radioactivity AUC0-24h. Additionally, 18 metabolites were identified in the blood following oral administration of remibrutinib, compared to 13 metabolites after i.v. administration. Similarly, 31 metabolites were identified in urine after oral dosing, whereas 27 were detected following i.v. administration. This difference in the number of metabolites is likely due to the extensive metabolism in the gastrointestinal tract and/or hepatic first-pass metabolism prior to entry into systemic circulation, leading to the formation of additional metabolites not observed with i.v. administration.

No major metabolites of remibrutinib were identified, as none exceeded 10% of the total AUC in blood. The most abundant metabolites, M68a and M68b, were polar, quaternary Phase II metabolites with low permeability, excreted in urine, and not considered reactive since the acrylamide moiety was metabolised and rendered inactive.

In the human ADME study, the cumulative recovery of total radioactivity after oral administration of [^{14}C]-remibrutinib solution was only 56.2% compared to 97% after i.v. administration. According to EMA DDI guideline (CPMP/EWP/560/95/Rev. 1 Corr. 2), the total recovery of radioactivity in urine and faeces should preferably exceed 90% of the administered dose, with more than 80% of the recovered radioactivity structurally identified. This result was unexpected, as preclinical studies in rats had demonstrated over 95% recovery of [^{14}C]-remibrutinib after both oral and i.v. administration.

To further investigate the low recovery, two additional participants received a 100 µg i.v. microdose of [^{14}C]-remibrutinib along with multiple 100 mg b.i.d. oral doses of unlabelled remibrutinib, mirroring the oral regimen in the study. Following i.v. administration, approximately 97% of total radioactivity was recovered. According to the Applicant, these results suggest that the issue of low recovery after oral dosing likely originates within the intestinal tract.

Despite comprehensive follow-up investigations, the exact reason for the incomplete recovery observed in the human ADME study could not be definitively established. However, based on all available evidence, the most plausible explanation for the low recovery following oral administration of remibrutinib is the inhomogeneous nature of the faecal samples, resulting in underestimation of the radioactivity excreted via faeces. Nevertheless, as the metabolism studies in both animals and humans provided a rather comprehensive characterisation of remibrutinib metabolic pathways, this issue was not pursued further by the CHMP.

Dose proportionality and time dependency

In both the SAD and MAD cohorts, Cmax and AUC increased with increasing doses across the entire range tested. However, dose proportionality was not observed over the full range, indicating a less than proportional increase in exposure with higher doses.

PopPK analysis demonstrated approximate dose linearity within the range of 10 mg to 200 mg. At doses above 100 mg b.i.d., absorption likely becomes the exposure-limiting factor, probably due to the low solubility of remibrutinib. Nevertheless, this is not relevant for the proposed clinical dose of 25 mg b.i.d. Since remibrutinib is dosed 25 mg b.i.d., dose non-proportionality observed is not expected to affect current dosing recommendations.

The PK of remibrutinib is time-dependent due to the influence of covalent target binding on its clearance. Since the proposed remibrutinib posology is twice daily, the impact of covalent target binding is expected only at the initiation of therapy, and therefore, no dosing adjustments are anticipated.

Population PK analysis

Estimates of PK parameters from the final model indicated fast clearance (CL/F=160 L/h) and large volume of distribution (central V1/F=58 L and peripheral V2/F=1180 L) in line with the results from FIH study X2101, although very high variability was observed.

Even though, all structural model parameters and standard deviation of the random effects were estimated with good precision, shrinkage is quite high and estimated IIV of intercompartmental clearance and deep volume compartment are extremely high. This could be due to majority of PK samples (coming from phase 3 studies) being collected around Cmax. This is a significant limitation for subsequent exposure-response analyses that used individual EBEs for PK parameters. With such high shrinkage, individual estimates would be pulled towards the typical population value and would

not reflect the true individual variability.

In the PopPK analysis, 76 (6.6%) individuals were healthy volunteers and 1076 (93.4%) were patients with CSU. The dataset is considered representative of CSU patients.

pcVPC plots stratified by study show overprediction of variability for studies with rich PK sampling (X1101, X2101, A02104), while the predictions overall capture adequately observed data in studies with sparse sampling.

Overall, based on the Pop PK analysis, it is agreed that no clinically relevant covariate effects were identified and statement in SmPC section 5.2 can be supported. However, the model is not considered to adequately account for inter-individual variability in exposure-responses analyses.

PBPK

The PBPK model was based on sufficient amount of *in vitro*, as well as *in vivo* clinical data.

Remibrutinib PK after SAD/MAD appears to be reasonably well predicted.

The developed PBPK model was applied to predict untested clinical scenarios including the DDI magnitude of remibrutinib with weak (fluvoxamine), moderate (erythromycin, fluconazole, efavirenz), and strong (ketoconazole, itraconazole, rifampin) CYP3A4 precipitants as well as the DDI potential of remibrutinib 25 mg b.i.d. with CYP and transporter sensitive substrates, including midazolam (CYP3A4 substrate), caffeine (CYP1A2 substrate), tolbutamide (CYP2C9 substrate), digoxin (P-gp substrate) and rosuvastatin (OATP1B/BCRP substrate). In addition, the effect of acid reducing agents (ARAs, such as proton pump inhibitors) in the presence and absence of a meal, as well as the effect of renal impairment at 25 mg b.i.d. and 100 mg b.i.d., on the PK of remibrutinib were also predicted. Uncertainty associated with model predictions was not reported. The PBPK model was only regarded as supportive, and relevant studies were conducted when needed.

Special populations

Renal impairment

No dedicated renal impairment study was conducted since elimination of remibrutinib via kidneys appeared to be minimal (<1% of oral dose in the first-in-human study and 2.93% of the IV dose in the mass-balance study). Impact of renal impairment on PK of remibrutinib was explored through evaluation of creatinine clearance as a covariate on remibrutinib CL/F in the population PK model, which is an acceptable approach. Even though renal function was not identified as a significant covariate, in the population PK dataset there was very limited number of subjects in categories 'moderate' (n=25; 2.2%) and 'severe' (n=1; 0.1%) renal impairment. Therefore, it is not possible to draw firm conclusions from the population PK analysis on the impact of moderate and severe RI on PK of remibrutinib. Moreover, in severe renal impairment other non-renal elimination pathways could also be affected, such as metabolising enzymes which could have an indirect effect on remibrutinib PK. However, any potential increase in exposure is not expected to be higher than the observed increase in exposure in subjects with severe hepatic impairment. PBPK modelling was supportive of that conclusion. Therefore, it is agreed that no dose adjustment is needed in patients with renal impairment. This is adequately described in the SmPC.

Hepatic impairment

Remibrutinib is extensively metabolised, with CYP3A4 metabolism being the predominant elimination pathway. Therefore, it is expected that hepatic impairment would have a significant impact on remibrutinib PK. Study A2101 evaluated the impact of varying degrees of impaired hepatic function (mild, moderate and severe according to Child Pugh categorisation) on the PK of remibrutinib following multiple dose administration (25 mg b.i.d.). Study results indicate increase in exposure with

increasing degree of hepatic impairment. AUClast,ss increased by 2.33-, 2.3- and 3.49-fold in subjects with mild, moderate and severe hepatic impairment, respectively. In subjects with severe HI, remibrutinib total blood Cmax,ss, AUCtau and AUClast,ss were approximately 1.99-, 3.12-, and 3.49-fold that of the healthy matched controls, respectively.

Fraction unbound was similar in subjects with different degree of HI, so similar results were obtained for unbound plasma remibrutinib PK parameters and reporting the results for total blood concentrations in section 5.2 of the SmPC is acceptable.

The supplementary exposure-safety analyses did not indicate any statistically significant relationship between remibrutinib exposure subgroup and occurrence of any AEs, serious AEs, Cytopenia AESI, Infection AESI and Bleeding AESI, although some small numerical trends toward higher proportion of events in higher exposure subgroup was observed for any AEs, Infection AESI and Bleeding AESI.

Given the observed high variability of AUCtau in CSU patient population, around 2-fold increase compared to the mean value is still considered to be within therapeutic exposure range for the given dose. Together with supplementary exposure-safety analyses provided, it is agreed that increase in exposure in patients with mild and moderate HI is not expected to impact significantly the safety profile of remibrutinib and that no further warnings are necessary.

On the contrary, in subjects with severe hepatic impairment, AUCtau increased 3.12 (90%CI 1.98-4.94-fold). Since upper boundary of the 90%CI covers even 5-fold higher exposures and no dose adjustment is possible, as a measure of precaution, the use of remibrutinib should be avoided in patients with severe hepatic impairment. This has been reflected in section 4.2 of the SmPC.

Gender, ethnic factors, weight, age

Based on population PK analysis, no clinically relevant effects of age, sex, race/ethnicity and body weight are expected on remibrutinib PK. This is adequately described in the SmPC.

Therapeutic window

According to the applicant, exposures relevant for safety evaluation are exposures achieved at 100 mg b.i.d.

Geometric mean AUCtau at 100 mg b.i.d was 3.7- (week 4) to 4.2-fold (week 12) higher than at 25 mg b.i.d. dose, while geometric mean Cmax at 100 mg b.i.d. was 3.1- (week 4) to 3.3-fold (week 12) higher than at 25 mg b.i.d. dose.

Clinical scenarios of high remibrutinib exposure include co-administration with CYP3A4/P-gp inhibitors and hepatic impairment.

The wide therapeutic window, based on safety data from patients treated with 4-fold higher dose (100 mg b.i.d.) in studies A2201 and A2201E was not found sufficiently substantiated for long-term treatment of CSU patients (see safety assessment). Moreover, lower bound of the therapeutic window has also not been defined.

Subsequently, exposures achieved during pivotal Phase 3 studies with the proposed 25 mg BID dose are considered representative of the therapeutic window in the CSU indication and this has consequences for the co-administration with strong CYP3A4 inhibitors, as well as for patients with severe hepatic impairment.

Pharmacokinetic interactions studies

Three in vivo DDI studies (X2102, X2103, and A02103) have been conducted to investigate drug–drug interaction (DDI) potential of remibrutinib both as an object and as a precipitant, based on positive results of the in vitro studies.

In study X2103, the effect of remibrutinib co-administration with ritonavir (a strong inhibitor of both intestinal and hepatic CYP3A4 and P-gp) and grapefruit juice (a moderate-to-strong inhibitor of intestinal CYP3A4) was investigated. Co-administration with ritonavir resulted in a 3.3-fold increase in Cmax and a 4.3-fold increase in AUC, while grapefruit juice led to approximately a 1.24-fold increase in Cmax and a 1.29-fold increase in AUC, indicating that remibrutinib is not a sensitive substrate for CYP3A4 inhibition. Given the extent of exposure increase when concomitantly administered with strong CYP3A4 inhibitors, the SmPC section 4.5 states that concomitant use with strong CYP3A4 inhibitor must be avoided.

Co-administration of moderate CYP3A4 inhibitors was allowed in pivotal Phase 3 studies and exposure in those patients (even though the numbers are limited) is within the therapeutic window of CSU patients taking remibrutinib 25 mg b.i.d., therefore it is agreed that co-administration may be allowed without dose modifications.

In study A02103, the effect of carbamazepine (a strong CYP3A4 inducer) on exposure of remibrutinib was evaluated. Co-administration with carbamazepine resulted in a 74% and 78% reduction in remibrutinib Cmax and AUC, respectively, indicating remibrutinib is a sensitive substrate to CYP3A4 induction. Therefore, concomitant use of remibrutinib with strong or moderate CYP3A4 inducers must be avoided.

In study X2102, the DDI potential of remibrutinib (100 mg b.i.d.) was evaluated with a monophasic oral contraceptive (ethinylestradiol and levonorgestrel) and with sensitive probe substrates for CYP3A4 (midazolam), CYP1A2 (caffeine), and CYP2C9 (tolbutamide). The available data suggest a weak CYP3A4 inhibition by remibrutinib, as indicated by modest increases in Cmax and AUC0-24h of ethinylestradiol (28%- and 16%), levonorgestrel (36% and 39%), and midazolam (36%- and 43%). However, the results may be different with the proposed therapeutic dose (25 mg b.i.d). In conclusion, a warning is included in the SmPC that remibrutinib should not be used concomitantly with CYP3A4 substrates of narrow therapeutic index.

For the sensitive CYP2C9 substrate tolbutamide concentration at 24 hours post-dose (C24h) increased by 27–30% following administration of the remibrutinib at 100 mg b.i.d., indicating a weak inhibitory effect (AUCR ≥ 1.25). The rationale for using the C24h value is unclear, as a single time-point concentration such as C24h does not adequately represent overall drug exposure required for a reliable DDI assessment. The DDI Guideline (EMA/CHMP/ICH/652460/2022) recommends using AUC to assess drug interactions. However, as in vitro studies showed no inhibition at clinically relevant concentrations of remibrutinib, and a 4-fold higher dose of 100 mg b.i.d. was used in the clinical DDI study, no clinically significant interactions with CYP2C9 are expected at the proposed posology of 25 mg b.i.d.

For the in vivo assessment of CYP1A2 inhibition, the totality of evidence from both in vitro and in vivo studies suggests that a clinically relevant inhibitory effect on CYP1A2 is unlikely.

In study A02103, remibrutinib was identified as a weak inhibitor of P-gp and BCRP, as indicated by increased exposure (AUC ≥ 1.25) of their sensitive substrates. In the presence of remibrutinib, Cmax of the P-gp substrate digoxin increased by 110% and AUC 40%, while for the BCRP substrate rosuvastatin, Cmax and AUC increased by 60% and 70%, respectively. Therefore, it is recommended to monitor patients more frequently when using remibrutinib with P-gp P-gp and BCRP substrates with a narrow therapeutic index. This has been included in the SmPC.

Pharmacodynamics

The mechanism of action of remibrutinib has been sufficiently characterised. Pharmacodynamics were characterised by assessing target occupancy (i.e., BTK occupancy) and distal pathway inhibition in basophils and B cells. BTK occupancy increased in a dose dependent manner, with almost complete

BTK occupancy observed starting at 30 mg remibrutinib (given as single dose) or total daily dose of 50 mg (given q.d.) which was sustained up to 48 hours after the last dose. Due to the covalent binding to the target and time needed for turn-over of the drug-protein complex, PD effects persist longer than systemic drug exposure. BTK occupancy returned to pre-dose levels approximately 2 to 3 weeks after the last dose.

Full inhibition of basophil activation measured by CD63 expression was observed at a dose of 50 mg q.d. remibrutinib or higher.

PD effects in the skin were evaluated by the decrease in the wheal diameter of the skin prick test. There was a dose-dependent trend up to 100 mg q.d.

Dose-dependent inhibition was also observed for the activation of B cells, starting at 30 mg single dose of remibrutinib.

In the FIH study, effect of remibrutinib on platelet function was observed as an increase in time taken for platelet aggregation from the baseline values and an increase in clotting time. For further evaluation of these effects in the form of bleeding AEs, see section 5.4 Clinical safety.

Study A2305 ruled out an increase of > 3 mmHg in 24-hour average systolic blood pressure at steady state (Week 4) compared to baseline, measured by ABPM. Analyses for secondary endpoints showed similar results as the primary analysis, showing no significant change in blood pressure at Week 4 compared to baseline. Although results from study A2305 appear reassuring, measurement was done only at 4 weeks' time point, long term safety data are missing, further data will be obtained with study CLOU064A2303B.

Due to its immunomodulatory activity, remibrutinib could alter immune response to vaccines. The effect of remibrutinib on the immune response following vaccination with influenza vaccine (T cell-dependent), pneumococcal polysaccharide (PPV-23) vaccine (T cell-independent) and keyhole limpet hemocyanin (KLH) vaccine (T cell-dependent) was evaluated for the interrupted (1 week prior and until 2 weeks after vaccination) and concomitant remibrutinib treatment.

The interrupted remibrutinib regimen was shown to be non-inferior to placebo in responder rates for one (Influenza B Austria) of the four antigens in influenza vaccine and for PPV-23 vaccine. Interrupted remibrutinib dosing was also non-inferior to placebo for anti-KLH IgG response, while did not show non-inferiority for anti-KLH IgM response.

The concomitant remibrutinib dosing showed lower antibody response compared to placebo for all 3 vaccines tested. Additional post-hoc supplementary analyses were performed of antibody levels characterised as protective against influenza infection (≥1:40) or against pneumococcal infection (≥1300 µg/L for 70% of 23 serotypes). These analyses were supportive of interrupted remibrutinib dosing, suggesting that stopping the treatment of remibrutinib 1 week prior to until 2 weeks after vaccination would not impair the generation of protective levels of antibodies after influenza or PPV-23 vaccination. A recommendation to consider interrupting the treatment with remibrutinib around planned vaccinations has been included in section 4.4 and 4.5 of the SmPC.

The safety of remibrutinib with live or live-attenuated vaccines has not been studied, these vaccines should not be given concomitantly with remibrutinib.

Exposure-response analyses

Provided exposure-response analyses are considered supportive only, without significant impact on benefit-risk evaluation. One of the major limitations of these analyses are the exposure metrics derived from individual empirical Bayes estimates. Due to high shrinkage in the Pop PK model, these estimates do not reflect the true inter-individual variability. This can lead to underestimation or failure

to detect real relationships. Moreover, exposure-safety analyses are based mostly on the exposure range from patients receiving proposed 25 mg b.i.d. dose which makes it difficult to characterize exposure-response trends. The Applicant suggests that remibrutinib has a wide therapeutic window, based on safety data from patients treated with 4-fold higher dose (100 mg b.i.d.). However, there was only a limited number of patients receiving this dose included in the analysis (Safety Pool 2) no firm conclusions can be drawn.

Exposure-efficacy analyses suggest that proposed dosing regimen (25 mg b.i.d.) results with PK exposures in the plateau of the exposure-response relationship for all explored endpoints. Response to treatment was comparable across different covariates explored, except for patients with low IgE levels at baseline, CU-Index positive patients at baseline and patients who had prior history of angioedema, who showed higher response to remibrutinib treatment.

All conducted exposure-safety analyses did not show any statistically significant relationship with remibrutinib Cavg,ss. Other parameters than Cavg,ss (e.g. Cmax,ss) that could be relevant for safety were not evaluated. However, this will not be requested due to exploratory nature of these analyses. Even though not statistically significant, some small numerical trends could be observed for increase in SAEs, bleeding, cytopenias and infections with increase in Cavg,ss for some of the safety pools. Nevertheless, no conclusions can be made.

Concentration-QTcF analysis was conducted on a pooled dataset containing matched PK and QTcF measurements from Studies X1101, X2101 and A2201. Based on the results from the analysis, the estimated increase in QTcF is not considered to be of clinical concern at the proposed dose regimen (25 mg b.i.d.), in the scenario of high clinical exposure (when co-administered with strong CYP3A4 inhibitor) nor at the exposures 2-fold of high clinical exposure. Additional information on methodology was presented as requested and it supports the validity of concentration-QTcF analysis. The results from the analysis support that no clinically significant prolongation of QTcF is expected with remibrutinib as stated in section 5.1 of SmPC.

5.2.6.2. Conclusions

A robust clinical pharmacology package has been provided to characterise PK and PD of remibrutinib. Available clinical data supports therapeutic window which is covering exposures achieved during pivotal Phase 3 studies with the proposed 25 mg BID dose. Safety of higher exposures as proposed by the Applicant (up to 4-fold) has not been substantiated for long-term treatment of CSU patients. Since it is not possible to adjust the dose, as a measure of precaution, the use of remibrutinib should be avoided in patients with severe hepatic impairment, and in patients co-administering strong CYP3A4 inhibitors. When receiving non-live vaccines, interruption of remibrutinib treatment should be considered in order to optimise immune response. Live vaccines should not be given concomitantly with remibrutinib.

5.3. Clinical efficacy

5.3.1. Dose response study

Methods

Study CLOU064A2201 (also referred to as Study A2201) was a randomised, double-blind, parallel-group, placebo-controlled dose-finding study to assess the adequate dose of remibrutinib in patients with CSU. Adult patients with presence of itch and hives for ≥ 6 consecutive weeks prior to screening and UAS7 score (range: 0 - 42) ≥ 16 and HSS7 score (range: 0 - 21) ≥ 8 during 7 days prior to

randomisation inadequately controlled by second generation H1-AHs were randomised in a 1:1:1:1:1:1:1 ratio to 6 remibrutinib arms (10 mg q.d., 35 mg q.d., 100 mg q.d., 10 mg b.i.d., 25 mg b.i.d., 100 mg b.i.d.) and were compared to placebo to select a dosing regimen for the Phase III program. The patients were stratified by prior anti-IgE biologic use (i.e., had previous treatment with anti-IgE biologic or not) and geographical region. The total study duration was up to 18 weeks (2 weeks of screening period, 12 weeks of treatment period, and 4 weeks of treatment-free follow-up period).

Throughout the study, all patients were on a stable, locally standard approved dose of a second generation H1-AHs ("background medication"). Patients could take an additional second generation H1-AHs, different from the H1-AHs used as background medication, on an as-needed basis to treat CSU flare-ups of unbearable symptoms. Key efficacy evaluation criteria were the reduction of signs (hives) and symptoms (itch) of CSU measured with UAS7 and the improvement of health-related QoL as measured by DLQI.

The primary efficacy objective of the study was to characterise a dose-response relationship between remibrutinib administered in the above-mentioned range of doses and regimens compared to placebo with respect to change from baseline in UAS7 at Week 4 (primary endpoint). The key secondary endpoints were change from baseline in UAS7 score at Week 12 and over time, percentage of patients with complete absence of itch and hives (UAS7 = 0) over time, and percentage of patients with disease activity control (UAS7 $\leq$ 6) over time.

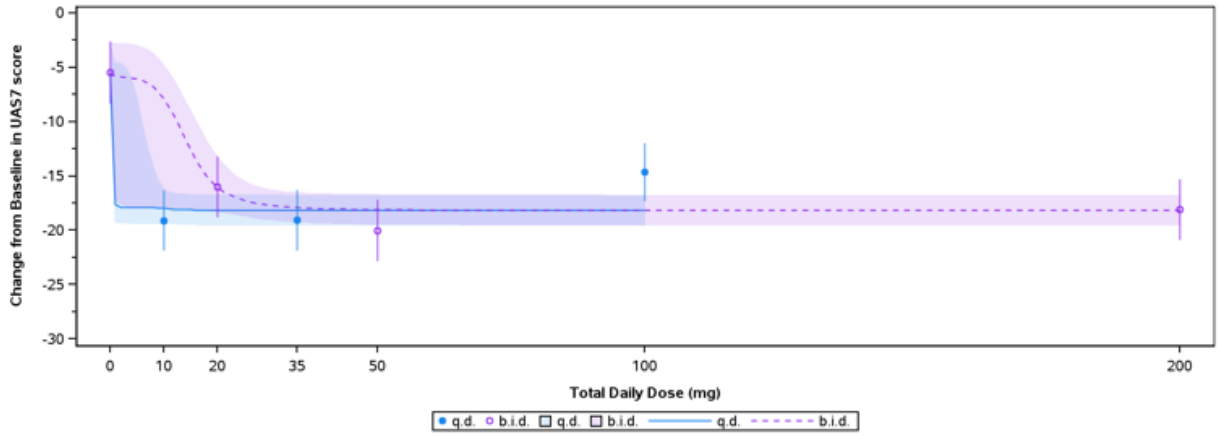
Results

The efficacy of remibrutinib in patients who remain symptomatic despite H1-AH treatment was assessed in a total of 311 randomised adult patients for the following dose regimens: 10 mg q.d. (n = 44), 35 mg q.d. (n = 44), 100 mg q.d. (n = 47), 10 mg b.i.d. (n = 44), 25 mg b.i.d. (n = 44), 100 mg b.i.d. (n = 45) vs. placebo (n = 43).

The study demonstrated clinical efficacy of remibrutinib in the treatment of CSU, with all tested doses showing superior efficacy over placebo at Week 4 and Week 12.

A dose-response was observed for remibrutinib treatment compared to placebo with respect to change from baseline in UAS7 score at Week 4, with the dose-response plateau achieved at 10 mg q.d. and 25 mg b.i.d., based on an MCP-mod approach (max T-statistics: 6.67, one-sided p-value < 0.0001).

Figure *13*: Dose response shape based on change from baseline UAS7 score at Week 4 (FAS)

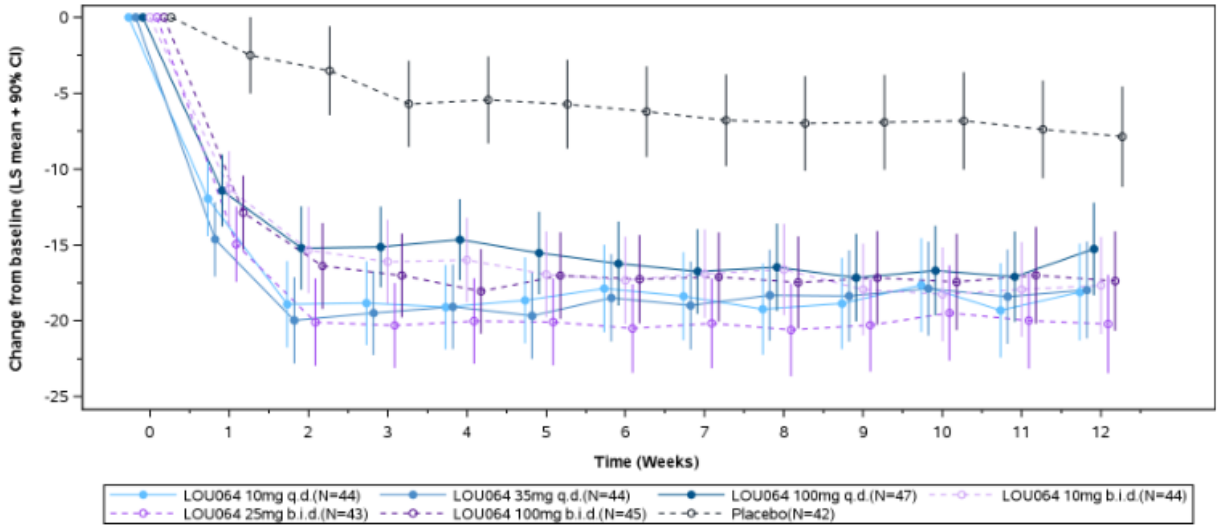


The dose response curve shows the median value from 5000 bootstrap samples.
The shade area displays the 90% prediction interval from 5000 bootstrap samples.
The dots with the error bar represent LS mean and 90% CI from MMRM model.
LS Mean: least square mean; MMRM: mixed effect model for repeated measurements.
Source: [Study A2201-Figure 14.2-1]

At Week 12, higher reductions in UAS7 score from baseline were observed in all remibrutinib treatment arms when compared to placebo. Across all remibrutinib treatment arms, the largest treatment difference in LS means (90% CI; p-value) compared to placebo was observed with the remibrutinib 25 mg b.i.d. arm (-12.35, 90% CI: -16.82, -7.87; one-sided p-value < 0.0001).

Over time, higher reductions in UAS7 score from baseline were observed in all remibrutinib arms (range: −11.29 to −20.61) compared to placebo (−2.50 to −7.87) at all time-points. Reductions in UAS7 score were observed as early as Week 1, continued to reduce at Week 2 and thereafter remained constant up to Week 12 in all remibrutinib arms. Except for the 100 mg q.d. arm, reductions in LS mean UAS7 score were comparable between the treatment arms.

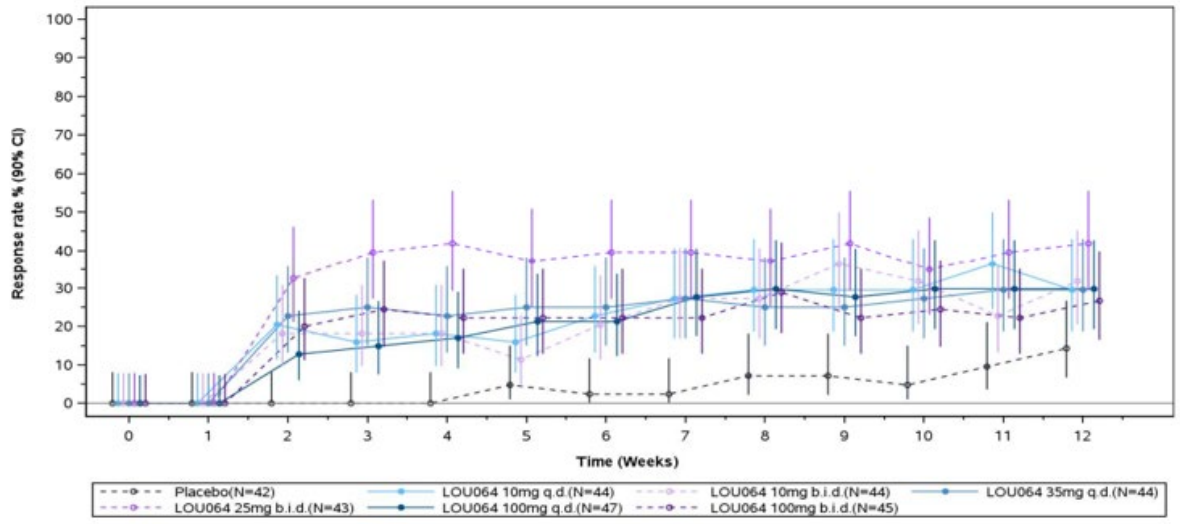
Figure *14*: Mixed-effect repeated measurement analysis of UAS7 score change from baseline - Treatment period (FAS)



Source: Figure 14.2-2_c

At Week 12, the number of patients with complete absence of itch and hives (UAS7 = 0) was higher in all remibrutinib arms compared to the placebo arm; however, the remibrutinib 25 mg b.i.d. arm had the highest proportion of UAS7 = 0 responders (41.9%) compared to all other active treatment arms (remibrutinib 10 mg q.d.: 29.5%, 35 mg q.d.: 29.5%, 100 mg q.d.: 29.8%, 10 mg b.i.d.: 31.8%, and 100 mg b.i.d.: 26.7%), and placebo (14.3%) (non-responder imputation). This was observed as early as Week 2, after which the rate of UAS7 = 0 increased and was maintained up to Week 12.

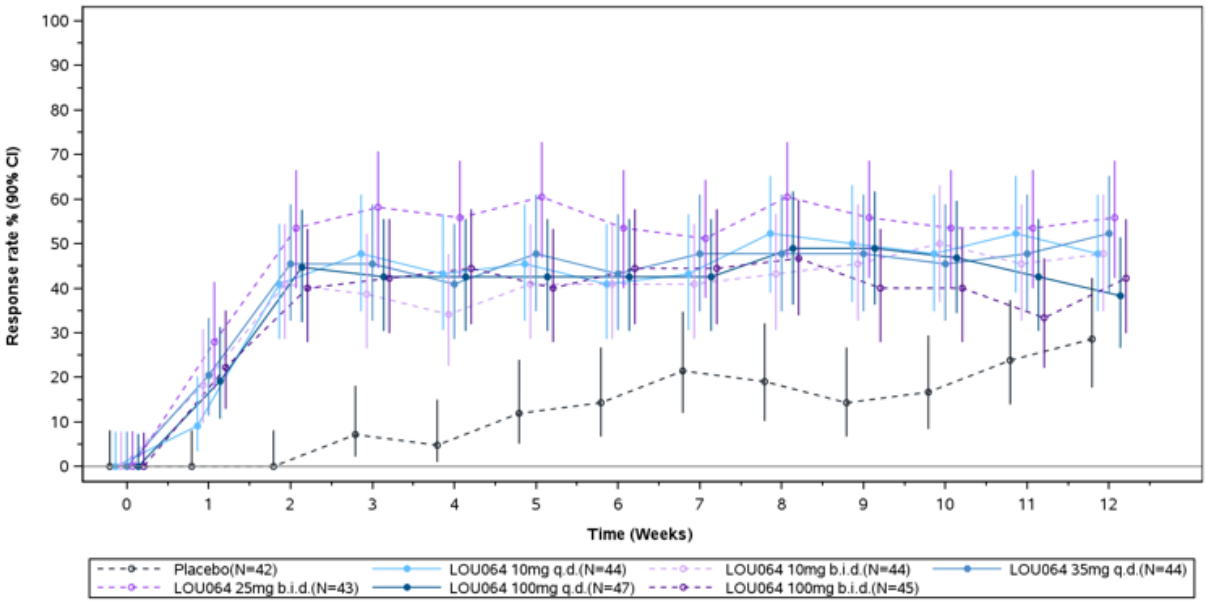
Figure *15*: UAS7 = 0 response rate over time by treatment arm - Treatment period (non-responder imputation) (FAS)



Source: [Study A2201-Figure 14.2-4.2]

Similarly, at Week 12, the remibrutinib 25 mg b.i.d. arm had the highest proportion of patients (55.8%) achieving disease activity control (UAS7 ≤ 6) compared to all other active treatment arms (remibrutinib 10 mg q.d.: 47.7%, 35 mg q.d.: 52.3%, 100 mg q.d.: 38.3%, 10 mg b.i.d.: 47.7%, and 100 mg b.i.d.: 42.2%), and compared to the placebo arm (28.6%). The highest proportion of patients with UAS7 ≤ 6 in all remibrutinib arms compared to placebo was also observed in the 25 mg b.i.d. arm as early as Week 1.

Figure *16*: UAS7 ≤ 6 response rate over time by treatment arm - Treatment period (non-responder imputation) (FAS)



Source: [Study A2201-Figure 14.2-4.1]

A higher proportion of patients with AAS7 = 0 response (absence of angioedema) for cumulative of 12 weeks was observed in all remibrutinib arms (31.1% to 52.3%) compared to the placebo arm (28.6%). The mean duration of cumulative number of weeks with AAS7 = 0 response was higher in all remibrutinib arms (9.2 weeks to 10.5 weeks) compared to the placebo arm (8.2 weeks).

The proportions of patients with DLQI score of 0 or 1 (no impact on patients' dermatology-related QoL) was higher in all remibrutinib arms compared to the placebo arm at Week 4 and Week 12. Across all remibrutinib arms, proportions of patients with DLQI score of 0 or 1 was highest in the remibrutinib 25 mg b.i.d. arm at Week 4 (remibrutinib 25 mg b.i.d.: 51.2% vs. placebo: 16.7%) (non-responder imputation) and Week 12 (remibrutinib 25 mg b.i.d.: 53.5% vs. placebo: 28.6%) (non-responder imputation).

A lower b.i.d. dose (10 mg b.i.d.) or q.d. dosing did not enable patients to achieve the maximum efficacy, which could be achieved with 25 mg b.i.d. dosing, especially when considering the UAS7 score. Achievement of disease activity control (UAS7 ≤ 6) and complete absence of itch and hives (UAS7 = 0) are therapeutic objectives for patients with CSU. At the same time, higher dosing regimens, such as 100 mg b.i.d., are not required to reach maximum efficacy. Hence, the 25 mg b.i.d. dose regimen has been chosen for the Phase III studies.

5.3.2. Main studies

Note: Studies A2301 and A2302 were identical in design and are presented and assessed together. Any difference between the studies will be highlighted. These two studies are pivotal studies in this MAA.

5.3.2.1. Study CLOU064A2301 (Study A2301) and Study CLOU064A2302 (Study A2302)

5.3.2.1.1. Study title

Study CLOU064A2301: A multicenter, randomised, double-blind, placebo-controlled Phase 3 study of remibrutinib (LOU064) to investigate the efficacy, safety, and tolerability for 52 weeks in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines.

EU CT number: 2021-000471-37

NCT number: NCT05030311

Study CLOU064A2302 A multicenter, randomised, double-blind, placebo-controlled Phase 3 study of remibrutinib (LOU064) to investigate the efficacy, safety, and tolerability for 52 weeks in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines.

EU CT number: 2021-000424-35

NCT number: NCT05032157

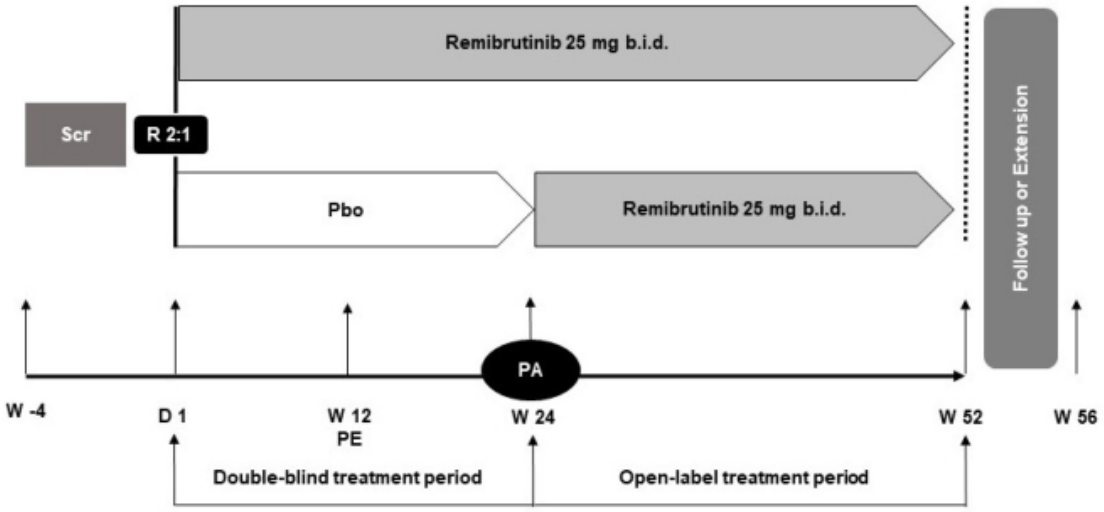
5.3.2.1.2. Study design

Studies A2301 and A2302 were identical in design. They were two global, multicenter, randomised, double-blind, parallel-arm, placebo-controlled Phase III studies, investigating the safety, tolerability, and efficacy of remibrutinib (25 mg b.i.d.) in adult patients with CSU inadequately controlled by second generation H1-AHs. The studies consisted of four periods and the total study duration was up to 60 weeks:

- Screening period: up to 4 weeks.
- Double-blind treatment period: 24 weeks of double-blind treatment with remibrutinib or placebo.
- Open-label treatment period: 28 weeks of open-label treatment with remibrutinib.
- Follow-up period: 4 weeks of treatment-free follow-up.

An extension Phase IIIb study, CLOU064A2303B, was initiated to allow eligible patients to roll over after completion of the open-label treatment period.

Figure *17*: Study schema (Studies A2301 and A2302)



D 1: Day 1, Pbo: placebo, PA: Primary Analysis, PE: Primary Endpoint; Scr: Screening, W: Week.
Source: Appendix 16.1.1-Protocol-Figure 3-1

5.3.2.1.4.1. Treatment

Novartis Global Clinical Supply supplied oral FCTs (remibrutinib 25 mg and remibrutinib 25 mg matching placebo (both blinded) and remibrutinib 25 mg (open-label)) in both pivotal studies in appropriately labelled bottles.

Rationale for choice of control drug

Placebo was chosen as a comparator to adjust for the fluctuating nature of CSU, which can result in a pronounced placebo effect.

Investigational or other study treatment dose adjustments were not permitted.

Study treatment interruptions were foreseen to manage the following events:

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

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

5.3.2.1.4.1. Randomisation

At the randomisation visit, all eligible patients were randomised in a 2:1 ratio via IRT to one of the treatment arms. The Investigator or his/her delegate contacted the IRT after confirming that the

patient fulfilled all the inclusion/exclusion criteria. The IRT assigned a randomisation number to the patient, which was used to link the patient to a treatment arm and specified a unique medication number for the first package of study treatment to be dispensed to the patient.

Randomisation was stratified by prior anti-IgE biologic use (Yes/No) and geographic region (LaCAN (Latin America, Caribbean and Canada), RE (Region Europe), US, AMEA (Asia, Middle East & Africa), Japan (Study A2301 only), China (Study A2302 only).The maximum number of participants with prior exposure to anti-IgE biologics was limited to approximately 30% of the total study population.

5.3.2.1.4.1. Blinding

Patients, Investigator, staff, persons performing the assessments, and the study team directly involved with the conduct of the study remained blinded to the identity of the treatment during the double-blind treatment period (i.e., up to Week 24), from the time of randomisation until the final database lock. At the time of the Week 24 analysis, a selected applicant team created and reviewed unblinded results (used to further inform decision-making for the remibrutinib development program). No access to the unblinding information was given to the study team conducting the study until the final database lock.

Unblinding a single participant at the study site for safety reasons (necessary for participant management) could occur via an emergency system in place at the site. As a result, the participant should be discontinued from the study treatment.

5.3.2.1.4.1. Patient population

Key inclusion criteria

- Male and female adult patients ≥ 18 years of age at the time of screening.
- CSU duration for ≥ 6 months prior to screening (defined as the onset of CSU determined by the Investigator based on all available supporting documentation).
- Diagnosis of CSU inadequately controlled by second generation H1-AHs at the time of randomisation defined as:
    - The presence of itch and hives for ≥ 6 consecutive weeks prior to screening despite the use of second generation H1-AHs during this time period
    - UAS7 score (range: 0 - 42) ≥ 16, ISS7 score (range: 0 - 21) ≥ 6 and HSS7 score (range: 0 - 21) ≥ 6 during the 7 days prior to randomisation (Day 1)
- Documentation of hives within three months before randomisation (either at screening and/or at randomisation; or documented in the patient's medical history).
- Willing and able to complete an urticaria patient daily diary (UPDD) for the duration of the study and adhere to the study protocol.
- Patients should not have had more than one missing UPDD entry (either morning or evening) in the 7 days prior to randomisation (Day 1).

Key exclusion criteria

- Patients with clearly defined predominant or sole trigger of their chronic urticaria (chronic inducible urticaria/CINDU) including urticaria factitia (symptomatic dermographism), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria.

- Other diseases with symptoms of urticaria or angioedema, including but not limited to urticaria vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary urticaria, or drug-induced urticaria.
- Any other skin disease associated with chronic itching that might influence in the Investigator's opinion the study evaluations and results, e.g., atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or psoriasis.
- Participants taking medications prohibited by the protocol.
- Evidence of clinically significant cardiovascular (such as but not limited to myocardial infarction, unstable ischemic heart disease, New York Heart Association Class III/IV left ventricular failure, arrhythmia, and uncontrolled hypertension within 12 months prior to Visit 1), neurological, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic, hematological disorders, gastrointestinal disease or immunodeficiency that, in the Investigator's opinion, would compromise the safety of the patient, interfere with the interpretation of the study results or otherwise preclude participation or protocol adherence of the patient.
- Significant bleeding risk or coagulation disorders.
- History of gastrointestinal bleeding, e.g., in association with use of nonsteroidal anti-inflammatory drugs, that was clinically relevant (e.g., where intervention was indicated or requiring hospitalisation or blood transfusion).
- Requirement for anti-platelet medication, except for acetylsalicylic acid up to 100 mg/d or clopidogrel up to 75 mg/d. The use of dual anti-platelet therapy (e.g., acetylsalicylic acid + clopidogrel) was prohibited.
- Requirement for anticoagulant medication (for e.g., warfarin or novel oral anti-coagulants).
- History or current hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or ALT/AST levels of > 1.5 × ULN or INR of > 1.5 at Screening.

Concomitant and rescue therapies

Background therapy

Throughout the studies, patients were required to take a second generation H1-AH at a locally label approved dose. Background therapy was not to be changed until the Week 12 visit and could only be changed thereafter if medically required (i.e., adverse reactions that are attributable to background therapy as per Investigator's judgment).

Rescue therapies

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

Table 23: Standardisation of different rescue H1-AH doses used

Rescue H1-AHs	Doses used in study	Dosing Standard
BEPOTASTINE BESILATE		
	10 mg	1
BILASTINE		
	20 mg	1
CETIRIZINE		
	10 mg	1
CETIRIZINE HYDROCHLORIDE		
	10 mg	1
	5 mg	1/2
CHLORPHENAMINE MALEATE		
	4 mg	1
CLEMASTINE FUMARATE		
	1 mg	1
DESLORATADINE		
	5 mg	1
	8.8 mg	1.76
DIPHENHYDRAMINE		
	25 mg	1
DIPHENHYDRAMINE HYDROCHLORIDE		
	25 mg	1
EBASTINE		
	10 mg	1
	20 mg	2
EMEDASTINE FUMARATE		
	2 mg	1
EPINASTINE HYDROCHLORIDE		
	10 mg	1
	20 mg	2
FEXOFENADINE		
	120 mg	2/3
	180 mg	1
	360 mg	2
	60 mg	1/3
FEXOFENADINE HYDROCHLORIDE		
	120 mg	2/3
	180 mg	1
	60 mg	1/3
KETOTIFEN		
	1 mg	1
LEVOCETIRIZINE		
	5 mg	1
	10 mg	2
LEVOCETIRIZINE DIHYDROCHLORIDE		
	5 mg	1
	10 mg	2
LORATADINE		
	10 mg	1
MIZOLASTINE		
	10 mg	1
OLOPATADINE HYDROCHLORIDE		
	5 mg	1
RUPATADINE		
	10 mg	1
RUPATADINE FUMARATE		
	10 mg	1
	12.8 mg	1.28

Upon request, the usage of rescue H1-AH was also expressed as per the fold-dose (0-fold to 4-fold) of the approved dose based on the following criteria: 0-fold: no rescue medication used; 1-fold: > 0 to < 2; 2-fold: ≥ 2 to < 3; 3-fold: ≥ 3 to < 4; 4-fold: ≥ 4. The highest fold-dose per participant from Week 1 to Week 12 was identified to assess its impact on primary and secondary efficacy endpoints at Week 12.

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

Rescue medication was sourced locally. Use of H1-antihistamine rescue medication only for CSU had to be recorded in the eDiary by the participant (number of tablets taken) and the name and dose were captured on the appropriate electronic Case Report Form (eCRF).

Prohibited therapies

Prohibited medications included biologics for treatment of CSU (including omalizumab and ligelizumab), routine (i.e., more than three doses over a 5-day period) oral corticosteroids (oral corticosteroids were only allowed as an additional rescue therapy for CSU after Week 12), i.v./i.m./i.a. corticosteroids, leukotriene antagonists (including montelukast and zafirlukast), H2-AHs, first generation AHs, second generation AHs other than the patients defined background medication and rescue medication, other immunosuppressive/immunomodulating medication with or without known effect on CSU including but not limited to hydroxychloroquine, methotrexate, cyclosporine A, cyclophosphamide, tacrolimus, and mycophenolate mofetil; intravenous Igs or plasmapheresis, UV therapy, any other therapy intended for the treatment of urticaria including but not limited to herbal therapies.

Also, live attenuated vaccines, strong inhibitors of CYP3A4, moderate and strong inducers of CYP3A4, anticoagulant medications, antiplatelet medication (except for acetylsalicylic acid up to 100 mg/d or clopidogrel up to 75 mg/d) were not allowed in the study. The use of dual anti-platelet therapy (e.g., acetylsalicylic acid + clopidogrel) was prohibited.

Study assessments

All efficacy assessments were measured by patient reported outcomes (PROs).

All patients were provided with an electronic device (eDiary) to complete daily UPDD and angioedema activity score (AAS), as well as additional PROs.

eDiary daily assessments were performed for UPDD and AAS:

- UPDD, which assesses the following components:
    - UAS (*morning* and *evening* assessment)
        - Itch severity
        - Number of hives
    - Sleep interference (*morning* assessment)

- Activity interference (*evening* assessment)
- H1-AHs rescue medication use (*evening* assessment)
- Number of calls to doctor, nurse or nurse practitioner (*evening* assessment)
- Angioedema occurrence and its management (*evening* assessment)

- AAS
- Other PRO assessments: DLQI, EQ-5D-5L, WPAI, UCT, PGIS, PGIC

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

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

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

Table 24: Hives severity score

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

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

Table 25: Itch severity score

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

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

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

The DLQI, PGIS, PGIC, UCT, EQ-5D-5L, and WPAI questionnaires were given during respective visits on site and had to be completed prior to any other study specific procedure. Site personnel had to allow participants to complete the questionnaire on their own without any assistance from the site staff. In the case that participants couldn't come on site, the DLQI, PGIS, PGIC, UCT, EQ-5D-5L and WPAI were available on their electronic device.

Table 26: DLQI score bands and impact on patient's life

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

The UAS7, AAS7, and UCT scores are unified, simple, and validated tools, recommended by the current urticaria guidelines for the assessment of disease activity and treatment response in patients with CSU.

5.3.2.1.3. Objectives and estimands

5.3.2.1.3.1 Primary objective

There were two primary objective scenarios reflecting different regulatory expectations. For EMA, UAS7 was used as the primary efficacy endpoint; for the FDA, ISS7 and HSS7 were used as co-primary endpoints. These two primary objective scenarios were tested in two distinct testing strategies. Distinctions in the secondary objectives reflected the corresponding scenario: the primary objective in one scenario was presented as secondary objective(-s) in another. The other secondary and all exploratory objectives were identical in both scenarios.

In both scenarios, the goal was to demonstrate that remibrutinib (25 mg twice daily) provides superior clinical benefit compared to placebo in patients with chronic spontaneous urticaria (CSU);

$$H_0: \mu_{remibrutinib} \geq \mu_{placebo} \text{ vs. } H_A: \mu_{remibrutinib} < \mu_{placebo.}$$

In **Scenario 1**, the Urticaria Activity Score over 7 days (UAS7) was selected as the primary efficacy endpoint.

Null Hypothesis (H_0): The average absolute change from baseline in UAS7 at Week 12 in the remibrutinib group is greater than or equal to that in the placebo group (i.e., no superiority).

Alternative Hypothesis (H_1): The average absolute change from baseline in UAS7 at Week 12 in the remibrutinib group is significantly smaller (i.e., more negative) than in the placebo group, indicating greater symptom reduction.

Hypothesis Type: Superiority

In **Scenario 2**, the weekly Itch Severity Score (ISS7) and Hive Severity Score (HSS7) were used as co-primary efficacy endpoints.

Table 27: Primary, secondary and exploratory objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
To demonstrate that remibrutinib (25 mg b.i.d.) is superior to placebo in patients with CSU with respect to change from baseline in UAS7 at Week 12	Absolute change from baseline in UAS7 at Week 12
Secondary objectives	**Endpoints for secondary objectives**
To demonstrate that a greater proportion of patients achieve disease activity control (UAS7 ≤ 6) at Week 12 who are treated with remibrutinib compared to placebo-treated patients	Achievement of UAS7 ≤ 6 (yes/no) at Week 12
To demonstrate that a greater proportion of patients achieve complete absence of hives and itch (UAS7 = 0) at Week 12 who are treated with remibrutinib compared to placebo-treated patients	Achievement of UAS7 = 0 (yes/no) at Week 12
To demonstrate the superiority of remibrutinib treated patients with respect to a reduction from baseline in the weekly itch severity score at Week 12 compared to placebo-treated patients	Improvement of severity of itch, assessed as absolute change from baseline in ISS7 score at Week 12
To demonstrate the superiority of remibrutinib treated patients with respect to a reduction from baseline in the weekly hive severity score at Week 12 compared to placebo-treated patients	Improvement of severity of hives, assessed as absolute change from baseline in HSS7 score at Week 12
To demonstrate that a greater proportion of patients achieve UAS7 ≤ 6 at Week 2 who are treated with remibrutinib compared to placebo-treated patients	Achieving early onset of disease activity control, as defined as achievement of UAS7 ≤ 6 (yes/no) at Week 2
To demonstrate that a greater proportion of patients who are treated with remibrutinib achieve DLQI = 0-1 at Week 12 compared to placebo-treated patients	No impact on patients' dermatology-related QoL, as defined by achievement of DLQI = 0-1 (yes/no) at Week 12
To demonstrate that remibrutinib treated patients maintain disease activity control (defined as UAS7 ≤ 6) for more weeks compared to placebo treated patients over 12 weeks	Achieving sustained disease activity control, assessed as cumulative number of weeks with an UAS7 ≤ 6 response between baseline and Week 12
To demonstrate that remibrutinib treated patients have more angioedema occurrence-free weeks over 12 weeks compared with placebo-treated patients	Number of weeks without angioedema, assessed by the cumulative number of weeks with an AAS7 = 0 response between baseline and Week 12
To demonstrate the safety and tolerability of remibrutinib	Occurrence of treatment emergent AEs and SAEs during the study
Exploratory objectives	**Endpoints for exploratory objectives**
To explore the efficacy of remibrutinib on further UPDD-related efficacy parameters: • Achievement and maintenance of complete hive response at Week 12 and over time • Achievement and maintenance of complete itch response at Week 12 and over time • Achievement and maintenance of complete UAS7 response over time • Achievement and maintenance of UAS7 ≤ 6 response over time • Profile of change from baseline in HSS7, ISS7, and UAS7 over time • To explore the effect of remibrutinib treatment on sleep interference and activity interference as assessed by the UPDD	• Achievement of HSS7 = 0 (yes/no) at Week 12 and by visit over time • Achievement of ISS7 = 0 (yes/no) at Week 12 and by visit over time • Achievement of UAS7 = 0 (yes/no) response by visit over time • Achievement of UAS7 ≤ 6 (yes/no) response by visit over time • Absolute score and change from baseline in UAS7, ISS7, and HSS7 by visit over time • Change from baseline of weekly sleep interference score, weekly activity interference score, and complete absence of CSU interference assessed on sleep and activity score over time, respectively
To explore the impact of disease characteristics at baseline on the efficacy of remibrutinib • CU Index status (+ or -) • Serum concentrations of total IgE • Disease duration before baseline • Diagnosis of concomitant CINDU	Additional subgroup analysis by CU Index status, IgE levels, disease duration, and the diagnosis of concomitant CINDU (all at baseline) on: • UAS7 (co-primary endpoints ISS7/HSS7) change from baseline over time • Achievement of UAS7 ≤ 6 over time • Achievement of UAS7 = 0 over time

Objectives	Endpoints
Impact of study treatment on the following PRO assessments:	
• DLQI total score	• Improvement of patients' dermatology-related QoL, assessed as absolute and relative change from baseline of DLQI score at Week 12. Absolute change from baseline of DLQI by visit over time. Achievement of DLQI = 0-1 by visit over time
• AAS	• Absolute change from baseline of AAS7 by visit over time in patients with AAS7 > 0 at baseline. • Absolute change from baseline of AAS7 by visit over time. • Achievement of AAS7 = 0 by visit over time. • Angioedema burdened days by visit over time.
• UCT	• Change from baseline in UCT score over time
• WPAI	• Absolute change from baseline of WPAI component scores and the absolute WPAI component score by visit over time
• EQ-5D-5L	• EQ-5D-5L domain results by visit over time and by baseline disease severity (defined by UAS7 categories)
• PGIS score • PGIC score	• Change from baseline in PGIS scores by visit over time • PGIC scores by visit over time
To evaluate the use of rescue medication	Total weekly doses of rescue medication by visit over time
To explore the impact of treatment with remibrutinib on total levels of IgG, IgM, IgA, and IgE	Levels of immunoglobulins (IgG, IgM, IgA, and IgE) by visit over time
To assess the PK profile of remibrutinib as well as PK/PD and PK/safety	Concentration of remibrutinib by visit over time and relationship of population PK compared to efficacy and safety
To explore the impact of treatment with remibrutinib on B cell count and the B cell subsets in peripheral blood - substudy; at selected sites only	B cell count and analysis of the B cell subsets over time for a subset of patients
To explore the impact of remibrutinib on concomitant symptomatic dermographism in patients with a positive provocation test at baseline	Change from baseline in Fric Test threshold at Week 12 and Week 52
To perform exploratory pharmacogenetic analysis based on blood samples for DNA (optional assessments)	Evaluate the relationship of genetic polymorphisms data with drug metabolism, the indication, the drug target pathway, and treatment response
To perform exploratory biomarker analysis based on blood samples for biomarkers (optional assessments)	Identification of potential biomarkers associated with treatment response to remibrutinib or possibly correlating with the severity or disease course of CSU

5.3.2.1.3.2 Estimand for the primary objective

Table 28: Estimands for primary objective

Population	Adult patients with inadequately controlled CSU despite treatment with second generation H1-AHs who have CSU duration ≥ 6 months, a UAS7 score ≥ 16, ISS7 ≥ 6, and HSS7 score ≥ 6 in the last 7 days prior to randomisation.
Treatment condition	Randomised study treatment (remibrutinib or placebo), with background medication of locally approved dose second generation H1-AHs, and a different second generation H1-AH as rescue medication.
Endpoint (variable)	Change in UAS7 from baseline at Week 12.
Population-level summary	The mean difference between treatment arms.
Intercurrent events and strategy to handle them	
Discontinuation of study treatment due to any reason	Treatment policy
Intake of strongly confounding prohibited medication (e.g., biologics treatment at any time before Week 12, cyclosporin after Week 8, systemic corticosteroids after Week 8)	Composite (measurements after this event will be excluded from the analysis and will be imputed using the worst value of the endpoint)
Intake of rescue medication, switch of background medication, intake of other prohibited medication, or patients non-compliant to treatment prior to Week 12	Treatment policy

The primary clinical question of interest is: What is the effect of remibrutinib treatment versus placebo on the change from baseline in UAS7 score after 12 weeks treatment in adult participants with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of discontinuation from study treatment for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication as an unfavourable outcome?

The UAS7 is the sum of the HSS7 score and the ISS7 score, and ranges from 0-42. Weekly scores (HSS7 and ISS7 scores) are derived by adding up the average daily scores of the 7 days preceding the visit. HSS and ISS are recorded by the participant twice daily (morning, evening) in their eDiary, on scale of 0 to 3. The daily score of HSS and ISS is calculated by averaging the morning and evening HSS and ISS score, respectively (possible range 0-3). If one of the morning or evening scores is missing, the non-missing score for that day (morning or evening) is then used as the daily score. If both of the morning and evening scores are missing, the daily score for that day is missing. If the questionnaires in eDiary are completed more than once per session (morning, evening) on the same day, then the worst score is used for that day. If one or more of the daily scores are missing, the following principles were applied to handle the missing data:

- If a participant has at least 4 non-missing daily scores within the 7 days, HSS7 or ISS7 is calculated as the sum of the available scores of that week, divided by the number of non-missing days, multiplied by 7.

- If there are less than 4 non-missing daily scores within the 7 days, HSS7 or ISS7 are considered as missing for that week.

5.3.2.1.3.3 Statistical methods for estimation and sensitivity analysis on primary estimands

Primary Objective: To assess the effect of remibrutinib versus placebo on change from baseline in UAS7 at Week 12.

Endpoint: Absolute change in UAS7 score from baseline to Week 12.

Population: Full Analysis Set (FAS).

Statistical Method: Mixed model for repeated measures (MMRM), including treatment, baseline score, stratification variables, time, and interaction terms (treatment by week, baseline UAS7 score by week) as fixed effects. Repeated measures within participants will be modeled using an unstructured covariance structure for error terms. Least Square (LS) mean and 95% CI, along with p-value for treatment comparison will be presented.

Missing Data: Addressed via multiple imputation (MI), using Missing at Random (MAR) or Jump to Reference (J2R) assumptions based on RDO (Retrieved Drop Out, data collected after discontinuation) availability:

- For patients in the active treatment arms, if sufficient RDO data were available, MI was performed using the observed data within the corresponding active arm. If sufficient RDO data were not available, missing data were imputed under a J2R assumption, using observed placebo arm data.
- For patients in the placebo arm, if sufficient RDO data were available, MI was performed using observed placebo arm data. If sufficient RDO data were not available, missing data were imputed under a MAR assumption based on the placebo arm data.

Sensitivity Analysis: Different assumption for handling the intercurrent event of "Intake of strongly confounding prohibited medication (e.g. biologics treatment at any time before Week 12, cyclosporin after Week 8 to Week 12, systemic corticosteroids after Week 8 to Week 12)". The change from baseline in UAS7 score up to week 12 will be imputed using zero.

Supplementary analyses: The supplementary analysis was implemented with the same target population, the primary variables and the summary measure as for the primary estimand but using hypothetical strategy for Intake of strongly confounding prohibited medication intercurrent event. Measurements after this event will be excluded from the analysis and will be imputed via a modeling approach.

- For participants in the active treatment arms, hypothetical data will be imputed using multiple imputation under missing at random (MAR) assumptions using LOU064 data.
- For participants in the placebo arm, hypothetical data will be imputed using multiple imputation under MAR assumptions using Placebo data.

5.3.2.1.3.4 Secondary objectives

The secondary objectives for the scenario with UAS7 as the primary efficacy endpoint were**:**

- To demonstrate that a greater proportion of participants achieve disease activity control (UAS7 ≤ 6) at Week 12 who are treated with remibrutinib (25 mg b.i.d.) compared to placebo-treated participants

$$H_{02}: p_{remibrutinib} \leq p_{placebo} \text{ vs. } H_{A2}: p_{remibrutinib} > p_{placebo}$$

where p is the proportion of patients achieving UAS7 ≤ 6 at Week 12.

- To demonstrate that a greater proportion of participants achieve complete absence of hives and itch (UAS7 = 0) at Week 12 who are treated with remibrutinib (25 mg b.i.d.) compared to placebo-treated participants

$$H_{03}: p_{remibrutinib} \leq p_{placebo} \text{ vs. } H_{A3}: p_{remibrutinib} > p_{placebo}$$

where p is the proportion of patients achieving UAS7=0 at Week 12.

- To demonstrate the superiority of remibrutinib (25 mg b.i.d.) treated participants with respect to a reduction from baseline in the weekly itch severity score at Week 12 compared to placebo treated participants

$$H_{04}: \mu_{remibrutinib} \geq \mu_{placebo} \text{ vs. } H_{A4}: \mu_{remibrutinib} < \mu_{placebo}$$

where μ is the mean change from baseline in ISS7 at Week 12.

- To demonstrate the superiority of remibrutinib (25 mg b.i.d.) treated participants with respect to a reduction from baseline in the weekly hive severity score at Week 12 compared to placebo treated participants

$$H_{05}: \mu_{remibrutinib} \geq \mu_{placebo} \text{ vs. } H_{A5}: \mu_{remibrutinib} < \mu_{placebo}$$

where μ is the mean change from baseline in HSS7 at Week 12.

- To demonstrate that a greater proportion of participants achieve UAS7 ≤ 6 at Week 2 who are treated with remibrutinib (25 mg b.i.d.) compared to placebo-treated participants

$$H_{06}: p_{remibrutinib} \leq p_{placebo} \text{ vs. } H_{A6}: p_{remibrutinib} > p_{placebo}$$

where p is the proportion of patients achieving UAS7 ≤ 6 at Week 2.

- To demonstrate that a greater proportion of participants who are treated with remibrutinib (25 mg b.i.d.) achieve DLQI = 0-1 at Week 12 compared to placebotreated participants

$$H_{07}: p_{remibrutinib} \leq p_{placebo} \text{ vs. } H_{A7}: p_{remibrutinib} > p_{placebo}$$

where p is the proportion of patients achieving DLQI = 0-1 at Week 12.

- To demonstrate that remibrutinib (25 mg b.i.d.) treated participants maintain disease activity control (defined as UAS7≤6) for more weeks compared to placebo treated participants over 12 weeks

$$H_{08}: \mu_{remibrutinib} \leq \mu_{placebo} \text{ vs. } H_{A8}: \mu_{remibrutinib} > \mu_{placebo}$$

where μ is the mean cumulative number of weeks that patients achieve UAS7 ≤ 6 response between baseline and Week 12.

- To demonstrate that remibrutinib (25 mg b.i.d.) treated participants have more angioedema occurrence-free weeks over 12 weeks compared with placebo-treated participants

$$H_{09}: \mu_{remibrutinib} \leq \mu_{placebo} \text{ vs. } H_{A9}: \mu_{remibrutinib} > \mu_{placebo}$$

where μ is the mean cumulative number of weeks that patients achieve AAS7=0 response between baseline and Week 12.

Derivation of AAS7 score: A weekly AAS7 score will be derived by adding up the daily scores (possible ranges 0 to 15) of the 7 days preceding the visit, and ranges from 0 to 105 (please refer to the assessment window in Section 2.1.1.5). If one or more of the daily scores are missing, the following principles will be applied to handle the missing data: If a participant has at least 4 non-missing daily scores within the 7 days, ASS7 will be calculated as the sum of the available scores of that week, divided by the number of non-missing days, multiplied by 7. If there are less than 4 non-missing daily scores within the 7 days, ASS7 will be considered as missing for that week.

- To demonstrate the safety and tolerability of remibrutinib (25 mg b.i.d.).

The list of secondary and exploratory endpoints is provided in **Table 27**.

5.3.2.1.3.5 Estimand for the secondary objective

For each secondary endpoint, the following secondary estimand were considered with the secondary clinical question of interest:

What is the effect of remibrutinib treatment versus placebo on secondary endpoints after 12 weeks treatment in adult participants with CSU who are inadequately controlled by H1-antihistamine and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of treatment discontinuation for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication as an unfavourable outcome?

Population: Patients with inadequately controlled CSU despite treatment with second generation H1-antihistamine who have CSU duration ≥6 months, a UAS7 score ≥ 16, ISS7 score ≥ 6 and HSS7 score ≥ 6 in the last 7 days prior to randomisation, assigned to remibrutinib or placebo.

Treatment conditions: Assignment to remibrutinib, regardless of discontinuation and added to background medication of a locally labeled second-generation H1-antihistamine, and a different second-generation H1-antihistamine as rescue medication as needed, compared to assignment to placebo, regardless of discontinuation, added to background medication of a locally labeled second-generation H1-antihistamine, and a different second-generation H1-antihistamine as rescue medication as needed.

Handling of intercurrent events: the intercurrent events are the same for the primary endpoint. For the handling of intercurrent events, please see below.

Table 29: Endpoint, population level summary and intercurrent events

Endpoint	Summary measurement	Handing of intercurrent event
UAS7 ≤ 6 at Week 12	Odds ratio between treatment groups	A treatment policy strategy: RDO data or data collected after the IE will be used. In case of missing values of RDO data, derivation based on the multiply imputed UAS7 will be applied. A composite strategy: UAS7 response after the intercurrent event will be excluded and UAS7 ≤ 6 will be derived from imputed UAS7 score using the worst value (i.e., 42).
UAS7 = 0 at Week 12	Odds ratio between treatment groups	Same as UAS7 ≤ 6 at Week 12.
ISS7 score change from baseline to Week 12	Mean difference between treatment groups	Same as the primary estimand
HSS7 score change from baseline to Week 12	Mean difference between treatment groups	Same as the primary estimand
UAS7 ≤ 6 at Week 2	Odds ratio between treatment groups	Same as UAS7 ≤ 6 at Week 12. Note: As this endpoint is for the score at W2, some intercurrent events, e.g. intake of strongly confounding prohibited medication, will not be considered.
DLQI 0/1 at Week 12	Odds ratio between treatment groups	Same as UAS7 ≤ 6 at Week 12. In case of missing values of RDO data, derivation based on the multiply imputed DLQI score with same approach as UAS7 will be applied.
Cumulative number of weeks with an UAS7 ≤6 response between baseline and Week 12	Ratio of response rate between treatment groups	Same as UAS7 ≤ 6 at Week 12. Derivation based on the multiply imputed UAS7 will be applied.
Cumulative number of weeks with an AAS7= 0 response between baseline and Week 12	Ratio of response rate between treatment groups	Same as UAS7 ≤ 6 at Week 12. Derivation based on the multiply imputed AAS7 with same approach as UAS7 will be applied.

5.3.2.1.3.6. Statistical methods for estimation and sensitivity analysis on the secondary estimand

Analysis plan for secondary endpoints:

Statistical methods**:**

- UAS7 ≤ 6 at Week 12: The proportion of participants with UAS7 ≤ 6 at Week 12 will be analysed using a logistic regression model, including treatment group, region, prior exposure to anti-IgE biologics, and baseline UAS7 score as covariates.
- UAS7 = 0 at Week 12: The proportion of participants with UAS7 = 0 at Week 12 will be analysed using a logistic regression model, including treatment group, region, prior exposure to anti-IgE biologics, and baseline UAS7 score as covariates.
- ISS7 Score Change from Baseline at Week 12: The absolute change from baseline in ISS7 score at Week 12 will be analysed using an MMRM model. The model will include treatment group, baseline ISS7 score, randomisation strata variables, week, and interactions of treatment by week and baseline ISS7 score by week as fixed effects.
- HSS7 Score Change from Baseline at Week 12: The absolute change from baseline in HSS7 score at Week 12 will be analysed using an MMRM model. The model will include treatment group, baseline HSS7 score, randomisation strata variables, week, and interactions of treatment by week and baseline HSS7 score by week as fixed effects.

- UAS7 ≤ 6 at Week 2: The proportion of participants with UAS7 ≤ 6 at Week 2 will be analysed using a logistic regression model, including treatment group, region, prior exposure to anti-IgE biologics, and baseline UAS7 score as covariates.
- DLQI = 0/1 at Week 12: The proportion of participants with DLQI ≤ 1 at Week 12 will be analysed using a logistic regression model, including treatment group, region, prior exposure to anti-IgE biologics, and baseline DLQI score as covariates.
- Cumulative Number of Weeks with UAS7 ≤ 6 Response Between Baseline and Week 12: The cumulative number of weeks achieving UAS7 ≤ 6 response will be modelled using a negative binomial regression model with a log link. The model will adjust for treatment group, region, prior exposure to anti-IgE biologics, and the varying lengths of participants' time in the treatment period (offset variable based on the natural log of the proportion of time spent in treatment).
- Cumulative Number of Weeks with AAS7 = 0 Response Between Baseline and Week 12: The cumulative number of weeks achieving AAS7 = 0 response will be modelled using a negative binomial regression model with a log link. The model will adjust for treatment group, region, prior exposure to anti-IgE biologics, baseline AAS7 = 0 status, and the varying lengths of participants' time in the treatment period (offset variable based on the natural log of the proportion of time spent in treatment).

Missing data: Same as stated in Scenario 1 for missing data of continuous variables. Missing data of response variables will be derived using the multiply imputed data for corresponding continuous variables.

Sensitivity: None.

Supplementary analyses: For binary variables (UAS7 ≤ 6 at Week 12, UAS7 = 0 at Week 12, UAS7 ≤ 6 at Week 2, DLQI 0/1 at Week 12), the treatment difference adjusting covariates as region, prior exposure to anti IgE biologics and baseline UAS7 score will be provided.

Multiple testing strategy: The study uses a closed testing procedure to control family-wise error rate. The testing strategy is hierarchical, meaning: Primary endpoint is tested first. Only if the primary hypothesis is rejected, will secondary endpoints be tested. Secondary endpoints are tested in a pre-specified order (e.g. UAS7 ≤ 6 at Week 12, UAS7 = 0 at Week 12, ISS7 score change, etc.). Each hypothesis test (primary and secondary) is tested at the full significance level (0.025, one-sided), but testing stops as soon as any null hypothesis is not rejected.

Formal testing of the primary endpoint and key secondary endpoints are only performed at the primary analysis time point; thus, no adjustment for multiplicity is required. The primary analysis is conducted when all participants have completed their Week 24 visit or discontinued early and when a minimum of 150 participants across both Phase 3 pivotal studies (A2301 and A2302) have completed the 52-week treatment period.

Planned subgroup analyses

Subgroup analyses will explore the impact of baseline disease characteristics on efficacy for endpoints like UAS7 change, achievement of UAS7 ≤ 6, and achievement of UAS7 = 0 over time. Key subgroups include:

- CU-index status (Positive/Negative)
- IgE levels (Normal/High vs. Low)
- Duration of CSU (≤1 year, >1 to 3 years, >3 to 5 years, >5 years)

- Concomitant CINDU diagnosis (Yes/No)

Subgroup analyses will be performed for the primary endpoint and secondary endpoints using the randomisation strata subgroups. If the actual stratum is different to the assigned stratum in IRT, the actual stratum will be used in the analysis.

Randomisation strata:

- Previous exposure to anti-IgE biologics (Yes/No)
- Geographic region: LaCAN (Latin America, Caribbean and Canada), RE (Region Europe), US, AMEA (Asia, Middle East & Africa), Japan (Study A2301 only), China (Study A2302 only);

5.3.2.1.4. Results

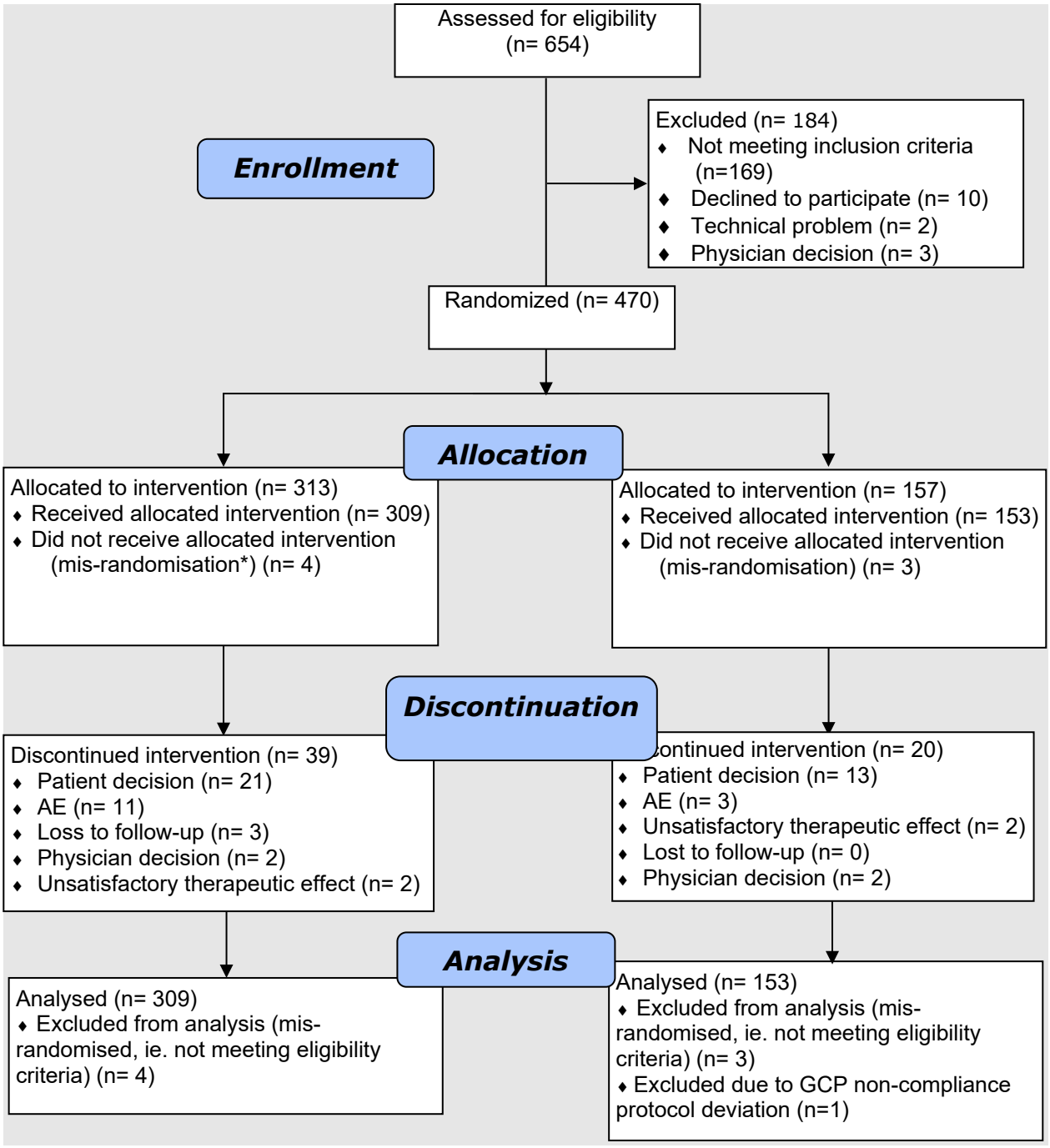
5.3.2.1.4.1. Participant flow and numbers analysed

Study initiation and completion dates

Study	Study initiation date (first patient first visit)	Study completion date (last patient last visit)
A2301	30-Nov-2021	19-Jan-2024
A2302	01-Dec-2021	05-Jan-2024

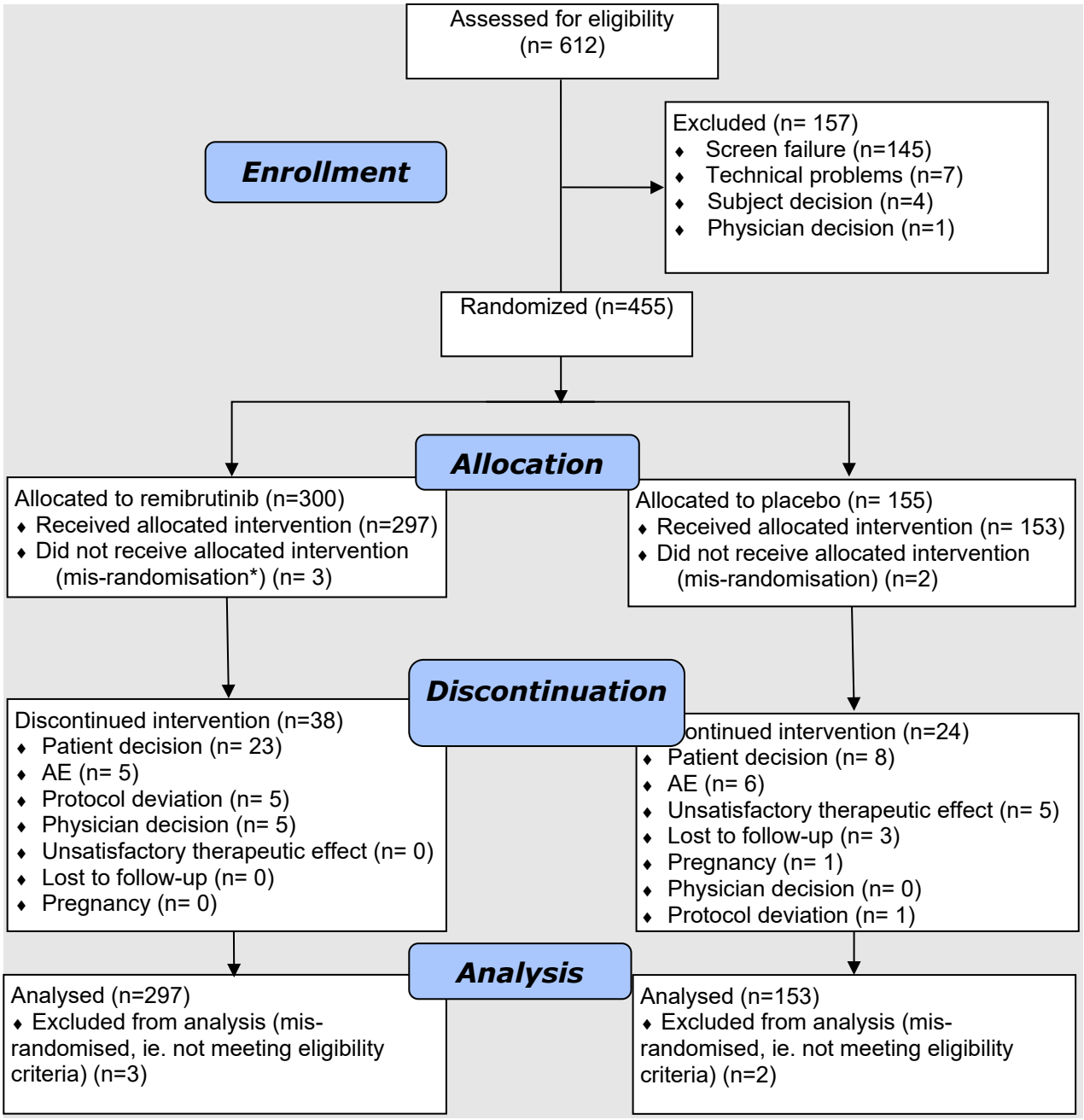
Patient disposition

Figure *18*: Participant flow (Study A2301; double-blind treatment period)



* Mis-randomised patients were defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomisation eligibility and no study medication was administered to the patient.

Figure *19*: Participant flow (Study A2302; double-blind treatment period)



* Mis-randomised patients were defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomisation eligibility and no study medication was administered to the patient.

Data sets analysed

Table 30: Study A2301 Analysis sets (all screened patients)

Analysis population	LOU064 25 mg b.i.d. n	Placebo n	Placebo - LOU064 25 mg b.i.d. n[a]	Transitioned to LOU064 25 mg b.i.d. n[b]	Total n
Screened					654
Randomized analysis set	313	157	-	-	470
Double-blind treatment period					
Full analysis set	309	153	-	-	462
Safety set	309	153	-	-	462
Entire study period					
Full analysis set	309	-	153	-	462
Safety set[c]	309	153	-	133	462

[a] Placebo - LOU064 25 mg b.i.d.: Included patients initially randomized to placebo regardless of entering the open-label period, i.e., including patients who discontinued during double-blind treatment period and not entered into open-label period and patients who entered into open-label period and switched to LOU064.
[b] Transitioned to LOU064 25 mg b.i.d.: Included patients initially randomized to placebo and switched to remibrutinib.
[c] Total of Safety set for entire study period is from LOU064 25 mg b.i.d. and placebo, the transitioned to LOU064 25 mg b.i.d. does not contribute.
Source: Table 14.1-2

Table 31: Study A2302 Analysis sets (all screened patients)

Analysis population	LOU064 25 mg b.i.d. n	Placebo n	Placebo - LOU064 25 mg b.i.d. n[a]	Transitioned to LOU064 25 mg b.i.d. n[b]	Total n
Screened					612
Randomized analysis set	300	155	-	-	455
Double-blind treatment period					
Full analysis set	297	153	-	-	450
Safety set	297	153	-	-	450
Entire study period					
Full analysis set	297	-	153	-	450
Safety set[c]	297	153	-	129	450

[a] Placebo - LOU064 25 mg b.i.d.: Included patients initially randomized to placebo regardless of entering the open-label period, i.e., including patients who discontinued during double-blind treatment period and not entered into open-label period and patients who entered into open-label period and switched to LOU064.
[b] Transitioned to LOU064 25 mg b.i.d.: Included patients initially randomized to placebo and switched to remibrutinib.
[c] Total of Safety set for entire study period is from LOU064 25 mg b.i.d. and placebo, the transitioned to LOU064 25 mg b.i.d. does not contribute.
Source: Table 14.1-2

5.3.2.1.4.2 Deviations from study plan

Protocol amendments

Study A2301: The original protocol was dated 19 May 2021. The global study protocol was amended once (Version 1.0, 23 May 2022).

Study A2302: The original protocol was dated 19 May 2021. The global study protocol was amended once (Version 1.0, 23 May 2022) and there were 2 local study protocol amendments (UK: 30-Sep-2021, Germany: 12-Nov-2021).

The key rationale for the global study protocol amendment was to implement recommendation from the FDA regarding statistical analysis covering ICE handling for COVID-19 for treatment discontinuation

and the use of the same covariates in both primary and secondary endpoint. The other key aspect was to ensure consistency across the program involving both pivotal studies (CLOU64A2301 and CLOU64A2302).

Other changes in study conduct

Due to the geopolitical disruption in 2022, screening was stopped at all sites in Russia and no new patients were randomised, Russia's patient allocation was redistributed amongst the other countries/subdivisions. The randomised patients continued in the study and the blood and urine samples were analysed locally, if required. There was no impact on drug supplies and assessments. No other changes occurred in the study conduct.

Protocol deviations

Table 32: Study A2301: Protocol deviations by category (double-blind treatment)

	LOU064 25 mg b.i.d. N=313 n (%)	Placebo N=157 n (%)	Total N=470 n (%)
Patients with at least one protocol deviation	123 (39.3)	67 (42.7)	190 (40.4)
Protocol deviation			
Other	75 (24.0)	38 (24.2)	113 (24.0)
Prohibited concomitant medication	40 (12.8)	11 (7.0)	51 (10.9)
Selection criteria not met	27 (8.6)	13 (8.3)	40 (8.5)
Treatment deviation	14 (4.5)	9 (5.7)	23 (4.9)
Patient not withdrawn as per protocol	0	1 (0.6)	1 (0.2)
Patients with at least one COVID-19 related protocol deviation	2 (0.6)	1 (0.6)	3 (0.6)
COVID-19 related protocol deviation			
Health status related	2 (0.6)	1 (0.6)	3 (0.6)

A patient with multiple occurrences of a protocol deviation category was counted only once in the protocol deviation category.
Patients may have protocol deviations in more than one protocol deviation category.
Source: Table 14.1-3.1

Table 33: Study A2302: Protocol deviations by category (double-blind treatment)

	LOU064 25 mg b.i.d. N=300 n (%)	Placebo N=155 n (%)	Total N=455 n (%)
Patients with at least one protocol deviation	122 (40.7)	72 (46.5)	194 (42.6)
Protocol deviation			
Other	69 (23.0)	40 (25.8)	109 (24.0)
Treatment deviation	29 (9.7)	20 (12.9)	49 (10.8)
Prohibited concomitant medication	25 (8.3)	23 (14.8)	48 (10.5)

Selection criteria not met	23 (7.7)	12 (7.7)	35 (7.7)
Patients with at least one COVID-19 related protocol deviation	9 (3.0)	7 (4.5)	16 (3.5)
COVID-19 related protocol deviation			
Health status related	8 (2.7)	6 (3.9)	14 (3.1)
Lockdown / quarantine of patient	1 (0.3)	1 (0.6)	2 (0.4)
Patient concern	0	1 (0.6)	1 (0.2)

A patient with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category.
Patients may have protocol deviations in more than one protocol deviation category.
Source: Table 14.1-3.1

Upon request, the Applicant clarified that the category 'Other' Protocol deviations consisted of 17 sub-categories as follows: 1: randomised in error; 2: any assessment performed after withdrawal of consent; 3: DLQI not completed at scheduled timepoints; 4: post dose PK samples not taken when scheduled; 5: triplicate ECG not taken at scheduled timepoints; 6: urine pregnancy test not performed every 4 weeks; 7: UPDD entries not sufficient to calculate UAS7 score at scheduled timepoints; 8: ASS not completed; 9: participant randomised to an incorrect stratum; 10: serum pregnancy test not done/result missing at randomisation; 11: incorrect PK sample collection or processing; 12: severe GCP noncompliance of study site; 13: safety laboratory test not done; 14: missing efficacy and safety assessment due to missed site visit; 15: additional data collected not aligned with Protocol; 16: pharmacogenetic sample collected despite not having consent for it; 17: additional biomarker samples taken despite not having consent for it.

Sub-categories 3 and 7 were related to missing eDiary data (DLQI not completed and Urticaria Patient Daily Diary entries not sufficient to calculate UAS7 score) with a possible impact on the primary and secondary endpoints. Frequencies of these deviations were comparable between remibrutinib and placebo arms across both pivotal studies during the double-blind period. Incomplete DLQI were observed in 7.3% in remibrutinib vs 7.6% in placebo arms in Study A2301 and in 5.0% in remibrutinib vs 6.5% in placebo arms in Study A2302. UPDD entries insufficient to calculate UAS7 score were observed in 2.6% in remibrutinib vs 3.2% in placebo arms in Study A2301 and in 6.0% in remibrutinib vs 6.5% in placebo arms in Study A2302.

5.3.2.1.4.3. Baseline data

Table 34: Study A2301: Demographic characteristics (RAS)

Characteristic	LOU064 25 mg b.i.d. N=313	Placebo N=157	Total N=470
Age group -n (%)			
≥ 18 - <65 years	282 (90.1)	143 (91.1)	425 (90.4)
≥ 65 - <85 years	31 (9.9)	14 (8.9)	45 (9.6)
Age (years)			
n	313	157	470
Mean	44.6	45.9	45.0
SD	14.27	13.44	13.99
Min	18	18	18
Median	44.0	47.0	45.0
Max	79	79	79
Gender -n (%)			
Female	212 (67.7)	109 (69.4)	321 (68.3)
Male	101 (32.3)	48 (30.6)	149 (31.7)
Race -n (%)			
White	188 (60.1)	89 (56.7)	277 (58.9)
Asian	94 (30.0)	46 (29.3)	140 (29.8)
American Indian or Alaska Native	12 (3.8)	14 (8.9)	26 (5.5)
Black or African American	12 (3.8)	3 (1.9)	15 (3.2)
More than one race	6 (1.9)	2 (1.3)	8 (1.7)
Unknown	1 (0.3)	2 (1.3)	3 (0.6)
Native Hawaiian or Other Pacific Islander	0	1 (0.6)	1 (0.2)
Ethnicity -n (%)			
Not Hispanic or Latino	237 (75.7)	113 (72.0)	350 (74.5)
Hispanic or Latino	76 (24.3)	44 (28.0)	120 (25.5)
Geographic region -n (%)			
Asia, Middle East and Africa	99 (31.6)	50 (31.8)	149 (31.7)
US	81 (25.9)	40 (25.5)	121 (25.7)
Region Europe	63 (20.1)	32 (20.4)	95 (20.2)
Latin America, Caribbean and Canada	51 (16.3)	27 (17.2)	78 (16.6)
Japan	19 (6.1)	8 (5.1)	27 (5.7)
BMI (kg/m²)			
n	313	156	469
Mean	27.81	28.31	27.97
SD	6.377	6.475	6.407
Min	15.8	15.8	15.8
Median	26.94	27.49	27.11
Max	57.6	54.1	57.6
BMI group -n (%)			
<25 (kg/m²)	119 (38.0)	57 (36.3)	176 (37.4)
≥ 25 - <30 (kg/m²)	98 (31.3)	45 (28.7)	143 (30.4)
≥ 30 (kg/m²)	96 (30.7)	54 (34.4)	150 (31.9)

Age was collected at Screening.
BMI was calculated as (body weight in kilograms) / (height in meters)².
Source: Table 14.1-4.1

Table 35: Study A2302: Demographic characteristics (RAS)

Characteristic	LOU064 25 mg b.i.d. N=300	Placebo N=155	Total N=455
Age group -n (%)			
≥ 18 - <65 years	276 (92.0)	144 (92.9)	420 (92.3)
≥ 65 - <85 years	24 (8.0)	11 (7.1)	35 (7.7)
Age (years)			
n	300	155	455
Mean	41.9	41.3	41.7
SD	14.52	14.58	14.53
Min	18	18	18
Median	41.0	40.0	41.0
Max	80	81	81
Gender -n (%)			
Female	197 (65.7)	100 (64.5)	297 (65.3)
Male	103 (34.3)	55 (35.5)	158 (34.7)
Race -n (%)			
White	159 (53.0)	79 (51.0)	238 (52.3)
Asian	130 (43.3)	72 (46.5)	202 (44.4)
American Indian or Alaska Native	0	0	0
Black or African American	7 (2.3)	3 (1.9)	10 (2.2)
More than one race	3 (1.0)	1 (0.6)	4 (0.9)
Unknown	1 (0.3)	0	1 (0.2)
Native Hawaiian or Other Pacific Islander	0	0	0
Ethnicity -n (%)			
Not Hispanic or Latino	284 (94.7)	149 (96.1)	433 (95.2)
Hispanic or Latino	16 (5.3)	5 (3.2)	21 (4.6)
Not reported	0	1 (0.6)	1 (0.2)
Geographic region -n (%)			
China	43 (14.3)	22 (14.2)	65 (14.3)
Asia, Middle East and Africa	94 (31.3)	50 (32.3)	144 (31.6)
United States	56 (18.7)	30 (19.4)	86 (18.9)
Latin America, Caribbean and Canada	26 (8.7)	13 (8.4)	39 (8.6)
Region Europe	81 (27.0)	40 (25.8)	121 (26.6)
BMI (kg/m^2)			
n	300	155	455
Mean	26.97	26.98	26.97
SD	6.499	5.946	6.310
Min	15.4	18.0	15.4
Median	25.61	25.69	25.67
Max	53.2	51.4	53.2
BMI group -n (%)			
<25 (kg/m^2)	139 (46.3)	70 (45.2)	209 (45.9)
≥ 25 - <30 (kg/m^2)	84 (28.0)	50 (32.3)	134 (29.5)
≥ 30 (kg/m^2)	77 (25.7)	35 (22.6)	112 (24.6)

Age was collected at Screening.
BMI was calculated as (body weight in kilograms) / (height in meters)^2.
Source: Table 14.1-4.1

Table 36: Study A2301: Baseline disease characteristics (RAS)

Characteristic	LOU064 25 mg b.i.d. N=313	Placebo N=157	Total N=470
Baseline UAS7 Score			
n	312	157	469
Mean (SD)	30.63 (7.921)	29.58 (7.723)	30.28 (7.863)

Min	7.0	12.8	7.0
Median	30.00	29.50	30.00
Max	42.0	42.0	42.0
Baseline UAS7 category -n (%)			
Severe disease (28≤UAS7≤42)	205 (65.5)	93 (59.2)	298 (63.4)
Moderate disease (16≤UAS7<28)	104 (33.2)	61 (38.9)	165 (35.1)
Mild disease (6<UAS7<16)	3 (1.0)	3 (1.9)	6 (1.3)
Missing	1 (0.3)	0	1 (0.2)
Baseline ISS7 Score			
n	312	157	469
Mean (SD)	14.74 (4.224)	14.29 (4.023)	14.59 (4.159)
Min	1.5	5.5	1.5
Median	14.00	14.00	14.00
Max	21.0	21.0	21.0
Baseline HSS7 Score			
n	312	157	469
Mean (SD)	15.89 (4.625)	15.29 (4.645)	15.69 (4.636)
Min	0.0	5.5	0.0
Median	16.00	15.50	16.00
Max	21.0	21.0	21.0
Baseline AAS7 score			
n	312	157	469
Mean (SD)	27.94 (30.907)	23.46 (28.688)	26.44 (30.226)
Min	0.0	0.0	0.0
Median	12.92	11.67	12.00
Max	105.0	104.0	105.0
Baseline AAS7=0 response -n (%)			
Yes	108 (34.5)	64 (40.8)	172 (36.6)
No	204 (65.2)	93 (59.2)	297 (63.2)
Missing	1 (0.3)	0	1 (0.2)
Baseline DLQI score			
n	301	147	448
Mean (SD)	14.21 (6.983)	13.52 (6.827)	13.98 (6.932)
Min	1.0	0.0	0.0
Median	13.00	13.00	13.00
Max	30.0	30.0	30.0
Duration of CSU (years)			
n	313	157	470
Mean (SD)	6.91 (9.291)	6.13 (7.148)	6.65 (8.635)
Min	0.46	0.51	0.46
Median	3.780	3.850	3.785
Max	62.85	41.65	62.85
Duration of CSU (years) -n (%)			
≤1 year	53 (16.9)	25 (15.9)	78 (16.6)

Characteristic	**LOU064 25 mg b.i.d. N=313**	**Placebo N=157**	**Total N=470**
>1 - ≤3 years	80 (25.6)	45 (28.7)	125 (26.6)
>3 - ≤5 years	58 (18.5)	24 (15.3)	82 (17.4)
>5 years	122 (39.0)	63 (40.1)	185 (39.4)
Previous exposure to anti-IgE biologics -n (%)			
Yes	98 (31.3)	52 (33.1)	150 (31.9)
No	215 (68.7)	105 (66.9)	320 (68.1)
Previous experience of angioedema -n (%)			
Yes	173 (55.3)	70 (44.6)	243 (51.7)
No	140 (44.7)	87 (55.4)	227 (48.3)
Baseline CU-Index -n (%)			
Positive (≥ 10)	90 (28.8)	37 (23.6)	127 (27.0)
Negative (<10)	215 (68.7)	114 (72.6)	329 (70.0)
Missing	8 (2.6)	6 (3.8)	14 (3.0)
Baseline total IgE level -n (%)			
Normal/High (>43 IU/mL)	225 (71.9)	110 (70.1)	335 (71.3)
Low (≤43 IU/mL)	81 (25.9)	43 (27.4)	124 (26.4)
Missing	7 (2.2)	4 (2.5)	11 (2.3)

Duration of CSU = (inform consent date – diagnosis date + 1)/365.25.
Baseline total IgE level: 43 IU/mL corresponds to 103.2 µg/L.
Source: Table 14.1-4.2

Table 37: Study A2302: Baseline disease characteristics (RAS)

Characteristic	LOU064 25 mg b.i.d. N=300	Placebo N=155	Total N=455
Baseline UAS7 Score			
n	299	153	452
Mean (SD)	30.23 (8.011)	29.52 (7.552)	29.99 (7.857)
Min	6.5	8.0	6.5
Median	30.50	29.00	30.00
Max	42.0	42.0	42.0
Baseline UAS7 category -n (%)			
Severe disease (28≤UAS7≤42)	181 (60.3)	88 (56.8)	269 (59.1)
Moderate disease (16≤UAS7<28)	112 (37.3)	64 (41.3)	176 (38.7)
Mild disease (6<UAS7<16)	6 (2.0)	1 (0.6)	7 (1.5)
Missing	1 (0.3)	2 (1.3)	3 (0.7)
Baseline ISS7 Score			
n	299	153	452
Mean (SD)	14.31 (4.362)	13.85 (4.086)	14.15 (4.271)
Min	0.0	4.0	0.0
Median	14.00	14.00	14.00
Max	21.0	21.0	21.0
Baseline HSS7 Score			
n	299	153	452
Mean (SD)	15.93 (4.638)	15.67 (4.450)	15.84 (4.572)
Min	0.5	4.0	0.5
Median	16.50	15.50	16.50
Max	21.0	21.0	21.0
Baseline AAS7 score			
n	298	153	451
Mean (SD)	25.18 (30.812)	19.59 (27.610)	23.28 (29.852)
Min	0.0	0.0	0.0
Median	10.00	4.00	8.00
Max	105.0	105.0	105.0
Baseline AAS7=0 response -n (%)			
Yes	125 (41.7)	75 (48.4)	200 (44.0)
No	173 (57.7)	78 (50.3)	251 (55.2)
Missing	2 (0.7)	2 (1.3)	4 (0.9)
Baseline DLQI score			
n	294	149	443
Mean (SD)	14.00 (7.539)	13.58 (6.701)	13.86 (7.263)
Min	0.0	2.0	0.0
Median	13.00	13.00	13.00
Max	30.0	30.0	30.0
Duration of CSU (years)			
n	300	155	455
Mean (SD)	5.511 (7.587)	4.638 (6.227)	5.214 (7.158)
Min	0.45	0.47	0.45
Median	3.010	2.230	2.780
Max	46.05	38.78	46.05
Duration of CSU (years) -n (%)			
≤1 year	65 (21.7)	44 (28.4)	109 (24.0)
>1 - ≤3 years	84 (28.0)	42 (27.1)	126 (27.7)
>3 - ≤5 years	60 (20.0)	26 (16.8)	86 (18.9)
>5 years	91 (30.3)	43 (27.7)	134 (29.5)
Previous exposure to anti-IgE biologics -n (%)			
Yes	90 (30.0)	50 (32.3)	140 (30.8)
No	210 (70.0)	105 (67.7)	315 (69.2)
Previous experience of angioedema -n (%)			
Yes	143 (47.7)	69 (44.5)	212 (46.6)
No	157 (52.3)	86 (55.5)	243 (53.4)
Baseline CU-Index -n (%)			
Positive (≥ 10)	77 (25.7)	48 (31.0)	125 (27.5)
Negative (<10)	166 (55.3)	76 (49.0)	242 (53.2)
Missing	57 (19.0)	31 (20.0)	88 (19.3)
Baseline total IgE level -n (%)			
Normal/High (>43 IU/mL)	224 (74.7)	107 (69.0)	331 (72.7)
Low (≤43 IU/mL)	71 (23.7)	45 (29.0)	116 (25.5)
Missing	5 (1.7)	3 (1.9)	8 (1.8)

Duration of CSU = (inform consent date – diagnosis date + 1)/365.25.
Baseline total IgE level: 43 IU/mL corresponds to 103.2 µg/L.
Source: Table 14.1-4.2

Background second generation H1-AH medication

Study A2301: Almost all patients (309 patients in the remibrutinib arm (98.7%) and 153 patients in the placebo arm (97.5%)) were treated with background second generation H1-AHs medication at the locally label approved dose (once daily), as required by the study protocol. The remaining 8 patients were excluded from analysis and did not receive the study treatment, as 7 were mis-randomised and 1 patient was excluded due to GCP non-compliance protocol deviation.

Study A2302: Almost all patients (297 patients in the remibrutinib arm (99.0%) and 153 patients in the placebo arm (98.7%)) were treated with background second generation H1-AHs medication at the locally label approved dose (once daily), as required by the study protocol. The remaining 5 patients were excluded from analysis, as they were mis-randomised and did not take the study treatment.

Table 38: Background medication used in ≥ 10% of patients in any arm in pivotal studies in randomised set

Medication	**Study A2301** (remi vs placebo)	**Study A2302** (remi vs placebo)
Bilastine	12.8 % vs 9.6 %	17.7 % vs 14.8 %
Cetirizine	14.7 % vs 8.9 %	12.0 % vs 9.7 %
Cetirizine hydrochloride	11.2 % vs 15.3 %	—
Levocetirizine dihydrochloride	10.2 % vs 10.2 %	—
Fexofenadine	8.6 % vs 14.6 %	—
Fexofenadine hydrochloride	—	9.7 % vs 11.0 %

Rescue medication

In addition to being used as background medication, the use of a different second generation H1-AH was allowed as rescue medication, on an 'as-needed' basis for patients with CSU flare-ups of unbearable symptoms. Oral corticosteroids were also allowed as an additional rescue medication, only after the Week 12 primary endpoint.

Study A2301: Almost all patients across the two arms were prescribed rescue medication with second generation H1-AHs (99.0% in the remibrutinib arm and 100% in the placebo arm), which differed from the background H1-AHs medication.

Study A2302: Almost all patients across the two arms were prescribed rescue medication with second generation H1-AHs (99.3% in both arms), which differed from the background H1-AHs medication.

Table 39: Rescue medication used in ≥ 10% of patients in any arm in pivotal studies in safety set

Medication	**Study A2301** (remi vs placebo)	**Study A2302** (remi vs placebo)
Fexofenadine	18.1 % vs 17.0 %	14.5 % vs 9.2 %
Levocetirizine dihydrochloride	11.7 % vs 9.8 %	—
Cetirizine hydrochloride	11.3 % vs 7.8 %	—
Cetirizine	10.4 % vs 17.0 %	—
Fexofenadine hydrochloride	9.1 % vs 11.1 %	—
Bilastine	5.5 % vs 10.5 %	5.7 % vs 10.5 %
Loratadine	—	11.4 % vs 14.4 %
Desloratadine	—	10.4 % vs 8.5 %

Additionally, in Study A2301 oral corticosteroids were used as rescue medication by 1 patient (0.3%, prednisone) in the remibrutinib arm and 3 patients (2.0%, i.e., prednisolone in 1.3% and prednisone in 0.7%) in the placebo arm. In Study A2302, oral corticosteroids were used as rescue medication by 3 patients (1.0%, methylprednisolone, prednisolone and prednisone) in the remibrutinib arm and 3 (2.0%, all used prednisolone) in the placebo arm.

5.3.2.1.4.4. Outcomes and estimation

The outcomes and estimations will be presented in the following way: An overview table of primary and all secondary results for both pivotal studies will be presented first, followed by more details for each outcome.

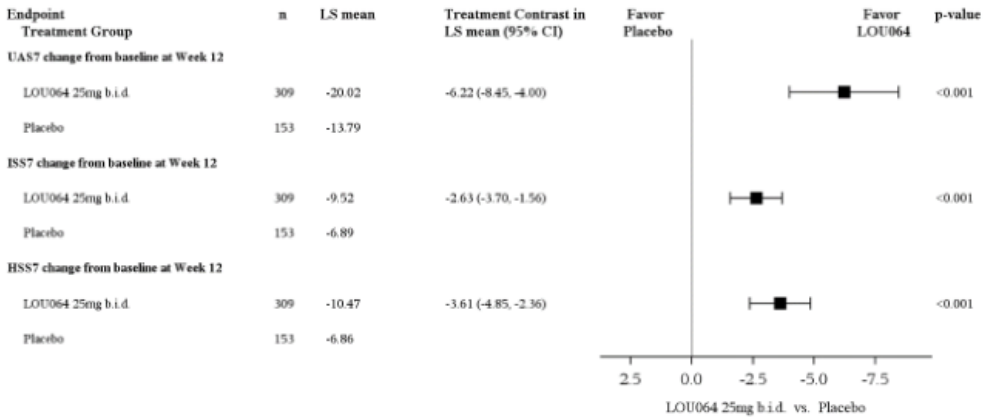
Table 40: Overview of primary and secondary efficacy endpoints in Studies A2301 and A2302 (FAS)

Endpoint	Measure	Study A2301			Study A2302		
		Remibrutinib 25 mg b.i.d. N = 309	Placebo N = 153	Comparison vs. placebo	Remibrutinib 25 mg b.i.d. N = 297	Placebo N = 153	Comparison vs. placebo
Primary endpoint							
H_1 : UAS7 score change from baseline at Week 12	n1	309	153		297	153	
	LS mean [1]	-20.02	-13.79	-6.22	-19.41	-11.73	-7.68
	95% CI [1]			(-8.45, -4.00)			(-9.91, -5.46)
	p-value (adjusted)			<0.001			<0.001
Secondary endpoints							
H_2 : Disease activity control (UAS7 ≤ 6) at Week 12	n2/M	154/309	38/153		139/297	30/153	
	Response rate (%)	49.8	24.8	25.44 [2]	46.8	19.6	27.61 [2]
	95% CI [2]			(16.48, 34.39)			(19.14, 36.08)
	p-value (adjusted)			<0.001			<0.001
H_3 : Complete absence of itch and hives (UAS7 = 0) at Week 12	n2/M	96/309	16/153		83/297	10/153	
	Response rate (%)	31.1	10.5	20.55 [2]	27.9	6.5	21.60 [2]
	95% CI [2]			(13.35, 27.75)			(15.10, 28.10)
	p-value (adjustedl)			<0.001			<0.001
H_4 : ISS7 score change from baseline at Week 12	n1	309	153		297	153	
	LS mean [1]	-9.52	-6.89	-2.63	-8.95	-5.72	-3.23
	95% CI [1]			(-3.70, -1.56)			(-4.29, -2.16)
	p-value (adjusted)			<0.001			<0.001
H_5 : HSS7 score change from baseline at Week 12	n1	309	153		297	153	
	LS mean [1]	-10.47	-6.86	-3.61	-10.47	-6.00	-4.47
	95% CI [1]			(-4.85, -2.36)			(-5.71, -3.23)
	p-value (adjusted)			<0.001			<0.001
H_6 : Disease activity control (UAS7 ≤ 6) at Week 2	n2/M	104/309	5/153		89/297	9/153	
	Response rate (%)	33.7	3.3	30.20 [2]	30.0	5.9	24.55 [2]
	95% CI [2]			(24.30, 36.10)			(18.31, 30.80)
	p-value (adjusted)			<0.001			<0.001
H_7 : No impact on patients' dermatology-related quality of life (DLQI = 0-1) at Week 12	n2/M	120/308	34/153		106/297	28/153	
	Response rate (%)	39.0	22.2	17.65 [2]	35.7	18.3	18.21 [2]
	95% CI [2]			(9.14, 26.16)			(9.96, 26.45)
	p-value (adjusted)			<0.001			<0.001
H_8 : Cumulative number of weeks with UAS7 ≤ 6 response between baseline and Week 12	n1	309	153		297	153	
	Average counts of weeks [3]	5.17	1.92		4.50	1.38	
	Rate ratio [3]			2.69			3.26
	95% CI [3]			(2.01, 3.61)			(2.26, 4.71)
	p-value (adjusted)			<0.001			<0.001
H_9 : Cumulative number of weeks with AAS7= 0 response between baseline and Week 12	n1	309	153		297	153	
	Average counts of weeks [3]	8.43	6.72		8.81	6.68	
	Rate ratio [3]			1.25			1.32
	95% CI [3]			(1.12, 1.41)			(1.17, 1.49)
	p-value (adjusted)			<0.001			<0.001

n1 : The number of patients included in the analysis for each treatment arm.
n2 : Average number of patients with response in 100 imputations.
N : The total number of patients in the corresponding treatment arm.
M : The total number of patients in the treatment arm with response variable defined.
Adjusted p-value: One-sided p-value was adjusted according to testing strategy with level of significance 0.025.
Multiple imputation techniques were implemented for missing data.
[1] Statistical model used a MMRM adjusting for treatment group, geographical region, prior exposure to anti-IgE biologics, visit week, baseline score and both interaction of treatment by visit week and interaction of baseline score by visit week.
[2] Treatment difference and 95% CI are estimated with a statistical model that used logistic regression adjusting for treatment arm, geographical region, prior exposure to anti-IgE biologics and baseline UAS7 (or DLQI) score.
[3] A rate ratio >1 favors the remibrutinib treatment arm. Statistical model used a negative binomial regression with log link that included treatment arm as fixed effect, geographical region, prior exposure to anti-IgE biologics (and baseline AAS7 = 0 status for the cumulative number of weeks with AAS7 = 0 between baseline and Week 12) as covariates. Natural log of (number of weeks with the response variable in treatment period/12 weeks) is used as an offset variable.
Source : [Study A2301-Table 14.2-1.4, Table 14.2-1.5, Table 14.2-1.1, Table 14.2-4.1, Table 14.2-4.2, Table 14.2-4.3, Table 14.2-4.4, Table 14.2-2.1, Table 14.2-2.2, Table 14.2-2.6], [Study A2302-Table 14.2-1.4, Table 14.2-1.5, Table 14.2-1.1, Table 14.2-4.1, Table 14.2-4.2, Table 14.2-4.3, Table 14.2-4.4, Table 14.2-2.1, Table 14.2-2.2, Table 14.2-2.6]

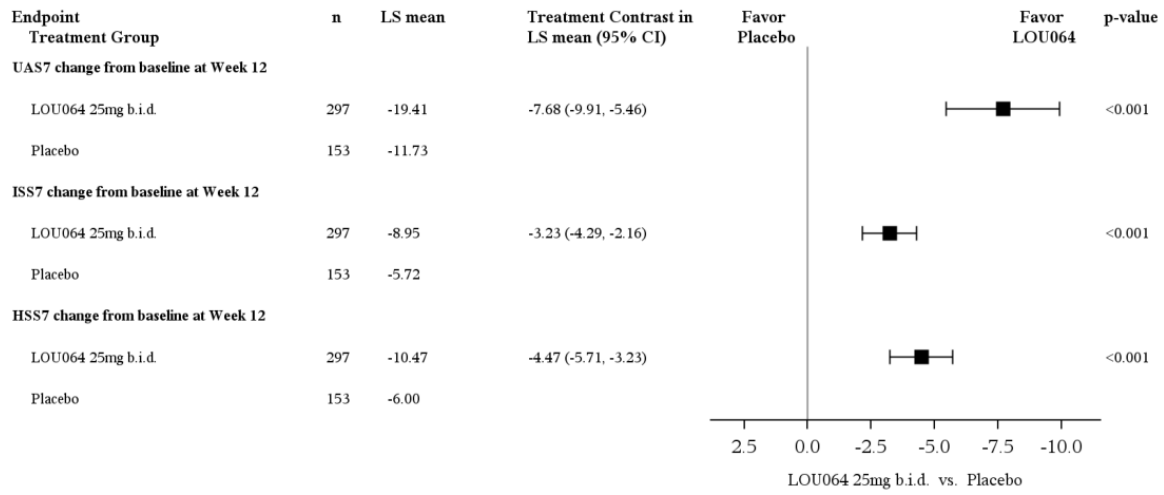
Primary endpoint results: change from baseline in UAS7 score at Week 12

Figure *20*: Study A2301: Forest plot of the LS mean difference in change from baseline for UAS7, ISS7 and HSS7 at Week 12 (Estimand, MMRM) (FAS)



p-value: one-sided p-value.
Statistical model used MMRM adjusting for treatment arm, geographical region, prior exposure to anti-IgE biologics, visit week, baseline score and both interaction of treatment by visit week and interaction of baseline score by visit week.
Source: Figure 14.2-1.1

Figure *21*: Study A2302: Forest plot of the LS mean difference in change from baseline for UAS7, ISS7 and HSS7 at Week 12 (Estimand, MMRM) (FAS)



LS Mean: Least squares mean, SE: standard error, CI: confidence interval, p-value: one-sided p-value.
Statistical model used a mixed effect model with repeated measures (MMRM) adjusting for treatment group, geographical region, prior exposure to anti-IgE biologics, visit week, baseline score and both interaction of treatment by visit week and interaction of baseline score by visit week.
Source: Table 14.2-1.1, Table 14.2-1.4 and Table 14.2-1.5.

Intercurrent events up to week 12

Table 41: Study A2301: Summary of intercurrent events up to Week 12 (FAS)

Parameter	LOU064 25mg b.i.d. N=309	Placebo N=153
Total number of subjects with intercurrent events for primary/secondary estimands	254 (82.2)	144 (94.1)
Number of subjects with treatment discontinuation prior to Week 12 due to any reason	19 (6.1)	13 (8.5)
Number of subjects with use of rescue medication as per protocol, or switch of background medication, or intake of other prohibited medication, or non-compliant to treatment prior to Week 12	252 (81.6)	142 (92.8)
Number of subjects with intake of strongly confounding prohibited medication	1 (0.3)	0

A subject with multiple occurrences of an intercurrent event category is counted only once in the intercurrent event category.
Subjects may have intercurrent events in more than one intercurrent event category.
Switch of background medication: subjects who had multiple medications with different medication name.

The Applicant's original definition of ICE 'use of strongly confounding prohibited medications' included biologics treatment at any time before Week 12, cyclosporin after Week 8 and systemic corticosteroids after Week 8. It was considered that the use of these medications at any point prior to week 12 could have impacted efficacy; hence broadening of the definition to include the use of these medicinal products from baseline to Week 12 was requested.

In Study A2301, with the broader definition, intake of strongly confounding prohibited medication was reported in 2.3% (7 patients) in the remibrutinib arm vs. 0.7% (1 patient) in the placebo arm. In the CSR, with the initial definition, intake of strongly confounding prohibited medication was reported in 0.3% (1 patient) in the remibrutinib arm vs. 0% in the placebo arm.

In Study A2302, with the broader definition, intake of strongly confounding prohibited medication was reported in 1% (3 patients) in the remibrutinib arm vs. 2% (3 patients) in the placebo arm. In the CSR, with the initial definition, intake of strongly confounding prohibited medication was reported in 0.3% (1 patient) in the remibrutinib arm vs. 0.7% (1 patient) in the placebo arm.

Cumulatively for both pivotal studies, the broader definition identified 8 additional patients in remibrutinib and 3 in placebo arms who took strongly confounding medicines. These patients took corticosteroids prior to Week 8. The Applicant provided the requested additional analyses using this broader definition for the primary and secondary endpoints, including also the sensitivity and supplementary analysis for the primary endpoint. The results were in line with the primary results.

The tables below represent the requested disaggregated intercurrent event data.

Table 42: Study A2301: Summary of intake of rescue medication, switch of background medication, intake of other prohibited medication, and treatment non-compliance up to Week 12 (Full Analysis Set)

Parameter	LOU064 25 mg b.i.d. N=309	Placebo N=153
Number of subjects with intake of rescue medication as per protocol prior to Week 12	247 (79.9)	141 (92.2)
Number of subjects with switch of background medication prior to Week 12	0	3 (2.0)
Number of subjects with intake of other prohibited medication (except for strongly confounding prohibited medication) prior to Week 12	15 (4.9)	7 (4.6)
Number of subjects non-compliant to treatment prior to Week 12	10 (3.2)	3 (2.0)

A subject with multiple occurrences of an intercurrent event category is counted only once in the intercurrent event category.
Subjects may have intercurrent events in more than one intercurrent event category.
Switch of background medication: subjects who had multiple medications with different medication name.
Source: [Responses to D120 Clinical Appendix 5-Table ADAR070-1-1]

Table 43: Study A2302: Summary of intercurrent events up to Week 12 (FAS)

Parameter	LOU064 25mg b.i.d. N=297	Placebo N=153
Total number of subjects with intercurrent events for primary/secondary estimands	241 (81.1)	136 (88.9)
Number of subjects with treatment discontinuation prior to Week 12 due to any reason	25 (8.4)	17 (11.1)
Number of subjects with use of rescue medication as per protocol, or switch of background medication, or intake of other prohibited medication, or non-compliant to treatment prior to Week 12	238 (80.1)	135 (88.2)
Number of subjects with intake of strongly confounding prohibited medication	1 (0.3)	1 (0.7)

A subject with multiple occurrences of an intercurrent event category is counted only once in the intercurrent event category.
Subjects may have intercurrent events in more than one intercurrent event category.
Switch of background medication: subjects who had multiple medications with different medication name.

Table 44: Study A2302: Summary of intake of rescue medication, switch of background medication, intake of other prohibited medication, and treatment non-compliance up to Week 12 (Full Analysis Set)

Parameter	LOU064 25 mg b.i.d. N=297	Placebo N=153
Number of subjects with intake of rescue medication as per protocol prior to Week 12	232 (78.1)	128 (83.7)
Number of subjects with switch of background medication prior to Week 12	6 (2.0)	4 (2.6)
Number of subjects with intake of other prohibited medication (except for strongly confounding prohibited medication) prior to Week 12	10 (3.4)	10 (6.5)
Number of subjects non-compliant to treatment prior to Week 12	13 (4.4)	13 (8.5)

A subject with multiple occurrences of an intercurrent event category is counted only once in the intercurrent event category.
Subjects may have intercurrent events in more than one intercurrent event category.
Switch of background medication: subjects who had multiple medications with different medication name.
Source: [Responses to D120 Clinical Appendix 5-Table ADAR070-1-2]

Missing primary outcome data

In Study A2301, 25 patients (8.1%) in the remibrutinib arm and 14 patients (9.2%) in the placebo arm had missing UAS7/ISS7/HSS7 scores at Week 12. Of those, 19 patients in remibrutinib and 13 in placebo prematurely discontinued study treatment prior to Week 12. These were considered as RDO patients. Among RDO patients, 1 patient (5.3%) in the remibrutinib arm and 2 patients (15.4%) in the placebo arm had UAS7/ISS7/HSS7 scores at Week 12.

In Study A2302, 33 patients (11.1%) in the remibrutinib arm and 19 patients (12.4%) in the placebo arm had missing UAS7/ISS7/HSS7 scores at Week 12. Of those, 24 patients in the remibrutinib arm and 14 patients in the placebo arm who prematurely discontinued study treatment prior to Week 12. These were considered as RDO patients. Among RDO patients, 3 patients (12.5%) in the remibrutinib arm had UAS7/ISS7/HSS7 scores at Week 12. None of the patients in the placebo arm had UAS7/ISS7/HSS7 scores at Week 12.

Sensitivity analysis

The change from baseline in UAS7 scores up to Week 12 were imputed using zero (i.e., no clinical improvement from baseline, rather than the worst value of the endpoint (i.e., 42 for UAS7)) for the intercurrent event of 'Intake of strongly confounding prohibited medication' handled with composite strategy.

In Study A2301, the LS mean treatment difference in UAS7 score at Week 12 was -6.29 (95% CI: -8.49, -4.08; one-sided p-value < 0.001). In Study A2302, the LS mean treatment difference was -7.64 (95%CI: -9.83, -5.44), p<0.001.

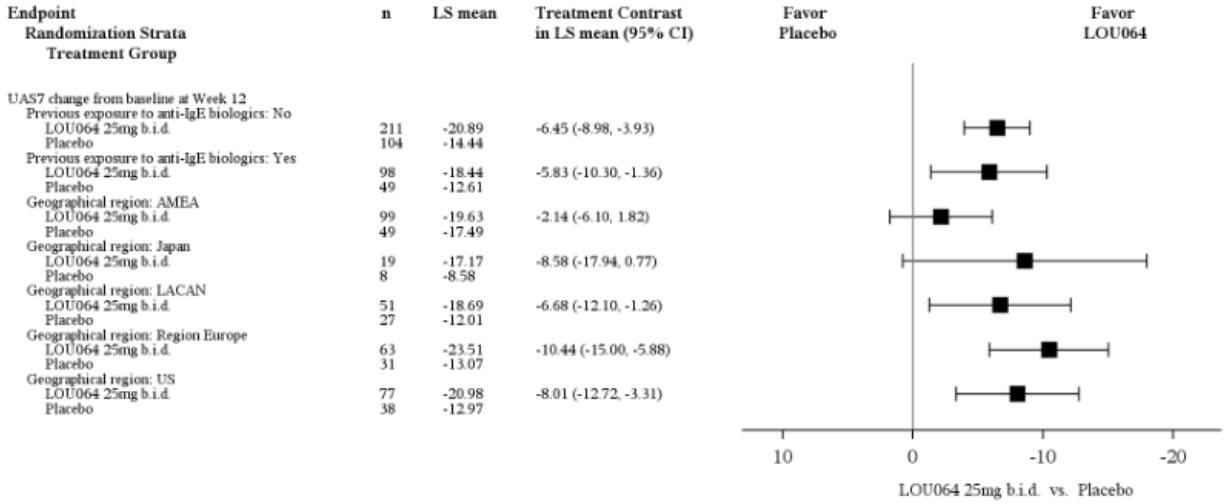
Supplementary analysis

In the supplementary analysis, for the intercurrent event of 'Intake of strongly confounding prohibited medication', hypothetical strategy was applied. Measurements after these events were excluded from the analysis and were imputed via a modeling approach.

In Study A2301, the LS mean treatment difference in UAS7 score at Week 12 was -6.36 (95% CI: -8.56, -4.16; one-sided p-value < 0.001). In Study A2302, the LS mean treatment difference in UAS7 score at Week 12 was -7.69 (95%CI: -9.86, -5.47), p<0.001.

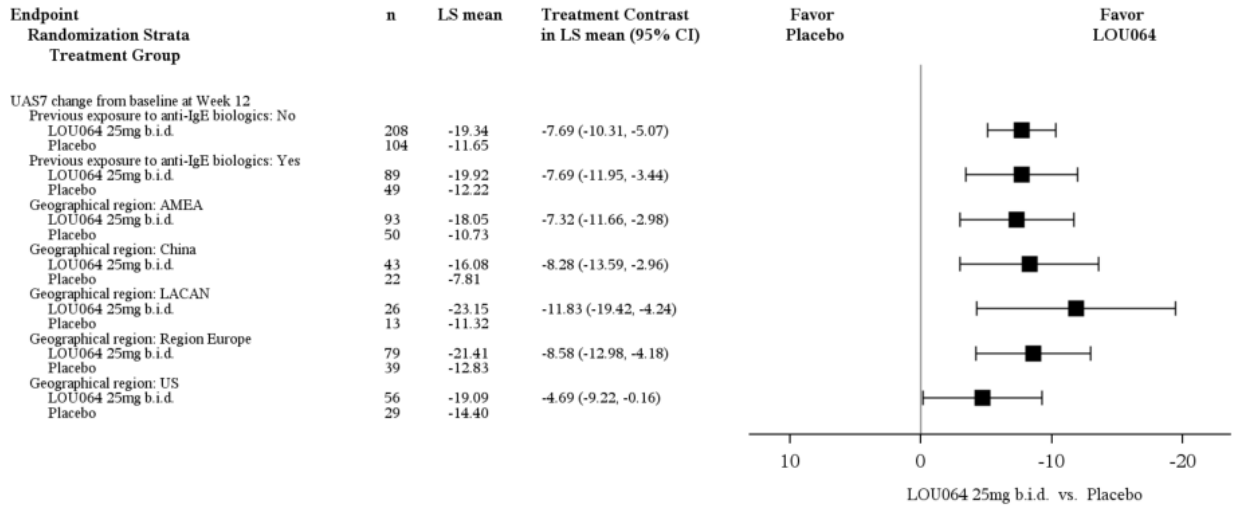
Subgroup analysis by randomisation strata

Figure *22*: Study A2301: Forest plot of the LS mean difference in CFB for UAS7 at Week 12 (Estimand, MMRM) by randomisation strata (FAS)



LS Mean: Least squares mean, CI: confidence interval.
Statistical model used a mixed effect model with repeated measures (MMRM) adjusting for treatment group,geographical region (excluded in the analysis of the geographical region subgroups), prior exposure to anti-IgE biologics (excluded in the analysis of the prior exposure to anti-IgE biologics subgroups), visit week, baseline score and both interaction of treatment by visit week and interaction of baseline score by visit week.
Source: Table 14.2-1.1a, Table 14.2-1.4a and Table 14.2-1.5a.

Figure *23*: Study A2302: Forest plot of the LS mean difference in CFB for UAS7 at Week 12 (Estimand, MMRM) by randomisation strata (FAS)



LS Mean: Least squares mean, CI: confidence interval.
Statistical model used a mixed effect model with repeated measures (MMRM) adjusting for treatment group,geographical region (excluded in the analysis of the geographical region subgroups), prior exposure to anti-IgE biologics (excluded in the analysis of the prior exposure to anti-IgE biologics subgroups), visit week, baseline score and both interaction of treatment by visit week and interaction of baseline score by visit week.
Source: Table 14.2-1.1a. Table 14.2-1.4a and Table 14.2-1.5a.

Rescue medication

In the CSR of both pivotal studies rescue medications were presented under Exploratory analyses. However, as they are vital to the interpretation of efficacy results, they are included here.

Total weekly dose of second generation H1-AHs

In Study A2301, the mean total weekly doses of H1-AHs rescue medication used at baseline was 532.21 mg in the remibrutinib arm and 520.37 mg in the placebo arm. The mean percent change in the total weekly doses of second generation H1-AHs rescue medication used at Week 12 in the remibrutinib arm compared to the placebo arm was -34.65% vs. -16.86%.

In the remibrutinib arm, the mean percent change in the total weekly doses of second generation H1-AHs rescue medication used were -37.44% at Week 24 and -33.66% at Week 52.

In the placebo-remibrutinib transitioned patients, the mean percent change in the total weekly doses of second generation H1-AHs rescue medication used were -25.10% at Week 24 and -53.18% at Week 52.

Table 45: Study A2301: Summary of CFB in H1-AH (rescue medication) dose in mg (FAS, original table only partially shown)

Table 14.2-9.26 (Page 1 of 27)
Summary of change from baseline in H1-AH (rescue medication) dose (mg) up to the end of study (Observed data)
Full Analysis Set

		LOU064 25mg b.i.d. N=309				Placebo - LOU064 25mg b.i.d. N=153			
Time point	Statistics	Base	Post	Change	Percentage Change	Base	Post	Change	Percentage Change
Baseline	n	298				145			
	Mean	532.21				520.37			
	SD	1022.868				1018.851			
	Minimum	0.0				0.0			
	Median	112.50				140.00			
	Maximum	5400.0				7560.0			
Week 1	n	298	298	298	257	144	144	144	127
	Mean	532.21	360.26	-171.95	-21.72	523.50	387.96	-135.54	-19.41
	SD	1022.868	881.499	858.375	108.505	1021.708	899.711	415.148	75.770
	Minimum	0.0	0.0	-5400.0	-100.0	0.0	0.0	-2700.0	-100.0
	Median	112.50	60.00	-15.00	-38.46	140.00	75.00	-20.00	-22.22
	Maximum	5400.0	7380.0	6120.0	733.3	7560.0	5400.0	1080.0	600.0

Base=Baseline, Post=Post baseline, Change=Post-Base, Percentage Change=(Post-Base)*100/Base.
For each post-baseline week, only subjects with a value at both baseline and the respective week are included.
Total weekly dose of H1-AH (in mg) will be calculated by multiplying the total number of tablets used per week from UPDD eDiary data and the dose (in mg) per tablet from eCRF.

Table 14.2-9.26 (Page 7 of 27)
Summary of change from baseline in H1-AH (rescue medication) dose (mg) up to the end of study (Observed data)
Full Analysis Set

		LOU064 25mg b.i.d. N=309				Placebo - LOU064 25mg b.i.d. N=153			
Time point	Statistics	Base	Post	Change	Percentage Change	Base	Post	Change	Percentage Change
Week 12	n	278	278	278	239	133	133	133	118
	Mean	540.05	288.79	-251.26	-34.65	543.71	609.75	66.04	-16.86
	SD	1039.272	814.523	1000.354	162.367	1052.850	1743.816	1315.404	128.502
	Minimum	0.0	0.0	-5220.0	-100.0	0.0	0.0	-2160.0	-100.0
	Median	110.00	15.00	-40.00	-75.00	140.00	60.00	-40.00	-42.86
	Maximum	5400.0	9000.0	7740.0	2000.0	7560.0	12600.0	11340.0	900.0
Week 13	n	274	274	274	235	131	131	131	116
	Mean	547.15	280.66	-266.49	-34.10	549.38	578.58	29.20	-18.26
	SD	1045.195	954.277	1155.288	171.824	1059.870	1712.067	1323.342	131.789
	Minimum	0.0	0.0	-5220.0	-100.0	0.0	0.0	-2700.0	-100.0
	Median	112.50	5.00	-40.00	-80.00	140.00	60.00	-40.00	-43.22
	Maximum	5400.0	12600.0	11340.0	2000.0	7560.0	12600.0	11340.0	900.0

Base=Baseline, Post=Post baseline, Change=Post-Base, Percentage Change=(Post-Base)*100/Base.
For each post-baseline week, only subjects with a value at both baseline and the respective week are included.
Total weekly dose of H1-AH (in mg) will be calculated by multiplying the total number of tablets used per week from UPDD eDiary data and the dose (in mg) per tablet from eCRF.

In Study A2302, the mean total weekly doses of H1-AHs rescue medication used at baseline was 585.38 mg in the remibrutinib arm and 324.69 mg in the placebo arm. The mean percent change in the total weekly doses of second generation H1-AHs rescue medication used at Week 12 in the remibrutinib arm compared to the placebo arm was -37.84% vs. -7.14%.

In the remibrutinib arm, the mean percent change in the total weekly doses of second generation H1-AHs rescue medication used were -37.10% at Week 24 and -58.82% at Week 52.

In the placebo-remibrutinib transitioned patients, the mean percent change in the total weekly doses of second generation H1-AHs rescue medication used were -5.54% at Week 24 and -58.04% at Week 52.

Table 46: Study A2302: Summary of CFB in H1-AH (rescue medication) dose in mg (FAS, original table only partially shown)

Table 14.2-9.26 (Page 1 of 27)
Summary of change from baseline in H1-AH (rescue medication) dose (mg) up to the end of study (Observed data)
Full Analysis Set

		LOU064 25mg b.i.d. N=297				Placebo - LOU064 25mg b.i.d. N=153			
Time point	Statistics	Base	Post	Change	Percentage Change	Base	Post	Change	Percentage Change
Baseline	n	277				142			
	Mean	585.38				324.69			
	SD	1451.903				816.853			
	Minimum	0.0				0.0			
	Median	75.00				70.00			
	Maximum	12600.0				5040.0			
Week 1	n	277	277	277	222	142	142	142	111
	Mean	585.38	459.69	-125.69	-15.99	324.69	311.12	-13.57	-6.31
	SD	1451.903	1206.946	754.744	98.893	816.853	776.223	338.711	80.890
	Minimum	0.0	0.0	-9000.0	-100.0	0.0	0.0	-1800.0	-100.0
	Median	75.00	50.00	-5.00	-27.53	70.00	70.00	0.00	-11.11
	Maximum	12600.0	10800.0	2340.0	800.0	5040.0	5040.0	1440.0	500.0

Base=Baseline, Post=Post baseline, Change=Post-Base, Percentage Change=(Post-Base)*100/Base.
For each post-baseline week, only subjects with a value at both baseline and the respective week are included.
Total weekly dose of H1-AH (in mg) will be calculated by multiplying the total number of tablets used per week from UPDD eDiary data and the dose (in mg) per tablet from eCRF.

Table 14.2-9.26 (Page 7 of 27)
Summary of change from baseline in H1-AH (rescue medication) dose (mg) up to the end of study (Observed data)
Full Analysis Set

		LOU064 25mg b.i.d. N=297				Placebo - LOU064 25mg b.i.d. N=153			
Time point	Statistics	Base	Post	Change	Percentage Change	Base	Post	Change	Percentage Change
Week 12	n	252	252	252	199	127	127	127	98
	Mean	561.67	324.23	-237.44	-37.84	348.39	255.40	-92.99	-7.14
	SD	1447.693	1052.699	926.554	107.298	860.206	665.557	583.554	149.351
	Minimum	0.0	0.0	-9000.0	-100.0	0.0	0.0	-3960.0	-100.0
	Median	72.50	5.00	-27.50	-72.73	70.00	35.00	0.00	-22.92
	Maximum	12600.0	12600.0	1440.0	1000.0	5040.0	4320.0	1260.0	1200.0
Week 13	n	250	250	250	196	126	126	126	97
	Mean	553.44	292.18	-261.26	-37.19	350.36	237.06	-113.30	-22.22
	SD	1438.945	722.623	1100.829	123.116	863.352	646.944	668.856	82.660
	Minimum	0.0	0.0	-9540.0	-100.0	0.0	0.0	-5040.0	-100.0
	Median	70.00	0.00	-20.00	-72.90	70.00	35.00	0.00	-30.00
	Maximum	12600.0	4500.0	1980.0	1100.0	5040.0	5040.0	1440.0	400.0

Base=Baseline, Post=Post baseline, Change=Post-Base, Percentage Change=(Post-Base)*100/Base.
For each post-baseline week, only subjects with a value at both baseline and the respective week are included.
Total weekly dose of H1-AH (in mg) will be calculated by multiplying the total number of tablets used per week from UPDD eDiary data and the dose (in mg) per tablet from eCRF.

Total weekly dose of oral corticosteroids

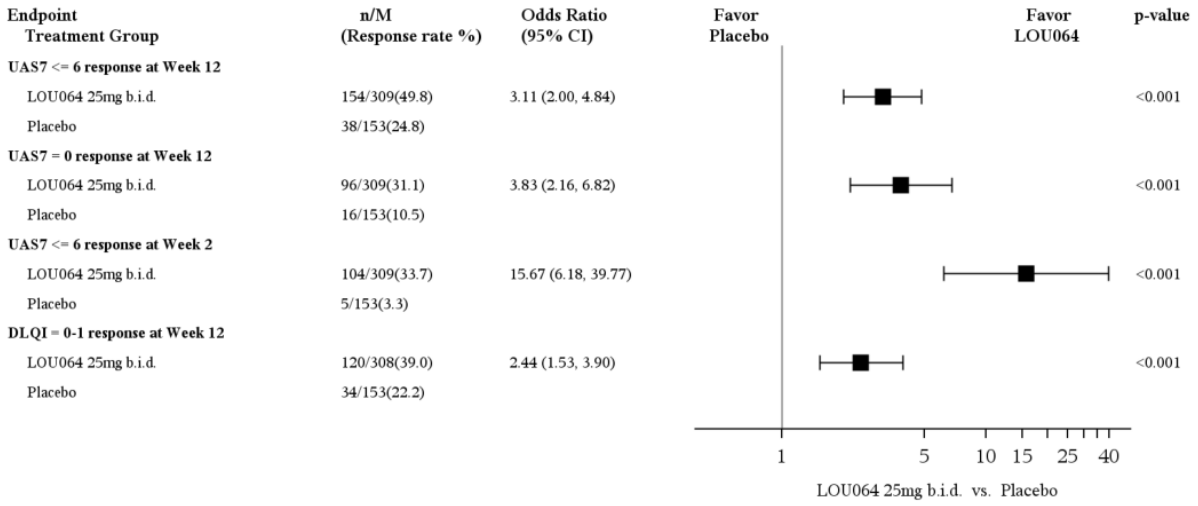
Oral corticosteroids were allowed as rescue medication only after the Week 12 primary endpoint. Very few patients required oral corticosteroids in both pivotal studies. In Study A2301 in the double-blind

period, 0.3% vs. 2.0% patients in the remibrutinib vs. placebo arms and in the entire study period, 8 patients (2.6%) in the remibrutinib arm and 2 patients (1.5%) in the patients who transitioned to remibrutinib used oral corticosteroids. In Study A2302 in the double-blind period, 1.0% vs. 2.0% patients in the remibrutinib vs. placebo arms and in the entire study period, 6 patients (2.0%) in the remibrutinib arm and 4 patients (3.1%) in the patients who transitioned to remibrutinib used oral corticosteroids.

Secondary endpoint results

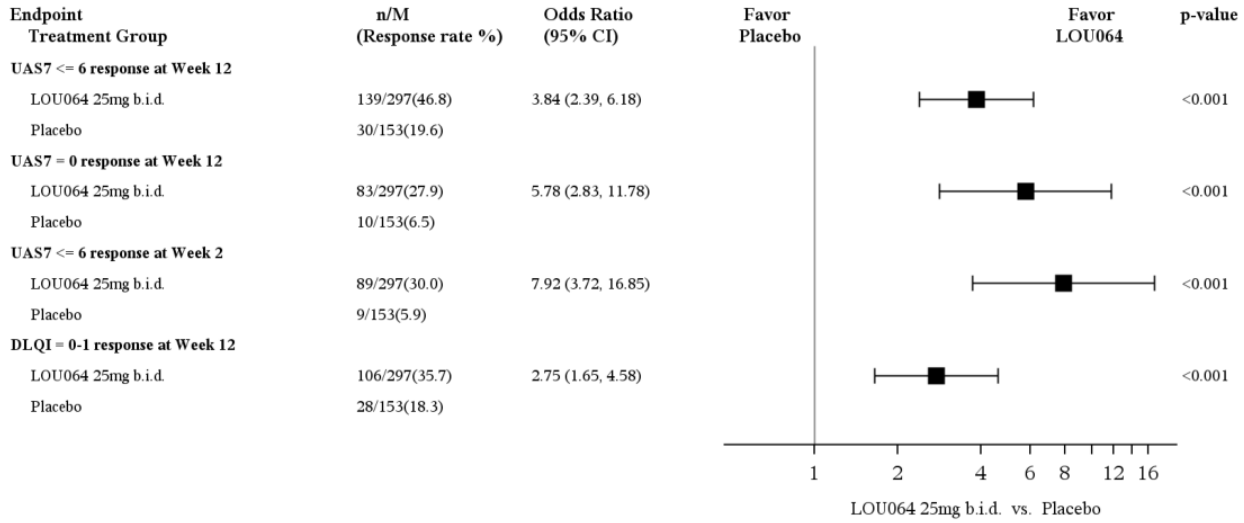
Secondary endpoint results for both pivotal studies are already summarised in **Table 40**. Additional data will be presented below.

Figure *24*: Study A2301: Forest plot of the odds ratio for UAS7≤6 at W12, UAS7=0 at W12, UAS7≤6 at W2 and DLQI 0-1 at W12 (Estimand) (FAS)



CI: confidence interval, p-value: one-sided p-value.
Statistical model used logistic regression adjusting for treatment group, geographical region, prior exposure to anti-IgE biologics and baseline score.
Source: Table 14.2-1.2, Table 14.2-1.3, Table 14.2-1.6 and Table 14.2-1.7.

Figure *25*: Study A2302: Forest plot of the conditional odds ratio for UAS7 ≤ 6 at W12, UAS7=0 at W12, UAS7 ≤6 at W2 and DLQI 0-1 at W12 (Estimand) (FAS)



CI: confidence interval, p-value: one-sided p-value.
Statistical model used logistic regression adjusting for treatment group, geographical region, prior exposure to anti-IgE biologics and baseline score.
Source: Table 14.2-1.2, Table 14.2-1.3, Table 14.2-1.6 and Table 14.2-1.7.

Supplementary analyses for the secondary outcomes

In supplementary analyses, for binary variables (UAS7 ≤ 6 at Week 12, UAS7 = 0 at Week 12, UAS7 ≤ 6 at Week 2, DLQI = 0-1 at Week 12), the treatment difference adjusting for region, prior exposure to anti-IgE biologics and baseline score was provided.

UAS7 ≤ 6 at Week 12: In Study A2301, the treatment difference between rembrutinib and placebo response rate was 25.44% (95% CI 16.48, 34.39) favouring remibrutinib. In Study A2302, the treatment difference was 27.61% (95% CI 19.14, 36.08) favouring remibrutinib.

UAS7 = 0 at Week 12: In Study A2301, the treatment difference between rembrutinib and placebo response rate was 20.55% (95% CI 13.35, 27.75) favouring remibrutinib. In Study A2302, the treatment difference was 21.60% (95% CI 15.10, 28.10) favouring remibrutinib.

UAS7 ≤ 6 at Week 2: In Study A2301, the treatment difference between remibrutinib and placebo response rate was 30.20 (95% CI 23.30, 36.1) favouring remibrutinib. In Study A2303, the treatment difference was 24.55 (95% CI 18.31, 30.8) favouring remibrutinib.

DLQI = 0-1 at Week 12: In Study A2301, the treatment difference was 17.65% (95%CI 9.14, 26.16) favouring remibrutinib. In Study A2302, the treatment difference was 18.21% (95% CI 9.96, 26.45) favouring remibrutinib.

Subgroup analyses by randomisation strata

UAS7 ≤ 6 at Week 12: The results of the subgroup analysis by randomisation strata in Study A2301 showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 1 in regions Japan, AMEA and LACAN. In Study A2302, subgroup analyses by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata.

UAS7 = 0 at Week 12: In Study A2301, the results of the subgroup analysis by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 1 in regions Japan, AMEA and LACAN. In Study A2302, the results of the subgroup analysis by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 1 in regions China and LACAN.

Change from baseline in ISS7 score at Week 12: In Study A2301, the results of the subgroup analysis by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 0 in regions Japan and AMEA. In Study A2302, the results of the subgroup analysis by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 0 in region US.

Change from baseline in HSS7 score at Week 12: In Study A2301, the results of the subgroup analysis by randomszation strata showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 0 in regions Japan and AMEA. In Study A2302, the results of the subgroup analysis by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata.

UAS7 ≤ 6 at Week 2: In Study A2301, the results of the subgroup analysis by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 0 in regions Japan, AMEA and LACAN. In Study A2302, the results of the subgroup analysis by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 1 in region LACAN.

DLQI = 0-1 at Week 12: In Study A2301, the results of the subgroup analysis by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 1 in regions Japan, AMEA and LACAN. In Study A2302, the results of the subgroup analysis by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 1 in regions AMEA, China, LACAN and the US.

Cumulative number of weeks with UAS7 ≤ 6 up to Week 12: In Study A2301, the subgroup analysis by randomisation strata results showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 1 in region Japan. In Study A2302, the results of the subgroup analysis by randomisation strata showed a treatment effect in favour of the remibrutinib arm across the strata.

Cumulative number of weeks with AAS7 = 0 up to Week 12: In Study A2301, the subgroup analysis by randomisation strata results showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 1 in the subgroup of patients who had previous exposure to anti-IgE biologic and in the region LACAN, while the LS mean was not estimable in the region Japan. In Study A2302, the subgroup analysis by randomisation strata results showed a treatment effect in favour of the remibrutinib arm across the strata, although with the CI crossing 1 in regions AMEA, China and the US.

Exploratory endpoint results

Of note, only those exploratory endpoint results considered of clinical interest from Study A2301 and A2302 will be presented below; for complete results of exploratory endpoint results please refer to their respective CSRs.

Exploratory endpoints at Week 24 (end of double-blind period)

Absolute change from baseline of UAS7, ISS7 and HSS7 scores at Week 24

In Study A2301, the LS mean values reported at Week 24 in the remibrutinib vs. placebo arms were as follows:

- UAS7: -20.74 vs. -16.02 with a treatment difference of -4.73 (95% CI: -6.98, -2.48)
- ISS7: -9.81 vs. -8.00 with a treatment difference of -1.81 (95% CI: -2.88, -0.73)
- HSS7: -10.88 vs. -7.97 with a treatment difference of -2.91 (95% CI: -4.16, -1.66)

In Study A2302, the LS mean values reported at Week 24 in the remibrutinib vs. placebo arms were as follows:

- UAS7: -20.41 vs. -13.73 with a treatment difference of -6.68 (95% CI: -9.06, -4.31)
- ISS7: -9.49 vs. -6.46 with a treatment difference of -3.03 (95% CI: -4.16, -1.90)
- HSS7: -10.92 vs. -7.31 with a treatment difference of -3.61 (95% CI: -4.92, -2.29)

Proportion of patients achieving disease activity control (UAS7 ≤ 6) at Week 24

Study A2301: proportions of patients achieving disease control at week 24 were 54.7% vs 35.3 % in remibrutinib vs placebo arms, respectively.

Study A2302: proportions of patients achieving disease control at week 24 were 51.9 vs 27.5% in remibrutinib vs placebo arms, respectively.

Proportion of patients achieving complete absence of itch and hives (UAS7 = 0) at Week 24

Study A2301: The proportion of patients achieving UAS7=0 at week 24 was 35.6% vs. 19.6% in remibrutinib vs placebo arm, respectively.

Study A2302: The proportion of patients achieving UAS7=0 at week 24 was 35.7% vs. 15.7% in remibrutinib vs placebo arm, respectively.

DLQI = 0-1 (No impact on patient's dermatology-related QoL) at Week 24

Study A2301: The proportion of patients achieving DLQI = 0-1 at week 24 was 46.1% vs. 28.1% in remibrutinib vs placebo, respectively.

Study A2302: The proportion of patients achieving DLQI = 0-1 at week 24 was 40.7% vs. 20.3% in remibrutinib vs placebo, respectively.

Cumulative number of weeks with disease activity control (UAS7 ≤ 6) up to Week 24

Study A2301: Up to Week 24, the patients in the remibrutinib arm continued to maintain disease activity control (UAS7 ≤ 6) for more weeks, approximately 2 times more than that of the placebo arm patients (LS mean: 11.66 weeks vs. 5.63 weeks, respectively; rate ratio: 2.07 with 95% CI: 1.55, 2.77).

Study A2302: Up to Week 24, the patients in the remibrutinib arm continued to maintain disease activity control (UAS7 ≤ 6) for more weeks, approximately 2.5 times more than that of the placebo arm patients (LS mean: 10.44 weeks vs. 4.18 weeks, respectively; rate ratio: 2.50 with 95% CI: 1.79, 3.49)

Cumulative number of angioedema-free weeks (AAS7 = 0) up to Week 24

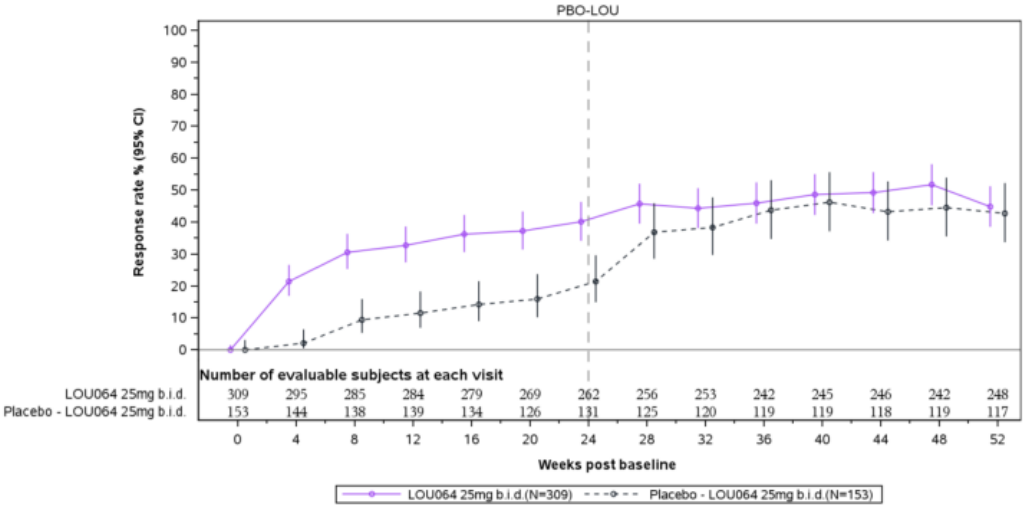
Study A2301: Up to Week 24, the patients in the remibrutinib arm continued to have more angioedema-free weeks than the placebo arm patients (LS mean: 17.43 weeks vs. 14.45 weeks, respectively; rate ratio: 1.21 with 95% CI: 1.07, 1.36).

Study A2302: Up to Week 24, the patients in the remibrutinib arm continued to have more angioedema-free weeks than the placebo arm patients (LS mean: 18.03 weeks vs. 13.97 weeks, respectively; rate ratio: 1.29 with 95% CI: 1.12, 1.48).

Exploratory endpoints over time

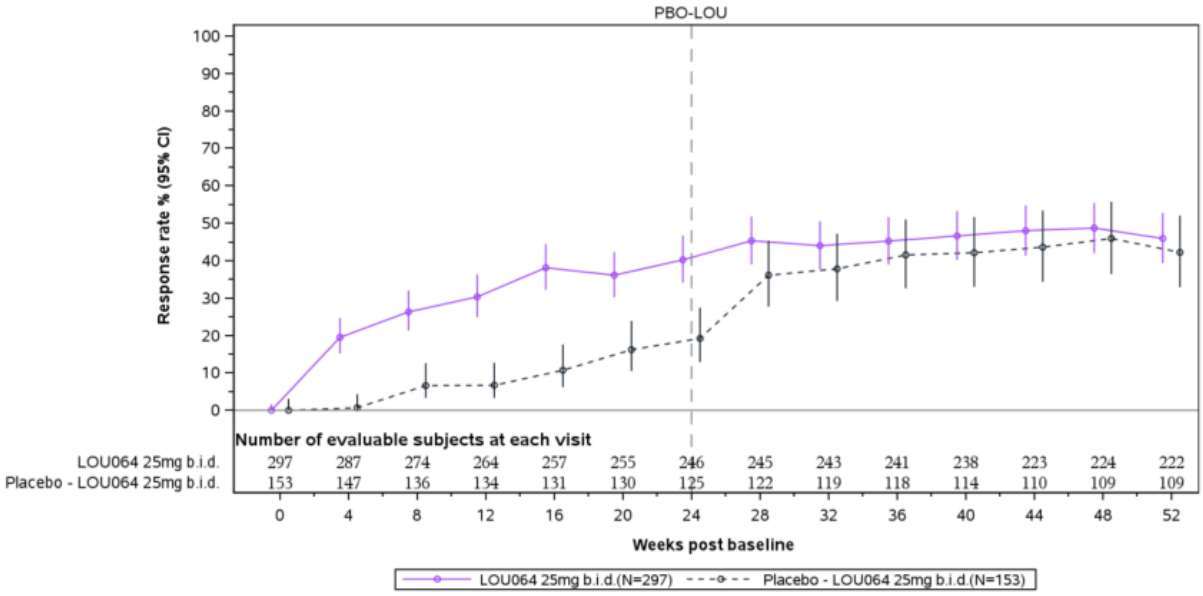
Complete absence of itch and hives (UAS7 = 0) over time

Figure *26*: Study A2301: UAS7 = 0 response rate by 4 weeks up to the end of the study by treatment arm (Observed data) (FAS)



Source: Figure 14.2-3.1

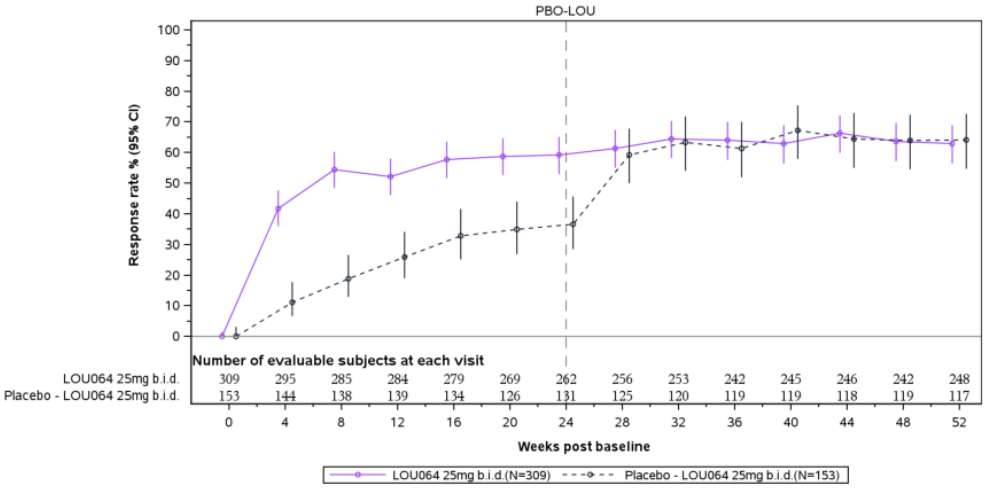
Figure *27*: Study A2302: UAS7 = 0 response rate by 4 weeks up to the end of the study by treatment arm (Observed data) (FAS)



Source: Figure 14.2-3.1

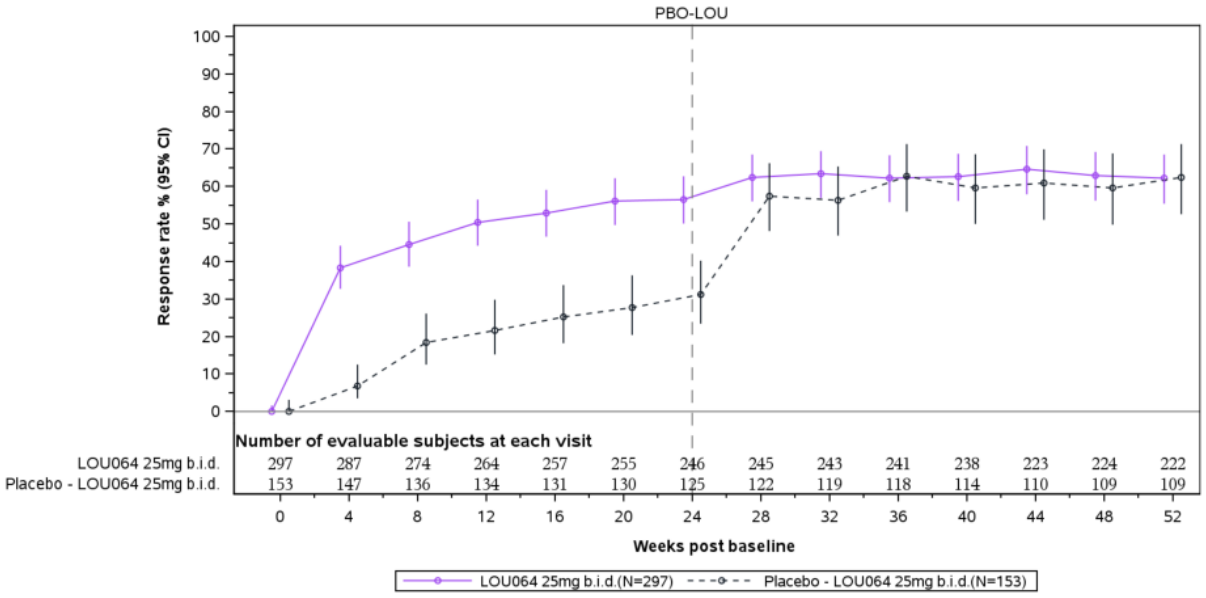
Disease activity control (UAS7 ≤ 6) over time

Figure *28*: Study A2301: UAS7 ≤ 6 response rate by 4 weeks up to the end of the study (Observed data) (FAS)



Source: Table 14.2-9.4.

Figure *29*: Study A2302: UAS7 ≤ 6 response rate by 4 weeks up to the end of study (Observed data) (FAS)

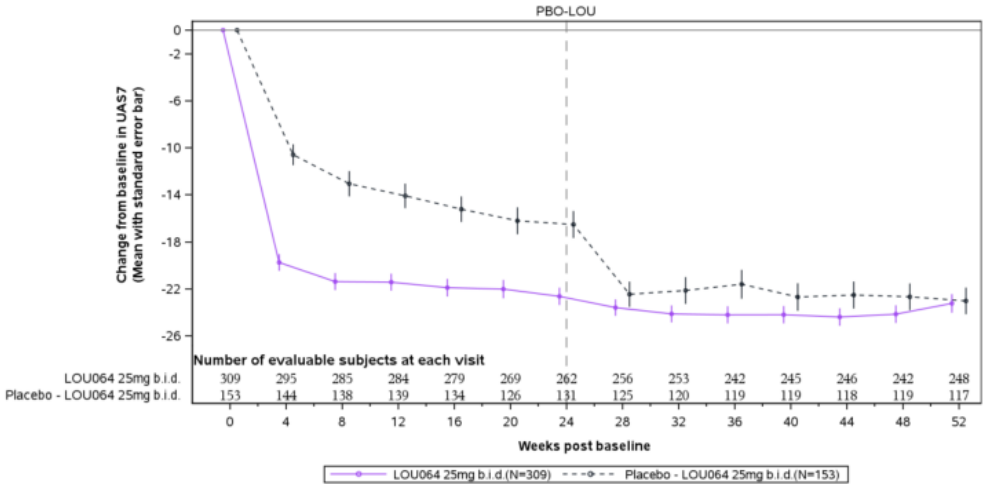


Source: Table 14.2-9.4.

/vob/CLOU064A/CLOU064A2302/csr_2/pgm/eff/fbline.sas 25FEB24:20:39 Final Version

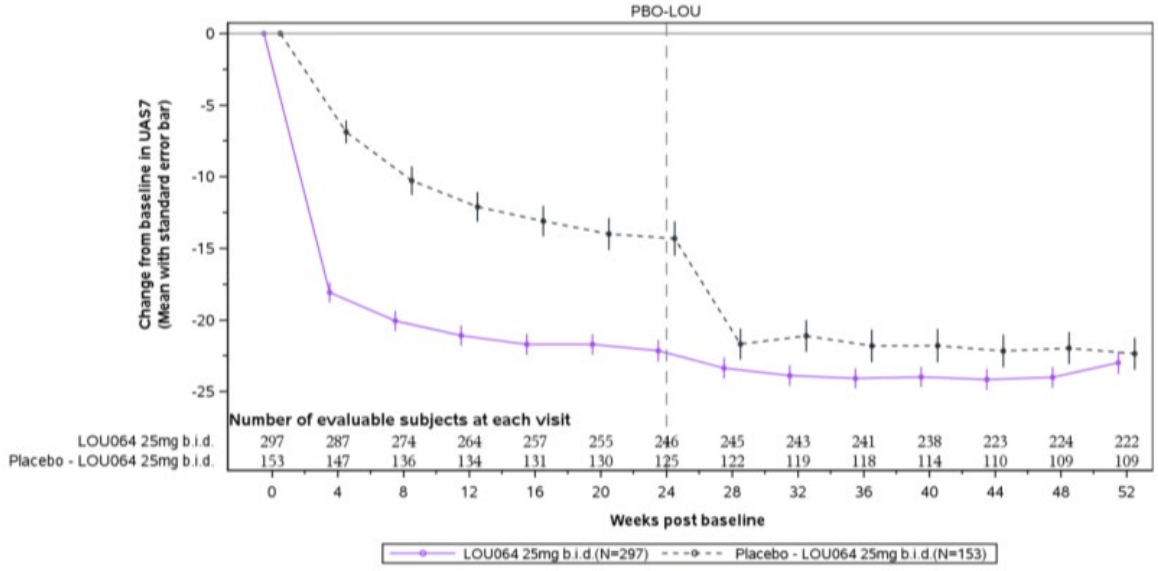
Absolute change from baseline in UAS7 over time

Figure *30*: Study A2301: UAS7 mean change from baseline by 4 weeks up to the end of the study (Observed data) (FAS)



Source: Figure 14.2-3.3

Figure *31*: Study A2302: UAS7 mean change from baseline by 4 weeks up to the end of the study (Observed data) (FAS)



Source: Figure 14.2-3.3

Angioedema-free (AAS7=0) over time

Study A2301: At baseline, 34.6% of the patients in the remibrutinib arm and 40.5% of the patients in the placebo arm were free of angioedema. At Week 24, 83.7% of the patients in the remibrutinib arm were angioedema-free (AAS7 = 0) compared to 74.2% in the placebo arm. At Week 52, 86.0% of the patients in the remibrutinib arm and 87.4% of the placebo-remibrutinib transitioned patients were angioedema-free (AAS7 = 0).

Study A2302: At baseline, 41.9% of the patients in the remibrutinib arm and 49.0% of the patients in the placebo arm were free of angioedema. At Week 24, 85.2% of the patients in the remibrutinib arm were angioedema-free (AAS7 = 0) compared to 72.1% in the placebo arm. At Week 52, 90.2% of the

patients in the remibrutinib arm and 89.7% of the placebo-remibrutinib transitioned patients were angioedema-free (AAS7 = 0).

5.3.2.1.4.5 Pre-defined and post-hoc subgroup analyses

Subgroup analysis of UAS7, ISS7 and HSS7 change from baseline scores and achievement of disease activity control (UAS7 ≤ 6) and complete absence of itch and hives (UAS7 = 0) over time

By baseline CU-Index: In general, and in both pivotal studies, patients who were CU-Index positive showed a better improvement in the UAS7, ISS7, and HSS7 scores and achieved disease activity control (UAS7 ≤ 6) or complete absence of itch and hives (UAS7 = 0) in greater proportion compared to the CU-Index-negative patients in the remibrutinib arm up to Week 24. The treatment effect sustained up to Week 52 in the remibrutinib arm. In the placebo-remibrutinib transitioned patients also, CU-Index positive patients showed better response after transitioning to remibrutinib.

By baseline total IgE levels: In both pivotal studies, patients with low levels of IgE (≤ 43 IU/mL) at baseline showed greater improvements in UAS7, ISS7, and HSS7 scores and achieved disease activity control (UAS7 ≤ 6) or complete absence of itch and hives (UAS7 = 0) in greater proportion compared to the patients with normal/high levels (> 43 IU/mL) in the remibrutinib arm up to Week 24, and sustained thereafter up to Week 52. In the placebo-remibrutinib transitioned patients, the treatment effect was generally similar for both low and normal/high IgE levels groups after transitioning to remibrutinib.

By disease duration: In both pivotal studies in the remibrutinib arm, patients in all CSU duration subgroups showed similar improvements in the UAS7, ISS7, and HSS7 scores and achieved disease activity control (UAS7 ≤ 6) or complete absence of itch and hives (UAS7 = 0) in similar proportion up to Week 24, and sustained thereafter up to Week 52. In the placebo-remibrutinib transitioned patients, patients with prolonged CSU (over 3 years of duration and more) showed worse results compared to patients with shorter disease duration after transitioning to remibrutinib.

By diagnosis of concomitant CINDU: In general, and in both pivotal studies, patients with and without concomitant CINDU at baseline showed similar UAS7, ISS7, and HSS7 scores and achieved disease activity control (UAS7 ≤ 6) or complete absence of itch and hives (UAS7 = 0) up to Week 24, and sustained thereafter up to Week 52. In placebo-remibrutinib transitioned patients, similar findings were observed after transitioning to remibrutinib.

5.3.2.1.4.6 Pre-defined and post-hoc sensitivity analyses

Sensitivity analyses are reported under the primary endpoint results, while no sensitivity analyses were performed for the secondary endpoints.

5.3.3. Clinical studies in special populations

Table 47: Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	1/1221	0/215
Hepatic impairment** patients (Subjects number /total number)	0/1221	0/215
Paediatric patients <18 years (Subjects number /total number)	0/1221	0/215
Older patients; Age 65-74 (Subjects number /total number)	92/1221	17/215
Age 75-84 (Subjects number /total number)	17/1221	1/215
Age 85+ (Subjects number /total number)	0/1221	0/215
Other (Subjects number /total number)	1111/1221	197/215

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

5.3.4. Supportive studies

Study CLOU064A1301 was a single country, multi-center, open-label, single arm Phase III study investigating the safety, tolerability and efficacy of remibrutinib (25 mg b.i.d.) in Japanese patients with CSU inadequately controlled by second generation H1-AHs with total duration of 60 weeks. Background and rescue medications were used in the same way as in the pivotal studies. A total of 71 patients were enrolled in the study and received open-label remibrutinib 25 mg b.i.d. A total of 68 patients (95.8%) completed the 52-week treatment period and 3 patients (4.2%) discontinued.

The main efficacy results are:

- The mean absolute change from baseline in UAS7 score at Week 12 was -18.14.
- The proportion of patients achieving disease activity control (UAS7 ≤ 6) at baseline was 0% and 42.3% at Week 12.
- The proportion of patients achieving complete absence of itch and hives (UAS7 = 0) at baseline was 0% and 21.1% at Week 12.
- The mean absolute change from baseline in ISS7 score at Week 12 was -8.01.
- The mean absolute change from baseline in HSS7 score at Week 12 was -10.12
- The proportion of patients achieving disease activity control as early as Week 2 was 40.8%.
- The proportion of patients who had no impact on their dermatology-related QoL (DLQI = 0-1) at baseline was 0% and 54.9% at Week 12.
- The mean cumulative number of weeks with disease activity control (UAS7 ≤ 6) up to Week 12 was 4.6 weeks.
- The mean cumulative number of angioedema-free weeks (AAS7 = 0) up to Week 12 was 10 weeks.

Study CLOU064A2201E1 was an open-label, single arm, multicenter, long-term safety and tolerability extension study for CSU patients rolling over from Study A2201. The study conducted differs from the pivotal studies in terms of remibrutinib dosing and study design (efficacy endpoints were assessed at week 4 until when no background medication was used).

Study CLOU064A2305 was a small study with 144 participants treated with sg H1-AHs and remibrutinib. The primary objective of the study was to evaluate the effect of remibrutinib on ABPM measures.

Study A2303B is a Phase IIIb multicenter, double-blind, placebo-controlled, RW, and open-label extension study to evaluate the efficacy and safety of remibrutinib in adult participants with CSU who had completed one of the preceding Phase III core studies: Study A2301, Study A2302, Study A1301, and the ABPM Study A2305. The study consists of two Epochs (Epoch 1 and Epoch 2), and the total study duration is approximately 160 weeks. Only data from Epoch 1 are currently available.

5.3.5. Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analysis across pivotal studies A2301 and A2302

As presented in the Main studies section, Studies A2301 and A2302 were identical in design, enabling the pooling of the results. Results from the pooled analysis of the primary and secondary efficacy endpoints will be presented below. Additionally, results from the pooled analysis of the exploratory endpoints (consisting of endpoints analysed at week 24 and exploratory analysis over time) will be presented further below.

Table 48: Pooled (Studies A2301 and A2302) analysis of the primary and secondary efficacy endpoints (Estimand) (Pooled FAS)

Endpoint	Measure	Pooled data from Study A2301 and Study A2302		
		Remibrutinib 25 mg b.i.d. N = 606	Placebo N = 306	Comparison vs. placebo
UAS7 score change from baseline at Week 12	n1	606	306	
	LS mean [1]	-19.93	-12.98	-6.95
	95% CI [1]			(-8.52, -5.38)
	p-value			<0.001
ISS7 score change from baseline at Week 12	n1	606	306	
	LS mean [1]	-9.36	-6.44	-2.92
	95% CI [1]			(-3.68, -2.17)
	p-value			<0.001
HSS7 score change from baseline at Week 12	n1	606	306	
	LS mean [1]	-10.59	-6.55	-4.04
	95% CI [1]			(-4.92, -3.16)
	p-value			<0.001
Disease activity control (UAS7 ≤ 6) at Week 12	n2/M	294/606	68/306	
	Response rate (%) [2]	48.5	22.2	26.53
	95% CI [2]			(20.33, 32.72)
	p-value			<0.001
Complete absence of itch and hives (UAS7 = 0) at Week 12	n2/M	180/606	26/306	
	Response rate (%) [2]	29.7	8.5	21.02
	95% CI [2]			(16.15, 25.90)
	p-value			<0.001
Disease activity control (UAS7 ≤ 6) at Week 2	n2/M	192/606	14/306	
	Response rate (%) [2]	31.7	4.6	27.41
	95% CI [2]			(23.10, 31.72)
	p-value			<0.001
	n2/M	226/605	61/306	
	Response rate (%) [2]	37.4	19.9	17.85

No impact on patients' dermatology-related quality of life (DLQI = 0-1) at Week 12	95% CI [2]			(11.90, 23.80)
	p-value			<0.001
Cumulative number of weeks with an UAS7 ≤ 6 response between baseline and Week 12	n1	606	306	
	Average counts of weeks[3]	4.83	1.68	
	Rate ratio [3]			2.87
	95% CI [3]			(2.28, 3.61)
	p-value			<0.001
Cumulative number of weeks with an AAS7= 0 response between baseline and Week 12	n1	606	306	
	Average counts of weeks[3]	8.64	6.70	
	Rate ratio [3]			1.29
	95% CI [3]			(1.19, 1.40)
	p-value			<0.001

n1: The number of patients included in the analysis for each treatment group.
n2 : The number of patients who responded.
N: The total number of patients in the corresponding treatment group
M: The total number of patients in the treatment group with response variable defined.
p-value : one-sided nominal p-value.
Multiple imputation techniques were implemented for missing data.
[1] Statistical model used a MMRM adjusting for treatment group, geographical region, prior exposure to anti-IgE biologics, visit week, baseline score, study and both interaction of treatment by visit week and interaction of baseline score by visit week.
[2] Statistical model used logistic regression adjusting for treatment group, geographical region, prior exposure to anti-IgE biologics, baseline score and study.
[3] A rate ratio >1 favors the remibrutinib treatment group. Statistical model used a negative binomial regression with log link includes treatment group as fixed effect, geographical region, prior exposure to anti-IgE biologics and study (and baseline AAS7 = 0 status for the cumulative number of weeks with AAS7 = 0 between baseline and Week 12) as covariates. Natural log of (number of weeks with the response variable in treatment period/12 weeks) as offset variable.
Source: [SCE Appendix 1-Table 3.1.1-1.1, Table 3.1.3-1.1, Table 3.1.2-1.1, Table 3.1.8-1.1, Table 3.1.5-1.1, Table 3.1.8-1.4, Table 3.1.11-1.1, Table 3.1.9-1.1, Table 3.1.14-1.1]

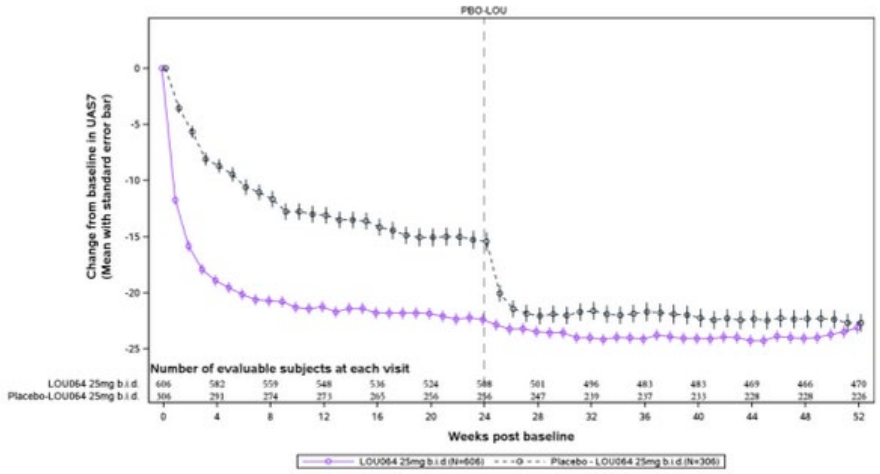
Table 49: Exploratory endpoint results for Study A2301 (FAS), Study A2302 (FAS), and pooled analysis (Pooled FAS) at Week 24

Endpoint	Measure	Study A2301			Study A2302			Pooled data from Study A2301 and Study A2302		
		Remibrutinib 25 mg b.i.d. N = 309	Placebo N = 153	Comparison vs. placebo	Remibrutinib 25 mg b.i.d. N = 297	Placebo N = 153	Comparison vs. placebo	Remibrutinib 25 mg b.i.d. N = 606	Placebo N = 306	Comparison vs. placebo
UAS7 score change from baseline at Week 24	n1	309	153		297	153		606	306	
	LS mean [1]	-20.74	-16.02	-4.73	-20.41	-13.73	-6.68	-20.79	-15.09	-5.70
	95% CI [1]			(-6.98, -2.48)			(-9.06, -4.31)			(-7.34, -4.06)
	p-value			< 0.001			< 0.001			< 0.001
ISS7 score change from baseline at Week 24	n1	309	153		297	153		606	306	
	LS mean [1]	-9.81	-8.00	-1.81	-9.49	-6.46	-3.03	-9.78	-7.36	-2.41
	95% CI [1]			(-2.88, -0.73)			(-4.16, -1.90)			(-3.19, -1.63)
	p-value			< 0.001			< 0.001			< 0.001
HSS7 score change from baseline at Week 24	n1	309	153		297	153		606	306	
	LS mean [1]	-10.88	-7.97	-2.91	-10.92	-7.31	-3.61	-11.03	-7.77	-3.26
	95% CI [1]			(-4.16, -1.66)			(-4.92, -2.29)			(-4.17, -2.36)
	p-value			< 0.001			< 0.001			< 0.001
Disease activity control (UAS7 ≤ 6) at Week 24	n2/M	169/309	54/153		154/297	42/153		323/606	96/306	
	Response rate (%)	54.7	35.3	20.05 [2]	51.9	27.5	24.57 [2]	53.3	31.4	22.23 [2]
	95% CI [2]			(10.45, 29.66)			(15.21, 33.92)			(15.48, 28.98)
	p-value			< 0.001			< 0.001			< 0.001
Complete absence of itch and hives (UAS7 = 0) at Week 24	n2/M	110/309	30/153		106/297	24/153		216/606	55/306	
	Response rate (%)	35.6	19.6	16.05 [2]	35.7	15.7	19.61 [2]	35.6	18.0	17.80 [2]
	95% CI [2]			(7.60, 24.49)			(11.39, 27.83)			(11.92, 23.68)
	p-value			< 0.001			< 0.001			< 0.001
	n2/M	142/308	43/153		121/297	31/153		263/605	74/306	

No impact on patients' dermatology-related quality of life (DLQI = 0-1) at Week 24	Response rate (%)	46.1	28.1	18.24 [2]	40.7	20.3	20.49 [2]	43.5	24.2	19.45 [2]
	95% CI [2]			(9.12, 27.36)			(11.69, 29.28)			(13.08, 25.82)
	p-value			< 0.001			< 0.001			< 0.001
Cumulative number of weeks with an UAS7 ≤ 6 response between baseline and Week 24	n1	309	153		297	153		606	306	
	Average counts of weeks [3]	11.66	5.63		10.44	4.18		11.04	4.94	
	Rate ratio [3]			2.07			2.50			2.23
	95% CI [3]			(1.55, 2.77)			(1.79, 3.49)			(1.79, 2.78)
	p-value			< 0.001			< 0.001			< 0.001
Cumulative number of weeks with an AAS7= 0 response between baseline and Week 24	n1	309	153		297	153		606	306	
	Average counts of weeks [3]	17.43	14.45		18.03	13.97		17.77	14.21	
	Rate ratio [3]			1.21			1.29			1.25
	95% CI [3]			(1.07, 1.36)			(1.12, 1.48)			(1.14, 1.37)
	p-value			0.001			< 0.001			< 0.001

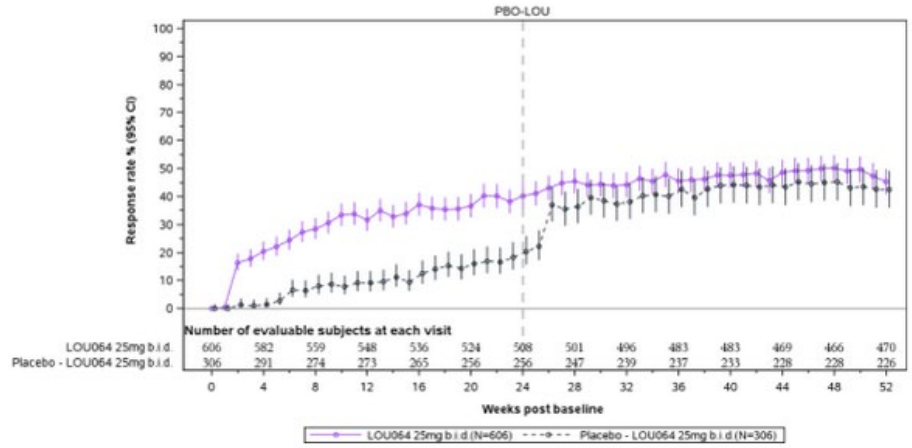
n1: The number of patients included in the analysis for each treatment group.
n2 : Average number of patients with response in 100 imputations.
N: The total number of patients in the corresponding treatment arm/group
M: The total number of patients in the treatment group with response variable defined.
p-value: one-sided nominal p-value.
Multiple imputation techniques were implemented for missing data.
[1] Statistical model used a MMRM adjusting for treatment arm/group, geographical region, prior exposure to anti-IgE biologics, visit week, baseline score, both interaction of treatment by visit week and interaction of baseline score by visit week (and study for the pooled data).
[2] Treatment difference and 95% CI are estimated adjusting for treatment group, geographical region, prior exposure to anti-IgE biologics and baseline UAS7 (or DLQI) score (and study for the pooled data)
[3] A rate ratio >1 favors the remibrutinib treatment arm/group. Statistical model used a negative binomial regression with log link includes treatment arm/group as fixed effect, geographical region, prior exposure to anti-IgE biologics (and baseline AAS7 = 0 status for the cumulative number of weeks with AAS7 = 0 between baseline and Week 12) (and study for the pooled data) as covariates. Natural log of (number of weeks with the response variable in treatment period/24 weeks) as an offset variable.
Source: [SCE-Table 3-15, Table 3-16, Table 3-17, Table 3-18, Table 3-19, Table 3-20, Table 3-21, Table 3-22]

Figure *32*: Pooled analysis: UAS7 mean change from baseline by visit up to Week 52 (observed data) (Pooled FAS)



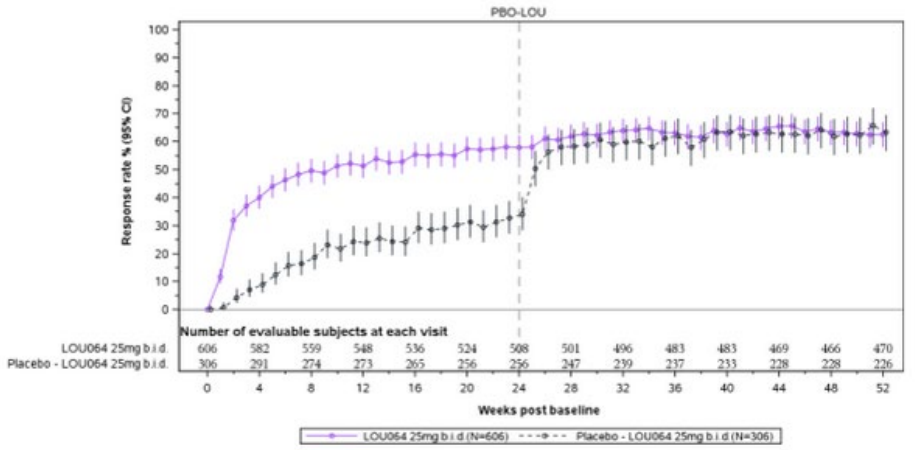
Apparent shift between timepoints is a visual effect to prevent graphical overlap of error bars.
Source: [SCE Appendix 1-Figure 3.1.1-1.3]

Figure *33*: Pooled analysis: UAS7=0 by 4 weeks up to Week 52 (Observed data) (Pooled FAS)



Apparent shift between timepoints is a visual effect to prevent graphical overlap of error bars.
Source: [SCE Appendix 1-Figure 3.1.5-1.3]

Figure *34*: Pooled analysis: UAS7 ≤ 6 by 4 weeks up to Week 52 (Observed data) (Pooled FAS)



Apparent shift between timepoints is a visual effect to prevent graphical overlap of error bars.
Source: [SCE Appendix 1-Figure 3.1.8-1.3]

Indirect treatment comparison for efficacy of remibrutinib to omalizumab

A report of an indirect comparison of remibrutinib and omalizumab was submitted. The report describes the analysis results from the indirect comparison of remibrutinib (25 mg b.i.d.) to omalizumab (Xolair) (300 mg q.4.w.) in the treatment of CSU, using available individual patient data during the 24-week placebo-controlled double-blind treatment period from four pivotal phase III studies conducted by Novartis:

- Remibrutinib data from two identical studies CLOU064A2301 (A2301; REMIX 1) and CLOU064A2302 (A2302; REMIX 2),
- Omalizumab data from two identical studies CQGE031C2302 (C2302; PEARL 1) and CQGE031C2303 (C2303; PEARL 2).

Feasibility of indirect comparison

The Population, Intervention, Comparator, Outcomes and Study design (PICOS) criteria (Richardson et al 1995) can provide a systematic approach to determine the feasibility of the ITC and any important difference that should be adjusted for in the analysis.

- Population: Based on inclusion and exclusion criteria, only minor differences were observed between the A2301/A2302 and C2302/C2303 study populations. A2301/A2302 studies enrolled only adult patients (at least 18 years of age) whereas C2302/C2303 studies recruited both adults and adolescents. Only adult patients from C2302/C2303 will be used in this analysis. The studies did differ in minimum requirements in the ISS7 (A2301/A2302: at least 6 versus C2302/C2303: no minimum requirement) and HSS7 (A2301/A2302: at least 6 versus C2302/C2303: at least 8) components of the UAS7 score. Since both studies required a total UAS7 score of at least 16 during the 7 days prior to randomisation, this difference was not expected to impact this analysis.
- Intervention: LOU064 is an oral tablet taken twice daily, and omalizumab is an s.c. injection administered once every 4 weeks.
- Comparator: Since the REMIX placebos are administered twice daily and PEARL placebo is an s.c. injection administered once every 4 weeks, a common placebo arm was not assumed and the individual placebo arms were treated as separate treatment arms. This is supported by the consistently higher placebo responses reported in the A2301/A2302 studies than in C2301/C2302 studies (Table below):

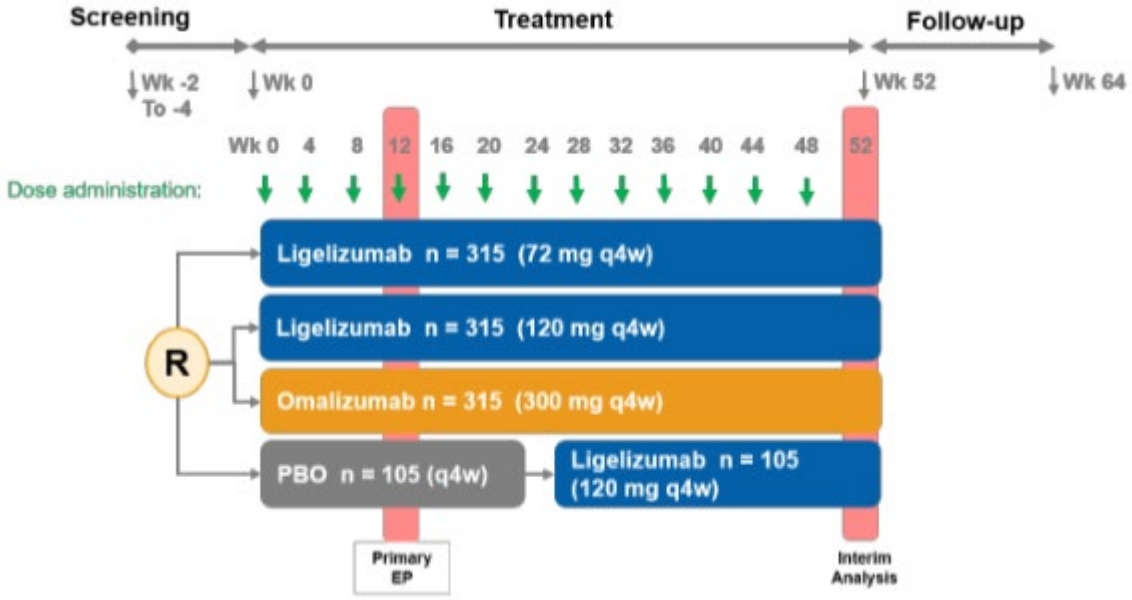
Table 50: Placebo response in CLOU064A2301/A2302 (REMIX) studies and QGE031C2302/2303 (PEARL) studies (FAS)

Study	n	Change from baseline in UAS7 at Week 12 LS mean (SE)	UAS7 = 0 n (%)
A2301	153	-13.79	16 (10.5)
A2302	153	-11.73	10 (6.5)
C2302	106	-11.4	8 (8)
C2303	103	-9.2	4 (4)

n: number of patients included in the analysis.
LS mean: Least squares mean,
n: Number of subjects with response.
Source: [A2301 CSR], [A2302 CSR], Maurer et al 2024

- Outcome: Based on regional regulatory precedent and Health Authorities' feedback, A2301/A2302 studies had two primary objective scenarios. The C2302/C2303 studies only considered one primary objective scenario: Absolute change from baseline (CFB) in UAS7 at Week 12.
- Study design: The screening and double-blinded treatment periods study designs were comparable between A2301/A2302 and C2302/C2303 studies. In the C2302/C2303 studies, the 52-week double-blind treatment period was followed by a 12-week treatment free follow-up period. The designs of Study C2302/C2303 are displayed below:

Figure *35*: Study C2302/C2303 study designs



Objectives and endpoints

The primary clinical question of interest is: What is the effect of remibrutinib treatment versus omalizumab on the change from baseline in UAS7 score at Week 12 after treatment in adult participants with CSU who remain symptomatic despite H1-AH treatment and receiving a stable locally label approved dose of a second generation H1-antihistamine, regardless of treatment discontinuation for any reason and regardless of intake of a different second generation H1-antihistamine as rescue medication and considering strongly confounding prohibited medication as an unfavourable outcome?

One difference noted in the estimands between A2301/A2302 and C2302/C2303 studies was the inclusion of strongly confounding prohibited medication as an intercurrent event in A2301/A2302 studies. After a review of unblinded data, only one patient in each arm in A2302 study and one patient in remibrutinib arm in A2301 experienced this intercurrent event (due to intake of corticosteroids before Week 12). In C2302/C2303 studies, corticosteroids were taken before Week 12 by 8 patients (2.6%) in the omalizumab arm in each study, 4 (3.8%) and 3 (2.9%) patients in the placebo arms of C2303 and C2303 studies, respectively. Given these low proportions, no adjustments were made to further align the two sets of studies.

The objectives and endpoints used for the indirect treatment comparison (ITC) are provided below:

Table 51: Objectives and related endpoints of the indirect treatment comparison of remibrutinib vs omalizumab

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
To compare remibrutinib (25 mg b.i.d.) to omalizumab (300 mg q.4.w.) in CSU patients with respect to change from baseline in UAS7 at Week 12	Absolute change from baseline in UAS7 at Week 12
To compare remibrutinib (25 mg b.i.d.) to omalizumab (300 mg q.4.w.) in CSU patients with respect to reduction from baseline in the weekly itch severity score at Week 12	Absolute change from baseline in ISS7 score at Week 12
To compare remibrutinib (25 mg b.i.d.) to omalizumab (300 mg q.4.w.) in CSU patients with respect to reduction from baseline in the weekly hives severity score at Week 12 compared	Absolute change from baseline in HSS7 score at Week 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
To compare remibrutinib (25 mg b.i.d.) to omalizumab (300 mg q.4.w.) with respect to the proportion of CSU patients who achieve disease activity control (UAS7 ≤ 6) at Week 12	Achievement of UAS7 ≤ 6 (yes/no) at Week 12
To compare remibrutinib (25 mg b.i.d.) to omalizumab (300 mg q.4.w.) with respect to the proportion of CSU patients who achieve complete absence of hives and itch (UAS7 = 0) at Week 12	Achievement of UAS7 = 0 (yes/no) at Week 12
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
To compare remibrutinib (25 mg b.i.d.) to omalizumab (300 mg q.4.w.) in CSU patients with respect to all primary and secondary objectives at Week 24	Primary and secondary endpoints at Week 24

Statistical methods

Pooled Full Analysis Set (PFAS) comprised all adult patients (≥18 years old) that were identified on the Full Analysis Set (FAS) in each individual study (A2301, A2302, C2302, and C2303). PFAS was used for all efficacy variables.

Linear mixed models with repeated measures (MMRM) were used to estimate treatment differences for change from baseline in the primary endpoints (UAS7, ISS7, and HSS7) at Week 12, based on the PFAS. Each MMRM model included treatment group (4 levels: remibrutinib 25 mg b.i.d., REMIX placebo, omalizumab 300 mg q.4.w., PEARL placebo), baseline score, geographic region, ITC adjustment variables (sex, duration of CSU, previous experience of angioedema, baseline CU-index status, and baseline total IgE level), week and both interaction of treatment by week and interaction of baseline score by week as fixed effects. Patients with missing baseline ITC adjustment variables were excluded from the analysis. Repeated measures within patient were modelled using an unstructured covariance of the error terms. Data up to Week 12 was used in the model.

Results

Disposition

A total of 1734 adult patients treated with remibrutinib 25 mg b.i.d., omalizumab 300 mg q.4.w., or placebo across the 4 studies were included in this analysis (912 patients from pooled A2301/A2302 and 822 from pooled C2302/C2303).

The proportion of patients who discontinued study treatment up to Week 24 was slightly higher in the pooled A2301/A2302 treatment and placebo arms compared to the pooled C2302/C2303 treatment and placebo arms.

Table 52: Patient disposition of study treatment - up to Week 24 (Pooled full analysis set)

Disposition/Reason	Remibrutinib 25 mg b.i.d. N=606 n (%)	REMIX Placebo N=306 n (%)	Omalizumab 300 mg q.4.w N=613 n (%)	PEARL Placebo N=209 n (%)
Completed 24-week treatment period	529 (87.3)	262 (85.6)	577 (94.1)	190 (90.9)
Discontinued 24-week treatment period	77 (12.7)	44 (14.4)	36 (5.9)	19 (9.1)
Primary reason for discontinuation of 24-week treatment period				
Adverse event	16 (2.6)	9 (2.9)	6 (1.0)	7 (3.3)
Lack of efficacy	NA	NA	4 (0.7)	2 (1.0)
Lost to follow-up	3 (0.5)	3 (1.0)	1 (0.2)	1 (0.5)
Physician decision	7 (1.2)	2 (0.7)	1 (0.2)	1 (0.5)
Pregnancy	0	1 (0.3)	0	1 (0.5)
Protocol deviation	5 (0.8)	1 (0.3)	10 (1.6)	1 (0.5)
Subject decision	44 (7.3)	21 (6.9)	13 (2.1)	6 (2.9)
Technical problems	0	0	1 (0.2)	0
Unsatisfactory therapeutic effect	2 (0.3)	7 (2.3)	NA	NA

N = Number of patients in the Pooled Full Analysis Set.
The primary reason for discontinuation as given by the investigator on the Treatment Disposition eCRF is summarized.
NA reported when primary reason for discontinuation of 24-week treatment period was not available as a response in Treatment Disposition eCRF.
Source: Appendix Table 1.1-1.1

Demographics

The demographic characteristics of the pooled A2301/A2302 and pooled C2302/C2303 were generally comparable.

Primary efficacy results

The main analysis showed that remibrutinib was comparable to omalizumab with respect to the absolute change from baseline in UAS7, ISS7 and HSS7 scores at Week 12.

- With respect to change from baseline in UAS7: LS mean (SE) was -19.83 (0.526) in remibrutinib and -19.92 (0.544) in omalizumab, resulting in no treatment difference between remibrutinib and omalizumab (LS mean treatment contrast: 0.09; 95% CI: -1.30, 1.49; p=0.896).
- With respect to change from baseline in ISS7: LS mean (SE) was -9.04 (0.248) in remibrutinib and -9.09 (0.256) in omalizumab, resulting in no treatment difference between remibrutinib and omalizumab (LS mean treatment contrast: 0.04; 95% CI: -0.62, 0.70; p=0.895).
- With respect to change from baseline in HSS7: LS mean (SE) was: -10.79 (0.299) in remibrutinib and -10.83 (0.312) in omalizumab, resulting in no treatment difference between remibrutinib and omalizumab (LS mean treatment contrast: 0.04; 95% CI: -0.76, 0.84; p=0.919).
- The results from the sensitivity analysis, using observed data, were consistent with the primary analysis results with respect to all three primary endpoints at Week 12.
- As a supplementary analysis, a placebo adjusted ITC was performed for the primary efficacy endpoints, considering placebo as the anchor treatment when comparing remibrutinib and omalizumab. This analysis relies on the assumption that the placebo arms across the REMIX and PEARL programs are common, which may not be verified considering the differences in

frequency and route of administration. This is supported by the consistently higher placebo responses reported in the A2301/A2302 studies than in C2301/C2302 studies.

- With respect to change from baseline in UAS7 scores at Week 12, a higher placebo response in the pooled REMIX placebo than in the pooled PEARL placebo (UAS7: -12.96 (SE: 0.721) vs. -10.02 (SE: 0.870)) resulted in significantly higher change from baseline in omalizumab as compared to remibrutinib (LS Mean difference: 3.04; 95% CI: 0.47, 5.60). The change in ISS7 was not significantly different when comparing remibrutinib and omalizumab at Week 12 (LS Mean difference: 1.15; 95% CI: -0.06, 2.35), whereas the change in HSS7 was significantly different when comparing remibrutinib and omalizumab at Week 12 (LS Mean difference: 1.92; 95% CI: 0.46, 3.38).

Secondary efficacy results

- The proportion of patients with UAS7 $\leq$ 6 and UAS7 = 0 response at Week 12 were lower in remibrutinib (48.4% and 29.7%, respectively) compared to omalizumab (54.4% and 34.7%, respectively), but the odds ratios for UAS7 $\leq$ 6 and UAS7 = 0 at Week 12 comparing remibrutinib to omalizumab (OR=0.86 and OR=0.86, respectively) were not statistically significant (p=0.263 and p=0.259, respectively), leading to no treatment difference between remibrutinib and omalizumab.
- The anchored (placebo adjusted) supplementary analysis results were consistent with the unanchored analysis results but with a larger treatment effect between remibrutinib and omalizumab for both UAS7 $\leq$ 6 and UAS7 = 0 at Week 12 (OR = 0.67 and OR = 0.46, respectively) although not statistically significant (p=0.145 and 0.068, respectively).
- The REMIX placebo response rates at Week 12 were higher compared to PEARL placebo. With REMIX placebo at Week 12, 22.3% achieved UAS7 $\leq$ 6 and 8.4% achieved UAS7 = 0, but with PEARL placebo at Week 12, 19.5% achieved UAS7 $\leq$ 6 and 5.4% achieved UAS7 = 0.

Exploratory efficacy results

- For the exploratory efficacy endpoints absolute change from baseline in UAS7, ISS7, and HSS7 score at Week 24, as well as the response rates for UAS7 $\leq$ 6 and UAS7 = 0 at Week 24, remibrutinib was comparable to omalizumab. The results at Week 24 were consistent with the results at Week 12, but the response rate for UAS7 = 0 at Week 24 was significantly lower in remibrutinib as compared to omalizumab (OR (95% CI): 0.72 (0.56, 0.94)).

5.3.6. Patient experience data (PED)

The input of the European Federation of Allergy and Airways Diseases Patients' Associations was received and is summarised below:

Disease burden

The persistent itch, heat, and heartbeat sensations in the wheals can be constant without effective treatment. The intense itch may lead patients to underperform in their daily activities, impacting their finances and mental well-being. Patients might reduce their hygiene practices and avoid activities that typically help manage stress, such as exercising. This is particularly problematic for patients who are professionally exposed to irritants. Additionally, coping mechanisms can add to the mental burden and self-stigmatization. Patients may avoid showing their skin. Patients struggle to perform simple tasks that require concentration, such as having a conversation. CSU disrupts sleep patterns and deprives

patients of restorative sleep. The spontaneous and nomad nature of CSU makes it even more exhausting and during periods of remission patients may experience anxiety about the next flare-up.

Standard treatments

The standard treatments prescribed for CSU flare-ups in the European region are antihistamines and cortisone. However, both treatments have side effects and may not provide significant relief, control, or prevention of CSU symptoms. In the absence of effective and specific treatments for CSU, some patients turn to homeopathy for relief during flare-ups.

Unmet medical need

The first unmet need for patients is access to early detection and accurate diagnosis, as diagnosis relies on medical history, and the duration and frequency of flare-ups, meaning that patients need to first experience the exhausting effects of the disease several times before getting their diagnosis.

It is important for general practitioners and dermatologists to be more familiar with urticaria guidelines, including the treatment and management with antihistamines. When H1 antihistamines are not effective enough, patients should have rapid access to other treatments that address CSU more effectively. It would also lead to better define in which cases to use H1 antihistamines, rather than increasing doses of a medication that may already be ineffective for treating CSU.

New medicine

There is a significant need for medicines that specifically target the nature and mechanisms of CSU, and have less side-effects to better treat patients. Patients treated with the biological medicine omalizumab for severe urticaria generally experience minimal side effects. Importantly, patients welcome treatments than cure and prevent CSU, rather than treatments for systemic control. Patients would prefer a medicine whose efficacy remains stable regardless of environmental conditions (hot/cold, wet/dry, winter/summer). There is a preference for oral medicines, as patients perceive them as more conscious medicine choices. Preventive treatments administered via syringe are also welcomed for their long-lasting protective effect.

Patients are concerned about long-term side effects (e.g., decreased efficacy), as well as symptoms upon discontinuation (e.g., increased vulnerability to infections, risk of more severe flare-ups).

Patients also value additional information on the use and interaction of the medicine with other inflammatory diseases and female hormones. It is highly desired that pregnant and breastfeeding women can be treated safely for urticaria. Women with CSU expect clear information on the effects of stopping treatment to fulfil their wish of becoming pregnant.

5.3.7. Healthcare professional engagement

The input of the European Academy of Allergy and Clinical Immunology (EAACI) was received with the following main points:

- The goal of CSU treatment is complete disease control (UCT=16 or UAS7=0), which is achieved by 30% of patients treated with omalizumab.
- Clinical relevance refers to a UAS7<6 achieved in at least half of the patients, and the minimally important difference for UAS7 is 11 points.
- Updosing of antihistamines is the recommended approach over mixing different AHs and is mainly used by practitioners. Adding another sg-AH as rescue treatment is not useful and may

increase adverse effects. However, patients and some physicians tend to combine two sg-AHs rather than increase the dose due to fear of side effects.

- The general approach to CSU treatment is *Treat the disease until it is gone*. There is a need for a disease-modifying treatment with long-term efficacy.
- The subpopulation of CSU patients with autoimmune CSU is difficult to treat and needs a new treatment option.
- Some advantages of new medicine would be: oral form, a rapid onset of action, long term safety, no lab monitoring required.

5.3.8. Overall discussion and conclusions on clinical efficacy

5.3.8.1. Discussion

The clinical development program for remibrutinib in chronic spontaneous urticaria consists of a dose-finding study (A2201) and 2 identical pivotal studies (A2301 and A2302). Additional efficacy data come from 3 open-label single arm studies (extension study A2201E1, Japanese study A1301 and an ABPM study A2305). Apart from the dose-finding study and the extension study, in all other studies remibrutinib was administered at the proposed marketing dose of 25 mg BID.

The initially proposed indication for remibrutinib was: "Remibrutinib is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment", while the final indication is: **"Remibrutinib is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients with inadequate response to H1 antihistamine treatment"**.

Overall, the extent of the clinical development program is adequate for evaluation of remibrutinib in CSU in adults.

Design and conduct of clinical studies

Dose response study

Study A2201 was a randomised, double-blind, placebo-controlled trial to determine the optimal dose of remibrutinib in patients with CSU. The study included adults CSU inadequately controlled by second-generation H1-antihistamines. Participants were randomised in 1:1:1:1:1:1:1 ratio to 6 remibrutinib arms (10 mg q.d., 35 mg q.d., 100 mg q.d., 10 mg b.i.d., 25 mg b.i.d., 100 mg b.i.d.) and were compared to placebo.

The study assessed dose-response by measuring changes in UAS7 scores at Weeks 4 and 12, along with other endpoints like complete absence of symptoms and quality of life improvements. With 311 participants randomised, all remibrutinib doses showed a dose-response at Weeks 4 and 12. At week 12, 25 mg b.i.d. demonstrated highest reduction in UAS7 score from baseline compared to placebo and other doses. 25 mg b.i.d. also had higher responder rate for absence of itch and hives and highest proportion with disease activity control compared to placebo and other tested doses.

Based on these data the applicant concluded that lower b.i.d. or q.d. doses were not optimal to achieve the maximum efficacy while the higher dosing regimen (100 mg b.i.d.) did not demonstrate additional benefit over 25 mg b.i.d. dose. This is endorsed by the CHMP.

Pivotal studies A2301 and A2302

Study design and treatments

Studies A2301 and A2302 were identical in design. They were multicentre, randomised, double-blind, placebo-controlled phase 3 studies to evaluate the efficacy and safety of remibrutinib in patients with CSU inadequately controlled by an approved dose of H1-antihistamines. The studies consisted of 4 parts: a 4-week screening period to assess eligibility, a 24-week double-blind period in which participants were randomised to receive remibrutinib or placebo (although the primary and secondary efficacy endpoints were evaluated at Week 12), a 28-week open-label period in which all participants received remibrutinib, and a 4-week follow-up period. The use of placebo in the study population was considered to be appropriate since patients additionally received a background therapy of second generation H1-AH and had access to additional rescue medication with a different second generation H1-AH.

The overall design is adequate. However, as the study did not include a randomised-withdrawal phase, it cannot provide controlled evidence on long-term maintenance of efficacy, rebound effects after discontinuation, or time to relapse. Further evidence will be collected in the post-marketing setting in study CLOU064A2303B as detailed in the approved RMP. The study will assess the efficacy of remibrutinib in CSU patients with a UAS7 <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.

Study population

The study population consisted of adults diagnosed with CSU, with itches and hives for ≥6 weeks prior to screening despite the use of second-generation H1-AHs during this period, and who had a UAS7 score ≥ 16, ISS7 and HSST score ≥ 6 during 7 days prior to randomisation. This definition of CSU is consistent with international guidelines (Zuberbier et al. 2022) and indicates moderate or severe disease. Patients with clearly defined CINDU or other diseases with symptoms of urticaria or angioedema were excluded. For safety reasons, participants with significant bleeding, coagulation disorders or taking anticoagulants or antiplatelet medication were excluded.

Both studies were carried out globally. The representation of European countries was good in both studies.

Background and rescue therapies

All patients were on a stable, locally approved dose of a second generation H1-AH (background therapy) throughout the entire study (starting a minimum of 7 days prior to randomisation). To treat unbearable symptoms, patients were allowed to use another second generation H1-AH on an as-needed basis in doses up to 4-fold of the locally approved dose (rescue therapy).

In the two pivotal studies, background therapy was limited to a standard (single) dose of H1-AH, while the up-titration was done through rescue therapy which consisted of a different second generation H1-AH used on an as needed basis in doses up to 4-fold of the approved dose. To evaluate if an imbalance in the use of rescue antihistamines possibly impacting efficacy existed, additional analyses were requested during the assessment. It was concluded that background and rescue therapies did not confound efficacy results.

Oral corticosteroids were prohibited before week 12 but were allowed as rescue medication for up to 3 days after week 12 as 20 to 50 mg prednisone or equivalent.

Patients previously treated with anti-IgE treatment were eligible to be included in the studies, with a minimum 4-month withdrawal period prior to randomisation. The number of patients with prior exposure to anti-IgE biologics was limited to approximately 30% of the total study population.

Randomisation and Blinding

Participants were randomised in a 2:1 ratio to remibrutinib versus control. Previous use of anti-IgE biologics and geographic region were used as stratification factors. SA advised to stratify based on CSU severity as per UAS7 score but this has not been implemented by the applicant. This would have been desirable; however, risk of over stratification is acknowledged. Slight disbalance in disease severity is observed between the arms in both studies, with remibrutinib having higher frequency of severe patients compared to placebo. The study was double-blinded for the first 24 weeks; afterwards the study was open-label.

Study assessments

All efficacy assessments were measured by PROs – patients were provided with an eDiary to daily capture the signs and symptoms of urticaria. The assessment of efficacy is based on the Urticaria Activity Score (UAS) and the Angioedema Activity Score (AAS), which are validated PROs used in the clinical setting and in the studies to assess disease activity in patients with CSU. The UAS7 (0-42) is a weekly score composed of the HSS7 (Hives Severity Score, 0-21) and the ISS7 (Itch Severity Score, 0-21). According to the feedback from European Academy of Allergy and Clinical Immunology, for a new treatment to be of clinical relevance, it should be providing relief (UAS7<6) in at least half of the patients.

However, the scoring for hives used by the Sponsor differs from the scoring for hives used in EAACI guidelines (Zuberbier et al. 2021) in that the Sponsor uses approximately 50% more 'lenient' cut-off values for different scores, e.g. score 3 is given for >12 hives/12 hours (EAACI: >50/24 hours). This discrepancy has potentially dual implications. Firstly, baseline severity was artificially inflated in some patients and secondly, the magnitude of the observed effect may be overestimated in some patients (e.g. the same biological improvement (15 → 5 hives/day) appears as a 7-point improvement under the Applicant scoring and no improvement under the EAACI scoring). Although the Applicant was asked to recalculate HSS7 score, since the raw data only recorded the categorical HSS scores (0–3) rather than the actual number of hives, it was not possible to recalculate UAS7 using the EAACI-recommended method. Consequently, the precise extent to which baseline disease severity might have been inflated and the treatment effect overestimated cannot be definitively determined. However, this uncertainty is not considered likely to substantially alter the overall conclusions on efficacy.

Endpoints and estimands

The primary endpoint was an absolute change from baseline in UAS7 score at week 12, while the primary objective was to demonstrate superiority of remibrutinib over placebo. The UAS7 score is a validated clinical instrument for assessing CSU activity and symptom severity, widely used in clinical trials, and sensitive to change.

Three groups of intercurrent events were defined: discontinuation of study treatment due to any reason (handled with the treatment policy strategy), intake of strongly confounding prohibited medications (handled with the composite strategy, assigning unfavourable outcome) and intake of rescue medication, other prohibited medication, switch of background medication or non-compliance (handled with the treatment policy strategy).

Secondary objectives were to demonstrate superiority of remibrutinib over placebo for disease activity control, achievement of symptom clearance, reduction of individual symptom severity and improvement in the quality of life.

The secondary endpoints were hierarchically tested.

A limitation in the study design is the assessment of the primary and all secondary outcomes at week 12, while endpoints at later timepoints were assessed in an exploratory manner, uncontrolled for the

type I error and with a more lenient approach to rescue medications. This does not allow any conclusions to be drawn about long-term efficacy, which is particularly important in a chronic disease such as CSU. Further long-term efficacy data will be obtained in the post marketing setting with study CLOU064A2303B.

Exploratory endpoints were defined to further explore the effect of remibrutinib on HSS7, ISS7 and UAS7 over time and the effect of remibrutinib on other components of the UPDD (sleep interference, activity interference) and on the QoL measures and the use of rescue medication, as well as to further explore the PK profile.

While the estimand for secondary endpoints applies the same intercurrent event handling as for the primary endpoint, this approach is not entirely appropriate for quality-of-life outcomes, which are likely to be more sensitive to events such as treatment discontinuation. The Applicant submitted the results of the additional analysis for the DLQI 0/1 at week 12 endpoint with a jump-to-reference imputation after the ICE permanent discontinuation. The results obtained are consistent with the results of the secondary estimand analysis as presented in the CSP.

Statistical methods

The efficacy analyses are mainly performed using the Full Analysis Set (FAS).

The primary endpoint is analysed using Mixed model for repeated measures (MMRM), including treatment, baseline score, stratification variables, time, and interaction terms (treatment by week, baseline UAS7 score by week) as fixed effects. Repeated measures within participants are modelled using an unstructured covariance structure for error terms. The proposed approach is acceptable.

Missing data for the primary endpoint are addressed via multiple imputation (MI), using Missing at Random (MAR) or Jump to Reference (J2R) assumptions based on RDO (Retrieved Drop Out, data collected after discontinuation) availability. The Applicant adequately clarified the definition, scope, and contribution of RDO data, noting that missing data rates at Week 12 include RDO subjects. However, no RDO data was collected at Week 24 and Week 52. Since not sufficient RDO data were available, missing data in the remibrutinib arm were imputed under a J2R assumption, using observed placebo arm data and missing data in the placebo arm were imputed under a MAR assumption based on the placebo arm data. This approach is appropriate to ensure conservative estimate of the treatment effect

The UAS7 score is calculated from recordings taken twice daily for 7 days prior to evaluation. As defined, the patients needed to have at least 4 non-missing daily (morning or evening, ie. on different days) scores within the 7 days prior to the study visit (ie. 4 out of 14 possible), and the weekly score for HSS or ISS is calculated as the sum of the available eDiary scores of the week, divided by the number of non-missing days, and multiplied by 7. Upon request, the Applicant's analyses showed that most weekly scores were based on complete daily data, and the consistency of mean changes and variability across treatment arms confirmed that the UAS7 calculation method did not affect the observed treatment effect.

Regarding statistical methods for secondary endpoints, for binary outcomes (proportion of participants with UAS7 ≤ 6 or 0, DLQI = 0/1), a logistic regression model was used, including treatment group, region, and prior exposure to anti-IgE biologics as factors. The baseline UAS7 or DLQI score was included as a covariate for the corresponding endpoints. The count variables (the cumulative number of weeks achieving UAS7≤6 and AAS7= 0 responses between baseline and Week 12) were modelled using a negative binomial regression model with log link, using treatment group, region, and prior exposure to anti-IgE biologics. Offset variable based on the natural log of the proportion of time spent in treatment is used to adjust for the varying lengths of patient's time in the randomised treatment period. For the endpoint Cumulative Number of Weeks with AAS7 = 0 response the model is also

adjusted for baseline AAS7 = 0 status. The continuous endpoints (absolute change from baseline in ISS7 and HSS7 score at Week 12) are analysed using the same method as for the primary endpoint.

Methods for handling missing data of continuous variables are the same as for primary endpoint. For the endpoints Cumulative number of weeks with AAS7 =0 / UAS7 ≤ 6 Response Between Baseline and Week 12 - if the AAS7 = 0 or UAS7≤6 assessment is missing, it is considered as a nonresponse for the cumulative number of weeks that participants achieve AAS7= 0 / UAS7≤6 response calculation.

A hierarchical approach was used to control the overall Type-1 error rate at one-sided significance level of alpha of 0.025 to adjust for the primary and eight secondary hypotheses. The proposed approach was adequately prespecified and is considered overall methodologically acceptable.

The planned statistical methods are acceptable and well-suited for this type of trial, although additional analyses were required as described above.

Efficacy data and additional analyses

Protocol amendments, deviations and treatment compliance

The original protocols for both pivotal studies were dated 19 May 2021 and were globally amended once (May 2022) to change the ICE handling of COVID-19, the use of covariates and to ensure consistency across both pivotal studies. This amendment did not have a negative impact on study validity. Both pivotal studies were conducted during the same time period (from Nov/Dec 2021 to Jan 2024).

Although comparable within study arms and across pivotal studies, the incidence of protocol deviations was quite high: 39.3% and 42.7% of patients in remibrutinib and placebo arms, respectively, in Study A2301 and 40.7% and 46.5% of patients in remibrutinib and placebo arms, respectively, in Study A2302 had at least one protocol deviation. Prohibited concomitant medications were more frequently taken by patients in the remibrutinib arm compared to the placebo arm in Study A2301, but the opposite occurred in Study A2302; therefore, any impact on the results in one study would be offset in the other study. Upon request, the Applicant clarified that the category 'other' Protocol deviations consisted of 17 sub-categories, of which sub-categories related to missing eDiary data (DLQI not completed and Urticaria Patient Daily Diary entries not sufficient to calculate UAS7 score) could have an impact on the primary and secondary endpoints. Since these deviations occurred with similar frequencies in remibrutinib and placebo arms during the double blind period (incomplete DLQI in ~7.5% in Study A2301 and in ~5.8% Study A2302; UPDD entries insufficient to calculate UAS7 score in ~2.9% Study A2301 and in ~6.3% in Study A2302), an impact on the primary and secondary enpoints is not expected.

Participant flow

The majority of patients in both treatment arms completed the double-blind period in both pivotal studies (overall approximately 85%), with comparable frequencies between treatment arms. The frequency of discontinuations of the double-blind period was approximately 12-13% for remibrutinib arms in both pivotal studies and for placebo in Study A2301, while it was slightly higher (15.5%) in placebo arm in Study A2302. Reasons for discontinuations and their frequencies were comparable between treatment arms and across both pivotal studies, the most frequent reason being patient's decision followed by adverse events. Losses to follow-up during the double-blind treatment were overall rare (3 patients or <1% in each study).

The efficacy analyses were performed with the FAS. This set excluded the mis-randomised patients (7 in Study A2301 and 5 in Study A2302) and excluded one patient from the placebo arm in Study A2301 due to GCP non-compliance protocol deviation. Therefore, the FAS sets include 309 patients in remibrutinib and 153 in placebo arms in Study A2301 and 297 patients in remibrutinib and 153 in

placebo arms in Study A2302. Although excluding patients after randomisation is not in accordance with the ITT principle, given the small number of excluded patients (in total 13 out of 925 randomised) an impact on the results is not expected.

Baseline data

The mean age of participants included was 45 (Study A2301) and 41 (Study A2302), the majority were females of White race with a BMI of 27-28 (mean). In total, 95 (20.2%) and 121 participants (26.6%) in Study A2301 and A2302, respectively, were from Region Europe.

Although the eligibility criteria limited inclusion to patients with moderate or severe disease, 6 and 7 patients with mild disease (UAS7 score: 7 -15) were randomised in Studies A2301 and A2302, respectively. As explained above, the applicant was unable to recalculate the HSS7 score using the EAACI recommended scale. Therefore, no meaningful data on the mild disease population are available.

The majority of study populations in both pivotal studies had severe disease (63.4% in A2301; 59.1% in A2302), with the mean baseline UAS7 score 30 (across both studies). Previous angioedema was reported in around 50% of patients, although the incidences were higher in remibrutinib compared to placebo arms in both studies. The duration of CSU was balanced within each study but generally one year shorter in Study A2302 (6.65 and 3.78 mean and median, respectively, in A2301 and 5.2 and 2.78 mean and median, respectively, in A2302). Baseline DLQI score was above 13 in all 4 treatment arms, indicating a very large effect on patient's quality of life. The majority of patients had a normal/high level of IgE (over 70% in all 4 treatment arms across both studies). Approximately 30% of the study population in both pivotal studies had concomitant CINDU.

Overall, demographic and baseline characteristics were well balanced within treatment arms in each pivotal study, generally comparable across both pivotal studies and representative of CSU patients with moderate or severe disease.

Primary endpoint results

Both pivotal studies met their respective primary and all hierarchically tested secondary outcomes (all evaluated at 12 weeks). The primary and the secondary endpoint results are consistent across both pivotal studies and show a statistically significant and clinically relevant effect of remibrutinib compared to placebo.

A greater reduction from baseline in UAS7 score at Week 12 was shown for remibrutinib compared to placebo in both pivotal studies. In Study A2301, LS mean CFB for remibrutinib was -20.02 compared to -13.79 for placebo. In Study A2302, LS mean CFB was -19.41 for remibrutinib and -11.73 for placebo. The improvement in both itch and hives (ISS7 and HSS7) contributed to the overall improvement. It is important to note that the MID of 10 points is defined as a within-patient change (ie., on an individual level), not for group differences. The between-group difference was a UAS7 reduction of -6.22 (95%CI -8.45, -4.00) in A2301 and -7.68 (95%CI -9.91, -5.46) in A2302, which is below the threshold of MID. Although the control group used the background and rescue therapy, participants by definition were unresponsive to H1-AHs. The notable effect in placebo/control is more likely due to the fluctuating nature of the disease. Therefore, the secondary outcomes of the proportion of patients who achieve disease control and disappearance of symptoms are of great importance.

The vast majority of participants across the pivotal studies had *intercurrent events* (between 81% and 94%). The distribution of patients with events per ICE category was similar between treatment arms within each study and across both studies. Only a negligible number of participants took strongly confounding prohibited medications (from 0 to 1 participant per treatment arm; handled with a composite strategy). Upon request, this ICE was broadened to include biologics, cyclosporin and

systemic corticosteroids before Week 12. Cumulatively for both pivotal studies, the broader definition identified 8 additional patients in remibrutinib and 3 in placebo arms who took strongly confounding medicines. These patients took corticosteroids prior to Week 8. The additional primary and secondary results were in line with the primary results.

The treatment policy strategy was used to handle the remaining 2 categories of ICEs. Between approximately 6% and 11% of participants permanently discontinued treatment before week 12. By far the ICE category with the largest number of patients with events (a subject with multiple occurrence of an intercurrent event category is counted once in that category) is 'use of rescue medication as per protocol, switch of background medication, intake of other prohibited medication, non-compliant to treatment prior to W12'. There were 81.6% vs 92.8% in remi vs placebo arms in Study A2301 and 80.1% vs 88.2% in remi vs placebo arms in Study A2302 with an event from this category. Upon request, the Applicant disaggregated intercurrent event data from this broad category, and the frequency of individual events is generally balanced between remibrutinib and placebo arms in both pivotal studies.

Although the amount of *missing data* for the primary outcome is not negligible (between approximately 8% and 12%, mainly due to premature study discontinuation), the imputations used are conservative enough to be acceptable for regulatory purposes.

Both the *sensitivity* and the *supplementary analysis* examined different imputations for the ICE 'Intake of strongly confounding prohibited medication'. Given the very limited number of these ICEs, it is not surprising that the results were consistent with the primary analyses in both pivotal studies.

Subgroup analyses by randomisation strata revealed no significant difference in study results with respect to prior IgE use. However, the results by geographic region were somewhat less robust, with the 95% CI of the mean treatment difference crossing (or being very close to) 0 in several geographical regions (AMEA and Japan in A2301 and US in AS302). However, as the subgroups are limited in size and further discussions are not expected to impact the regulatory decision making in Europe, this issue was not pursued.

The Applicant reported that the use of *rescue antihistamines* (any H1-AH different from the background H1-AH) declined at week 12 in both study arms, with the larger drop in the remibrutinib arm; after crossover to open-label remibrutinib (weeks 24–52) the placebo/remibrutinib arm showed the greatest further decline. Yet the summary metric used—mean milligrams of rescue drug per week—was almost impossible to interpret. Upon request, all rescue H1-AHs were normalised to a 'dosing standard'. This allowed for a calculation of a total weekly standardised dose for each patient, enabling the comparison of rescue use between treatment arms. According to this method, in the pooled analysis set, the mean weekly standardised rescue medication at baseline was 11.33 in remibrutinib compared to 10.99 in placebo. At week 12, this was 5.99 in remibrutinib compared to 10.353 in placebo (a -36.89 percent change in remibrutinib compared to a -13.11 percent change in placebo).

In both pivotal studies a larger proportion of patients in remibrutinib arms either didn't use a rescue or used a lower dose of rescue antihistamine, while 3-fold and 4-fold dose of rescue antihistamines were more frequently used in placebo arms.

The total number of days without rescue medication use was requested. The Applicant showed this data as a cumulative number of days without rescue antihistamines by 4 weeks up to Week 12. Across all 4-week intervals in both pivotal studies, both the mean and median number of days without rescue antihistamines were higher in remibrutinib compared to placebo arm. In Study A2301, between baseline and day 28, median number of days without rescue was 11 in remibrutinib vs 3 in placebo, between day 29 and 56, median was 15 days in remibrutinib vs 4 in placebo; between day 57 and 84,

median was 18 days in remibrutinib vs 3 in placebo. In Study A2302, between baseline and day 28, median number of days without rescue was 11 in remibrutinib vs 6 in placebo, between day 29 and 56, median was 17 days in remibrutinib vs 7.50 in placebo; between day 57 and 84, median was 19 days in remibrutinib vs 6 in placebo.

Upon request, the Applicant presented the daily rescue burden (-fold) per participant per treatment arm per study, for a cumulative period starting at baseline and ending at week 12 and for a cumulative period starting at week 12 and ending at week 24. In Study A2301, during the cumulative period between week 1 and week 12, the median of the average daily fold-dose of rescue H1-AH is lower in remibrutinib compared to placebo arm (0.56 vs. 1.00), and the same is observed during the cumulative period between week 13 and week 24 (0.23 vs. 0.97). In Study A2302, during the cumulative period between week 1 and week 12, the median of the average daily-fold dose of rescue H1-AH was 0.40 in remibrutinib vs. 0.99 in placebo arm and 0.14 in remibrutinib vs. 0.66 in placebo arm during the cumulative period between week 13 and week 24. These results indicate that patients took less daily standardised rescue medication in the remibrutinib arm compared to the placebo arm during the double-blind period of pivotal studies.

In line with the pivotal trial design and permitted background treatments a potential specification of remibrutinib as 'add-on' to H1-antihistamine treatment was considered for the indication, but this terminology was ultimately omitted from the final wording. In the two pivotal studies, participants were on stable standard dose of H1-AH without adequate response. These doses were maintained throughout the study. While rescue treatments with additional H1-AH were allowed, the additional analysis provided by the applicant showed lower use of rescue treatments in remibrutinib arm up to week 12 compared to placebo arm. In patients who respond to remibrutinib, continuous treatment with H1-AH might not be necessary. Specific treatment for an individual patient can be decided by the physician in line with clinical guidance. Section 5.1 of the SmPC contains information that background therapy consisted of second generation H1-AHs, and additional information regarding rescue treatment was added.

Secondary endpoint results

Disease activity control (UAS7≤6 at Week 12) was achieved in 49.8% of participants in remibrutinib compared to 24.8% participants in placebo arm in Study A2301. In Study A2302 the results were similar: 46.8% vs 19.6% in remibrutinib vs placebo arms, respectively.

According to the EAAC's input during early stakeholder consultations, a new treatment should provide relief (UAS7 < 6) in at least half of the patients to be considered clinically relevant. Although this benchmark was not achieved in the pivotal studies, the observed effect is still deemed relevant given the limited treatment options for CSU patients who remain symptomatic despite standard therapy with H1-AH.

The complete elimination of itch and hives (UAS7=0 at Week 12) was achieved by 31.1% of patients in remibrutinib and 10.5% in placebo arm in Study A2301. In Study A2302 the results were similar: 27.9% vs 6.5% in remibrutinib vs placebo arms, respectively. The achievement of UAS7=0 is the treatment goal in CSU, therefore of great clinical relevance.

Absolute change from baseline in ISS7 score at 12 weeks was -9.52 compared to -6.89 in the placebo arm in Study A2301. In Study A2302 the results were similar: -8.95 vs -5.72 in remibrutinib vs placebo, respectively. The reduction in itch severity in both the remibrutinib and placebo arms is considered clinically relevant (Mathias et al. 2015).

Absolute change from baseline in HSS7 score at 12 weeks was -10.47 in remibrutinib compared to -6.86 in the placebo arm in Study A2301. In Study A2302 the results were similar: -10.47 vs -6.00 in remibrutinib vs placebo, respectively. The reduction in the number of hives in both the remibrutinib and placebo arms is considered clinically relevant (Mathias et al. 2015).

Early onset of disease activity control (UAS7 ≤ 6 at Week 2) was achieved in 33.7% of participants in remibrutinib compared to 3.3% of participants in the placebo arm in Study A2301. In Study A2302 the results were similar: 30% vs 5.9% in remibrutinib vs placebo, respectively.

At baseline, the mean DLQI score was 14.21 in remibrutinib and 13.52 in the placebo arm in Study A2301 and 14 in remibrutinib and 13.58 in placebo arm in Study A2302, denoting a very large effect on patient's life. A DLQI score of 0-1 at week 12, denoting no impact on patient's life, was achieved by 39.0% of patients in remibrutinib and 22.2% in placebo arm in Study A2301 and in 35.7% in remibrutinib and 18.3% in placebo arm in Study A2302.

The cumulative number of weeks with UAS7 ≤ 6 (disease activity control) up to Week 12 is expressed based on available data (ie. missing UAS7 data are left out of the calculations). The average cumulative number of weeks with disease activity control (UAS7 ≤ 6) up to Week 12 was 5.17 weeks in remibrutinib compared to 1.92 weeks in placebo arm in Study A2301. Similarly, in Study A2302, 4.5 weeks in remibrutinib compared to 1.38 weeks in placebo arms.

The cumulative number of weeks with AAS7 = 0 (angioedema-free weeks) up to Week 12 is expressed based on available data (ie. missing AAS7 data are left out of the calculations). The average cumulative number of angioedema-free weeks (AAS7 = 0) up to Week 12 was 8.43 weeks in remibrutinib compared to 6.72 weeks in placebo arm in Study A2301. Similarly, in Study A2302, 8.81 weeks in remibrutinib compared to 6.68 weeks in placebo arms.

No sensitivity analyses were performed for the secondary endpoints. In *supplementary analyses* for the binary secondary outcomes (ie. UAS7 ≤ 6 at Week 12, UAS7 = 0 at Week 12, UAS7 ≤ 6 at Week 2, DLQI = 0-1 at Week 12), treatment differences were estimated adjusting for covariates as region, prior exposure to anti-IgE biologics, and baseline UAS7 or DLQI score. All performed supplementary analyses confirmed the primary analyses. Upon request, the applicant provided the proportion of patients with missing daily AAS scores. Although the handling of missing daily AAS scores was not fully explored through sensitivity analyses, available data indicate that different imputation methods would unlikely change the study outcomes.

The *subgroup analysis by randomisation strata* (previous exposure to anti-IgE biologics and geographical region) results showed a treatment effect in favour of the remibrutinib arm across the secondary outcomes and in both pivotal studies. However, occasionally the 95%CI crossed the value of no difference between treatments for some regions and only once for the previous IgE treatment (only for the outcome cumulative number of weeks with AAS7 = 0 up to Week 12 in Study A2301, for patients preciously exposed to anti-IgE biologic). Therefore, it is concluded that the subgroup analyses by randomisation strata generally point in the same direction as the primary analyses, although with some variations that could be explained by the limited sample sizes of the subgroups.

Exploratory endpoint results

Out of many exploratory endpoints, the focus of this assessment is on the endpoints evaluated at week 24 and on the analyses over time.

The results at week 24 numerically favour remibrutinib over placebo. However, the treatment difference was generally smaller due to patients receiving placebo improving more compared to patients receiving remibrutinib. While this can be due to many reasons, it still introduces uncertainty about the sustained benefit of remibrutinib.

Regarding exploratory analyses over time (up to week 52), the results indicate that benefit of remibrutinib over placebo exists at each timepoint up until week 24. After all patients transition to remibrutinib, former placebo-patients catch up with patients continuing on remibrutinib after about 4 weeks; afterwards a similar benefit in both treatment arms is observed up until week 52.

Although the benefit of remibrutinib over placebo was observed over time, long-term efficacy remains unknown. Since a substantial proportion of patients did not achieve disease control (approximately 50%) or complete control (approximately 70%) at weeks 12 and 24, the need to continue treatment should be evaluated on an individual basis. Therefore, the following statements were included in section 4.1 of the SmPC: Prescribers are advised to periodically reassess the need for continued therapy. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment for CSU.

Subgroup analyses

Subgroups were performed by CU index, total IgE levels, disease duration and diagnosis of concomitant CINDU. The results were consistent with the main analysis and remibrutinib showed efficacy in all subgroups compared to placebo. Slightly greater efficacy of remibrutinib was observed in CU index-positive patients (also after transitioning from placebo to remibrutinib) and in patients with low IgE levels. After transitioning from placebo to remibrutinib at week 24, patients with a longer duration of CSU showed lower efficacy compared to a shorter duration of the disease.

Additional subgroup analysis according to baseline CSU severity showed that the effect of remibrutinib is similar across baseline UAS7 score and disease severity (moderate or severe), and consistent with the findings in the overall population.

Supportive studies

Study A1301 study was a single- arm open-label phase 3 study in adult Japanese patients with CSU, primarily designed to evaluate the safety of remibrutinib 25mg BID. Efficacy was a secondary endpoint. The study included 71 patients (mainly females with median age of 43 and mostly with severe disease). All the patients used rescue medication and the same efficacy endpoints were assessed at weeks 12, 24 and 52. Although the results are consistent with those of the pivotal studies, the study is of limited value for the assessment of efficacy.

Study A2201E1 was a phase 2 extension study for CSU patients who participated in the A2201 dose-finding study. The design of this study is not comparable to those of the pivotal studies; for example, participants were administered a different dose (200 mg per day compared to 50 mg per day in the pivotal studies), efficacy endpoints were assessed at week 4 until no background medication was used. The results obtained are in favour of remibrutinib, but no conclusion on the efficacy in the required indication can be drawn from this study.

Study A2305 study included 144 participants treated with sg H1-AHs and remibrutinib. The primary objective of the study was to evaluate the effect of remibrutinib on ABPM measures, but the disease efficacy measures were also included as an exploratory objective. The study showed clinical benefit in CSU patients. The results from open-label Study A2303B, which includes a 24-week randomised withdrawal period to assess the durability of treatment response suggest sustained effect of remibrutinib over time. However, no claim about long-term efficacy can be made.

Indirect treatment comparison

The applicant provided an indirect treatment comparison between remibrutinib and omalizumab for CSU treatment. The comparison is based on individual patient data, as both remibrutinib and omalizumab were developed by the same company. Four studies were included in the analysis (two remibrutinib studies: A2301/A2302 [REMIX studies] and two omalizumab studies: C2302/C2303

[PEARL studies]). Although the omalizumab studies had a different duration of the double-blind phase (52 weeks in the C2302/C2303 studies compared to 24 weeks in the A2301/A2302 studies) and follow-up period, this is not considered crucial for the comparison as the primary and secondary endpoints were assessed at week 12, until when the studies are comparable in terms of study design.

Despite some differences (omalizumab including patients with HSS7≥ 8, rather than 6 as in the remibrutinib studies), the study population of remibrutinib and omalizumab studies are considered comparable and representing the population with moderate or severe CSU.

The proposed primary and secondary endpoints for this comparison included CFB in UAS7/ISS7/HSS7 at w12, achievement of UAS7 ≤6 and achievement of UAS7=0, which are clinically relevant and acceptable endpoints for this comparison.

A total of 1734 adult patients were included in this analysis (912 from remibrutib and 822 from omalizumab studies). The proportion of patients who discontinued 24-week treatment was higher in remibrutinib studies (12.7%, 14.4% vs. 5.9%, 9.1%), mainly due to subject decision (7.3%, 6.9% vs. 2.1%, 2.9%), in the remibrutinib and REMIX pbo groups vs. the omalizumab and PEARL pbo groups, respectively.

The efficacy results of CFB in UAS7, ISS7, HSS7 at week 12 showed a similar effect of remibrutinib and omalizumab. The results on the secondary endpoints (the proportion of patients with a response of UAS7 ≤ 6 and UAS7 = 0 at week 12) showed a better response with omalizumab than with remibrutinib. A higher response to placebo was observed in the remibrutinib studies than in the omalizumab studies.

5.3.8.2. Conclusions on the clinical efficacy

Remibrutinib demonstrated statistically significant and clinically relevant improvements over placebo at 12 weeks in patients with CSU when used as an add-on therapy to a standard dose of sg H1-AH and topped up with a rescue dose of another sg H1-AH in doses up to 4-fold the standard dose. The primary and all secondary endpoints were met in both pivotal studies. Therefore, the CHMP concluded that the efficacy of remibrutinib 25mg bid has been demonstrated for the treatment of chronic spontaneous urticaria (CSU) in adult patients with inadequate response to H1 antihistamine treatment.

5.4. Clinical safety

Please refer to the table of studies in section 5.3.2

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for

example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The safety analysis was performed in two pools as of the cut-off date of 04-Aug-2024:

- **Pool 1** included safety data from the two pivotal studies (A2301 and A2302)
- **Pool 2** included data from 2 pivotal Phase III studies plus the CSU Phase II supportive studies (A2201 and its extension A2201E1) and the Phase III Japanese local study (A1301).

Pool 2 included both randomised and open-label single arm studies, within which confounding by the "trial" variable could not be controlled in the analysis, and hence, direct comparison with the control group was not considered.

Table 53: Summary of the safety pooling strategy

Pooled Database	Population	Analysis Period	Domain	Studies	Treatment labels
Pooled database 1	CSU patients inadequately controlled by H1-antihistamines	Placebo-controlled period (24 weeks)	Disposition, Exposure, Demography, medical history, Disease characteristics, concomitant medications, AEs, labs, ECG, vital signs	A2301, A2302	1.LOU064 25 mg b.i.d.[a] 2.Placebo[d]
Pooled database 1	CSU patients inadequately controlled by H1-antihistamines	Entire study period (up to 56 weeks)	Disposition, Exposure, Demography, medical history, Disease characteristics, concomitant medications, AEs, Labs, ECG, VS	A2301, A2302	1.LOU064 25 mg b.i.d.a 2.Transitioned to LOU064 25 mg b.i.d.c 3.Any LOU064 25 mg b.i.d.
Pooled database 2	CSU patients inadequately controlled by H1-antihistamines	Entire study period (up to 72 weeks)	Disposition, Exposure, Demography, disease characteristics, medical history, AEs	A2201, A2201E1, A2301, A2302, A1301	1.LOU064 any dose 2.Any LOU064 25 mg b.i.d.

[a]LOU064 25 mg b.i.d.: excluding patients switching from placebo to LOU064 25 mg b.i.d.

[b]LOU064 any dose (10 mg q.d., 35 mg q.d., 100 mg q.d., 10 mg b.i.d., 25 mg b.i.d., 100 mg b.i.d.), including those patients transitioned from placebo to LOU064 for the first time (from Study A2201 to Study A2201E1, or from Study A2301 and Study A2302).

[c]Transitioned to LOU064 25 mg b.i.d.: placebo patients' data after the switch to LOU064.

[d]Placebo: placebo patients' data before the switch to LOU064 25 mg b.i.d.

Source: [Statistical Overview-Table 4-1]

Additional supportive safety information consisted of SAEs and cases of "exposure during pregnancy" (initial cases as well as cases with significant follow-up information) collected in the Novartis Safety Database (up to 04-Aug-2024) from ongoing CSU and non-CSU clinical studies of remibrutinib.

The investigator had the responsibility for managing the safety of individual participant and identifying adverse events. The occurrence of adverse events was sought by non-directive questioning of the participant at each visit during the study or reported by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

The pivotal studies included a data monitoring committee (DMC) which assessed at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

5.4.2. Patient exposure

Table 54: Patient exposure from the remibrutinib pivotal and supportive CSU studies (cut off 04-Aug-2024)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data	
				≥ 6 months	≥ 12 months
Blinded studies (placebo-controlled)	1236	1135***	911	772	438
Blinded studies (active-controlled)	NA	NA	NA	NA	NA
Open studies	409	243#	215	247##	216##
Post marketing	NA	NA	NA	NA	NA
Compassionate use	NA	NA	NA	NA	NA

NA = not applicable.
* Received at least 1 dose of active treatment.
** In general, this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.
*** Including patients who received at least one dose of remibrutinib in Studies A2301 and A2302, randomised to placebo and switched to open-label active treatment at Week 24.
# Patients who received placebo in Study A2201 and then received remibrutinib for the first time in Study A2201E1.
Remibrutinib exposure in Study A2201 is taken into account for patients who rolled-over into Study A2201E1.
Exposure duration (years) = ((date of last treatment + 28) - (date of first treatment) + 1))/ 365.25.
Blinded CSU studies: A2301, A2302, A2201 (completed).
Open-label CSU studies: A1301, A2305, A2201E1 (completed).

Pool 1 (Pivotal studies)

This pool includes safety data from 606 patients treated with remibrutinib 25 mg b.i.d. and an additional 262 patients who switched from placebo to remibrutinib at Week 24.

During the placebo-controlled period, the median duration of exposure was similar between treatment groups (24 weeks) with a range of 0.1 to 29.4 weeks for the remibrutinib 25 mg b.i.d. group and 0.3 to 30.3 weeks for the placebo group. The cumulative exposure was 261.57 patient-years for the remibrutinib 25 mg b.i.d. group and 129.55 patient-years for the placebo group.

During entire study period, for the any remibrutinib 25 mg b.i.d. group, median duration of exposure was 52.00 weeks (range 0.1 to 60.6 weeks), with a cumulative exposure of 671.55 patient-years.

Overall, 715 patients have completed the studies and 438 have been exposed to remibrutinib 25 mg b.i.d. for at least 52 weeks. In total, the pivotal data represent 671.55 patient-years of exposure to remibrutinib 25 mg twice daily.

Pool 2 (Phase II and Phase III studies) – entire study period

For the remibrutinib any dose group, the median duration of exposure was 52.00 weeks (range 0.1 to 69.9 weeks), with a cumulative exposure of 971.94 patient-years.

For the any remibrutinib 25 mg b.i.d. group, the median duration of exposure was 52.00 weeks (range 0.1 to 60.6 weeks), with a cumulative exposure of 751.47 patient-years.

Demographic and disease characteristics of study population

The eligibility criteria were aligned across the 5 clinical studies with a population representative of the target population, male and female adult patients with CSU who remain symptomatic despite H1-AH treatment. Patients with significant bleeding risk, coagulating disorders, ongoing chronic or recurrent infections, chronic or acute hepatic disease and evidence of ongoing Hepatitis C or B, history of renal disease, and history of malignancy within the past 5 years were excluded from these studies.

In Pool 1, the population was primarily White (55.3%), female (66.6%), with a mean (SD) BMI of 27.47 (6.394), a mean (SD) age of 43.4 (14.30) years and 8.4% of participants being ≥65 years of age. The majority of patients had severe (62.2%) or moderate disease (37%).

In Pool 2, the baseline demographic and disease characteristics of the safety population in any remibrutinib 25 mg b.i.d. arm were comparable to those observed in Pool 1.

5.4.3. Adverse events

Pool 1

Placebo-controlled period

Table 55: Overview of treatment-emergent adverse events during the placebo-controlled period (Pool 1 Safety set)

	LOU064 25 mg b.i.d. N=606 n (%)	Placebo N=306 n (%)
	Total PY = 265.1	**Total PY = 132.5**
Patients with AE(s)	393 (64.9)	198 (64.7)
Patients with at least one AE		
Mild	213 (35.1)	121 (39.5)
Moderate	163 (26.9)	70 (22.9)
Severe	17 (2.8)	7 (2.3)
Patients with serious or other significant events		
Death	0	0
SAE(s)	20 (3.3)	7 (2.3)
Discontinued study treatment due to any AE(s)	17 (2.8)	9 (2.9)
Discontinued study treatment due to any SAE(s)	2 (0.3)	1 (0.3)
Treatment interruption due to AE(s)	47 (7.8)	27 (8.8)
Treatment interruption due to SAE(s)	9 (1.5)	4 (1.3)

N = number of patients in the corresponding treatment group.
n = number of patients with the event.
Total PY = cumulative patient-years of on-treatment exposure from all patients in the corresponding treatment group.
Source: [SCS Appendix 1-Table 2.1-6.1p1], [SCS Appendix 1-Table 2.1-2.1p1]

Table 56: Most frequent (≥ 3.0% of patients in any treatment group) treatment-emergent adverse events by preferred term during the placebo-controlled period (Pool 1 Safety set)

Preferred term	LOU064 25 mg b.i.d. N=606 n (%) EAIR (95% CI)	Placebo N=306 n (%) EAIR (95% CI)	LOU064 25 mg b.i.d. vs. Placebo EAIR difference (95% CI)
	Total PY = 265.1	Total PY = 132.3	
Any preferred term	393 (64.9) 276.4 (249.7, 305.1)	198 (64.7) 273.5 (236.8, 314.4)	2.9 (-51.8, 56.2)
COVID-19	65 (10.7) 26.0 (20.1, 33.2)	35 (11.4) 28.0 (19.5, 38.9)	-1.9 (-13.7, 9.0)
Nasopharyngitis	40 (6.6) 15.7 (11.2, 21.4)	14 (4.6) 10.9 (5.9, 18.3)	4.8 (-3.3, 12.2)
Headache	38 (6.3) 15.0 (10.6, 20.6)	19 (6.2) 14.8 (8.9, 23.2)	0.2 (-8.7, 8.3)
Petechiae	23 (3.8) 8.9 (5.7, 13.4)	1 (0.3) 0.8 (0.0, 4.2)	8.2 (3.5, 12.1)
Urinary tract infection	19 (3.1) 7.3 (4.4, 11.4)	8 (2.6) 6.1 (2.6, 12.1)	1.2 (-4.8, 6.4)
Urticaria	15 (2.5) 5.7 (3.2, 9.5)	15 (4.9) 11.7 (6.5, 19.2)	-5.9 (-13.2, 0.6)

A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
Preferred terms are sorted in descending frequency of AE in the first column (LOU064 25 mg b.i.d.)
MedDRA Version 26.1 has been used for the reporting of adverse events.
N = number of patients in the corresponding treatment group in the analysis set; Total PY = cumulative patient-years of on-treatment exposure from all patients in the corresponding treatment group; n = number of patients with the event; EAIR = exposure-adjusted incidence rate, defined as the number of patients with the event per 100 patient-years of exposure, where the exposure time at risk is event-specific (terminated by incident events); CI = confidence interval for the rate (Garwood 1936) or the rate difference (Scosyrev, Pethe 2022).
Source: [SCS Appendix 1-Table 2-3p1]

Entire study period

Table 57: Overview of treatment-emergent adverse events during the entire study period (Pool 1 Safety set)

	LOU064 25 mg b.i.d. N=606 n (%)	Transitioned to LOU064 25 mg b.i.d. N=262 n (%)	Any LOU064 25 mg b.i.d. N=868 n (%)
	Total PY = 551.1	**Total PY = 141.9**	**Total PY = 693.1**
Patients with AE(s)	446 (73.6)	133 (50.8)	579 (66.7)
Patients with at least one AE			
Mild	219 (36.1)	74 (28.2)	293 (33.8)
Moderate	206 (34.0)	51 (19.5)	257 (29.6)
Severe	21 (3.5)	8 (3.1)	29 (3.3)
Patients with serious or other significant events			
Death	0	0	0
SAE(s)	25 (4.1)	3 (1.1)	28 (3.2)
Discontinued study treatment due to any AE(s)	28 (4.6)	4 (1.5)	32 (3.7)
Discontinued study treatment due to any SAE(s)	4 (0.7)	1 (0.4)	5 (0.6)
Treatment interruption due to AE(s)	54 (8.9)	9 (3.4)	63 (7.3)
Treatment interruption due to SAE(s)	10 (1.7)	0	10 (1.2)

N = number of patients from the corresponding treatment group; N for the Transitioned to LOU064 25 mg b.i.d. group refers to the number of patients transitioned to LOU064; N for Any LOU064 25 mg b.i.d. refers to number of patients in LOU064 25 mg b.i.d. group or switched to LOU064 25 mg b.i.d. group from placebo from the corresponding analysis set.
n = number of patients with the event.
Total PY = cumulative patient-years of on-treatment exposure from all patients in the corresponding treatment group.
Source: [SCS Appendix 1-Table 2.1-6.2p1], [SCS Appendix 1-Table 2.1-2.2p1]

Table 58: Most frequent (≥3% in any treatment group) treatment emergent adverse events, by preferred term during the entire study period (Pool 1 Safety set)

Preferred term	LOU064 25 mg b.i.d. N=606 n (%) EAIR (95% CI)	Transitioned to LOU064 25 mg b.i.d. N=262 n (%) EAIR (95% CI)	Any LOU064 25 mg b.i.d. N=868 n (%) EAIR (95% CI)
	Total PY = 551.1	Total PY = 141.9	Total PY = 693.1
Any preferred term	446 (73.6) 199.8 (181.7, 219.3)	133 (50.8) 144.8 (121.2, 171.6)	579 (66.7) 183.8 (169.1, 199.4)
COVID-19	94 (15.5) 19.0 (15.4, 23.3)	19 (7.3) 14.1 (8.5, 22.1)	113 (13.0) 18.0 (14.8, 21.6)
Nasopharyngitis	55 (9.1) 10.7 (8.0, 13.9)	9 (3.4) 6.5 (2.9, 12.2)	64 (7.4) 9.8 (7.5, 12.5)
Headache	47 (7.8) 9.0 (6.6, 12.0)	4 (1.5) 2.8 (0.8, 7.3)	51 (5.9) 7.7 (5.8, 10.2)
Upper respiratory tract infection	34 (5.6) 6.4 (4.4, 8.9)	11 (4.2) 7.9 (4.0, 14.2)	45 (5.2) 6.7 (4.9, 8.9)
Urinary tract infection	28 (4.6) 5.2 (3.5, 7.6)	4 (1.5) 2.8 (0.8, 7.3)	32 (3.7) 4.7 (3.2, 6.7)
Petechiae	24 (4.0) 4.5 (2.9, 6.7)	7 (2.7) 5.0 (2.0, 10.4)	31 (3.6) 4.6 (3.1, 6.6)
Urticaria	20 (3.3) 3.7 (2.3, 5.7)	7 (2.7) 5.0 (2.0, 10.3)	27 (3.1) 4.0 (2.6, 5.8)
Cough	19 (3.1) 3.5 (2.1, 5.5)	2 (0.8) 1.4 (0.2, 5.1)	21 (2.4) 3.1 (1.9, 4.7)
Nausea	19 (3.1) 3.5 (2.1, 5.5)	1 (0.4) 0.7 (0.0, 3.9)	20 (2.3) 2.9 (1.8, 4.6)
Influenza	18 (3.0) 3.3 (2.0, 5.3)	8 (3.1) 5.8 (2.5, 11.3)	26 (3.0) 3.8 (2.5, 5.6)

Pool 2

Table 59: Overview of treatment-emergent adverse events during the entire study period (Pool 2 Safety set)

	LOU064 any dose N=1234 n (%)	Any LOU064 25 mg b.i.d. N=982 n (%)
	Total PY = 1023.0	**Total PY = 776.0**
Patients with AE(s)	863 (69.9)	667 (67.9)
Patients with at least one AE		
Mild	448 (36.3)	346 (35.2)
Moderate	370 (30.0)	291 (29.6)
Severe	44 (3.6)	30 (3.1)
Unknown	1 (0.1)	0
Patients with serious or other significant events		
Death	0	0
SAE(s)	42 (3.4)	33 (3.4)
Discontinued study treatment due to any AE(s)	51 (4.1)	34 (3.5)
Discontinued study treatment due to any SAE(s)	9 (0.7)	6 (0.6)
Treatment interruption due to AE(s)	88 (7.1)	70 (7.1)
Treatment interruption due to SAE(s)	12 (1.0)	11 (1.1)

N: For LOU064 any dose group, N refers to the number of patients in any LOU064 treatment group or switched to LOU064 from the corresponding analysis set.
For Any LOU064 25 mg b.i.d., N refers to number of patients in LOU064 25 mg b.i.d. group or switched to LOU064 25 mg b.i.d. group from placebo from the corresponding analysis set.
n = number of patients with the event.
Total PY = cumulative patient-years of on-treatment exposure from all patients in the corresponding treatment group
Source: [SCS Appendix 1-Table 2.1-6.1p2], [SCS Appendix 1-Table 2.1-2.1p2]

In the remibrutinib any dose group, the most frequently reported AEs (by PT) (≥ 3% of patients) were COVID-19 (11.8%), nasopharyngitis (8.2%), headache (7.9%), upper respiratory tract infection (4.5%), CSU (3.4%), diarrhoea (3.3%), UTI (3.2%) and petechiae (3.2%).

In the any remibrutinib 25 mg b.i.d. group, the most frequently reported AEs (by PT) (≥ 3% of patients) were COVID-19 (12.9%), nasopharyngitis (7.6%), headache (6.7%), upper respiratory tract infection (4.9%), petechiae (3.6%), UTI (3.2%) and urticaria (3.0%).

5.4.3.1. Adverse drug reactions

Pool 1

Placebo-controlled period

Table 60: Most frequent (≥1.0% in any treatment group) treatment emergent adverse events related to study treatment, by primary system organ class and preferred term during the placebo-controlled period (Pool 1 Safety set)

Primary system organ class Preferred term	LOU064 25 mg b.i.d. N=606 n (%) EAIR (95% CI)	Placebo N=306 n (%) EAIR (95% CI)	LOU064 25 mg b.i.d. vs. Placebo EAIR difference (95% CI)
	Total PY = 265.1	**Total PY = 132.5**	
Patients with at least one AE	115 (19.0) 50.2 (41.4, 60.2)	39 (12.7) 32.1 (22.8, 43.8)	18.1 (3.4, 32.1)
Gastrointestinal disorders	23 (3.8) 9.0 (5.7, 13.4)	2 (0.7 1.5 (0.2, 5.5)	7.4 (2.5, 11.7)
Nausea	10 (1.7) 3.8 (1.8, 7.0)	1 (0.3) 0.8 (0.0, 4.2)	3.1 (-0.6, 6.0)
Nervous system disorders	17 (2.8) 6.6 (3.8, 10.5)	6 (2.0) 4.6 (1.7, 10.0)	2.0 (-3.5, 6.7)
Headache	11 (1.8) 4.2 (2.1, 7.5)	4 (1.3) 3.0 (0.8, 7.8)	1.2 (-3.5, 5.1)
Skin and subcutaneous tissue disorders	35 (5.8) 13.8 (9.6, 19.2)	10 (3.3) 7.7 (3.7, 14.2)	6.1 (-1.2, 12.6)
Petechiae	20 (3.3) 7.7 (4.7, 12.0)	1 (0.3) 0.8 (0.0, 4.2)	7.0 (2.5, 10.7)
Ecchymosis	7 (1.2) 2.7 (1.1, 5.5)	1 (0.3) 0.8 (0.0, 4.2)	1.9 (-1.5, 4.5)

A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
System organ classes are presented in alphabetical order; Preferred terms are sorted in descending frequency of AE in the first column (LOU064 25 mg b.i.d.)
MedDRA Version 26.1 has been used for the reporting of adverse events.
N = number of patients in the corresponding treatment group in the analysis set; Total PY = cumulative patient-years of on-treatment exposure from all patients in the corresponding treatment group; n = number of patients with the event; EAIR = exposure-adjusted incidence rate, defined as the number of patients with the event per 100 patient-years of exposure, where the exposure time at risk is event-specific (terminated by incident events); CI = confidence interval for the rate (Garwood 1936) or the rate difference (Scosyrev, Pethe 2022).
Total PY = cumulative patient-years of on-treatment exposure from all patients in the corresponding treatment group.
Source: [SCS Appendix 1-Table 2-7p1]

The most frequently reported AEs considered related to study treatment (≥ 3.0% of patients in either the remibrutinib 25 mg b.i.d. group or in the placebo group), respectively, by SOC included skin and subcutaneous tissue disorders (5.8% vs. 3.3%), and gastrointestinal disorders (3.8% vs. 0.7%).

The most frequently reported related events by PT in the remibrutinib 25 mg b.i.d. and placebo groups (≥ 1.0% of patients in either group), respectively, were petechiae (3.3% vs. 0.3%), headache (1.8% vs. 1.3%), nausea (1.7% vs. 0.3%), and ecchymosis (1.2% vs. 0.3%).

Entire study period

Remibrutinib 25 mg b.i.d. group in the entire study period: A total of 129 patients (21.3%) had AEs considered related to study treatment during the entire study period, including 14 patients (2.3%) in the remibrutinib 25 mg b.i.d. group with AEs considered related to study treatment after completion of the placebo-controlled period (during the open-label period).

The AEs considered related to study treatment most frequently reported (≥ 3.0% of patients) in the entire study period were in the SOCs of skin and subcutaneous tissue disorders (6.6%), investigations

(5.0%), gastrointestinal disorders (4.1%), infections and infestations (3.3%), and nervous system disorders (3.1%).

The most frequently reported related events by PT (≥ 1% of patients) in the entire study period were petechiae (3.5%), nausea (1.8%), headache (2.0%), ecchymosis (1.3%), nasopharyngitis (1.0%), and contusion (1.0%).

Patients who transitioned to remibrutinib: In these patients, 6.5% had at least 1 AE considered related to study treatment. The following related events (by SOC) were reported in ≥1% of patients: skin and subcutaneous disorders (2.7%), metabolism and nutrition disorders (1.1%), and investigations (1.1%). By PT, no related events were reported in ≥1% of patients, except for petechiae (1.5%).

Pool 2

In the remibrutinib any dose group, 229 patients (18.6%) had at least 1 AE considered related to study treatment. The most frequently reported AEs considered related to study treatment (≥ 3.0% of patients) by SOC were skin and subcutaneous disorders (5.9%), gastrointestinal disorders (4.0%), infections and infestations (3.1%), and investigations (3.4%).

Adverse events by PT considered related to study treatment that occurred in ≥ 1% of patients in the remibrutinib any dose group included petechiae (2.5%), headache (1.9%), nausea (1.5%), nasopharyngitis (1.2%), and diarrhoea (1.1%).

In the any remibrutinib 25 mg b.i.d. group, 175 patients (17.8%) had at least 1 AE considered related to study treatment. The most frequently reported AEs considered related to study treatment (≥ 3.0% of patients) by SOC were skin and subcutaneous disorders (6.2%), investigations (3.7%), and gastrointestinal disorders (3.2%).

Adverse events by PT considered related to study treatment that occurred in ≥ 1% of patients in the any remibrutinib 25 mg b.i.d. group included petechiae (3.0%), headache (1.5%), and nausea (1.2%).

Table 61: Summary of ADRs proposed for inclusion by the applicant in the SmPC

Infections and infestations	
Upper respiratory tract infections	Very common (14.7%)
Skin and subcutaneous tissue disorders	
Petechiae	Common (3.8%)
Contusion	Common (2.3%)
Ecchymosis	Common (1.5%)
Purpura	Uncommon (0.8%)
Vascular disorders	
Epistaxis	Uncommon (0.8%)
Conjunctival bleeding	Uncommon (0.3%)
Gingival bleeding	Uncommon (0.2%)

Identification of ADRs for remibrutinib was performed in 3 steps:

(1) Selection of pre-qualified ADR candidates based on the prior evidence of causality,
(2) Statistical screening of clinical study data for ADRs, and

(3) Medical evaluation of ADR candidates identified in Steps 1 and 2.

Step 1. Selection of pre-qualified ADR candidates

Pre-qualified ADR candidate selection was based on:

- AESIs: Infection, Bleeding and Cytopenia (based on the mechanism of action, preclinical and clinical data).
- ADRs of approved BTK inhibitors in hematological indications (ibrutinib, acalabrutinib and zanubrutinib) not specific to oncology: Supraventricular tachyarrhythmias, Malignant or unspecified tumors, Gastrointestinal disorders, and Pressor effect on blood pressure.
- Other safety topics: These included the topics defined in the development safety profiling plan (dSPP) but not already classified as AESI or ADRs for other class compounds - Teratogenicity and Drug related hepatic disorders.
- Designated medical events (DMEs): All Novartis-defined DMEs.

Step 2. Statistical screening

Statistical screening of AEs for ADRs was based on data from the 2 pivotal Studies CLOU064A2301 and CLOU064A2302 and based on the data from the Phase IIb dose-finding Study CLOU064A2201.

Comparison 1. Phase III Studies A2301/A2302 (Pool 1), 24-week placebo-controlled period: remibrutinib 25 mg b.i.d. vs. placebo, with a test for difference in proportions between the 2 groups.

Comparison 2. Phase IIb dose-finding Study in CSU, A2201 from Pool 2 Safety set, 12-week placebo-controlled period: remibrutinib pooled doses (ranging from 10 mg q.d. to 100 mg b.i.d.) vs. placebo, with a test for trend in proportions across the increasing doses.

The purpose of Comparison 1 was to estimate the dose-specific effect of remibrutinib 25 mg b.i.d. vs. placebo during the 24-week placebo-controlled period of the studies. The purpose of Comparison 2 was to examine the dose-averaged effect of remibrutinib vs. placebo during the 12-week placebo-controlled period of the study and look for evidence of a dose-response pattern. Comparison 1 was considered the main comparison for this analysis, while Comparison 2 played a supportive role.

For each AE term, a risk estimate in a given intervention arm was calculated as the number of patients with the event divided by the number of patients at risk (baseline sample size) × 100%. Additionally, risk differences were estimated for remibrutinib vs. placebo, with 95% CIs constructed by the method of (Agresti and Caffo 2000). Nominal screening p-values were calculated based on the two-sided Fisher's exact test in Comparison 1 or the Cochran-Armitage exact trend test (Agresti 2002) in Comparison 2. Terms with two-sided $p<0.05$ (unadjusted for multiplicity) were flagged for medical evaluation in Step 3.

Step 3. Medical evaluation of ADR candidates identified in Steps 1 and 2

Review of pre-qualified ADR candidates and additional ADR candidates flagged on screening was based on cross-functional assessment of causality, taking into account temporality, biological plausibility / mechanism of action considerations, estimated magnitude and precision of effect, evidence of a dose-response, pre-clinical safety findings, known class effects, investigator-assessed causality (not viewed as definitive evidence but taken into consideration), and positive de-challenge / re-challenge if relevant based on the event type. Patient-level baseline medical history was considered, if relevant in the review of DMEs and other serious events.

Results

Bleeding

In the analysis of prequalified ADR candidates in Comparison 1, a statistical hit ($p<0.05$) was observed for 1 group term – Bleeding (Hemorrhage). Within this group term defined by a customized MedDRA query (CMQ) (combination of SMQs and/or individual PTs capturing all terms relevant to the topic), a significant difference in event frequency on remibrutinib vs. placebo was present for the PT petechiae ($p<0.001$). While no other PT under this CMQ met the screening criteria ($p<0.05$), notable imbalances in event frequencies were present for PTs contusion, ecchymosis, and purpura.

In the analysis of all reported AEs at MedDRA levels SOC to PT in Comparison 1, a statistical hit was present for the HLGT skin vascular abnormalities, consisting of a single observed HLT purpura and related conditions, comprising PTs ecchymosis, petechiae, and purpura.

Additionally, PTs epistaxis, conjunctival haemorrhage, and gingival bleeding were classified as ADRs of remibrutinib based on the mechanistic plausibility considerations. Although the number of patients reporting these events was low with remibrutinib, and the difference vs. placebo was too small to constitute statistical evidence of causality, medical evidence of causality was considered adequate for classification of these events as ADRs.

Upper respiratory tract infection

In Comparison 2, the PT viral upper respiratory tract infection was flagged.

In Comparison 1, PT viral upper respiratory tract infections was reported with a frequency of 0.8% on remibrutinib vs. 0 patients on placebo, but no statistical hit was seen.

In Comparison 1, the frequency of HLT upper respiratory tract infections was comparable between remibrutinib (11.4%) and placebo (11.1%). Under this HLT, PT nasopharyngitis (6.6% vs. 4.6%) and pharyngitis (1.0% vs. 0.7%) were reported more frequently with remibrutinib. Also, more patients reported AEs under HLT influenza viral infections with remibrutinib (2.6%) vs. placebo. In addition, incidence of upper respiratory tract infections (including nasopharyngitis, pharyngitis) reported as related by investigator was higher in remibrutinib group vs placebo.

Despite limited statistical evidence, given a plausible mechanism of action for this AE and minor numerical imbalances seen in Comparison 1, upper respiratory tract infection (including PTs upper respiratory tract infection, acute sinusitis, chronic sinusitis, H1N1 influenza, influenza, laryngitis, nasopharyngitis, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection bacterial, viral upper respiratory tract infection) is classified as an ADR of remibrutinib.

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Adverse events of special interest (AESI)

Infection AESIs

Pool 1

Placebo-controlled period

Table 62: Treatment-emergent Infections AESIs (occurring in ≥ 1% of patients in either group) by risk level during the placebo-controlled period (Pool 1 safety set)

SOC PT	LOU064 25 mg b.i.d. N=606 n (%) EAIR (95% CI)	Placebo N=306 n (%) EAIR (95% CI)	LOU064 25 mg b.i.d. vs. Placebo EAIR difference (95% CI)
	Total PY = 265.1	**Total PY = 132.5**	
Infections and infestations (SOC)	203 (33.5) 95.6 (82.9,109.7)	105 (34.3) 98.1 (80.2,118.7)	-2.5 (-26.1, 20.1)
Bronchitis	7 (1.2) 2.7 (1.1, 5.5)	3 (1.0) 2.3 (0.5, 6.6)	0.4 (-3.6, 3.6)
COVID-19	65 (10.7) 26.0 (20.1, 33.2)	35 (11.4) 28.0 (19.5, 38.9)	-1.9 (-13.7, 9.0)
Cystitis	5 (0.8) 1.9 (0.6, 4.4)	3 (1.0) 2.3 (0.5, 6.7)	-0.4 (-4.3, 2.7)
Gastroenteritis	6 (1.0) 2.3 (0.8, 5.0)	7 (2.3) 5.3 (2.1, 11.0)	-3.1 (-8.1, 1.2)
Influenza	15 (2.5) 5.7 (3.2, 9.4)	4 (1.3) 3.0 (0.8, 7.8)	2.7 (-2.2, 6.8)
Nasopharyngitis	40 (6.6) 15.7 (11.2, 21.4)	14 (4.6) 10.9 (5.9, 18.3)	4.8 (-3.3, 12.2)
Pharyngitis	6 (1.0) 2.3 (0.8, 4.9)	2 (0.7) 1.5 (0.2, 5.5)	0.8 (-2.9, 3.6)
Sinusitis	3 (0.5) 1.1 (0.2, 3.3)	8 (2.6) 6.1 (2.6, 12.0)	-5.0 (-10.1, -0.6)
Suspected COVID-19	9 (1.5) 3.4 (1.6, 6.5)	5 (1.6) 3.8 (1.2, 8.9)	-0.4 (-5.1, 3.6)
Upper respiratory tract infection	18 (3.0) 6.9 (4.1, 10.9)	6 (2.0) 4.6 (1.7, 10.0)	2.3 (-3.2, 7.1)
Urinary tract infection	19 (3.1) 7.3 (4.4, 11.4)	8 (2.6) 6.1 (2.6, 12.1)	1.2 (-4.8, 6.4)

Total PY = cumulative patient-years of on-treatment exposure from all patients in the corresponding treatment group.
Source: [SCS Appendix 1-Table 2.1-7.4p1]

The percentages of patients with Infection AESIs in the remibrutinib 25 mg b.i.d. and placebo groups were 33.5% vs. 34.3% of patients, respectively. The median time to onset of the first Infection AESI was 63 and 83 days respectively, and median event duration was 8 days in both groups. For patients in both groups, no action was taken with study treatment for most events (>90%); study treatment was withdrawn once due to an Infection AESI in the remibrutinib 25 mg b.i.d. group (COVID-19). Study treatment was interrupted in 8.4% of events for the remibrutinib 25 mg b.i.d. Per Investigator's assessment, 9.1% vs. 7.2% events in the remibrutinib 25 mg b.i.d. and placebo groups, respectively, were considered related to study treatment. Serious Infection AESIs were reported in 5 patients (0.8%) in the remibrutinib 25 mg b.i.d. group (appendicitis, COVID-19, gastrointestinal infection, wound abscess, and food poisoning).

Infection by HLGT (pathogen): Infection AEs were most frequently reported (in ≥ 5% of patients in either group) in the following HLGTs for the remibrutinib 25 mg b.i.d. vs. placebo groups, respectively:

- Infections - pathogen unspecified (19.3% of patients in the remibrutinib 25 mg b.i.d. group vs. 20.6% of patients in the placebo group)
    - The most frequently reported PTs (in ≥ 3% of patients in either group) including nasopharyngitis (6.6% vs. 4.6%), upper respiratory tract infection (3.0% vs. 2.0%), and urinary tract infection (3.1% vs. 2.6%).

- Infections - viral infectious disorders (15.8% in the remibrutinib 25 mg b.i.d. group vs. 16.3% in the placebo groups)
    - The most frequently reported PT included COVID-19 (10.7% vs. 11.4%).

Entire study period

Remibrutinib 25 mg b.i.d. group in the entire study period: A total of 277 patients (45.7%) had Infection AESIs. The median time to onset of events was 99 days, and median event duration was 8 days. Overall, 8.6% of the events were considered related to study treatment. No action was taken with study treatment for most of the events (91.7%); 1.1% of the events of Infection AESIs led to study treatment discontinuation (in 3 patients: COVID-19; molluscum contagiosum, pyelonephritis, upper respiratory tract infection; urinary tract infection). Study treatment was interrupted for 6.6% of the events.

Patients who transitioned to remibrutinib: The percentage of patients with Infection AESIs was 26.3%. The median time to onset of events was 56 days, and the median event duration was 10.0 days. Overall, 1 event of body tinea (1.1%) was considered related to study treatment. For most events (90.5%), no action was taken with study treatment; study treatment was interrupted for 7 events (7.4%); 1 event of an Infection AESI led to study treatment discontinuation for 1 (1.1%) patient (moderate tooth abscess).

Pool 2

In the remibrutinib any dose group, 40.8% of patients had Infection AESIs. Per Investigator assessment, 7.8% of the events were considered related to study treatment. In the any remibrutinib 25 mg b.i.d. group, 40.7% of patients had Infection AESIs. One of these AESIs, renal abscess in Study A2201 (remibrutinib 25 mg b.i.d.) was considered related to study treatment.

Bleeding AESIs

Pool 1

Placebo-controlled period

Table 63:Treatment-emergent Bleeding AESIs by risk level during the placebo-controlled period (Pool 1 Safety set)

SMQ PT	LOU064 25 mg b.i.d. N=606 n (%) EAIR (95% CI)	Placebo N=306 n (%) EAIR (95% CI)	LOU064 25 mg b.i.d. vs. Placebo EAIR Difference (95% CI)
	Total PY = 265.1	**Total PY = 132.5**	
Haemorrhages (SMQ) (broad)	64 (10.6) 26.1 (20.1, 33.4)	16 (5.2) 12.5 (7.1, 20.3)	13.7 (4.1, 22.4)
Haemorrhage laboratory terms (SMQ) (broad)	15 (2.5) 5.8 (3.2, 9.5)	6 (2.0) 4.6 (1.7, 10.0)	1.2 (-4.2, 5.8)
Activated partial thromboplastin time prolonged	7 (1.2) 2.7 (1.1, 5.5)	4 (1.3) 3.0 (0.8, 7.8)	-0.4 (-4.7, 3.2)
Bleeding time prolonged	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Coagulation time prolonged	0 (0.0) 0 (0.0, 1.4)	1 (0.3) 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Haemoglobin decreased	3 (0.5) 1.1 (0.2, 3.3)	0 (0.0) 0 (0.0, 2.8)	1.1 (-1.3, 2.8)
International normalised ratio increased	1 (0.2) 0.4 (0.0, 2.1)	1 (0.3) 0.8 (0.0, 4.2)	-0.4 (-3.1, 1.6)
Prothrombin time prolonged	5 (0.8) 1.9 (0.6, 4.4)	3 (1.0) 2.3 (0.5, 6.7)	-0.4 (-4.3, 2.7)
Urinary occult blood positive	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Haemorrhage terms (excl laboratory terms) (SMQ) (broad)	56 (9.2) 22.7 (17.1, 29.4)	10 (3.3) 7.7 (3.7,14.1)	15.0 (6.7, 22.5)
Abnormal uterine bleeding	0 (0.0) 0 (0.0, 1.4)	2 (0.7) 1.5 (0.2, 5.5)	-1.5 (-4.6, 0.8)
Conjunctival haemorrhage	2 (0.3) 0.8 (0.1, 2.7)	0 (0.0) 0 (0.0, 2.8)	0.8 (-1.6, 2.3)
Contusion	13 (2.1) 5.0 (2.6, 8.5)	2 (0.7) 1.5 (0.2, 5.5)	3.5 (-0.7, 6.9)
Ecchymosis	9 (1.5) 3.4 (1.6, 6.5)	1 (0.3) 0.8 (0.0, 4.2)	2.7 (-0.9, 5.5)
Epistaxis	5 (0.8) 1.9 (0.6, 4.4)	1 (0.3) 0.8 (0.0, 4.2)	1.1 (-2.0, 3.5)
Gingival bleeding	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Haematoma	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Haematuria	6 (1.0) 2.3 (0.8, 5.0)	1 (0.3) 0.8 (0.0, 4.2)	1.5 (-1.7, 4.0)
Haemorrhagic ovarian cyst	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Heavy menstrual bleeding	2 (0.3) 0.8 (0.1, 2.7)	1 (0.3) 0.8 (0.0, 4.2)	0.0 (-2.8, 2.1)
Increased tendency to bruise	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Intermenstrual bleeding	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Menometrorrhagia	0 (0.0) 0 (0.0, 1.4)	1 (0.3) 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Petechiae	23 (3.8) 8.9 (5.7, 13.4)	1 (0.3) 0.8 (0.0, 4.2)	8.2 (3.5, 12.1)
Purpura	5 (0.8) 1.9 (0.6, 4.4)	0 (0.0) 0 (0.0, 2.8)	1.9 (-0.8, 3.9)

SMQ PT	LOU064 25 mg b.i.d. N=606 n (%) EAIR (95% CI)	Placebo N=306 n (%) EAIR (95% CI)	LOU064 25 mg b.i.d. vs. Placebo EAIR Difference (95% CI)
	Total PY = 265.1	**Total PY = 132.5**	

Total PY = cumulative patient-years of on-treatment exposure from all patients in the corresponding treatment group.
Source: [SCS Appendix 1-Table 2.1-7.4p1]

The percentages of patients with Bleeding AESIs were 10.6% vs. 5.2% in the remibrutinib 25 mg b.i.d. and placebo groups, respectively. Median time to event onset was 29.5 vs. 81.5 days, and median event duration was 26 vs. 36 days, respectively. Two serious Bleeding AESIs occurred in the remibrutinib 25 mg b.i.d. group: one contusion of the chest related to an accident and one haematuria in a patient with chronic urocystitis with squamous metaplasia.

The imbalance of Bleeding AESIs was primarily driven by cutaneous bleeding events: petechiae in 23 patients (3.8%) in the remibrutinib 25 mg b.i.d. group vs. 1 patient (0.3%) in the placebo group, contusion in 13 patients (2.1%) vs. 2 patients (0.7%), ecchymosis in 9 patients (1.5%) vs. 1 patient (0.3%), and purpura in 5 patients (0.8%) vs. zero in the placebo group.

The majority of Bleeding AESIs in the remibrutinib 25 mg b.i.d. group (67.0% of events) were considered related to study treatment versus 20.0 % of events in the placebo group. No action was taken with study treatment for most of the events of Bleeding AESIs (87.0% of events in the remibrutinib 25 mg b.i.d), although study treatment was interrupted for 9.6% of the events. Study treatment was discontinued for 2.6% of the events in the remibrutinib 25 mg b.i.d. group (3 patients reporting single events of purpura, petechiae, and contusion).

Bleeding AESIs by time to first occurrence: In the remibrutinib 25 mg b.i.d. group, first occurrence of bleeding AESIs was highest during the 0 to ≤ 4 weeks interval followed by the > 8 to ≤ 12 weeks interval and the > 4 to ≤ 8 weeks interval.

Entire study period

Remibrutinib 25 mg b.i.d. group during the entire study period: Overall 11.7% of patients had Bleeding AESIs, including 7 patients with events occurring after completion of the placebo-controlled period (during the open-label period). The median time to event onset was 32 days, and the median event duration was 27.5 days. Most of the events were resolved (82.1%), and 67.1% of the events were considered related to study treatment. No action was taken with study treatment for the majority of the events (86.4%); study treatment was interrupted for 7.9% of the events. Study treatment was discontinued for 4.3% of the events.

Patients who transitioned to remibrutinib: In these patients, 6.9% of patients had Bleeding AESIs. The median time to event onset was 47.5 days, with a median event duration of 43.0 days. The majority of the events were resolved (71.4%), and 33.3% were considered related to study treatment; no action was taken with study treatment for the majority of events (85.7%). Study treatment was interrupted for 1 event (4.8%) and withdrawn for 1 event (4.8%).

Bleeding events by PT: During the entire study period, the most frequently reported events by PT (> 0.5% of patients) in the SMQ of haemorrhages (excl laboratory terms) in the remibrutinib 25 mg b.i.d. group were petechiae in 24 patients (4.0%), contusion in 13 patients (2.1%), ecchymosis in 10 patients (1.7%), haematuria in 6 patients (1.0%), epistaxis in 5 patients (0.8%), purpura in 5 patients (0.8%), and conjunctival haemorrhage in 3 patients (0.5%).

Pool 2

In the remibrutinib any dose group, 10.5% of patients had Bleeding AESIs. 60.6% of the events were considered related to study treatment. In the any remibrutinib 25 mg b.i.d. group, 10.8% of patients had Bleeding AESIs. 62.2% of the events were considered related to study treatment.

Bleeding events by PT: In the remibrutinib any dose group, the most frequently reported events by PT (> 0.5% of patients) in the SMQ of haemorrhages (excl laboratory terms) were petechiae (3.2%), contusion (1.4%), purpura (1.1%), ecchymosis (1.0%), haematuria (0.7%), and epistaxis in (0.6%). One serious Bleeding AESI of melaena occurred in a patient in Study A2201E1 taking remibrutinib 100 mg b.i.d. The bleeding was reported as due to bariatric surgery.

In the any remibrutinib 25 mg b.i.d. group, the most frequently reported events (> 0.5% of patients) in the SMQ of haemorrhages (excl laboratory terms) were petechiae (3.6%), contusion (1.5%), purpura (1.1%), ecchymosis (1.0%), haematuria (0.6%), and epistaxis in (0.6%).

Cytopenia AESIs

Pool 1

Placebo-controlled period

Table 64: Treatment-emergent Cytopenias AESIs by risk level during the placebo-controlled period (Pool 1 safety set)

SMQ PT	LOU064 25 mg b.i.d. N=606 n (%) EAIR (95% CI)	Placebo N=306 n (%) EAIR (95% CI)	LOU064 25 mg b.i.d. vs. Placebo EAIR difference (95% CI)
	Total PY = 265.1	Total PY = 132.5	
Haematopoietic cytopenias (SMQ) (broad)	22 (3.6) 8.5 (5.3, 12.8)	6 (2.0) 4.6 (1.7, 10.0)	3.9 (-1.9, 8.9)
Haematopoietic erythropenia (SMQ) (broad)	8 (1.3) 3.0 (1.3, 6.0)	3 (1.0) 2.3 (0.5, 6.7)	0.7 (-3.4, 4.1)
Anaemia	5 (0.8) 1.9 (0.6, 4.4)	3 (1.0) 2.3 (0.5, 6.7)	-0.4 (-4.3, 2.7)
Haemoglobin decreased	3 (0.5) 1.1 (0.2, 3.3)	0 (0.0) 0 (0.0, 2.8)	1.1 (-1.3, 2.8)
Haematopoietic leukopenia (SMQ) (broad)	12 (2.0) 4.6 (2.4, 8.0)	2 (0.7) 1.5 (0.2, 5.5)	3.1 (-1.0, 6.4)
Leukopenia	3 (0.5) 1.1 (0.2, 3.3)	0 (0.0) 0 (0.0, 2.8)	1.1 (-1.3, 2.9)
Lymphopenia	0 (0.0) 0 (0.0, 1.4)	1 (0.3) 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Monocytopenia	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Neutropenia	7 (1.2) 2.7 (1.1, 5.5)	1 (0.3) 0.8 (0.0, 4.2)	1.9 (-1.4, 4.5)
Neutrophil count decreased	2 (0.3) 0.8 (0.1, 2.7)	0 (0.0) 0 (0.0, 2.8)	0.8 (-1.6, 2.3)
White blood cell count decreased	3 (0.5) 1.1 (0.2, 3.3)	0 (0.0) 0 (0.0, 2.8)	1.1 (-1.3, 2.9)
Haematopoietic thrombocytopenia (SMQ) (broad)	3 (0.5) 1.1 (0.2, 3.3)	1 (0.3) 0.8 (0.0, 4.2)	0.4 (-2.6, 2.6)
Thrombocytopenia	3 (0.5) 1.1 (0.2, 3.3)	1 (0.3) 0.8 (0.0, 4.2)	0.4 (-2.6, 2.6)

Total PY = cumulative patient-years of on-treatment exposure from all patients in the corresponding treatment group.
Source: [SCS Appendix 1-Table 2.1-7.4p1]

The overall percentages of patients with Cytopenia AESIs was 3.6% (22 patients) vs. 2.0% (6 patients) in the remibrutinib 25 mg b.i.d. and placebo groups, respectively. The difference between the treatment groups in Cytopenia AESIs was primarily driven by hematopoietic leukopenia (SMQ) (12 patients, 2.0% vs. 2 patients, 0.7%), with the most frequent PTs being related to neutropenia (neutropenia PT) reported in 7 patients (1.2%) in the remibrutinib 25 mg b.i.d. group vs. 1 patient (0.3%) in the placebo group; neutrophil count decreased PT reported in 2 patients (0.3%) vs. no patients, respectively. Few patients reported leukocyte count decreases - WBC count decreased in 3 patients (0.5%) vs. zero, and leukopenia in 3 patients (0.5%) vs zero.

Most of the events resolved (90.6% vs. 88.9%), and 31.3% of events in remibrutinib 25 mg b.i.d. group and 22.2% of events in placebo group were considered related to study treatment. The median time to event onset was 70.0 and 35.0 days and median event duration was 26.0 days (range 5 to 153 days) and 28.0 days (range 15 to 162 days) in the remibrutinib 25 mg b.i.d. group and the placebo group, respectively. In the remibrutinib 25 mg b.i.d. group, study treatment was discontinued for 1 (3.1%) event, and 3 events led to study treatment interrupted.

Entire study period

Remibrutinib 25 mg b.i.d. group during the entire study period: Overall, 5.9% of patients had Cytopenia AESIs, including 14 patients (2.3%) with events that occurred after completion of the placebo-controlled period (during the open-label period). The median time to event onset was 113.5 days and the median event duration was 36 days. 32.7% of the events were considered related to study treatment. No action was taken with study treatment for most of the events (87.8%); study treatment was interrupted for 6.1% of the events; study treatment was discontinued for 4.1% of the events.

Patients transitioned to remibrutinib: In these patients, the percentage of patients with Cytopenia AESIs was 1.5%. The median time to event onset was 28.0 days, with a median event duration of 79.0 days.

Pool 2

The overall percentages of patients with Cytopenias AESIs was 4.5% for the remibrutinib any dose group (29.3% of events were considered related to study treatment) and 4.6% for the any remibrutinib 25 mg b.i.d. group (30.6% of events were considered related to study treatment).

Cytopenia AESIs by PT: For Pool 2 in the remibrutinib any dose group, the most frequently reported Cytopenia AESI events by PT (>0.5% of patients) in the SMQ of haematopoietic leukopenias were as follows: neutropenia in 16 patients (1.3%), neutrophil count decreased in 9 patients (0.7%), leukopenia in 7 patients (0.6%), and WBC count decreased in 7 patients (0.6%).

For Pool 2 in the any remibrutinib 25 mg b.i.d. group, the most frequently reported Cytopenia AESIs (>0.5% of patients) in the SMQ of haematopoietic leukopenias were similar, specifically neutropenia in 11 patients (1.1%), neutrophil count decreased in 8 patients (0.8%), leukopenia in 6 patients (0.6%), and WBC count decreased in 6 patients (0.6%).

Additional safety topics

Cardiac arrythmias

For Pool 1 during the placebo-controlled period, 10 patients (1.7%) in the remibrutinib 25 mg b.i.d group vs. 4 patients (1.3%) in the placebo group had at least 1 AE in the SMQ Cardiac arrhythmias. The most frequent events occurred in both groups and included conduction defects (SMQ) (1.0% vs. 0.7%), disorders of the sinus node function (SMQ) (0.5% vs. 0.3%) and tachyarrhythmias (SMQ)

(0.5% vs. 0.7%). During the entire study period, EAIR did not increase with no new remarkable events. Under the SMQ Conduction defects, electrocardiogram QT prolonged was reported in 2 patients in remibrutinib 25 mg b.i.d. group. In both cases, QT elevation was marginal with maximum up to 470 msec. During the entire study period, 2 patients who transitioned from placebo to remibrutinib reported AEs of electrocardiogram QT prolonged. One patient baseline QTcF interval higher as compared to the value at the time of the report, when the value was below 450 ms. The other patient reported an AE before starting open-label treatment with remibrutinib, and the value was below baseline value and below 450 ms.

Overall, there was no significant finding for QT interval based on the data in Pool 1. Under the Tachyarrhythmia's SMQ, no atrial fibrillation AE was reported during entire study period. ECG evaluation also did not reveal any safety concern related to arrhythmias. No safety concern with remibrutinib was observed in the analysis of AEs reported under SMQ Cardiac arrhythmias.

Hypertension

The clinical studies comprising Pool 1 permitted the enrolment of patients with pre-existing hypertension - there were 20.3% and 17.0% patients with hypertension (PT) in the remibrutinib 25 mg b.i.d. group and in the placebo group at baseline.

In the Pool 1 placebo-controlled period, for hypertension (SMQ), the percentages of patients with events were 1.5% vs. 0.7%, respectively. In the remibrutinib 25 mg b.i.d. group, the AEs of hypertension (by PT) were mild to moderate in severity, and reflected transient blood pressure elevations, rather than newly occurring sustained hypertension. Mean changes in SBP and DBP from baseline during the placebo-controlled period were comparable between treatment groups (7.8 mmHg and 8.2 mmHg, respectively for SBP and 5.6 mmHg and 6.2 mHg, respectively, for DBP). During the entire study period after completion of the placebo-controlled period, 7 additional patients reported hypertension AEs (SMQ) in the remibrutinib 25 mg b.i.d. group.

To characterise blood pressure effect with remibrutinib treatment (according to the draft FDA guidance - Assessment of Pressor Effects of Drugs - Guidance for Industry, February 2022), the Phase III ABPM Study CLOU064A2305 (Study A2305) investigated the effects of remibrutinib 25 mg b.i.d. open-label on SBP measured as a change in 24-hour weighted average SBP from baseline to Week 4 assessed by ABPM. The primary objective of Study A2305 was to rule out an increase of >3 mm Hg in 24-hour SBP at steady state (Week 4) compared to baseline, assessed by the evaluation of change from baseline in 24-hour average SBP at Week 4 measured by ABPM. The study results showed that the mean change from baseline to Week 4 in 24-hour SBP measured by ABPM was a decrease of -1.3 mm Hg (95% CI: -2.3, -0.3). The upper limit of the 95% CI was -0.3 mm Hg, which was less than the prespecified upper limit of an increase of 3 mm Hg, as based on the draft FDA guidance. No clinically relevant effect of remibrutinib on blood pressure was noted.

Serious adverse events

Pool 1

<u>Placebo-controlled period</u>

For Pool 1 during the placebo-controlled period, the percentages of patients with SAEs were 3.3% in the remibrutinib 25 mg b.i.d. group and 2.3% in the placebo group.

Table 65: Treatment-emergent serious adverse events by primary system organ class and preferred term during the placebo-controlled period (Pool 1 Safety set)

Primary system organ class Preferred term	LOU064 25 mg b.i.d. N=606 n (%) EAIR (95% CI)	Placebo N=306 n (%) EAIR (95% CI)	LOU064 25 mg b.i.d. vs. Placebo EAIR difference (95% CI)
	Total PY = 265.1	**Total PY = 132.5**	
Patients with at least one AE	20 (3.3) 7.7 (4.7, 11.9)	7 (2.3) 5.3 (2.2, 11.0)	2.3 (-3.5, 7.4)
Cardiac disorders (SOC)	2 (0.3) 0.8 (0.1, 2.7)	0 (0.0) 0.0 (0.0, 2.8)	0.8 (-1.6, 2.3)
Angina pectoris	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Arteriosclerosis coronary artery	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Ear and labyrinth disorders (SOC)	0 (0.0) 0.0 (0.0, 1.4)	1 (0.3) 0 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Vestibular disorder	0 (0.0) 0.0 (0.0, 1.4)	1 (0.3) 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Gastrointestinal disorders (SOC)	2 (0.3) 0.8 (0.1, 2.7)	0 (0.0) 0.0 (0.0, 2.8)	0.8 (-1.6, 2.3)
Food poisoning	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Gastrointestinal wall thickening	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Hepatobiliary disorders (SOC)	0 (0.0) 0.0 (0.0, 1.4)	1 (0.3) 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Cholecystitis	0 (0.0) 0.0 (0.0, 1.4)	1 (0.3) 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Immune system disorders (SOC)	0 (0.0) 0.0 (0.0, 1.4)	1 (0.3) 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Drug hypersensitivity	0 (0.0) 0.0 (0.0, 1.4)	1 (0.3) 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Infections and infestations (SOC)	4 (0.7) 1.5 (0.4, 3.9)	2 (0.7) 1.5 (0.2, 5.5)	0.0 (-3.4, 2.7)
Appendicitis	1 (0.2) 0.4 (0.0, 2.1)	1 (0.3) 0.8 (0.0, 4.2)	-0.4 (-3.1, 1.6)
COVID-19	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Gastrointestinal infection	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Wound abscess	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Pneumonia	0 (0.0) 0.0 (0.0, 1.4)	1 (0.3) 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Injury, poisoning and procedural complications (SOC)	2 (0.3) 0.8 (0.1, 2.7)	0 (0.0) 0.0 (0.0, 2.8)	0.8 (-1.6, 2.3)
Contusion	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Face injury	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Head injury	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Metabolism and nutrition disorders (SOC)	2 (0.3) 0.8 (0.1, 2.7)	0 (0.0) 0.0 (0.0, 2.8)	0.8 (-1.6, 2.3)
Diabetic ketoacidosis	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)

Primary system organ class Preferred term	LOU064 25 mg b.i.d. N=606 n (%) EAIR (95% CI)	Placebo N=306 n (%) EAIR (95% CI)	LOU064 25 mg b.i.d. vs. Placebo EAIR difference (95% CI)
	Total PY = 265.1	**Total PY = 132.5**	
Hypokalaemia	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Musculoskeletal and connective tissue disorders (SOC)	4 (0.7) 1.5 (0.4, 3.9)	0 (0.0) 0.0 (0.0, 2.8)	1.5 (-1.1, 3.4)
Back pain	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Intervertebral disc degeneration	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
intervertebral disc protrusion	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Spinal stenosis	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Spondylolisthesis	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.2) 0.4 (0.0, 2.1)	1 (0.3) 0.8 (0.0, 4.2)	-0.4 (-3.1, 1.6)
Mucinous adenocarcinoma of appendix	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Breast cancer	0 (0.0) 0.0 (0.0, 1.4)	1 (0.3) 0.8 (0.0, 4.2)	-0.8 (-3.4, 1.1)
Renal and urinary disorders (SOC)	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Haematuria	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Nasal polyps	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Skin and subcutaneous tissue disorders (SOC)	2 (0.3) 0.8 (0.1, 2.7)	1 (0.3) 0.8 (0.0, 4.2)	0.0 (-2.8, 2.1)
Angioedema	1 (0.2) 0.4 (0.0, 2.1)	0 (0.0) 0.0 (0.0, 2.8)	0.4 (-1.8, 1.8)
Chronic spontaneous urticaria	1 (0.2) 0.4 (0.0, 2.1)	1 (0.3) 0.8 (0.0, 4.2)	-0.4 (-3.1, 1.6)

A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
System organ classes are presented in alphabetical order; preferred terms are sorted within system organ classes in descending frequency of AEs in the first column (LOU064 25 mg b.i.d.).
MedDRA Version 26.1 has been used for the reporting of adverse events.
N = number of patients in the corresponding treatment group from the analysis set; Total PY = cumulative patient-years of on-treatment exposure from all patients in the corresponding treatment group; n = number of patients with the event; EAIR = exposure-adjusted incidence rate, defined as the number of patients with the event per 100 patient-years of exposure, where the exposure time at risk is event-specific (terminated by incident events); CI = confidence interval for the rate (Garwood 1936) or the rate difference (Scosyrev, Pethe 2022).
Source: [SCS Appendix 1-Table 2.1-5.1p1]

Entire study period

Remibrutinib 25 mg b.i.d. group in the entire study period: A total of 25 patients (4.1%) in the remibrutinib 25 mg b.i.d. group had at least 1 SAE during the entire study period, including 5 additional patients with an SAE after completion of the placebo-controlled period (during the open-label period).

Patients who transitioned to remibrutinib: Three patients had at least 1 SAE.

Pool 2

In the remibrutinib any dose group, 3.4% of patients had at least 1 SAE.

In the any remibrutinib 25 mg b.i.d. group, 3.4% of patients had at least 1 SAE.

Two SAEs occurred in Study A2201 that were considered related to study treatment, 1 SAE of renal abscess (remibrutinib 25 mg b.i.d.) and 1 SAE of CSU (remibrutinib 10 mg b.i.d.), and both led to study treatment discontinuation. Although considered not related to study treatment, 1 notable bleeding event, an SAE of moderate melaena (remibrutinib 100 mg b.i.d.), occurred in Study A2201E1.

Deaths

There were no deaths reported in the clinical studies.

5.4.4.1. Important additional safety topic – Neoplasms

Table 66: Treatment emergent adverse events, by primary system organ class of Neoplasms benign, malignant and unspecified and preferred term during the placebo-controlled and entire study period, Pool 1 Safety Set (selected data of interest, complete data can be found in source documentation)

Primary system organ class	Placebo controlled period		After placebo controlled period	
	Placebo	**LOU064 25mg b.i.d.**	**LOU064 25mg b.i.d.**	**Transitioned to LOU064 25 mg b.i.d.**
	Malignant or potentially malignant neoplasms			
Neoplasms benign, malignant and unspecified	breast cancer	mucinous adenocarcinoma of appendix	pancreatic carcinoma	GIST
			small intestinal (duodenal) adenocarcinoma	
	Benign neoplasms and unspecified			
	FNH	skin papilloma (3 events) oesophageal leiomyoma	fibroma	acrochordon
		dysplastic naevus	benign renal neoplasm (oncocytoma)	sebborrhoeic keratosis
		haemangioma	haemangioma	
		lipoma	haemangioma of liver	
		pyogenic granuloma		

Source: Adapted from SCS Appendix 1, Table 2.1-1.1p1 and Table 2.1-1.3p1

Following review of all TEAEs within the SOC Neoplasms in Pool 1, neoplasm incidence rates were for remibrutinib 1.5%, EAIR: 3.4 vs. placebo 0.7%, EAIR: 1.5. Two malignant tumours were reported during placebo controlled period: mucinous adenocarcinoma of appendix in remibrutinib group, and breast cancer in placebo group. Regarding benign/unspecified neoplasms, except one event of FNH in placebo group, all other (8 events) were reported in remibrutinib group.

During the entire study period, 3 additional tumours were reported in patients receiving remibrutinib: GIST, disseminated pancreatic cancer, and small intestine adenocarcinoma. All malignant neoplasms occurred in gastrointestinal tract. Except for a single case of breast cancer in the placebo group, no other common tumours and no tumours usually associated with BTK inhibitors were reported during the pivotal studies.

At the CHMP request, the Applicant provided narratives of individual cases and available histology findings for neoplasms detected in pivotal studies. Three of the five reported events were finally

classified as malignant - appendiceal mucinous neoplasm (LAMN), duodenal adenocarcinoma, and metastatic pancreatic carcinoma. One event was benign leiomyoma of oesophagus. No conclusion is possible in a case of patient reported with GIST and large intestinal polyp. Time to onset was relatively short, ranging from 54 to 329 days.

The Applicant additionally conducted an analysis using pooled CSU data (referred to as Pool 3), including completed Phase II Studies (A2201, A2201E1) and Phase III Studies (A2301, A2302, Japanese open-label Study A1301, ABPM Study A2305) and an ongoing Phase IIIb extension Study A2303B (data cut-off date of 10-Mar-2025). In the study Pool 3 (exposure 2342.4 p-y), 52 neoplasms were reported, 16 were classified as malignant/unspecified. Out of those 16 malignant/unspecified events, 7 (43,8%) were located in the GI tract (PTs: Adenocarcinoma gastric, GIST, Mucinous adenocarcinoma of appendix, Oesophageal squamous cell carcinoma stage 0, Pancreatic carcinoma, Small intestine carcinoma, Colorectal adenoma). Additionally, 2 TEAEs of large intestinal polyps were observed in studies A2201E and A1301, along with a patient reported also with GIST in the pivotal study and one event of gastric polyps in study A2201.

5.4.5. Discontinuation due to adverse events

Pool 1

Placebo-controlled period

A total of 17 patients (2.8%) in the remibrutinib 25 mg b.i.d. group and 9 patients (2.9%) in the placebo group had AEs leading to study treatment discontinuation. The majority (12/17) of patients discontinued remibrutinib treatment during the first 12 weeks of the study. Of the 18 events reported in remibrutinib group, 3 were related to bleeding disorders (thrombocytopenia, petechiae and purpura), 2 events were related to high blood pressure (blood pressure increased and hypertension), and 2 events were related to liver toxicity (GGT increased and liver enzyme increased). Of those events, all but purpura and GGT increased were suspected to be related to remibrutinib treatment.

Entire study period

In the remibrutinib 25 mg b.i.d. group 11 additional patients (1.8%) discontinued study treatment due to AEs after completion of the placebo-controlled period. Reported PT's were as follows: increased tendency to bruise, angina pectoris (AP), cholecystitis, molluscum contagiosum, pyelonephritis, upper respiratory tract infection, urinary tract infection (UTI), aPTT prolonged, neutrophil count decreased, PT prolonged, pancreatic carcinoma, small intestine adenocarcinoma, Bell's palsy, menstrual disorder, and hypertensive crisis. Of reported events, all were suspected to be related to remibrutinib except AP, UTI, pancreatic carcinoma, small intestine adenocarcinoma and hypertensive crisis.

Of patients who transitioned to remibrutinib, 4 (1.5%) had at least 1 AE leading to study treatment discontinuation. These events included asthenia, tooth abscess, and dysaesthesia in 1 patient; and abortion spontaneous, urticaria, and Henoch-Schonlein purpura in 1 patient each (0.4%). Of reported events, asthenia and Henoch-Schonlein purpura were suspected to be related to remibrutinib treatment. Reported SAE of spontaneous abortion was not suspected to be related to remibrutinib.

SAEs leading to study treatment discontinuation

In Pool 1, six SAEs were reported that led to study treatment discontinuation. Five events were reported in remibrutinib treatment group during placebo-controlled period (spondylolisthesis, face injury, and abortus spontaneous) and open-label period (small intestinal adenocarcinoma, and pancreatic carcinoma). In placebo group one SAE of breast cancer led to treatment discontinuation. No SAE that led to study treatment discontinuation was considered related to study medication by

investigator.

Pool 2

In the remibrutinib any dose group, 51 patients (4.1%) had AEs leading to study treatment discontinuation. The following AEs occurred in 2 patients each (0.2%): diarrhoea, COVID-19, urinary tract infection, petechiae, purpura, and urticaria. The remaining AEs occurred in 1 patient each (0.1%).

In the any remibrutinib 25 mg b.i.d. group, 34 patients (3.5%) had AEs leading to study treatment discontinuation. Urinary tract infection and urticaria occurred in 2 patients each (0.2%); the remaining AEs occurred in 1 patient each (0.1%).

Adverse events leading to study treatment interruption

Pool 1

Placebo-controlled period

The percentages of patients with AEs leading to study treatment interruption were similar in the remibrutinib 25 mg b.i.d. and placebo groups (47 patients, 7.8% vs. 27 patients, 8.8%). The following events leading to study treatment interruption (by PT) occurred in more than 1 patient each: COVID-19 (1.5% and 1.0%), suspected COVID-19 (0.5% and 1.0%), petechiae (0.5% and 0%), neutropenia, headache, upper respiratory tract infection, aPTT prolonged, purpura (0.3% vs 0%); hepatic enzyme increased occurred in 0.3% in both groups.

Entire study period

Remibrutinib 25 mg b.i.d. group: A total of 54 patients (8.9%) had AEs leading to study treatment interruption, including 7 patients with AEs leading to study treatment interruption after completion of the placebo-controlled period as follows: COVID-19 in 3 patients; and suspected COVID-19, nasopharyngitis, pyrexia, blood pressure increased, blood uric acid increased, influenza-like illness, hyperglycaemia, leiomyoma, carpal tunnel syndrome, and diarrhoea in 1 patient each.

Patients who transitioned to remibrutinib: Nine patients (3.4%) had AEs leading to study treatment interruption as follows: COVID-19 in 2 patients (0.8%); the remaining events occurred in 1 patient each (0.4%) and included suspected COVID-19, nasopharyngitis, leukopenia, upper respiratory tract infection, gastroenteritis, Herpes zoster, electrocardiogram, QT prolonged, and epistaxis.

Pool 2

In the remibrutinib any dose group and in the any remibrutinib 25 mg b.i.d. group, 7.1% of patients had AEs leading to dose interruption. By PT, AES leading to study interruption were very similar to those reported for Pool 1.

5.4.6. Safety in special populations

The following subgroups were analysed for Pool 1:

- Age group (≥ 18 to < 65, ≥ 65 to < 85 years, ≥ 85 years)
- Gender (Male, Female)
- Age and gender combined (≥ 18 to < 65 & Male, ≥ 18 to < 65 & Female, ≥ 65 to < 85 years & Male, ≥ 65 to < 85 years & Female, ≥ 85 years & Male, ≥ 85 years & Female)
- Ethnicity (Hispanic or Latino, non-Hispanic and non-Latino)
- Race (White, Black or African American, Asian, Native Hawaiian or Pacific Islander, American Indian or Alaska native, more than one race)

Table 67: TEAEs by age range - during double-blind period (Pool 1 Safety Set)

	LOU064 25 mg b.i.d				Placebo			
MedDRA Terms	Age <65 n (%) N=553	Age 65-74 n (%) N=43	Age 75-84 n (%) N=10	Age 85+ n (%) N=0	Age <65 n (%) N=282	Age 65-74 n (%) N=22	Age 75-84 n (%) N=2	Age 85+ n (%) N=0
Total AEs	355 (64.2)	31 (72.1)	7 (70)	0	182 (64.5)	15 (68.2)	1 (50)	0
Serious AEs – Total	18 (3.3)	2 (4.7)	0	0	6 (2.1)	1 (4.5)	0	0
- Fatal	0	0	0	0	0	0	0	0
- Hospitalisation/prolong existing hospitalisation	18 (3.3)	2 (4.7)	0	0	4 (1.4)	0	0	0
- Life-threatening	1 (0.2)	0	0	0	0	0	0	0
- Disability/incapacity	0	0	0	0	0	0	0	0
- Other (medically significant)	3 (0.5)	0	0	0	3 (1.1)	1 (4.5)	0	0
AE leading to drop-out	15 (2.7)	1 (2.3)	1 (10.0)	0	7 (2.5)	2 (9.1)	0	0
Psychiatric disorders	12 (2.2)	0	0	0	4 (1.4)	0	0	0
Nervous system disorders	54 (9.8)	4 (9.3)	1 (10.0)	0	26 (9.2)	1 (4.5)	0	0
Accidents and injuries	27 (4.9)	6 (14.0)	2 (20.0)	0	7 (2.5)	0	0	0
Cardiac disorders	12 (2.2)	1 (2.3)	0	0	8 (2.8)	1 (4.5)	0	0
Vascular disorders	8 (1.4)	1 (2.3)	0	0	2 (0.7)	1 (4.5)	0	0
Cerebrovascular disorders	0	1 (2.3)	0	0	0	0	0	0
Infections and infestations	184 (33.3)	15 (34.9)	3 (30.0)	0	96 (34.0)	7 (31.8)	1 (50.0)	0
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	9 (1.6)	1 (2.3)	0	0	3 (1.1)	0	0	0
Other AEs (by PT) appearing more frequently in older patients								
Vertigo	3 (0.5)	2 (4.7)	0	0	1 (0.4)	0	0	0
Abdominal pain upper	7 (1.3)	2 (4.7)	0	0	3 (1.1)	0	0	0
Nasopharyngitis	36 (6.5)	4 (9.3)	0	0	12 (4.3)	2 (9.1)	0	0
COVID-19	60 (10.8)	4 (9.3)	0	0	30 (10.6)	4 (18.2)	0	0
Contusion	10 (1.8)	2 (4.7)	1 (10.0)	0	2 (0.7)	0	0	0
Hypokalaemia	1 (0.2)	2 (4.7)	0	0	0	0	0	0

	LOU064 25 mg b.i.d				Placebo			
MedDRA Terms	Age <65 n (%) N=553	Age 65-74 n (%) N=43	Age 75-84 n (%) N=10	Age 85+ n (%) N=0	Age <65 n (%) N=282	Age 65-74 n (%) N=22	Age 75-84 n (%) N=2	Age 85+ n (%) N=0
Arthralgia	10 (1.8)	2 (4.7)	0	0	6 (2.1)	1 (4.5)	0	0
Intervertebral disc degeneration	0	2 (4.7)	0	0	0	0	0	0
Back pain	10 (1.8)	2 (4.7)	1 (10.0)	0	2 (0.7)	0	0	0
Headache	35 (6.3)	3 (7.0)	0	0	19 (6.7)	0	0	0
Urticaria	12 (2.2)	3 (7.0)	0	0	12 (4.3)	3 (13.6)	0	0
Eczema	6 (1.1)	2 (4.7)	0	0	3 (1.1)	0	0	0
Bronchitis	5 (0.9)	0	2 (20)	0	3 (1.1)	0	0	0

A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
Source: [Responses to D120 Clinical Appendix 5-Table ADAR075 Q158-1.1, Table ADAR075 Q158-1.3].

Table 68: TEAEs by age range - during entire study period (Pool 1 Safety Set)

	Any LOU064 25 mg b.i.d				Placebo			
MedDRA Terms	Age <65 n (%) N=795	Age 65-74 n (%) N=61	Age 75-84 n (%) N=12	Age 85+ n (%) N=0	Age <65 n (%) N=282	Age 65-74 n (%) N=22	Age 75-85 n (%) N=2	Age 85+ n (%) N=0
Total AEs	529 (66.5)	42 (68.9)	8 (66.7)	0	182 (64.5)	15 (68.2)	1 (50)	0
Serious AEs – Total	23 (2.9)	5 (8.2)	0	0	6 (2.1)	1 (4.5)	0	0
Fatal	0	0	0	0	0	0	0	0
Hospitalisation/prolong existing hospitalisation	23 (2.9)	5 (8.2)	0	0	4 (1.4)	0	0	0
- Life-threatening	1 (0.1)	0	0	0	0	0	0	0
- Disability/incapacity	0	0	0	0	0	0	0	0
- Other (medically significant)	4 (0.5)	1 (1.6)	0	0	3 (1.1)	1 (4.5)	0	0
AE leading to drop-out	28 (3.5)	3 (4.9)	1 (8.3)	0	7 (2.5)	2 (9.1)	0	0
Psychiatric disorders	21 (2.6)	0	0	0	4 (1.4)	0	0	0
Nervous system disorders	82 (10.3)	7 (11.5)	1 (8.3)	0	26 (9.2)	1 (4.5)	0	0

Accidents and injuries	42 (5.3)	7 (11.5)	2 (16.7)	0	7 (2.5)	0	0	0
Cardiac disorders	22 (2.8)	2 (3.3)	0	0	8 (2.8)	1 (4.5)	0	0
Vascular disorders	17 (2.1)	2 (3.3)	0	0	2 (0.7)	1 (4.5)	0	0
Cerebrovascular disorders	0	1 (1.6)	0	0	0	0	0	0
Infections and infestations	316 (39.7)	25 (41.0)	3 (25.0)	0	96 (34.0)	7 (31.8)	1 (50.0)	0
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	13 (1.6)	1 (1.6)	0	0	3 (1.1)	0	0	0
Other AEs (by PTs) appearing more frequently in older patients								
Vertigo	9 (1.1)	2 (3.3)	0	0	1 (0.4)	0	0	0
Abdominal pain upper	14 (1.8)	2 (3.3)	0	0	3 (1.1)	0	0	0
Nasopharyngitis	59 (7.4)	5 (8.2)	0	0	12 (4.3)	2 (9.1)	0	0
COVID-19	102 (12.8)	9 (14.8)	2 (16.7)	0	30 (10.6)	4 (18.2)	0	0
Contusion	11 (1.4)	2 (3.3)	1 (8.3)	0	2 (0.7)	0	0	0
Hypokalaemia	2 (0.3)	2 (3.3)	0	0	0	0	0	0
Arthralgia*	17 (2.1)	3 (4.9)	0	0	6 (2.1)	1 (4.5)	0	0
Intervertebral disc degeneration	0	2 (3.3)	0	0	0	0	0	0
Back pain	16 (2.0)	3 (4.9)	1 (8.3)	0	2 (0.7)	0	0	0
Headache	48 (6.0)	3 (4.9)	0	0	19 (6.7)	0	0	0
Urticaria	21 (2.6)	6 (9.8)	0	0	12 (4.3)	3 (13.6)	0	0
Eczema	11 (1.4)	3 (4.9)	1 (8.3)	0	3 (1.1)	0	0	0
Bronchitis	12 (1.5)	1 (1.6)	2 (16.7)	0	3 (1.1)	0	0	0

Neutropenia	7 (0.9)	2 (3.3)	0	0	1(0.4)	0	0	0
Large intestine polyp	0	2 (3.3)	0	0	0	0	0	0
Urinary tract infection**	27 (3.4)	3(4.9)	2(16.7)	0	8 (2.8)	0	0	0
Upper respiratory tract infection	43 (5.4)	2 (3.3)	0	0	6 (2.1)	0	0	0
Procedural pain	1 (0.1)	2 (3.3)	0	0	0	0	0	0
Cough***	19 (2.4)	2 (3.3)	0	0	5 (1.8)	0	0	0

A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
*Arthralgia: two events occurred in one patient.
**Urinary tract infection: two events of occurred in one patient
***Cough: two events of cough occurred in one patient.
Source: [Responses to D120 Clinical Appendix 5-Table ADAR075 Q158-1.2], [SCS Appendix 1-Table 2.1-1.3p1_s1], [Study A2301-Listing 16.2.7-1], [Study A2302-Listing 16.2.7-1], [Responses to D120 Clinical Appendix 5-Table ADAR075 Q158-1.1, Table ADAR075 Q158-1.3].

Placebo-controlled period

During placebo-controlled period, 8.7% of patients receiving remibrutinib were older than 65 years; the oldest patient in the pivotal studies was 81 years old. Overall, compared to patients under 65 years old, older patients receiving remibrutinib experienced more injury, poisoning and procedural complications (EAIR 37.2 vs 14.2, most commonly contusions), musculoskeletal and connective tissue disorders (EAIR 40.1 vs 19.1, most commonly back pain), metabolism and nutrition disorders (EAIR 17.9 vs 12.9, most commonly hypokalaemia) and ear and labyrinth disorders (EAIR 8.7 vs 3.3, most commonly vertigo).

Entire study period

The AEs reported in the any remibrutinib 25 mg b.i.d. group during the entire study period (total PY 58.9) were similar to those reported during the placebo-controlled period. There was no increase in EAIRs in Pool 1 during the entire study period vs. the placebo-controlled period.

- Gender

Within Pool 1, about 66% of patients were female. With respect to gender, skin and subcutaneous tissue disorders were more common in females in both treatment groups. Blood and lymphatic system disorders were also more common in females in both treatment group, mostly due to PTs related to anaemia. Cytopenias were reported almost exclusively in female patients receiving remibrutinib.

- Ethnicity and race

Pivotal studies included about 85% of participants of not Hispanic or Latino ethnicity and about 55% of White and 37% of Asian race. With respect to ethnicity, patients of Hispanic or Latino ethnicity reported somewhat more metabolism and nutrition disorders, and nervous system disorders. No significant differences were observed with respect to White and Asian race (the number of patients in other race categories was too small to draw firm conclusions).

Impaired hepatic function

The impact of the severity of hepatic impairment on the exposure of remibrutinib was evaluated in Study A2101. This phase 1, open label study assessed the PK, safety, and tolerability of multiple-dose remibrutinib in patients with varying degrees of impaired hepatic function, covering the 3 Child-Pugh

categories: mild (N=8), moderate (N=8) and severe hepatic impairment (N=7). These patients were compared to matched healthy volunteers (N=15). All participants received 25 mg remibrutinib b.i.d. orally under fasting conditions on Days 1 and 2, and a morning oral dose of 25 mg remibrutinib on Day 3.

There were no deaths, no SAEs, and no participants discontinued due to AEs in this study. There were no participants with severe HI who reported TEAEs.

A total of 15 TEAEs were reported by 10 (26.3%) participants, including 4 (50.0%) participants with mild HI, 2 (25.0%) participants with moderate HI, and 4 (26.7%) healthy matched control participants. Of those TEAEs, 12 were mild (Grade 1) in severity, 3 were moderate (Grade 2, leukocyturia in 1 participant with mild HI and nausea and vomiting in 1 healthy matched control participant) in severity. The most common TEAE was headache, reported by 3 (7.9%) participants overall. All AEs by PT occurred in only 1 patient in a cohort. There were no treatment-related AEs or SAEs reported, and no clinically notable trends and no signal of liver toxicity across all degrees of hepatic impairment.

Impaired renal function

Remibrutinib excretion in urine is negligible and, therefore, no dedicated study to assess the impact of renal impairment on remibrutinib exposure was conducted (as agreed in consultation with the FDA and EMA). No dose adjustment is needed in patients with renal impairment.

Use in Pregnancy and Lactation

Remibrutinib induced fetal external malformations in pregnant rabbits at doses ≥ 300 mg/kg/day. See section 4. Non-clinical aspects for further details.

Overall, as of the cut-off date of 04-Aug-2025, a total of 19 pregnancies were reported, with the following outcomes:

- 6 full-term deliveries of normal newborns
- 1 spontaneous abortion in Study A2301 – a patient (30-35 years old) who was on oral contraceptives became pregnant on an unspecified date while receiving remibrutinib and had spontaneous abortion after initiation of remibrutinib. The event was reported as not related to study treatment considering risk factors such as overweight and use of oral contraceptives as per the investigator
- 4 elective terminations
- 2 lost to follow-up (the patients withdrew their consent)
- 6 pregnancies still ongoing with no outcomes yet available.

As required by study protocols, study treatment was discontinued when pregnancy was discovered.

It is not known if remibrutinib is transferred into human milk after administration. There are no data on the effects of remibrutinib on the breastfed child or on milk production.

Overdose

Based on preclinical data, it is concluded that remibrutinib has a low potential to cause acute toxicity (e.g., in case of accidental overdosing), due to low solubility and under-proportional exposure increases at doses >100 mg b.i.d. There is no experience with overdose in clinical trials with remibrutinib. Doses up to 600 mg per day were well tolerated in clinical trials with no evidence of dose-limiting AEs. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

Withdrawal and rebound

One patient in the placebo – remibrutinib group reported CSU-related SAEs and severe AEs of angioedema and urticarial chronic (0.7%) during follow-up period. Due to the limited number of patients who continued the treatment-free follow-up period (as most of the patients rolled over the extension study with no treatment-free follow-up period), the withdrawal and rebound profile of remibrutinib could not be fully characterised.

Ability to drive or operate machinery

The incidence of dizziness, fatigue, syncope, somnolence, impaired ability to use machinery, and impaired driving ability was low and similar in the treatment arms. All of the events were mild or moderate in severity; none were severe. During the entire study period, the frequency and severity of these events remained stable, with no concerns with longer treatment exposure. Additionally, preclinical findings support no expected impact on mental ability or ability to drive. These data suggest that remibrutinib is not expected to have an effect on ability to drive or operative machinery.

5.4.7. Immunological events

Not applicable.

5.4.8. Safety related to drug-drug interactions and other interactions

5.4.8.1. Vaccination immune response study

The purpose of Study F12101 was to assess the impact of concomitant or interrupted remibrutinib dosing on the immune response following administration of three different vaccines: a T cell-dependent (quadrivalent seasonal Influenza vaccine), a T cell-independent 23-valent pneumococcal polysaccharide vaccine (PPV-23, Pneumovax 23), and a T cell-dependent neoantigen vaccine (keyhole Limpet hemocyanin (KLH), Immucothel). The study consisted of a 28-day screening period, a 43-day treatment period, followed by a Study Completion evaluation (Day 57) within 2 weeks after last study drug administration. All participants were administered the 3 vaccines on Day 15. A safety follow-up call was performed approximately 30 days after the last study drug administration (Day 72).

The overall incidence of AEs was similar across the remibrutinib and placebo groups (86.3% for pooled remibrutinib group vs. 82.4% for placebo). The AE incidence was also comparable between the interrupted and concomitant remibrutinib groups (88.6% vs. 84.2%). The majority of SOCs showed comparable frequencies across the treatment groups. SOCs showing a numerical difference of $\geq$ 5% between the remibrutinib and placebo groups were General disorders and administration site conditions, Injury, poisoning and procedural complications, Nervous disorders and Gastrointestinal disorders. By PT, injection site reaction, injection related reaction, blood CPK increased and dizziness were numerically more frequent in interrupted remibrutinib group compared with the concomitant remibrutinib and placebo groups. Cough and COVID-19 were slightly more frequent in the concomitant remibrutinib group compared with the interrupted remibrutinib and placebo groups yet overall reported in a small number of participants in any treatment group. Headache was similarly more frequent in both remibrutinib groups compared with the placebo group. Rhinitis was reported only in the placebo group.

The majority of AEs were Grade 1 (83.2%) or Grade 2 (14.0%) (based on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials). A small and comparable number of participants in the remibrutinib and placebo groups had Grade 3 AEs (n=4, 11.4% in interrupted remibrutinib group; n=2, 5.9% in placebo group). One (2.6%) participant in the

concomitant remibrutinib group had a Grade 4 AE; this was a blood creatine phosphokinase (CPK) elevation in a participant with elevated baseline levels of CPK, considered by the investigator to be unrelated to remibrutinib, and resolved within 6 days after onset.

AEs led to discontinuation in a higher number of participants treated with remibrutinib (n=6, 8.2% in pooled remibrutinib group, of which 5 (13.2%) were in the concomitant remibrutinib group) compared with the placebo group (n=2, 5.9%). All except 2 of the AEs leading to discontinuation (rash maculopapular in concomitant remibrutinib and drug eruption in placebo group) were considered not related to study drug (remibrutinib/placebo).

There were no meaningful changes from baseline in vital signs or laboratory parameters in any treatment group throughout the study.

AESI

The overall incidence of infections and infestations (SOC) was similar between pooled remibrutinib group (19.2%) and placebo group (17.6%), although there was a numerically higher incidence in the concomitant remibrutinib group compared to the interrupted remibrutinib group (23.7% vs. 14.3%).

Bleeding AEs (all events were part of Hemorrhages broad SMQ) were reported in 3 participants each in the concomitant remibrutinib group (7.9%) and the placebo group (8.8%). None of the events led to treatment discontinuation.

No cytopenias AEs were reported in this study.

5.4.9. Vital signs and laboratory findings

- Haematology

In the remibrutinib 25 mg b.i.d. group, a downward shift in median neutrophil counts (from 4.00 x 10^9 cells/L at baseline to 3.75 x 10^9 cell/L at Week 2) and platelet counts (from 272 x10^9 cells/L at baseline to 243 x10^9 cells/L at Week 2) was observed compared to the placebo group, where values remained similar to baseline; importantly, median levels remained stable throughout the rest of study treatment and within the normal ranges. Median levels returned to baseline levels upon treatment cessation as observed at the end-of-study visit (safety follow-up, 4 weeks after last dose).

- Chemistry

There was a numerical imbalance between the treatment groups for Grade 3 and 4 lipase and amylase. None of the patients with Grade 3 or 4 lipase or amylase reported pancreatitis or related symptoms.

- IgM and IgG levels

In patients with normal IgG/IgM baseline values, in the remibrutinib 25 mg b.i.d. group, notable decreases below 3.0 g/L for IgG were seen in 1 patient and below 0.3 g/L for IgM were seen in 6 patients. No patients had IgG and IgM concurrently decreased. For all patients with IgG below 3.0 g/L and/or IgM below 0.3 g/L, 2 reported concurrent infections AESI (COVID-19 and ear infection, both non-serious, mild, recovered). In the placebo group with normal IgG/IgM baseline values, the decrease below 0.3 g/L for IgM was seen in 2 patients. One patient had a concurrent COVID-19 infection at the time of the decrease (non-serious, mild, recovered). No patient in the placebo group had IgG below 3.0 g/L.

During entire study period, there were 15 additional patients with IgM below 0.3 g/L, two patients reported concurrent infections: pharyngitis, and upper respiratory tract infection (all non-serious, mild, and recovered). None lead to treatment interruption or discontinuation and recovered in 6 days and in

3 days respectively. No IgG below 3.0 g/L was reported after the placebo-controlled period.

- Liver enzymes

During pivotal studies (entire study period) no Hy's Law cases were reported.

Newly occurring liver enzyme abnormalities, primarily represented by asymptomatic isolated liver transaminase (i.e., ALT and/or AST without concurrent increase of bilirubin) elevations, were infrequent and transient, and balanced between the remibrutinib and placebo groups. Most of the ALT liver enzymes elevations were between 3x and <5x ULN (i.e., CTCAE Grade 2), 6/8 patients in the remibrutinib 25 g b.i.d. group and 4/4 patients in the placebo group. Two patients in remibrutinib 25 mg b.i.d. group had ALT elevations >5x ULN.

Vital signs

- Blood pressure

Reference is made to Section 5.4.4.

Electrocardiogram

Reference is made to Section 5.4.4.

5.4.10. Post-marketing experience

Not applicable.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

Safety data from 5 completed studies in patients with CSU were submitted, and consisted of 1234 adult patients with CSU, treated with remibrutinib at doses ranging from 10 mg q.d. to 100 mg b.i.d., including 1172 patients treated with remibrutinib at 25 mg b.i.d. or 100 mg b.i.d. The safety analysis was performed in two pools.

The key safety evaluation of remibrutinib 25 mg b.i.d. was based on Pool 1, which included 868 adult patients with CSU (from the two pivotal studies), treated with remibrutinib 25 mg b.i.d for at least 6 months (772 patients) or for at least one year (438 patients). In total, the pivotal data represent 671.55 patient-years of exposure to remibrutinib 25 mg twice daily. Data from all phase 2 and phase 3 studies (Pool 2) provide a total exposure of 751.47 patient-years for remibrutinib 25 mg twice daily, and 971.94 patient-years for any dose of remibrutinib. Additional safety data were collected in specific clinical situations, i.e. patients with hepatic impairment (Study A2101), vaccination immune response study (Study F12101), and potential effect on hypertension was examined in a separate Study A2305. Any exposure during pregnancy was collected in the Novartis Safety Database (up to 04-Aug-2024) from ongoing CSU and non-CSU clinical studies of remibrutinib. Pooling strategies and collection of safety data were considered acceptable by the CHMP.

The percentage of patients who discontinued during the placebo-controlled period was low and comparable between groups (12.7% vs 14.4%, respectively). The majority of discontinuations occurred within the first 12 weeks of the study, and discontinuations due to adverse events were

relatively rare in both groups (about 3%). Over the entire study period, about 20% of participants discontinued, with AEs accounting for about 4% of discontinuations. Treatment interruptions were also relatively rare (about 8-9%), and TEAEs leading to study drug discontinuations or interruptions were generally consistent with the expected safety profile of remibrutinib and predefined AESIs, including bleeding related AEs, and infections and infestations.

Overall, the safety database is considered sufficiently large to assess the safety of remibrutinib in the target population. The extent of exposure and duration of follow-up meet current ICH E1 guideline requirements (CPMP/ICH/375/95) and are deemed adequate for the intended use of the product. The demographic and baseline disease characteristics are representative of the intended adult population with moderate to severe CSU.

AEs

In placebo-controlled period of studies in Pool 1, the most frequently reported AEs by SOC (occurring in ≥ 10% of patients in either group) for the remibrutinib 25 mg b.i.d. and placebo groups, respectively, were infections and infestations (33.3% vs. 34.0%), skin and subcutaneous tissue disorders (16.5% vs. 14.4%), gastrointestinal disorders (11.4% vs. 10.5%), and investigations (11.2% vs. 13.1%). The incidence of AEs was higher (≥ 2% of patient's difference) in the remibrutinib 25 mg b.i.d. vs. the placebo group for the SOCs of skin and subcutaneous tissue disorders (16.5% vs. 14.4%), musculoskeletal and connective tissue disorders (8.7% vs. 6.2%), and injury, poisoning and procedural complications (6.8% vs. 3.9%). This was mostly driven by the following PTs: contusion, petechiae, ecchymosis, purpura, and back pain. Results were similar for the entire study period of studies in Pool 1 as well as studies in Pool 2.

In placebo-controlled period of studies in Pool 1, the most frequently reported AEs by SMQs (≥ 5% of patients in either group) for the remibrutinib 25 mg b.i.d. and placebo groups, respectively, were COVID-19 (12.2% vs. 13.1%), hemorrhages (9.2% vs. 3.3%), gastrointestinal nonspecific inflammation and dysfunctional conditions (9.1% vs. 8.8%), gastrointestinal nonspecific symptoms and therapeutic procedures (7.8% vs. 6.5%), hypersensitivity (7.6% vs. 9.8%), accidents and injuries (5.8% vs. 2.3%), and angioedema (3.8% vs. 5.6%). The percentages of patients with AEs in SMQ accidents and injuries and SMQ hemorrhages were numerically higher in the remibrutinib 25 mg b.i.d. This is mostly due to cutaneous bleeding events that are adequately described in section 4.8 of the SmPC. Furthermore, some additional bleedings in relation to menstrual disorders (e.g. heavy menstrual bleeding, intermenstrual bleeding) were observed. However, there is insufficient evidence to currently firmly establish causal relationship with remibrutinib, and therefore, are not listed in section 4.8 of the SmPC. Results were similar for the entire study period of studies in Pool 1 as well as studies in Pool 2.

The PTs occurring more frequently in the remibrutinib 25 mg b.i.d. vs. the placebo group were the following: nasopharyngitis, headache, petechiae, and urinary tract infection. The most frequently reported AEs by PT (≥ 3% of patients) in the remibrutinib 25 mg b.i.d. group, in the entire study period, were COVID-19 (15.5%), nasopharyngitis (9.1%), headache (7.8%), upper respiratory tract infection (5.6%), petechiae (4.0%), urinary tract infection (4.6%), urticaria (3.3%), cough (3.1%), nausea (3.1%), and influenza (3.0%).

The safety profile of Remibrutinib is mainly based on data from safety Pool 1 where patients received Remibrutinib 25mg b.i.d. Data from safety pool 2, included all patients treated with Remibrutinib at any dose. Therefore, data from safety pool 2 are only considered supportive, and the safety profile studied and developed in the SmPC is at the approved dose of 25 mg b.i.d for CSU. There is not enough data to conclude on higher doses such as 100 mg b.i.d.

Considering CSU indication and taking into account known remibrutinib risks, such as bleedings, with currently limited safety data available regarding higher exposures with longer duration, it cannot be concluded that benefit-risk in that instances is favourable.

ADRs

The most frequently reported related events in the remibrutinib 25 mg b.i.d. group, in placebo-controlled period of studies in Pool 1, were petechiae, headache, nausea, and ecchymosis. Those events are included in section 4.8 of the SmPC.

In the entire study period in studies in Pool 1, nasopharyngitis and contusion, in addition to above mentioned events in placebo-controlled period, were commonly assessed as related by investigators. Those are listed ADRs in SmPC. In studies in Pool 2, diarrhoea was also frequently assessed as related.

Based on reporting differences between remibrutinib and placebo, as well as cases assessed as related or cases with positive dechallenge, the Applicant was requested, upon assessment, to include the following events as ADRs in section 4.8 of the SmPC: pyrexia, back pain, abdominal pain, herpes virus infection, headache, nausea and haematuria.

In addition, fatigue/ asthenia, arthralgia, hyperuricemia, vomiting, diarrhoea, constipation, dyspepsia, bronchitis, urinary tract infections, pneumonia, lower respiratory tract infections, skin infections, thrombocytopenia, neutropenia, anaemia, and hypertension were also considered for inclusion in the section 4.8 of the SmPC. Currently, no conclusion could be drawn on the association of these events with remibrutinib, and hence, they are not listed in section 4.8 of the SmPC.

AESI

Infection, bleeding, and cytopenia were chosen as AESIs. Those are known risks of approved BTK inhibitors. Cardiac arrhythmias and hypertension were followed as additional safety topics.

Infection AESIs

In the placebo-controlled period of studies in Pool 1, the percentages of patients with infection AESIs in the remibrutinib 25 mg b.i.d. and placebo groups were comparable, 33.5% vs. 34.3%, respectively. Serious and severe infections, as well as treatment discontinuations due to infections, were reported at comparable rates in both groups. Serious Infection AESIs were reported in 5 patients in the remibrutinib 25 mg b.i.d. group (appendicitis, COVID-19, gastrointestinal infection, wound abscess, and food poisoning)**.** The most frequently reported PTs (in $\geq$ 3% of patients in either group) were nasopharyngitis (6.6% vs. 4.6%), upper respiratory tract infection (3.0% vs. 2.0%), urinary tract infection (3.1% vs. 2.6%), and COVID-19 (10.7% vs. 11.4%). By pathogen, viral infections were the most common. Upper respiratory tract infections represent the most frequent ADRs and are adequately presented in section 4.8 of the SmPC.

Bleeding AESIs

In the placebo-controlled period of studies in Pool 1, the percentages of patients with bleeding AESIs were more common with remibrutinib 25 mg b.i.d. compared to placebo, 10.6% vs. 5.2%, respectively.

The following bleeding events were most frequently reported: petechiae (23 in remibrutinib group vs. 1 in placebo group), contusion (14 vs. 2), ecchymosis (9 vs. 1), epistaxis (5 vs. 1), purpura (5 vs. 0), haematuria (6 vs. 1), conjunctival bleeding (2 vs. 0), gingival bleeding (1 vs. 0). All those events are listed in the ADR table in section 4.8 of the SmPC.

The majority of Bleeding AESIs in the remibrutinib 25 mg b.i.d. group (67.0% of events) were considered related to study treatment versus 20.0 % of events in the placebo group. No action was

taken with study treatment for most of the events of Bleeding AESIs (87.0% vs. 90.0% of events in the remibrutinib 25 mg b.i.d. and placebo groups, respectively), although study treatment was interrupted for 9.6% vs. 10.0% of the events. Observations on the risk for bleeding were consistent with the understanding of the effect of remibrutinib on platelet function.

The Applicant was requested to include a warning regarding bleeding in section 4.4, together with information if treatment need to be interrupted if bleeding is observed or if surgery is planned (withholding remibrutinib 3 to 7 days before and after surgery should be considered), as well as precautions needed if antithrombotic agents or anticoagulants are used concomitantly.

Cytopenia AESIs

In the placebo-controlled period of studies in Pool 1, the overall percentages of patients with cytopenia AESIs were higher in the remibrutinib 25 mg b.i.d. than placebo group, 3.6% (22 patients) vs. 2.0% (6 patients), respectively. The majority of events were related to neutropenia (7 patients (1.2%) in the remibrutinib 25 mg b.i.d. group vs. 1 patient (0.3%) in the placebo group) and neutrophil count decreased (2 (0.3%) vs. 0), followed by leukocyte count decreases - WBC count decreased (3 (0.5%) vs. 0) and leukopenia (3 (0.5%) vs 0). Of those, 31.3% of events in remibrutinib 25 mg b.i.d. group was considered related. Taking into account remibrutinib 25 mg b.i.d. group in studies in Pool 2, neutropenia was reported in 11 patients (1.1%), neutrophil count decreased in 8 patients (0.8%), leukopenia in 6 patients (0.6%), and WBC count decreased in 6 patients (0.6%).

Cardiac arrhythmias

For Pool 1 during the placebo-controlled period, 10 patients (1.7%) vs. 4 patients (1.3%) in the remibrutinib 25 mg b.i.d. and placebo groups, respectively, had at least 1 AE in the SMQ Cardiac arrythmias. The most frequent events occurred in both groups and included conduction defects (SMQ) (1.0% vs. 0.7%), disorders of the sinus node function (SMQ) (0.5% vs. 0.3%) and tachyarrhythmias (SMQ) (0.5% vs. 0.7%). Low number of patients had events under SMQ Cardiac arrhythmias and so far, no safety concerns have been identified. No atrial fibrillation AE was reported under the Tachyarrythmias SMQ.

Hypertension

In the placebo-controlled period of studies in Pool 1, the incidence of SMQ Hypertension cases was higher in remibrutinib than placebo group (9 (1.5) vs. 2 (0.7%)). However, the incidence of high blood pressure (SBP ≥ 140 mmHg), during evaluation of vital signs, was comparable between remibrutinib and placebo (12.3% vs. 14.9%) and was similar to placebo (for 24 weeks) during the 52 weeks duration (14.2%).

No clinically relevant effect of remibrutinib on blood pressure was noted in Study A2305 that investigated effects of remibrutinib 25 mg b.i.d. open-label on SBP measured as a change in 24-hour weighted average SBP from baseline to Week 4 assessed by ambulatory blood pressure monitoring.

While no major safety concerns related to cardiac arrhythmias or hypertension were identified, it is important to note that the majority of the study population was under 65 years of age.

Serious adverse events

In Pool 1, during the placebo-controlled period, 20 patients in remibrutinib group experienced SAEs. Although each patient might have had more than one SAE, none of them were reported in more than one patient. None of them were assessed as related to study treatment by the investigator.

After completion of placebo-controlled period, additional SAEs were reported. None of them were assessed as related to study treatment by the investigator.

Taking into account Pool 2, 1 SAE of renal abscess (remibrutinib 25 mg b.i.d.) and 1 SAE of CSU (remibrutinib 10 mg b.i.d.) were assessed as related by the investigator, and both led to study treatment discontinuation. In addition, one notable bleeding event, an SAE of moderate melaena (after bariatric surgery), was reported and assessed as not related to remibrutinib.

Neoplasms

A significant imbalance in neoplasm incidence rates was observed between the remibrutinib and placebo groups (remibrutinib 1.5%, EAIR: 3.4 vs. placebo 0.7%, EAIR: 1.5).

Overall, five tumours were reported during entire study period in patients exposed to remibrutinib (vs one breast cancer in placebo group). Three of them were finally classified as malignant - appendiceal mucinous neoplasm (LAMN), duodenal adenocarcinoma, and metastatic pancreatic carcinoma. One event was benign leiomyoma of oesophagus. No conclusion was possible in a case of patient reported with GIST and large intestinal polyp. It is noteworthy that all malignant neoplasms occurred in gastrointestinal tract. Except the relatively more common pancreatic carcinoma (IR 13.8 per 100,000), reported malignant tumours are among rare tumours and it is not expected to observe several such tumours in relatively young patients and quite small population. Literature data indicate following incidence rates regarding observed tumours: mucinous adenocarcinoma of appendix 0.32 per 100 000 person-years, stomach GIST 0.62 per 100 000 person-years, small intestine adenocarcinoma 2.6 per 100,000 per years. Except for a single case of breast cancer in the placebo group, no other common tumours were reported during the pivotal studies, which would have been less unexpected. Also, no events of cancers usually associated with BTK inhibitors use were reported.

In the study Pool 3 (exposure 2342.4 p-y), 52 neoplasms were reported, 16 were classified as malignant/unspecified of which 7 (43,8%) were located in the GI tract. For patients exposed to remibrutinib in the Pool 3, the number of incident neoplasm diagnoses, both overall (malignant or benign) and malignant only, was compatible with the number expected based on the background rates in the general population, according to the 2021 Global Burden of Disease (GBD) Study data. Acknowledging the obvious limitations in the interpretation of the Pool 3 data (the relatively limited exposure, short follow-up, and lack of a control group), it nevertheless remains worrisome that nearly half of the malignant or unspecified neoplasms were located in the gastrointestinal tract (GI cancers account for about a quarter of global cancer incidence). Notably, all but pancreatic cancer occurred within the GI tract, and several cases represent rare cancer types.

At this point, the overall safety database is considered too limited in both the number of exposed patients and the duration of follow-up to allow confident conclusions or clear characterisation of a potential risk of neoplasms. Considering the observed imbalances in adverse events within the SOC Neoplasms for remibrutinib vs placebo in pivotal studies, and the reports of several rare and unexpected GI tumours in patients exposed to remibrutinib malignancies are included as important potential risk in RMP and will be followed up in the ongoing extension study for remibrutinib.

Subgroups

During placebo-controlled period, 8.7% of patients receiving remibrutinib were older than 65 years; the oldest patient in the pivotal studies was 81 years old. Although, the number of patients ≥ 65 years treated with remibrutinib is limited and no patients were included in the subgroup ≥ 85 years, based on PK data, safety data and information approved for BTK inhibitors no dose adjustment is required based on age. This is adequately reflected in the SmPC.

With respect to gender, cytopenias were reported almost exclusively in female patients receiving remibrutinib, females also reported more skin and subcutaneous tissue disorders, and males reported nervous system disorder.

No significant differences in the safety profile of remibrutinib were observed with respect to White and Asian race (the number of patients in other race categories was too small to draw firm conclusions).

Hepatic and renal impairment

In the study A2101 the administration of multiple oral doses of remibrutinib 25 mg b.i.d. was well-tolerated in participants across all degrees of hepatic impairment, including those with severe hepatic impairment. No trends were observed in number or severity of AEs in relation to severity of hepatic impairment, however it should be noted that the number of participants in each category was very small (n=7). Additionally, patients with pre-existing hepatic disease were excluded from pivotal studies, therefore the safety of remibrutinib in those patients remains uncertain.

Regarding dose recommendations in patients with hepatic impairment, please refer to Clinical pharmacology section.

Remibrutinib excretion in urine is negligible and the pop-PK analysis, which included patients with mild to moderate renal impairment and PK modelling data in patients with severe renal impairment, confirmed that renal function does not have an effect on remibrutinib exposure. No dose adjustment is needed.

Rebound

One event of rebound was reported, however due to the limited number of patients who continued the treatment-free follow-up period, the withdrawal and rebound profile of remibrutinib could not be fully characterised.

Overdose, abuse potential, impact on ability to drive or operate machinery

There is no experience with overdose in clinical trials with remibrutinib. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. No abuse potential or impact on ability to drive or operate machinery is anticipated for remibrutinib.

Pregnancy and lactation

Overall, as of the cut-off date of 04-Aug-2025, a total of 19 pregnancies were reported. Human data regarding pregnancies are lacking, however, remibrutinib induced foetal external malformations in pregnant rabbits at doses ≥ 300 mg/kg/day. See section 4. Non-clinical aspects for further details. Therefore, standard statements in accordance with The Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling (EMEA/CHMP/203927/2005), are included in the section 4.6 of the SmPC.

There are no data on the remibrutinib excretion in milk, its effects on the breastfed child or on milk production.

Vaccination

The safety profile of remibrutinib in healthy participants who received vaccination (Influenza, Pneumovax 23 and Immucothel vaccine) and concomitant or interrupted remibrutinib 100 mg b.i.d. dosing for 42 days was in general consistent with results from pivotal remibrutinib clinical studies and comparable to participants receiving placebo. See section 5.2 Clinical pharmacology for further details.

Laboratory findings

There was no clinically meaningful change from baseline in haematology and coagulation parameters. A downward shift in median neutrophil counts and platelet counts was observed compared to the placebo group, however median levels remained stable throughout the rest of study treatment and

within the normal ranges. No safety concerns for renal toxicity based on urinalysis results were observed.

No significant changes were observed in chemistry parameters, except more frequent Grade 4 increases in amylase and lipase in remibrutinib group during placebo-controlled period, reported in 6 patients receiving remibrutinib. Except for one patient with aggravated abdominal pain, all cases were asymptomatic, transient, and unrelated to pancreatitis. Four patients had elevated baseline values, and all had confounding comorbidities (five overweight or obese, one with hyperlipidaemia, and one using venlafaxine). No discontinuations occurred; one case required a temporary 1-day interruption with subsequent normalisation. Overall, these enzyme elevations were isolated, non-clinically relevant findings without current evidence of a drug-related safety signal.

Mild to moderate liver enzyme elevations (ALT or AST >3×ULN) were observed in a small proportion of patients (about 1% in each treatment group). However, ALT or AST >5x, 8x, or 10xULN occurred only in remibrutinib group, each occurring in 1-2 patients. Overall, liver enzyme and bilirubin elevations were uncommon, generally mild, and no cases suggestive of severe drug-induced liver injury (Hy's Law) were identified in either group.

Vital signs, ECG

There were no notable findings in the analysis of vital signs (pulse rate, SBP, DBP) in the placebo-controlled period and the entire period. Additionally, in a separate dedicated Study 2305, no clinically relevant effect of remibrutinib on blood pressure was observed.

There were no notable findings in the analysis of ECGs, and no clinically relevant QTc or QRS prolongation for the remibrutinib 25 mg b.i.d. group. Also, no safety concern with remibrutinib was identified in the analysis of AEs reported under SMQ Cardiac arrhythmias.

5.4.11.1.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 5.4.3.1 above.

The inclusion of proposed ADRs in section 4.8 of SmPC by the applicant was agreed by the CHMP. However, criteria for selection of ADRs were not completely acceptable. The Applicant has only taken into account AEs from placebo-controlled part of studies, medical evaluation was not presented into detail, investigator's assessment of causality was often absent, and therefore it couldn't be determined with certainty if every single event with a reasonable possibility was taken into account and which were the reasons why some events were not included particularly if there was a plausible mechanism (e.g. absence of statistical hit as stated by the Applicant is not sufficient). Therefore, some additional ADRs were proposed for consideration.

Based on reporting differences between remibrutinib and placebo, as well as cases assessed as related or cases with postive dechallenge, the Applicant was requested to include the following events as ADRs: nausea, headache, pyrexia, back pain, abdominal pain, herpes virus infection, and haematuria.

5.4.11.2. Conclusions on clinical safety

The available data suggest a generally manageable and tolerable safety profile for remibrutinib in the treatment of CSU.

The most frequently reported adverse events are bleedings and infections related events known as ADRs of approved BTK inhibitors. Cardiac arrhythmias, and severe, serious or opportunistic infections have not been identified as safety issues during remibrutinib clinical studies.

Since only a limited number of patients received remibrutinib for > 52 weeks, the safety profile of remibrutinib needs to be further characterised on the long-term use, data will be collected in study CLOU064A2303B.

The risk of malignany will also need to be further characterised, considering the seriousness and severity of this risk and the non-life-threatening target indication as well as taking into account that malignancies are included in safety specification of majority of BTK inhibitors. This risk is included as an important potential risk in the RMP and will be followed up in the post marketing setting in Study CLOU064A2303B.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 69: Summary of safety concerns in the proposed RMP

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

6.1.2. Discussion on proposed safety specification

The Applicant did not propose important identified risk to be included in safety specification which is agreed.
Regarding *Infections,* the Applicant states that *Infections* are considered as non-important identified risks and all events observed to date with remibrutinib have been assessed as not affecting the benefit-risk profile and no additional risk minimisation measures are deemed necessary. Taking into account the following: Infection AESI rates observed with remibrutinib were comparable to those with placebo, and no increase in the incidence of infections with long-term treatment was seen; serious infections were uncommon and rates were comparable between the remibrutinib and placebo groups; no opportunistic infections were reported and there was no evidence of risk of lower respiratory tract infections, herpes infections, or skin infections; no correlation was noted with neutrophil counts, no Hepatitis B reactivation was reported; no special monitoring is required and no warning is needed to be included in section 4.4., it is agreed with the Applicant that Infections do not need to be included in safety specification of the RMP as important identified risk. Instead, Infections should be monitored/followed as risk in PSURs.

The important potential risks proposed by the applicant: serious bleeding events, teratogenicity and malignancies are endorsed.

The potential mechanism of action (effect on platelets function based on pre-clinical evidence of bleeding) justifies the classification of serious bleeding as an important potential risk.
Pre-clinical evidence showed 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 twice daily based on AUC0-24h). Considering the clinical significance of the risk of teratogenicity in the general population, including in patients with CSU (predominantly young, female patients), the risk is classified as an important potential risk.
At CHMP request, the applicant included malignancies as an important potential risk (see section 5.4.11 for further details).

It is agreed to include long-term safety as missing information since number of patients who received remibrutinib for > 52 weeks is limited and it is important to determine whether there are new safety findings or known safety findings which worsen in severity after long-term treatment.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

The Applicant did not propose any routine pharmacovigilance activities beyond ADRs reporting and signal detection.

The Applicant has proposed the following additional pharmacovigilance activities:

Table 70: 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 authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
[Study CLOU064A2303B] A multicenter, double-blind, placebo-controlled, randomised 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

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond ADRs reporting and signal detection are considered necessary.

6.2.2.2. Additional pharmacovigilance activities

The Applicant proposes an ongoing open label extension study CLOU064A2303B as additional pharmacovigilance activity to study the important potential risk "Serious bleeding events" and missing information "Long-term safety". As requested by the CHMP, the study CLOU064A2303B has also been added to address the important potential risk "Malignancies" in the PhV plan.

The ongoing long-term extension study CLOU064A2303B is considered appropriate to further address the important potential risks Serious bleeding events and Malignancies and missing information Long-term safety in the pharmacovigilance plan. The selected safety monitoring assessments including laboratory assessments covering clinical safety laboratory tests, clinical and physical assessments, ECG monitoring and general AE assessment are well-established standard measures for close monitoring of

safety of the drug. The categorisation of the study as category 3 study in the pharmacovigilance plan is considered appropriate. As the final study report is foreseen in 2027, submission of interim reports is not considered necessary. The total duration of follow-up for 4 years and collection of AE data is considered sufficient to provide data on long-term safety including risk of malignancies.

There are no additional pharmacovigilance activities for the important potential risk teratogenicity in the agreed PhV plan. The potential risk is mitigated by the risk minimisation activities in the SmPC recommending specific clinical measures to address the risk (sexually active women of childbearing potential must use effective contraception, remibrutinib is not recommended during pregnancy). Routine pharmacovigilance monitoring of teratogenicity in upcoming PSURs is considered sufficient.

6.3. Plans for post-authorisation efficacy studies

Not applicable.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 71: Planned routine risk minimisation measures

Safety concern	Routine risk minimisation 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 minimisation 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 minimisation 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 minimisation activities recommending specific clinical measures to address the risk:**

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

The Applicant did not propose any additional risk minimisation measures.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The Applicant proposes routine risk minimisation activities recommending specific clinical measures to address the potential risks serious bleeding events (interrupting remibrutinib before and after surgery, co-administration with antithrombotic agents) and teratogenicity (sexually active women of childbearing potential must use effective contraception, remibrutinib is not recommended during pregnancy).

Routine risk minimisation measures are considered sufficient to minimise the risk of the product in the proposed indication.

6.4.2.2. Additional risk minimisation measures

The Applicant did not propose any additional risk minimisation measures. This is considered appropriate.

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

☒The CHMP and PRAC consider that the risk management plan version 1.2 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

☒The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the IBD. The IBD is 30.09.2025.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The approved indication is aligned with the population studied in the pivotal clinical trials.

8.1.2. SmPC section 5.1 justification

Section 5.1 presents the primary and the secondary endpoints of the two pivotal clinical trials. Additionally, the mean change form baseline in UAS7 score up to week 12 is presented as a figure, labelled as observed data.

8.2. Labelling

8.2.1. User consultation

8.2.1.1. Conclusion from the checklist for the review of user consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rhapsido (remibrutinib) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, therapeutic indication

Chronic spontaneous urticaria (CSU) is a skin disease characterised by the spontaneous and recurrent occurrence of itchy wheals (hives), angioedema or both over a period of at least 6 weeks. The pathogenesis is not fully understood. However, it partially depends on the production of autoantibodies that activate inflammatory cells that release histamine and cause symptoms of urticaria. The disease is more common in adults and women and is usually seen between the ages of 30-40. The disease resolves spontaneously, in 30 to 50% of adults by one year. The average duration of the disease is 2-5 years, but in some patients, symptoms may persist for more than five years. CSU affects both objective functioning and subjective well-being.

The agreed indication is: *Rhapsido is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients with inadequate response to H1 antihistamine treatment*.

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 2.1 of this document.

The aim of CSU treatment is to reduce disease activity with completely controlled symptoms (itching and hives) and normalized quality of life. As there is currently no disease-modifying treatment, the standard treatment is symptomatic treatment. The guidelines recommend 4 steps: standard dose of second generation H1-AH (step 1). If symptoms are not adequately controlled, the dose of sg-AH should be increased up to 4-fold after 2 to 4 weeks, although it is not an approved dosage (step 2). Mixing different sg-AHs is not recommended. In case of insufficient control with higher doses of sg-AHs, omalizumab should be added (step 3). The last step is the addition of ciclosporin (off label). Despite these available treatment options, complete disease control is not often observed, so patients who are inadequately treated with sg-H1-AH will require a new treatment.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2 of this document.

The evaluation of efficacy and safety is based on two identical, multicenter, randomised, double-blind, placebo-controlled pivotal studies A2301 and A2302. The studies involved patients with moderate and

severe CSU (baseline UAS7 ≥16) who were inadequately controlled with sg-H1-AH at the approved dose. Remibrutinib treatment (25 mg taken orally twice daily) was added to background therapy (standard dose of sg H1-AH) and compared to a placebo group that received only background therapy for 24 weeks. After 24 weeks, all patients received remibrutinib until week 52. Mixing of different sg H1-AH was frequently used in the studies.

9.3. Favourable effects

Both pivotal studies met their respective primary and all hierarchically tested secondary outcomes.

Primary endpoint: Change from baseline in UAS7 score at Week 12

Study A2301: At Week 12, LS mean absolute change from baseline in UAS7 score in the remibrutinib arm compared to placebo arm was -20.02 vs. -13.79 with a treatment difference in LS means of -6.22 (95% CI: -8.45, -4.00; one-sided p-value < 0.001).

Study A2302: At Week 12, LS mean absolute change from baseline in UAS7 score in the remibrutinib arm compared to placebo arm was -19.41 vs. -11.73 with a treatment difference in LS means of -7.68 (95% CI: -9.91, -5.46; one-sided p-value < 0.001).

Secondary endpoints (type 1 error controlled)

- **Disease activity control (UAS7 ≤ 6) at Week 12**
  Study A2301: 49.8% vs. 24.8%, in the remibrutinib group vs placebo group, with a treatment difference of 25.44% (95% CI: 16.48, 34.39; one-sided p-value < 0.001)
  Study A2302: 46.8% vs. 19.6%, in the remibrutinib group vs placebo group, with a treatment difference of 27.61% (95% CI: 19.14, 36.08; one-sided p-value < 0.001)
- **Complete absence of itch and hives (UAS7 = 0) at Week 12**
  Study A2301: 31.1% vs. 10.5% in the remibrutinib group vs. placebo group, with a treatment difference of 20.55% (95% CI: 13.35, 27.75; one-sided p-value < 0.001)
  Study A2302: 27.9% vs. 6.5% in the remibrutinib group vs. placebo group, with a treatment difference of 21.60% (95% CI: 15.10, 28.10; one-sided p-value < 0.001)
- **Change from baseline in ISS7 score at Week 12**
  Study A2301: -9.52 vs. -6.89 in the remibrutinib group vs. placebo group, with treatment difference in LS means of -2.63 (95% CI: -3.70, -1.56; one-sided p-value < 0.001)
  Study A2302: -8.95 vs. -5.72 in the remibrutinib group vs. placebo group, with a treatment difference in LS means of -3.23 (95% CI: -4.29, -2.16; one-sided p-value < 0.001)
- **Change from baseline in HSS7 score at Week 12**
  Study A2301: -10.47 vs. -6.86 in the remibrutinib group vs. placebo group, with a treatment difference in LS means of -3.61 (95% CI: -4.85, -2.36; one-sided p-value < 0.001)
  Study A2302: -10.47 vs. -6.00 in the remibrutinib group vs. placebo group, with a treatment difference in LS mean of -4.47 (95% CI: -5.71, -3.23; one-sided p-value < 0.001)
- **Early onset of disease activity control (UAS7 ≤ 6) at Week 2**
  Study A2301: 33.7% vs. 3.3% in the remibrutinib group vs. placebo group, with a treatment difference of 30.20% (95% CI: 24.30, 36.10; one-sided p-value < 0.001)
  Study A2302: 30.0% vs. 5.9% in the remibrutinib group vs. placebo group, with a treatment difference of 24.55% (95% CI: 18.31, 30.80; one-sided p-value < 0.001)
- **DLQI = 0-1 at Week 12**
  Study A2301: 39.0% vs. 22.2% in the remibrutinib group vs. placebo group, with a treatment difference of 17.65% (95% CI: 9.14, 26.16; one-sided p-value < 0.001)
  Study A2302: 35.7% vs. 18.3% in the remibrutinib group vs. placebo group, with a treatment difference of 18.21% (95% CI: 9.96, 26.45; one-sided p-value < 0.001)

- **Cumulative number of weeks with disease activity control (UAS7 ≤ 6) up to Week 12**
  Study A2301: 5.17 weeks in the remibrutinib group vs. 1.92 weeks in the placebo group, the mean cumulative number of weeks with disease activity control was 2.69 times (95% CI: 2.01, 3.61; one-sided p-value < 0.001) higher than the placebo group.
  Study A2302: 4.50 weeks in the remibrutinib group vs. 1.38 weeks in the placebo group, the mean cumulative number of weeks with disease activity control was 3.26 times (95% CI: 2.26, 4.71; one-sided p-value < 0.001) higher than the placebo group.
- **Cumulative number of angioedema-free weeks (AAS7 = 0) up to Week 12**
  Study A2301: 8.43 weeks in the remibrutinib group vs. 6.72 weeks in the placebo group, the mean cumulative number of angioedema-free weeks was 1.25 times (95% CI: 1.12, 1.41; one-sided p-value < 0.001) higher than the placebo group.
  Study A2302: 8.81 weeks in the remibrutinib group vs. 6.68 weeks in the placebo group, the mean cumulative number of angioedema-free weeks was 1.32 times (95% CI: 1.17, 1.49; one-sided p-value < 0.001) higher than the placebo group.

9.3.1. Uncertainties and limitations about favourable effects

The scoring for hives used by the Applicant differs from the scoring for hives used in EAACI guidelines. The Applicant was asked to recalculate HSS7 score using the EAACI-recommended method. However, since the raw data only recorded the categorical HSS scores (0–3) rather than the actual number of hives this was not possible. Therefore, the precise extent to which baseline disease severity might have been inflated and the treatment effect overestimated cannot be definitively determined. However, this uncertainty is not considered likely to substantially alter the overall conclusions on efficacy.

A limitation in the study design is the assessment of endpoints at later timepoints after primary evaluation at week 12. Indeed, they were assessed in an exploratory manner, uncontrolled for the type I error and with a more lenient approach to rescue medications. Although the reduction in the weekly intake of rescue medication is larger in remibrutinib compared to placebo arms at week 12, this trend reverses at around week 27 and stays reversed until week 52. Whether these findings could be indicative of reduced remibrutinib over time is not known.

Therefore, although the benefit of remibrutinib over placebo was observed over time, long-term efficacy will need to be further characterised in post-authorisation setting. Considering that a substantial proportion of patients did not achieve disease control (approximately 50%) or complete control (approximately 70%) at weeks 12 and 24, the need to continue treatment should be evaluated individually, and this information is reflected in the PI. Overall, it is acceptable that further long-term efficacy will be collected in post-authorisation setting in Study CLOU064A2303B.

The between-group difference was a UAS7 reduction of -6.22 (95%CI -8.45, -4.00) in A2301 and -7.68 (95%CI -9.91, -5.46) in A2302, which is below the threshold of minimal important difference (MID), albeit the MID of 10 points is defined as a within-patient, rather than a between-group difference. Nevertheless, efficacy was demonstrated (primary and secondary endpoints were statistically significant).

9.4. Unfavourable effects

In total, 715 patients have completed the studies and 438 have been exposed to remibrutinib 25 mg b.i.d. for at least 52 weeks. In total, the pivotal data represent 671.55 patient-years of exposure to remibrutinib 25 mg twice daily.

In placebo-controlled period of the two pivotal studies (Pool 1), the most frequently reported AEs in remibrutinib 25 mg b.i.d. group were the following (by PTs): nasopharyngitis (EAIR difference 4.8), headache (0.2), petechiae (8.2), and urinary tract infection (1.2). The most frequently reported related AEs in the remibrutinib 25 mg b.i.d. group, in placebo-controlled period of studies in Pool 1, were petechiae, headache, nausea, and ecchymosis. The most frequently reported AEs (by PTs) in the remibrutinib 25 mg b.i.d. group in the entire study period were COVID-19 (15.5%), nasopharyngitis (9.1%), headache (7.8%), upper respiratory tract infection (5.6%), petechiae (4.0%), urinary tract infection (4.6%), urticaria (3.3%), cough (3.1%), nausea (3.1%), and influenza (3.0%).

In the placebo-controlled period of studies in Pool 1, the percentages of patients with infection AESIs in the remibrutinib 25 mg b.i.d. and placebo groups were comparable, 33.5% vs. 34.3%, respectively. Serious and severe infections, as well as treatment discontinuations due to infections, were reported at comparable rates in both groups. Upper respiratory tract infections represent the most frequent ADRs and are included in section 4.8 of the SmPC.

The majority of bleeding AESIs in the remibrutinib 25 mg b.i.d. group were considered related to study treatment. These events are reflected in section 4.8 of the SmPC. In addition, a warning regarding bleeding events was added in section 4.4, together with information of treatment interruption if bleeding is observed or if surgery is planned, as well as precautions needed if antithrombotic agents or anticoagulants are used concomitantly. Finally, this risk will be followed up in the ongoing extension study for remibrutinib.

Based on reporting differences between remibrutinib and placebo, as well as cases assessed as related or cases with positive dechallenge, the following events were assessed as ADRs: headache, nausea, pyrexia, back pain, abdominal pain, herpes virus infection, and haematuria, and are included in section 4.8 of the SmPC.

An imbalance in neoplasm incidence rates was observed between the remibrutinib and placebo groups (remibrutinib 1.5%, EAIR: 3.4 vs. placebo 0.7%, EAIR: 1.5) in Pool 1. Several unexpected, rare gastrointestinal tumours were reported in patients exposed to remibrutinib (entire study period): mucinous adenocarcinoma of appendix, pancreatic cancer, small intestine adenocarcinoma, oesophageal leiomyoma, stomach GIST. Malignancies are also safety concern for other BTK inhibitors. Therefore, malignancies are included as important potential risk in RMP and will be followed up in the ongoing extension study CLOU064A2303B for remibrutinib.

9.4.1. Uncertainties and limitations about unfavourable effects

Malignancies are recognised safety concern with other BTK inhibitors. There were no pre-clinical concerns identified for carcinogenicity of remibrutinib, however during pivotal studies, several unexpected and rare malignant gastrointestinal tumours were reported in patients receiving remibrutinib. Although the time to onset of these events relative to first remibrutinib dose was not consistent with a causal relationship, the overall safety database is considered too limited in both the number of exposed patients and the duration of follow-up to allow confident conclusions or clear characterisation of a potential risk of neoplasms. Malignancies are included as important potential risk in RMP and will be followed up in the ongoing extension study for remibrutinib.

Since only a limited number of patients received remibrutinib for > 52 weeks, the safety profile of remibrutinib remains to be further characterised post approval in the long-term setting, data will be collected in study CLOU064A2303B.

9.5. Effects table

Table 72: Effects Table for Rhapsido for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment – Study CLOU064A2301, final database lock 23-Feb-2024; Study CLOU064A2302, final database lock: 14-Feb-2024 (FAS).

Effect	*Short description*	*Unit*	*Treatment REMI 25 mg b.i.d.*	*Control PBO*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable effects						
UAS7	Change from baseline in UAS7 score at Week 12 (PE)	Points	-20.02	-13.79	**SoE:** LS mean difference **-**6.22 (95% CI: -8.45, -4.00; p<0.001) **Unc:** large placebo effect, MID not reached	Study 301
			-19.41	-11.73	**SoE:** LS mean difference -7.68 (95% CI: -9.91, -5.46; p<0.001) **Unc:** large placebo effect, MID not reached	Study 302
UAS7≤6	Disease activity control (UAS7≤6) at Week 12 (SE type 1 error protected)	%	49.8%	24.8%	**SoE:** difference**=** 25.44% (95% CI: 16.48, 34.39; p< 0.001)	Study 301
			46.8%	19.6%	**SoE:** difference **=** 27.61% (95% CI: 19.14, 36.08, p<0.001)	Study 302
UAS7=0	Complete absence of itch and hives (UAS7 = 0) at Week 12 (SE type 1 error protected)	%	31.1%	10.5%	**SoE:** difference **=** 20.55% (95% CI: 13.35, 27.75, p<0.001)	Study 301
			27.9%	6.5%	**SoE:** difference **=** 21.60% (95% CI: 15.10, 28.10, p<0.001)	Study 302
ISS7	Change from baseline in ISS7 score at Week 12 (SE type 1 error protected)	Points	-9.52	-6.89	**SoE:** LS mean difference -2.63 (95% CI: -3.70, -1.56; p<0.001)	Study 301
			-8.95	-5.72	**SoE:** LS means difference -3.23 (95% CI: -4.29, -2.16; p < 0.001)	Study 302
HSS7	Change from baseline in HSS7 score at Week 12 (SE type 1 error protected)	Points	-10.47	-6.86	**SoE:** LS mean difference -3.61 (95% CI: -4.85, -2.36; p<0.001)	Study 301
			-10.47	-6.00	**SoE:** LS mean difference -4.47 (95% CI: -5.71, -3.23; p<0.001)	Study 302
UAS7≤6 at week 2	Early onset of disease activity control (UAS7 ≤6) at Week 2 (SE type 1 error protected)	%	33.7%	3.3%	**SoE:** treatment difference **=** 30.20% (95% CI: 24.30, 36.10; p< 0.001)	Study 301
			30.0%	5.9%	**SoE:** treatment difference **=** 24.55% (95% CI: 18.31, 30.80; p<0.001)	Study 302

Effect	Short description	Unit	Treatment REMI 25 mg b.i.d.	Control PBO	Uncertainties/ Strength of evidence	Ref
DLQI	DLQI = 0-1 at Week 12 (No impact on participants' dermatology quality of life) (SE type 1 error protected)	%	39.0%	22.2%	**SoE:** difference of 17.65% (95% CI: 9.14, 26.16; p< 0.001)	Study 301
			35.7%	18.3%	**SoE:** difference of 18.21% (95% CI: 9.96, 26.45; p< 0.001)	Study 302
UAS7 ≤6	Cumulative number of weeks with disease activity control (UAS7 ≤6) up to Week 12 (SE type 1 error protected)	No. of weeks	5.17	1.92	**SoE:** 2.69 (95% CI: 2.01, 3.61; p< 0.001)	Study 301
			4.50	1.38	**SoC**: 3.26 (95% CI: 2.26, 4.71; p< 0.001)	Study 302
ASS7=0	Cumulative number of angioedema-free weeks (AAS7 = 0) up to Week 12 (SE type 1 error protected)	No. of weeks	8.43	6.72	**SoE:** 1.25 (95% CI: 1.12, 1.41; p< 0.001)	Study 301
			8.81	6.68	**SoE:** 1.32 times (95% CI: 1.17, 1.49; p-value < 0.001)	Study 302
Unfavourable effects						
Upper respiratory tract infections			89 (14.7%)	36 (11.8%)	**SoE:** class effect	Pool 1
Petechiae			23 (3.8%)	1 (0.3%)	**SoE:** class effect	Pool 1
Contusion			14 (2.3%)	2 (0.7%)	**SoE:** class effect	Pool 1
Ecchymosis			9 (1.5%)	1 (0.3%)	**SoE:** class effect	Pool 1

Effect	Short description	Unit	Treatment REMI 25 mg b.i.d.	Control PBO	Uncertainties/ Strength of evidence	Ref
SOC Neoplasm benign, malignant and unspecified (incl. cysts and polyps)			9 (1.5%)	2 (0.7%)	**SoE:** known safety risk with other BTKi, imbalance between REMI and PBO **Unc:** 2 rare tumours reported in remibrutinib group (benign oesophageal leiomyoma, malignant mucinous adenocarcinoma of appendix) vs one breast cancer in PBO group.	Pool 1
- malignancies			1 (0.2%)	1 (0.3%)	3 additional GI malignant or potentially malignant tumours reported during OL period in patients receiving remibrutinib (pancreatic carcinoma, stomach GIST, duodenal adenocarcinoma)	

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; PE: primary endpoint; SE: secondary endpoint; REMI: remibrutinib; b.i.d. twice a day; PBO: placebo; UAS7: Weekly Urticaria Activity Score; HSS7: Weekly Hives Severity Score; ISS7: Weekly Itch Severity Score; DLQI: Dermatology Life Quality Index; PBO: placebo; GI: gastrointestinal; GIST: gastrointestinal stromal tumour; Pool 1: Study 301 and study 302

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The efficacy of remibrutinib 25 mg b.i.d. for the treatment of chronic spontaneous urticaria is based on the two pivotal studies 301 and 302, which demonstrated statistically significant and clinically relevant benefit. Although the between-group difference was a UAS7 reduction of -6.22 (95%CI -8.45, -4.00) in A2301 and -7.68 (95%CI -9.91, -5.46) in A2302, which is below the threshold of MID, the MID of 10 points is defined as a within-patient, rather than a between-group difference. In addition, a notable effect in placebo was observed, likely due to the fluctuating nature of the disease.

In support of the primary result, the secondary endpoints (type 1 error protected) showed statistically significant results indicating that remibrutinib can provide meaningful improvement for patients who do not respond to standard treatment of H1-AH.

The hives scoring system (HSS7) in the trial deviated from the the EAACI guideline. Consequently, the potential inflation of baseline disease severity and the possible overestimation of the treatment effect cannot be definitively determined. Nevertheless, this uncertainty is not expected to substantially alter the overall efficacy conclusions.

The primary and all secondary efficacy endpoints were evaluated at 12 weeks of treatment, representing a short period of time for treating a chronic disease such as CSU.

Therefore, long-term efficacy remains to be further characterised in post-authorisation setting in study CLOU064A2303B. In addition, since approximately 50% of patients did not achieve disease control and nearly 70% did not reach complete control at weeks 12 and 24, the need for continued therapy should be regularly assessed and treatment discontinuation should be considered in patients who show no response after 24 weeks as reflected in section 4.2 of the SmPC.

Although not studied, it is expected that the symptoms of the disease will return upon treatment

discontinuation as remibrutinib is a symptomatic, rather than a disease-modifying treatment.

Reported related adverse events are mostly known BTK class effects such as infections, and bleeding-related events. Adequate warnings have been included in section 4.4 to inform about this risk.

The safety profile of remibrutinib needs to be further characterised on the long-term use, data will be collected in study CLOU064A2303B.

In contrast to other approved BTK inhibitors, cardiac arrhythmias, and severe, serious or opportunistic infections have not been identified as safety issues during remibrutinib clinical studies.

Malignancies are recognised safety concern with other BTK inhibitors. There were no non-clinical concerns identified for carcinogenicity of remibrutinib, however during pivotal studies, several unexpected and rare malignant gastrointestinal tumours were reported in patients receiving remibrutinib. Consequently, malignancies have been included as important potential risk in RMP and will be followed up in the ongoing long-term extension study.

9.6.2. Balance of benefits and risks

The benefits of remibrutinib in the treatment of patients with CSU inadequately controlled with sg H1-AH are clinically relevant. Remibrutinib provides an alternative treatment option for CSU patients. Infections, bleeding-related events are the most frequently reported ADRs. In contrast to other approved BTK inhibitors, cardiac arrhythmias, severe, serious or opportunistic infections and tumours usually associated with BTK inhibitor use have not been reported during remibrutinib clinical studies. Several reports of rare malignant gastrointestinal tumours were identified, and although there is currently no evidence of causality, malignancies are included as important potential risk in RMP and will be followed up in the ongoing extension study for remibrutinib.

9.6.3. Additional considerations on the benefit-risk balance

9.6.3.1. Questions posed to additional experts

A consultation with the Nitrosamines Safety Operational Expert Group (NS OEG) is needed to aid with the assessment of the read-across approach and the decision on the acceptability of the proposed limit for the mutagenic impurity.

The following question was endorsed by CHMP for the NS OEG:

The NS OEG expert input on the appropriate approach (CPCA vs. read-across) to set an acceptable intake for the mutagenic impurity is requested. For this purpose, the NS OEG expert assessment of the Applicant’s response is essential.

9.6.3.2. Input from additional experts

The NS OEG experts’ response:

Based on the global similarity assessment and the unknown influence on metabolic activation of the gamma ether directly linked to the aromatic cycle the proposed molecule may not be an adequate surrogate. Taking into account the physio-chemical properties of impurity (higher TPSA, higher MW), and LogP and water solubility within the range of other molecules for which read across to the proposed surrogate was conducted, an AI of 100 ng/day is considered to be sufficiently conservative based on the data currently available.

9.7. Benefit-risk conclusions

9.7.1. At Day 210 – CHMP conclusions

The overall benefit/risk balance of Rhapsido is positive in the following indication:

Rhapsido is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients with inadequate response to H1 antihistamine treatment.