Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rhapsido

Active ingredient: Remibrutinib

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

June 2026

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
AEs	Adverse events
AESI	Adverse events of special interest
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration-time curve
BTK	Bruton's tyrosine kinase
CMI	Consumer Medicines Information
CSU	Chronic spontaneous urticaria
C_{max}	Maximum concentration
LS	Least squares
PI	Product Information
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
PSUR	Periodic safety update report
RMP	Risk management plan
TGA	Therapeutic Goods Administration
T_{max}	Time to maximum concentration
UAS7	Urticaria Activity Score 7

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Rhapsido
Active ingredient:	remibrutinib
Decision:	Approved
Date of decision:	7 May 2026
Approved therapeutic use for the current submission:	Rhapsido is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment.
Date of entry onto ARTG:	11 May 2026
ARTG number:	485465
▼*Black Triangle Scheme*	Yes
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Limited, 54 Waterloo Road, Macquarie Park, NSW 2113
Dose form:	Film coated tablet
Strength:	Each film coated tablet contains 25 mg of remibrutinib
Container and pack sizes:	PA/Al/PVC/Al blisters in either packs of 30 tablets or 60 tablets in a cardboard carton, or multipacks containing 180 tablets (3 packs of 60).
Route of administration:	Oral
Dosage:	25 mg taken orally twice daily For further information regarding dosage, refer to the Product Information.
Pregnancy category:	**Category D** Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register Rhapsido (remibrutinib) for the following proposed indication:[1]

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

Disease or condition

Urticaria is defined as a condition characterised by the development of wheals (hives), angioedema or both[2].

Acute urticaria is defined as the occurrence of wheals, angioedema, or both for 6 weeks or less. Chronic urticaria is defined as the occurrence of wheals, angioedema, or both for more than 6 weeks. Two categories of chronic urticaria have been identified:[2]

- Chronic inducible urticaria is characterised by the development of hives and/or wheals following exposure to specific identifiable triggers (e.g. cold, heat, pressure, vibration etc.);
- Chronic spontaneous urticaria (CSU) is characterised by the development of hives and/or wheals where no definite eliciting factor can be identified.

CSU is characterised by wheals with pale, central swelling and surrounding erythema. Lesions may range in size from a few millimetres to several centimetres in diameter and may occur over any part of the body. Pruritus is variable in severity. Wheals are typically transient, resolving within 24 hours but arising spontaneously on most days of the week for more than six weeks.[3,4,5]

Angioedema is characterised by a sudden, pronounced swelling of the deeper dermis or mucus membranes. It typically affects the face, extremities, or torso and causes discomfort rather than pruritus. Resolution of symptoms is slower than for hives (up to 72 hours).[3,4]

Most patients with CSU develop wheals only (57%), with 37% having both wheals and angioedema, and 6% having angioedema only.[6]

CSU is a common condition in adults, with a lifetime prevalence rate of approximately 1.8% of the general population. It occurs more commonly in females.[4] CSU may occur at any age, but peak incidence occurs between 20 and 40 years.[4]

The severity of CSU may fluctuate, and spontaneous remission may occur at any time.[2] Approximately 50% of people with CSU go into remission after 6 months to 5 years. Approximately 20% still have active disease after 10 years, and 10% after 20 years.[7] CSU may recur after months or years of full remission.[2]

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[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77(3):734-766. doi:10.1111/all.15090

[3] Lang DM. Chronic Urticaria. N Engl J Med. 2022; 387 (9): 824-831.

[4] Australasian Society of Clinical Immunology and Allergy (ASCIA). ASCIA Chronic Spontaneous Urticaria (CSU) Position Paper and Treatment Guidelines. 2020. Available from: https://www.allergy.org.au/images/stories/pospapers/ASCIA_HP_Position_Paper_CSU_2020.pdf

[5] Ben-Shoshan M, Kanani A, Kalicinsky C, Watson W. Urticaria. Allergy Asthma Clin Immunol. 2024; 20 (Suppl 3): 64.

[6] Wong D, Waserman S, Sussman GL. Endotypes of chronic spontaneous urticaria and angioedema. J Allergy Clin Immunol. 2025; 156 (1): 17-23

[7] Sabroe RA, Lawlor F, Grattan CEH et al. British Association of Dermatologists' Clinical Standards Unit. British Association of Dermatologists guidelines for the management of people with chronic urticaria 2021. Br J Dermatol. 2022; 186 (3): 398-413.

CSU may be associated with significant detrimental effects on quality of life due to severe itching, unpredictable occurrence and flare of symptoms, anxiety, fatigue, sleep disturbances, cosmetic problems, and adverse effects of off-label use of medication.[8]

Current treatment options

An international consensus clinical practice guideline has been developed on the treatment of urticaria, including CSU.[2] This guideline was developed by the following organisations:

- The European Academy of Allergology and Clinical Immunology (EAACI);
- The Global Asthma and Allergy European Network (GA2LEN);
- The European Dermatology Forum (EDF; EuroGuiDerm);
- The Asia Pacific Association of Allergy Asthma and Clinical Immunology (APAAACI).

The guideline has been endorsed by 50 national and/or international medical or scientific societies from 31 countries.

An Australian guideline has been developed by the Australasian Society of Clinical Immunology and Allergy (ASCIA).[4] Multiple other consensus guidelines have been developed.[5,7,8,9,10,11]

According to the updated international guideline[12] the treatment of CSU should be along the following lines:

1. First-line treatment should be a second generation (non-sedating) H1-antihistamine at a standard (approved) dose. The guideline specifically recommends *against* the use of first-generation antihistamines.
2. In subjects who do not respond, the dose of the second generation H1-antihistamine should be increased up to four-fold of the approved dose.
3. In unresponsive patients, the next agent prescribed should be either omalizumab, dupilumab or remibrutinib. Omalizumab is used as add-on therapy to the second generation H1-antihistamine and should be increased (up to 600 mg) and/or the dosage interval decreased (down to every 2 weeks) in unresponsive patients.
4. In unresponsive patients the dose of omalizumab should be increased (up to 600 mg) and/or the dosage interval decreased (down to every 2 weeks).
5. In subjects who do not respond to the second line agents (omalizumab, dupilumab or remibrutinib), the next agent prescribed should be ciclosporin (in combination with a second generation H1-antihistamine) at a dose of 3.5 – 5.0 mg/kg per day. Due to a high incidence of adverse effects, the guideline states that ciclosporin is recommended only for patients with severe disease refractory to any dose of antihistamine and omalizumab in combination.

[8] Maurer M, Abuzakouk M, Bérard F et al. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy. 2017; 72 (12): 2005-2016

[9] Maurer M, Weller K, Bindslev-Jensen C et al. Unmet clinical needs in chronic spontaneous urticaria. A GA^{2}LEN task force report. Allergy. 2011; 66 (3): 317-30.

[10] Bernstein JA, Lang DM, Khan DA et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014; 133 (5): 1270-7.

[11] Powell RJ, Leech SC, Till S et al. British Society for Allergy and Clinical Immunology. BSACI guideline for the management of chronic urticaria and angioedema. Clin Exp Allergy. 2015; 45 (3): 547-65.

[12] Zuberbier T, Abdul Hameed Ansari Z, Abdul Latiff AH, et al. The International Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. Allergy. Published online February 6, 2026. doi:10.1111/all.70210

6. The guideline mentions a number of other agents which have been used in the treatment of CSU, but which could not be recommended as standard therapy due to lack of clinical evidence. These include:
   - Leukotriene antagonists (e.g., montelukast);
   - H2-antihistamines (e.g. ranitidine);
   - Doxepin;
   - Other immunosuppressive agents (e.g., methotrexate, mycophenolate mofetil);
   - Sulphones (e.g., dapsone, sulphasalazine)

The guideline also states that a short-term course (up to 10 days) of systemic corticosteroids (doses between 20 and 50mg/day of prednisone equivalent) may be appropriate for the treatment of acute exacerbations of CSU.

The Australian ASCIA guideline (dated 2020) generally follows a similar treatment paradigm.[4] Differences of note are:

- A short-term trial of montelukast may be attempted prior to treatment with omalizumab;
- Up-dosing of omalizumab is not specifically recommended.

Clinical rationale

Remibrutinib is an oral, highly selective inhibitor of Bruton's tyrosine kinase (BTK). BTK is expressed in selected cells of the adaptive and innate immune system, including mast cells, basophils, macrophages, B cells and thrombocytes. Notably, BTK is not expressed in T cells and mature plasma cells, nonhematopoietic stem cells or in other somatic cells [13,14]. BTK plays an important role for signaling through the FcεR1 for IgE and activating FcγR for IgG, as well as the B cell antigen receptor.[15,16] It has been demonstrated that BTK inhibition leads to blockade of mast cell and basophil activation/degranulation in vitro and to reduced wheal sizes in skin prick tests with patients suffering from IgE-mediated diseases.[17,18,19,20,21] Based on this mechanism of

[13] Reynolds JA, Bruce IN (2021). Chapter 40 – Pipeline therapies and future drug development. In: Lahita RG, Costenbader KH, Bucala R, Manzi S, Khamashta MA, (eds) Lahita's systemic lupus erythematosus. pp. 661-71. Sixth edition. Academic Press, London, UK.
[14] [Sung L (2021)] Chapter Two – Covalent drugs in development for immune-mediated diseases. In: Ward RA, Grimster NP (eds) The Design of Covalent-Based Inhibitors. Annual Reports in Medicinal Chemistry. pp. 33-74. Volume 56. Academic Press, London, UK.
[15] Rip J, Van Der Ploeg EK, Hendriks RW, et al (2018). The Role of Bruton's Tyrosine Kinase in Immune Cell Signaling and Systemic Autoimmunity. Crit Rev Immunol; 38(1):17-62.
[16] McDonald C, Xanthopoulos C, Kostareli E (2021). The role of Bruton's tyrosine kinase in the immune system and disease. Immunology; 164(4):722-36.
[17] Smiljkovic D, Blatt K, Stefanzl G, et al (2017). BTK inhibition is a potent approach to block IgE-mediated histamine release in human basophils. Allergy; 72(11):1–11.
[18] Regan JA, Cao Y, Dispenza MC, et al (2017)] Ibrutinib, a Bruton's tyrosine kinase inhibitor used for treatment of lymphoproliferative disorders, eliminates both aeroallergen skin test and basophil activation test reactivity. J Allergy Clin Immunol; 140(3): 875-9.
[19] Dispenza MC, Pongracic JA, Singh AM, et al (2018). Short-term ibrutinib therapy suppresses skin test responses and eliminates IgE-mediated basophil activation in adults with peanut or tree nut allergy. J. Allergy Clin. Immunol; 141(5):1914-16.e7.
[20] Dispenza MC, Krier-Burris RA, Chhiba KD, et al (2020). Bruton's tyrosine kinase inhibition effectively protects against human IgE-mediated anaphylaxis. J Clin Invest; 130(9):4759-70.
[21] Kaul M, End P, Cabanski M, et al (2021). Remibrutinib (LOU064): A selective potent oral BTK inhibitor with promising clinical safety and pharmacodynamics in a randomized phase I trial. Clin Transl Sci; 14(5):1756-68.

action, and as supported by results from Phase II and Phase III studies, BTK inhibition is a therapeutic target for the treatment of CSU.[22],[23]

The sponsor also contended that there is a high unmet medical need for alternative second-line oral treatments for patients who remain symptomatic despite H1-antihistamine treatment:

- more than 50% of patients fail to achieve complete therapeutic benefit with antihistamines and omalizumab;
- response to omalizumab varies, with some patients having a delayed onset of response and requiring higher than approved doses, and many patients on omalizumab 300 mg fail to achieve complete response;
- while omalizumab is administered via subcutaneous injection, remibrutinib is an oral treatment. While there is no data on adherence for CSU in other indications, better patient adherence has been shown with oral therapies compared to injectables.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. Table1 summarises these submissions.

Table 1. International regulatory status at the time the TGA considered this submission

Country/Region	Submission date	Status	Proposed indication
United States of America	31 January 2025	Under evaluation	For the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment
European Union	26 February 2025	Under consideration	For the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment
Switzerland	19 May 2025 (planned)	-	-
Canada	4 December 2026 (planned)	-	-

[22] Metz M, Sussman G, Gagnon R, et al (2021). Fenebrutinib in H1 antihistamine-refractory chronic spontaneous urticaria: a randomized phase 2 trial. Nat Med; 27(11):1961-9.
[23] Maurer M, Berger W, Giménez-Arnau A, et al (2022)] Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria. J Allergy Clin Immunol; 150(6):1498-1506.e2.

Country/Region	Submission date	Status	Proposed indication
United Kingdom	March 2026 (planned)	-	-
Singapore	Q2 2025	-	-
New Zealand	Q2 2026	-	-

Registration timeline

Table 2 captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2. Timeline for Rhapsido (remibrutinib), submission PM-2025-01101-1-1

Description	Date
Submission dossier accepted evaluation commenced	3 June 2025
Evaluation completed	23 March 2026
Registration decision (Outcome)	7 May 2026
Registration in the ARTG completed	11 May 2026
Number of working days from submission dossier acceptance to registration decision*	190

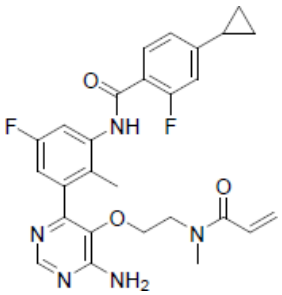
*Statutory timeframe for standard submissions is 255 working days

Assessment overview

Quality evaluation summary

Drug substance

Table 3. Remibrutinib drug substance

Name	Remibrutinib
Structure	

Chemical name	IUPAC *N*-(3-{6-Amino-5-[2-(*N*-methylprop-2-enamido)ethoxy]pyrimidin-4-yl}-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide
CAS Number	1787294-07-8
Molecular formula	$C_{27}H_{27}F_2N_5O_3$
Molecular weight	507.54 g/mol

The drug substance, remibrutinib, is produced from five starting materials in ten synthetic steps.

Remibrutinib is a white to pale yellow powder.

Remibrutinib is achiral.

Remibrutinib is practically insoluble in aqueous media across the physiologically relevant pH range. The drug substance is classified as a BCS Class II compound, characterised by low solubility and high permeability.

The proposed specification adequately controls the identity, potency, purity and chemical and physical properties of the drug substance relevant to the dose form.

The synthetic impurity limits are controlled to either ICH Q3A[24] or where higher were adequately qualified via toxicological assessment.

The drug substance subsequently undergoes wet milling as part of manufacture of the drug product, and thus particle size distribution is not considered a critical parameter of the drug substance.

Risk evaluations on the potential presence of nitrosamines and elemental impurities were performed. No significant risk was identified; however, a nitrosamine impurity is controlled in the drug product specification.

The analytical methods used to analyse the product were adequately described and validated.

The retest period is 24 months when stored at -20°C/ambient relative humidity.

Drug product

The remibrutinib 25 mg tablet is a light yellow, round, curved, unscored film-coated 7mm tablet, debossed with 'LV' on one side and the Novartis logo on the other side.

The product is supplied in PA/Al/PVC/Al blister packs of 30 or 60 tablets and multipacks of 180 tablets (3 packs of 60 tablets).

The drug product formulation contains no novel excipients, and no excipients are of animal origin.

[24] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline. Impurities In New Drug Substances Q3A(R2).

The drug product is manufactured by wet media milling, spray granulation, compression and aqueous film coating process. Acceptable in-process controls have been applied.

The drug product specifications adequately control the quality of the drug product at release and throughout the shelf-life. The impurities are controlled to either ICH Q3B[25] or where higher were adequately qualified. An issue regarding the total impurity limit remains outstanding, however is expected to be resolved soon.

A risk assessment on the potential contamination of the product with nitrosamine impurities identified a nitrosamine of the drug substance, JHZ933. This nitrosamine impurity is controlled in the drug product specification at a limit of 2.0 ppm (equivalent to the acceptable intake of 100 ng/day based on a maximum daily dose of 50 mg).

The dissolution limits were adequately justified based on the dissolution profiles of the pivotal clinical study batches.

The analytical methods used to analyse the product were adequately described and validated.

Stability data did not show any degradation trends on long term storage. The stability data submitted supports a shelf-life of 24 months when stored below 30 °C.

The drug product formulation used in the Phase 3 clinical studies is the same as the product formulation proposed for registration. No bridging studies were required.

Approval from a quality perspective is recommended.

Nonclinical evaluation summary

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of ICH M3(R2).[26] The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were GLP compliant.

In vitro, remibrutinib bound BTK with nanomolar affinity and is more selective for BTK compared to BTK-related enzymes. In cellular systems, remibrutinib inhibited B cell receptor (BCR) signalling in human and rodent B cells, and displayed antiproliferative effects against mouse splenocytes and human PBMCs. Histamine release in human primary mast cells and basophils was inhibited by remibrutinib. In vivo, remibrutinib reduced mast cell-mediated skin hypersensitivity in two different mouse models.

Remibrutinib inhibited collagen-induced platelet aggregation in vitro in human blood samples, suggesting a potential impact on haemostasis at clinically relevant exposures. Suppression of IgM and IgG levels in rodents indicate a possible increased infection risk, although no reactivation of dormant *M. tuberculosis* was observed in a human 3D granuloma model in vitro.

In secondary pharmacology screens, inhibition of other kinases and receptors was observed, but not at clinically relevant concentrations. No adverse effects on CNS, cardiovascular or respiratory function are predicted in patients.

Oral absorption of remibrutinib was rapid in laboratory animal species, and similar to humans. Oral bioavailability in mice, rats and dogs was low (cf. moderate in humans). Plasma half-life was short in rodents (~1–4 h), very long in dogs (~20 h) and long to very long in humans (~10–17 h). Plasma protein binding was moderate to high, and broadly similar across species. Rapid and

[25] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH harmonised tripartite guideline. Impurities in New Drug Products. Q3B(R2)

[26] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals - Scientific guideline. 2013.

wide tissue distribution of ^{3}H- or ^{14}C-remibrutinib-derived radioactivity was demonstrated in rats, with only limited penetration of the blood-brain barrier apparent. Remibrutinib binds to melanin.

Metabolism of remibrutinib N-demethylation and/or oxidation, O-dealkylation, N-oxidation and C-hydroxylation. CYP3A4/5 was identified as the main enzyme involved in the metabolism of remibrutinib. Formation of drug-protein adducts was demonstrated in vitro in human liver microsomes and hepatocytes. A potential for hepatic reactivity during clinical use cannot be excluded. Excretion of remibrutinib and/or its metabolites was predominantly via the faeces in rats, rabbits, dogs and humans. Biliary excretion was demonstrated in rats.

In vitro data indicate the potential for CYP3A4 inducers/inhibitors to alter remibrutinib exposure in patients and for remibrutinib to cause interactions through inhibition of intestinal CYP3A4/5, P-glycoprotein and BCRP.

Remibrutinib showed a low order of acute toxicity by the oral route in mice, rats and dogs.

Repeat-dose toxicity studies by the oral route were conducted in mice (4 weeks), rats (up to 6 months) and dogs (up to 9 months). The major targets for remibrutinib were haemostatic system and platelets (increases in bleeding time, inhibition of collagen-induced platelet aggregation and delayed clot lysis), and lymphoid organs (lymphoid depletion in lymph nodes and/or gut-associated lymphoid tissue frequently accompanying decreases in circulating B cells with increased T cells), which are considered consistent with BTK inhibition by remibrutinib.

Other effects were observed in the liver (reversible increases in the relative weight with decreased AST levels and occasional hepatocellular hypertrophy in rats), pancreas (irreversible pancreatic islet fibrosis in rats) and thyroid gland (reversible increases in follicular cell hypertrophy in rats). The effects on the platelet-related haemostasis and lymphoid system are considered clinically relevant. Due to the decreased haemostatic function, patients may have increased risk of bleeding events. The potential alteration in circulating lymphocyte subpopulations during treatment may be associated with an increased risk of infection or poor response to vaccines in patients.

Remibrutinib is not considered to be genotoxic and was not carcinogenic in transgenic mice or rats.

Fertility was unaffected in male and female rats treated with remibrutinib. Remibrutinib crossed the placenta in rats and could be detected in fetal tissue. In rabbits, fetal malformations (open/opaque eye, small mandible and hyperflexion in forelimbs) were seen at very high exposures (121 times the clinical AUC). Severe maternal toxicity was also noted at higher exposures. No teratogenicity was noted in rats. Transfer of remibrutinib into milk was not assessed. Severe maternotoxicity, increased stillborn pups, decreased litter size, increased pup mortality between birth and lactation day 1 were seen at very high exposures in pre- and post-natal development studies in rats.

Remibrutinib was not phototoxic and was not a skin irritant or skin sensitiser in in vitro studies.

The proposed limits for two impurities in the drug substance and one impurity in the drug product have been adequately qualified by submitted toxicity data.

There are no nonclinical objections to registration of Rhapsido for the proposed indication.

Clinical evaluation summary

Pharmacology

Pharmacokinetics

Absorption

An in vitro study in the gastrointestinal Caco-2 cell line (DMPK R1500096) was reported to show that the predicted absorption of remibrutinib was high (>90%). An efflux transporter effect was demonstrated at low remibrutinib concentrations. However, this appeared to be saturated at higher concentrations. The efflux transporter effect was abolished when an inhibitor of P-glycoprotein (P-gp) was added, suggesting that remibrutinib is a substrate for P-gp.

In the clinical PK studies absorption was rapid with median T_{max} values typically being approximately 1.0 hour. In the ADME study, following oral administration, unchanged remibrutinib in faeces accounted for only 1.21% of the administered dose, suggesting that remibrutinib is almost completely absorbed.

There were no clinical data examining sites and mechanism of absorption.

Bioavailability

Absolute bioavailability: In study CLOU064X2103, mean absolute bioavailability was estimated to be 33.8% (± 11.5%).

Bioequivalence of clinical trial and market formulations: Most of the clinical pharmacology studies used a hard gelatin capsule (HGC) formulation for oral administration. The pivotal efficacy and safety studies used a film-coated tablet (FCT) formulation which is identical to the one proposed for marketing. Study CLOU064X2105 compared the two formulations. The FCT formulation was associated with an approximate 20% reduction in AUC and an approximate 28% reduction in C_{max}.

Influence of food: In study CLOU064A02104, when a 25 mg dose of the FCT formulation was co-administered with a high-fat meal, AUC was increased by 33%. C_{max} was slightly decreased (by approximately 5%). Median T_{max} was increased from 1.0 to 2.0 hours.

In an earlier study using the HGC formulation (CLOU064X2101 – Part 3), co-administration with food resulted in an increase in AUC of approximately 30%, a decrease in C_{max} of approximately 20% and a delay in T_{max} of approximately 2 hours. Of note, the sponsor is proposing that the drug can be administered with or without food.

Dose proportionality: Four studies examined ascending doses of remibrutinib - CLOU064X2101 – Part 1, CLOU064X2101 – Part 2, CLOU064X2101 – Part 4 and CLOU064X1101. AUC and C_{max} increased with increasing dose but typically in a less than dose-proportional manner.

The nonlinear PK of remibrutinib was attributed to both target-mediated drug disposition at low doses (up to ~50 mg total daily dose) and solubility-limited absorption at high doses (above 200 mg total daily dose).

In the population PK analysis, the PK at steady state appeared to be dose proportional for doses between 10 and 200 mg per day.

The proposed dosage regimen is a fixed dose of 25 mg BD, without any dose reductions/ increase.

Bioavailability during multiple dosing: In multiple dose studies there was mild accumulation with repeated dosing (accumulation ratios < 2.0 for AUC). In study CLOU064X2101 (Part 2) there was a more notable increase in AUC with repeated dosing at low doses (10 and 25 mg OD). This was attributed to time-dependent changes in clearance due to covalent binding of remibrutinib to its target BTK. Such binding is saturated at higher doses and accumulation becomes less apparent.

Distribution

Volume of distribution

In the PK studies of oral administration values for apparent volume of distribution (V/F) were high (> 300 L). In study X2101 (Part 2) the mean apparent volume of distribution at steady state after daily doses of 25 mg was 407 L.

After IV administration of 100 mcg of a stable isotope of remibrutinib mean central volume of distribution (Vc) was 72.4L

In the population PK analysis, the final model estimated an apparent central volume of distribution (V1/F) of 58 L, and an apparent peripheral volume of distribution (V2/F) of 1180 L.

These data suggest that remibrutinib is extensively distributed into tissues.

Plasma protein binding

An in vitro study (DMPK R2300145) was reported to show that the protein binding of remibrutinib in plasma is high (94.9%). Binding was independent of plasma remibrutinib concentration over the range 5 – 5000 ng/mL. Most binding was to albumin, followed by alpha-1 acid glycoprotein and high density lipoprotein.

In study A2101, mean plasma protein binding was > 95% and was unaffected by degree of hepatic impairment.

Erythrocyte distribution

In study X2104, the total radioactivity exposure (AUC_{inf}) in whole blood was 85% of the AUC_{inf} for the total radioactivity found in plasma. These data suggest that there is no significant partitioning of drug-related material into red blood cells.

Metabolism

Sites of metabolism and mechanisms / enzyme systems involved

The involvement of cytochrome P450 and other metabolic enzymes in the metabolism of remibrutinib was investigated in an in vitro study (DMPK R1500124) using pooled human liver microsomes, S9 fractions, liver cytosol and human hepatocytes. It was reported that CYP3A4 was the major CYP enzyme responsible for the oxidative metabolism of remibrutinib in the liver with a possible minor contribution from CYP2C19 and extrahepatic CYP1A1.

In another in vitro study (DMPK R1600559) it was reported that CYP3A4 was the main hepatic enzyme catalysing the primary oxidative metabolism of remibrutinib in human liver microsomes with potentially partial low contributions from other enzymes such as CYP2C19, CYP3A5 and CYP2B6.

Non-renal clearance

Renal clearance of remibrutinib is low (see below), and the drug is predominantly cleared through metabolism.

Total clearance

In the PK studies remibrutinib was rapidly cleared from the blood. In the population PK analysis, the final model estimated an apparent clearance (CL/F) of 160 L per hour.

Metabolites identified in humans: active and other

In study X2104, the metabolism of remibrutinib was shown to be complex, with a large number of metabolites formed by multiple metabolic steps.

After oral administration of radiolabelled remibrutinib:

- Remibrutinib was the most abundant species in blood comprising 16.7% of 14C-AUC0-24h;
- A total of 18 metabolites were identified in blood. The most common were M68 (11.2%), M24 (6.33%) and M2 (4.95%);
- A total of 31 metabolites were identified in urine. The most common were M24 (3.49% of the total over 0-48 hrs) and M68 (2.99%). Unchanged remibrutinib accounted for 0.65%.
- A total of 21 metabolites were identified in faeces. The most common was M24 (7.22% of the total over 0-144 hrs). Unchanged remibrutinib accounted for 1.21%.

Pharmacokinetics of metabolites

As systemic exposure to individual metabolites was low, the PK of metabolites was not investigated.

Excretion

Routes and mechanisms of excretion

In study X2104, radiolabelled remibrutinib was administered IV to two subjects. Most of the radioactivity was recovered in faeces (67.1% and 71.7%) and excretion in urine was lower (29.7% and 25.5%).

Renal clearance

In study X2104, radiolabelled remibrutinib was administered IV to two subjects. Only a small proportion of the radioactivity was recovered in the urine as unchanged remibrutinib (2.2% and 5.0%), indicating that renal clearance of remibrutinib is low.

In studies of oral administration in which urine PK was examined (X2101-Parts 2 and 4, X1101) only a small fraction of the administered dose was excreted as unchanged remibrutinib in the urine. Mean renal clearance was low compared to mean total apparent clearance (CL/F).

Pharmacokinetics in the target population

In the PopPK analyses with data from participants with non-relapsing secondary progressive multiple sclerosis (nrSPMS; EFC16645 study) or relapsing multiple sclerosis (RMS; EFC16033), age, sex, and body weight were not identified as significant covariates affecting the PK of remibrutinib and the M2 metabolite (POH1142 and POH0855).

The PK variabilities in participants with nrSPMS and RMS in EFC16645 and EFC16033 studies were very high (CV%: 60% to 65% for Remibrutinib and 56% to 58% for M2), but consistent with the variabilities observed in healthy participants in Phase 1 studies.

The population PK analysis suggested that remibrutinib PK in CSU subjects was similar to that observed in healthy subjects.[

Pharmacokinetics in subjects with impaired hepatic function

In study A02101 systemic exposure to remibrutinib was increased in subjects with hepatic impairment. In subjects with severe impairment, C_{max} was increased 1.99-fold, and AUC was increased 3.12 – 3.49-fold.

Pharmacokinetics in subjects with impaired renal function

Renal clearance of remibrutinib is low and therefore renal impairment would not be expected to significantly alter the PK of the drug. No specific clinical studies were performed in subjects with renal impairment.

In the population PK analysis, degree of renal impairment was investigated as a potential covariate for remibrutinib clearance. No significant effect was detected. The population in the analysis only included one subject with severe renal impairment.

In the PBPK model, renal impairment was predicted to produce a modest increase in systemic exposure to remibrutinib. In subjects with severe impairment, C_{max} would be increased by 35% and AUC by 48%. The increased exposure was attributed to a lower abundance of CYP3A4 in renal impairment populations (compared to the healthy control population).

Pharmacokinetics related to genetic factors

In the population PK analysis, mainland Chinese, Japanese, and other Asian subjects had significantly decreased clearance and increased systemic exposure compared to Non-Asian subjects. Increases in AUC of up to approximately 30% were predicted. Given the high inter-individual variability of remibrutinib PK, these effects were considered by the sponsor to be not clinically significant.

Population pharmacokinetics

The PK of remibrutinib were adequately described by a two-compartment model with first-order absorption and a lag time and linear elimination. Bodyweight (both lean bodyweight and adipose tissue) and Asian race were found to be statistically significant covariates and were included in the model. However, simulations conducted with the model suggested that these covariate effects were unlikely to be clinically significant.

Effect of other medicines on remibrutinib PK

CYP3A4 inhibitors: In study X2103, coadministration of remibrutinib together with ritonavir (a strong inhibitor of CYP3A4) resulted in an approximately 4-fold increase in remibrutinib AUC.

Also in study X2103, coadministration of remibrutinib together with grapefruit juice (a moderate to strong inhibitor of CYP3A4 in the gut wall) resulted in a 1.29-fold increase in remibrutinib AUC.

CYP3A4 inducers: In study A02103, coadministration of remibrutinib together with carbamazepine (a strong inducer of CYP3A4) resulted in a 77% decrease in remibrutinib AUC.

P-glycoprotein (P-gp) inhibitors: In vitro studies were reported as demonstrating that remibrutinib is a substrate for (P-gp) in the gastrointestinal tract. The sponsor considered that inhibition of P-gp would be unlikely to affect remibrutinib PK for the following reasons:

- At the expected concentrations of remibrutinib in the intestinal lumen, P-gp transport is expected to be saturated.
- Remibrutinib is a highly permeable drug and P-gp transport would not be expected to modify the extent of absorption.

- The fast absorption rate observed across all doses suggests a low risk of interactions due to P-gp inhibition.

Pharmacodynamics

Primary pharmacodynamic effects

BTK occupancy

BTK is a cytoplasmic signalling protein expressed in a variety of immune cells, including mast cells, basophils, B lymphocytes, natural killer cells, macrophages, neutrophils, dendritic cells, monocytes, and osteoclasts[10]. The extent to which BTK was occupied following remibrutinib treatment was measured in several of the clinical pharmacology studies. A cell lysate was prepared from whole blood and total BTK and free BTK (not bound to remibrutinib) were measured using validated ELISA methods. These measurements were used to calculate BTK occupancy.

- With single doses of 30 mg and higher, complete BTK occupancy (>95%) was seen and was sustained beyond 4 hours. After 48 hours, BTK occupancy decreased (study X2101 – Parts 1 and 5, study X1101 – Part B);
- After multiple dosing for 12 days, BTK occupancy was > 95% at most timepoints at doses ≥ 10 mg per day. Occupancy began to decrease at 48 hours after the last dose (study X2101 – Parts 2 and 4);

Free BTK

In study X2101 – Part 6, subjects were treated with remibrutinib 100 mg BD for 29 days. Free BTK levels dropped to zero at the first measurement after 30 minutes and remained undetectable throughout the treatment period and up to 24 hours after the last dose.

In study X1101 – Part B, subjects were treated with remibrutinib 400 mg BD or placebo for 5 days. At predose on day 1, the mean concentration of free BTK in the remibrutinib group was 101.22 ng/mL This fell to 0.73 ng/mL by 0.5 hours on day 1 and remained at this level until 24 hours after the last (day 5) dose. Free BTK concentrations were unchanged in the placebo group.

Basophil activation

BTK has a role in the activation of basophils, and the extent of inhibition of such activation after remibrutinib treatment was measured in several of the clinical pharmacology studies. Whole blood was stimulated with anti-IgE and stained with fluorescence-labelled antibodies directed against CD63 and CD203c (markers of basophil activation). The percentages of CD63-positive and CD203c-positive cells were analysed by Fluorescence Activated Cell Sorting (FACS).

- After single doses of 50 mg and above, percent inhibition of CD63 +ve basophils was > 98% at 8hrs post dose (study X2101 – Parts 1 and 5). At doses of 100mg and higher, an inhibition level of > 88% or more was observed up to 48 hours post-treatment (study X2101 – Part 1).
- With multiple dosing for 12 days (at doses ≥ 50 mg daily) percent inhibition of CD63 +ve basophils was > 95% by day 2 predose (i.e. 24 hours after the first dose). Inhibition began to decline at 48 hours after the last dose and returned to baseline approximately 11 days after the last dose (study X2101 – Parts 2 and 4)
- In study X2101 – Part 6, subjects were treated with remibrutinib 100 mg or placebo BD for 29 days. In the remibrutinib arm percent inhibition of CD63 +ve basophils was > 97% from the first measurement (day 1, 8 hours) until 24 hours after the last dose (day 30). No inhibition was observed in the placebo arm.

In these studies, inhibition of CD203c-positive basophils was also observed although the effects were less pronounced than those observed for CD63+ basophils.

B-lymphocyte activation

BTK also has a role in the activation of B-lymphocytes, and the extent of inhibition of such activation after remibrutinib treatment was measured in study X1101.

Whole blood was stimulated with anti-IgM and recombinant human interleukin-4 (rhIL-4). Anti-IgM and rhIL-4 both stimulate B-cell activation and proliferation. A 4-colour flow cytometry assay using monoclonal antibodies was used to detect CD69 expression on B cells. CD69 is a cell surface protein which is a marker of lymphocyte activation.

- In Part A subjects were treated with single doses of remibrutinib ranging from 5 to 400 mg. Percent inhibition of CD69 +ve cells > 50% was achieved at doses ≥ 30 mg. The maximum level of inhibition observed was 65.98% at 24 hours post dose in the 200 mg dose group.
- In Part B subjects were treated with remibrutinib 400 mg BD or placebo for 5 days. Percent inhibition of > 50% was achieved by day 2 and was maintained until day 6. The maximum level of inhibition observed was 65.30% on day 2.

Skin prick testing

Study X2101 (Parts 2 and 4) enrolled healthy volunteers with a known allergic diathesis. This study examined the effect of remibrutinib (10 to 600 mg daily, for 12 days) on the size of skin wheals produced by skin prick testing with a known antigen. Treatment with remibrutinib resulted in a decrease in the wheal size produced by the known antigen. A dose-response effect was observed. Response appeared to plateau at a dose of 100 mg daily.

Secondary pharmacodynamic effects

Study F12101 examined the effect of remibrutinib treatment on antibody responses to vaccines. Vaccination concomitant with remibrutinib treatment generally resulted in a decreased antibody response compared to vaccination received while on placebo. This effect was decreased if remibrutinib treatment was interrupted for one week prior to, and two weeks after, vaccination.

This study was conducted with inactivated vaccines. The interaction between remibrutinib and live attenuated vaccines has not been studied.

The onset of action of remibrutinib is rapid, with complete BTK occupancy and absent free BTK at 30 minutes after administration. These effects lasted until 24 hours after the last dose.

Dosage selection for the pivotal studies

The dose of remibrutinib used in the pivotal studies was 25 mg BD.

Pharmacokinetics and pharmacodynamics: dose finding studies

With single doses of 30 mg and higher, complete BTK occupancy (>95%) was seen. After multiple dosing for 12 days, BTK occupancy was > 95% at most timepoints at doses ≥ 10 mg per day.

Inhibition of basophil activation was maximal at doses ≥ 50 mg daily. With skin prick testing, a dose-response effect was observed. Response appeared to plateau at a dose of 100 mg daily.

Study A2201explored various doses from 10 to 200 mg daily in subjects with CSU. The 25 mg BD dose was found to produce the greatest placebo-corrected improvement from baseline in efficacy parameters.

The dose chosen for the pivotal studies was appropriate.

A subsequent exposure-response analysis using efficacy data from the pivotal studies indicated that there was a steep relationship between systemic exposure to remibrutinib and efficacy

outcomes. Maximum response was achieved at low exposures (e.g. those predicted for a 10 mg BD dose), and the response plateaued at higher exposures. The response predicted at the systemic exposure achieved with the 25 mg BD dose was on this plateau.

Efficacy

Efficacy data to support the proposed indication is provided by two pivotal, identically designed, phase 3, randomised, double-blind, placebo-controlled trials (A2301 and A2302, Figure 1). One phase 2, randomised, double-blind, placebo-controlled, dose-ranging study (A2201) provides supportive evidence.

Studies CLOU064A2301 (REMIX-1) and CLOU064A2302 (REMIX-2)

Study design

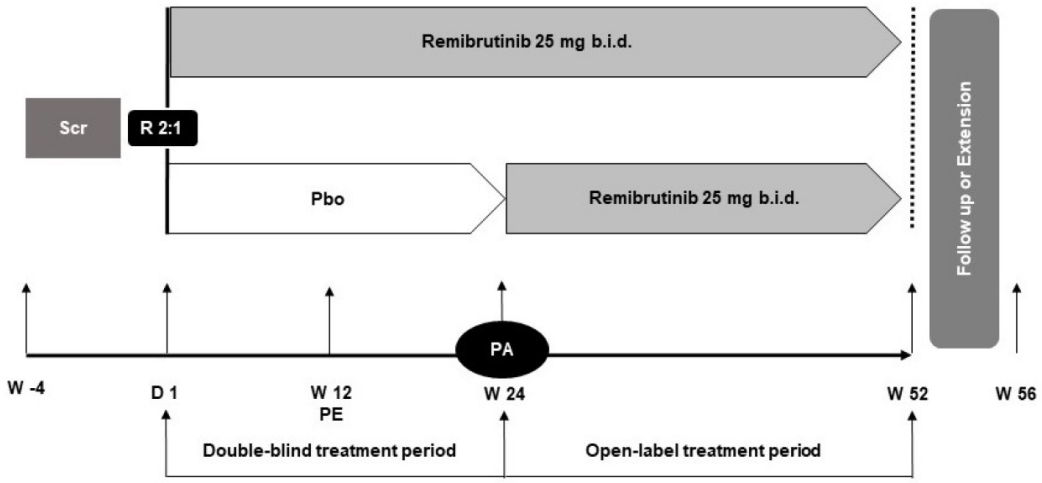
Each study was a phase 3, randomised (2:1), double-blind placebo-controlled trial with two parallel groups (remibrutinib vs. placebo).

Each study consisted of four periods, with a total study duration of up to 60 weeks:

- A screening period of up to 4 weeks (days -28 to -1);
- A double-blind treatment period of 24 weeks.
- An open-label treatment period of 28 weeks with open-label remibrutinib.
- A follow-up period of 4 weeks of treatment-free follow-up.

Study visits were scheduled during screening (between days -28 and -1), at baseline (day 1 of week 1), at weeks 2, 4, 8, 12, 16, 20, 24, 32 40 and 52 of treatment and at the end of the follow period (week 56).

Figure 1. Studies A2301 and A2302 – Study schema



D 1: Day 1, Pbo: placebo, PA: Primary Analysis, PE: Primary Endpoint; Scr: Screening, W: Week.

Study objectives and endpoints

Of note, the sponsor received different advice from the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) regarding the appropriate primary endpoint(s). The EMA recommended use of the UAS7 as the primary endpoint, whereas the FDA recommended the use of the Itch Severity Score over 7 days (ISS7) and Hive Severity Score over 7 days (HSS7) as co-primary endpoints. These three endpoints are explained below.

As a result, the sponsor constructed two "scenarios" for analysis of the data. The first scenario followed the EMA approach while the second scenario followed the FDA approach. The study objectives and study endpoints differed between the two scenarios. As the TGA typically adopts the approach of the EMA (e.g. EMA clinical guidelines), this evaluation report will focus on the first scenario.

Table 4 – Studies A2301 and A2302 – Study objectives

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

Inclusion and exclusion criteria

The key inclusion criteria were:

- Age ≥ 18 years.
- CSU duration for ≥ 6 months prior to screening.
- CSU inadequately controlled by second generation H1-antihistamines at the time of randomisation.

- Moderate to severe disease.

The key exclusion criteria were:

- Chronic Inducible Urticaria (CINDU) if the predominant or sole trigger of CU
- Other diseases with symptoms of urticaria or angioedema.
- Any other skin disease associated with chronic itching that might influence in the investigator's opinion the study evaluations and results.
- Evidence of clinically significant cardiovascular, neurological, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic, haematological disorders, gastrointestinal disease or immunodeficiency.

Sample size

The International Conference on Harmonisation (ICH) guideline on the extent of population exposure required to assess clinical safety suggests that 300-600 patients should be treated for 6 months, and 100 patients for 12 months.[27] The sample size was chosen in order to fulfill these requirements. For both studies, a sample size of 300 subjects in the active arm (and 150 in the placebo arm) was targeted. Hence, the total sample size was 450 randomised subjects in each study.

Participant flow

In study A2301, a total of 654 subjects were screened, and a total of 470 subjects were randomised. Of these, seven subjects were mis-randomised and therefore did not receive treatment. 309 subjects were randomised and treated in the remibrutinib arm, and 154 subjects were randomised and treated in the placebo arm.

In study A2302, a total of 612 subjects were screened, and a total of 455 subjects were randomised. Of these, five subjects were mis-randomised and therefore did not receive treatment. 297 subjects were randomised and treated in the remibrutinib arm, and 153 subjects were randomised and treated in the placebo arm.

Major protocol violations/deviations

Protocol deviations were not classified as major or minor.

Study A2301

Overall deviations occurred with a similar frequency in both arms. Use of prohibited concomitant medication was more common in the remibrutinib arm (12.8% vs. 7.0%).

Study A2302

Overall, deviations were more common in the placebo arm (46.5% vs. 40.7%). Use of prohibited medication was also more common in the placebo arm (14.8% vs. 8.3%).

Baseline data

Study A2301

Mean age of the study population was 45.0 years (range 18 – 79). 68.3% were female and 31.7% were male. The two treatment arms were well balanced with respect to these characteristics.

31.3% of the population had had prior exposure to anti-IgE agents such as omalizumab.

[27] ICH Topic E1. Population Exposure: The Extent of Population Exposure to Assess Clinical Safety. 1995.

More subjects in the remibrutinib arm had a prior history of angioedema (55.3% vs. 44.6%). However, baseline weekly Angioedema Activity Scores (AAS7) were similar in the two arms. The two arms were reasonably well balance with respect to other disease characteristics at baseline.

The two arms were also reasonably well balanced at baseline with respect to prior medications.

Results for the primary efficacy outcome

The primary endpoint was the absolute change from baseline in UAS7 at Week 12.

Study A2301

In the remibrutinib arm the LS mean change in UAS7 from baseline to week 12 was -20.02 points, compared with -13.79 points in the placebo arm. The LS mean difference between treatments was -6.22 points (95%CI: -8.45 to -4.00). The difference was statistically significant ($p < 0.001$).

Table 5. Study A2301 –Mean Change from baseline to week 12 in UAS7 (FAS)

		Within Treatment		Treatment Contrast in LS mean (change)				
Treatment group	n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
LOU064 25mg b.i.d.	309	-20.02	0.716	vs Placebo	-6.22	1.136	(-8.45 , -4.00)	<0.001
Placebo	153	-13.79	0.980					

LS Mean: Least squares mean, SE: standard error, CI: confidence interval, p-value: one-sided p-value.
n: number of subjects included in the analysis for each treatment group.
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.
Pre-specified intercurrent events are considered. Intake of strongly confounding prohibited medication: Composite strategy (the measurements after the event are excluded and imputed with the worst value). Discontinuation of study treatment due to any reason prior to Week 12: Treatment policy strategy; Intake of rescue medication as per protocol, switch of background medication, intake of other prohibited medication, or non-compliant prior to Week 12: Treatment policy strategy.

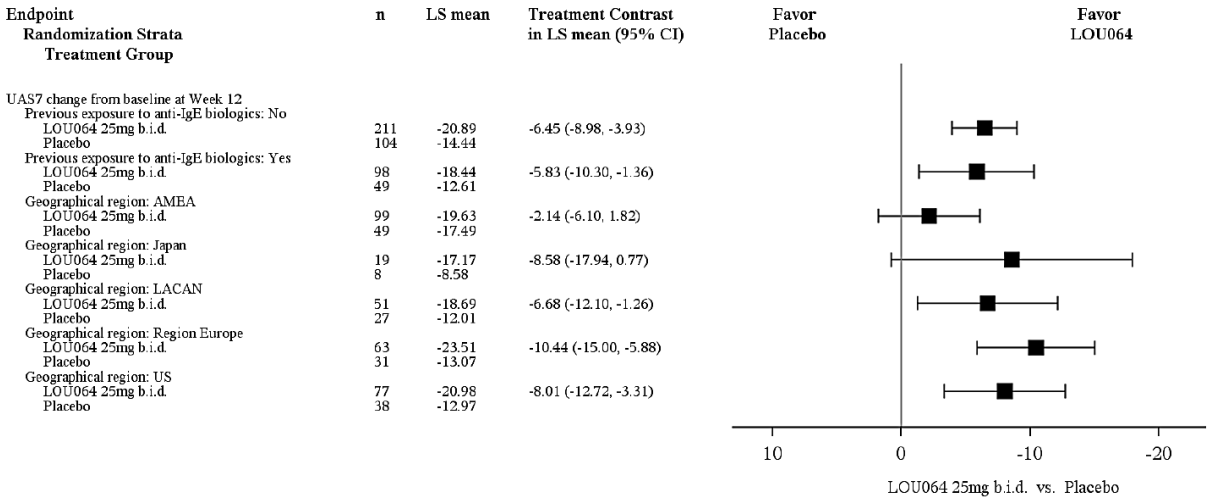
A sensitivity analysis was conducted. In this analysis in the case of intake of strongly confounding prohibited medication, the change from baseline in UAS7 scores up to Week 12 were imputed using zero (i.e., no clinical improvement from baseline), rather than using the worst possible value.

Using this method, in the remibrutinib arm the LS mean change in UAS7 from baseline to week 12 was -20.07 points, compared with -13.79 points in the placebo arm. The LS mean difference between treatments was -6.29 points (95%CI: -8.49 to -4.08). The difference was statistically significant ($p < 0.001$).

Subgroup analyses

Subgroup analyses were presented for the subgroups defined by the randomisation strata. Remibrutinib was superior to placebo in all subgroups. Prior use of anti-IgE biologics did not affect efficacy (Figure 2).

Figure 2 – Study A2301 – Subgroup analyses



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.

Study A2302

In the remibrutinib arm the LS mean change in UAS7 from baseline to week 12 was -19.41 points, compared with -11.73 points in the placebo arm. The LS mean difference between treatments was -7.68 points (95%CI: -9.91 to -5.46). The difference was statistically significant ($p < 0.001$).

Table 6. Study A2302 – Change from baseline to week 12 in UAS7

		Within Treatment		Treatment Contrast in LS mean (change)				
Treatment group	n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
LOU064 25mg b.i.d.	297	-19.41	0.702	vs Placebo	-7.68	1.136	(-9.91 , -5.46)	<0.001
Placebo	153	-11.73	0.948					

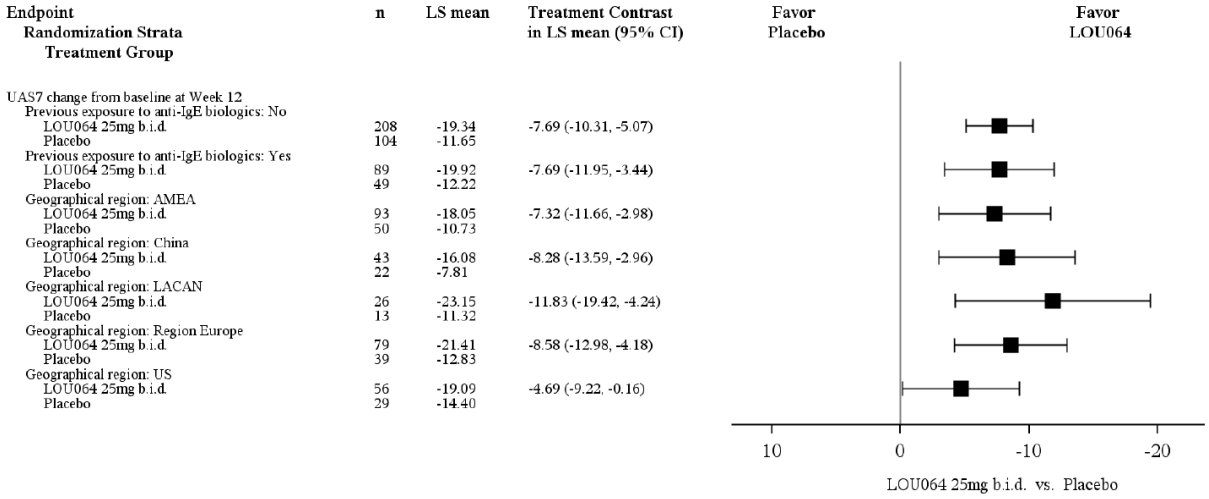
LS Mean: Least squares mean, SE: standard error, CI: confidence interval, p-value: one-sided p-value.
n: number of subjects included in the analysis for each treatment group.
Statistical model used a mixed effect model with repeated measures (MMRM) adjusting for treatment group, geographical region, 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.
Pre-specified intercurrent events are considered. Intake of strongly confounding prohibited medication: Composite strategy (the measurements after the event are excluded and imputed with the worst value). Discontinuation of study treatment due to any reason prior to Week 12: Treatment policy strategy; Intake of rescue medication as per protocol, switch of background medication, intake of other prohibited medication, or non-compliant prior to Week 12: Treatment policy strategy.
Sensitivity analysis

The same sensitivity analysis used in study A2301 was performed. Using this method, in the remibrutinib arm the LS mean change in UAS7 from baseline to week 12 was -19.49 points, compared with -11.85 points in the placebo arm. The LS mean difference between treatments was -7.64 points (95%CI: -9.83 to -5.44). The difference was statistically significant ($p < 0.001$).

Subgroup analysis

Subgroup analyses were presented for the subgroups defined by the randomisation strata. These are illustrated in Figure 3.

Figure 3. Forest plot of the LS mean difference in change from baseline for UAS7, ISS7 and HSS7 at Week 12 (Estimand, MMRM) by randomization strata (previous exposure to anti-IgE biologics, geographical region) Full Analysis Set



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.

Pooled analysis

In the remibrutinib arm (n=606) the LS mean change in UAS7 from baseline to week 12 was -19.93 points, compared with -12.98 points in the placebo arm (n=306). The LS mean difference between treatments was -6.95 points (95%CI: -8.52 to -5.38).

Results for secondary efficacy outcomes

Achievement of UAS7 ≤ 6 at week 12.

Study A2301: In the remibrutinib arm 49.8% of subjects achieved a UAS7 ≤ 6 at week 12 compared to 24.8% of subjects in the placebo arm. The estimated conditional odds ratio was 3.11 (95% CI: 2.00 to 4.84). The difference was statistically significant (p-value < 0.001).

Study A2302: In the remibrutinib arm 46.8% of subjects achieved a UAS7 ≤ 6 at week 12 compared to 19.6% of subjects in the placebo arm. The estimated conditional odds ratio was 3.84 (95% CI: 2.39 to 6.18). The difference was statistically significant (p-value < 0.001).

Pooled analysis: In the remibrutinib arm 48.5% of subjects achieved a UAS7 ≤ 6 at week 12 compared to 22.2% of subjects in the placebo arm. The estimated treatment difference was 26.53% (95% CI: 20.33 to 32.72).

Achievement of UAS7 = 0 at week 12

Study A2301: In the remibrutinib arm 31.1% of subjects achieved a UAS7 = 0 at week 12 compared to 10.5% of subjects in the placebo arm. The estimated conditional odds ratio was 3.83 (95% CI: 2.16 to 6.82). The difference was statistically significant (p-value < 0.001).

Study A2302: In the remibrutinib arm 27.9% of subjects achieved a UAS7 = 0 at week 12 compared to 6.5% of subjects in the placebo arm. The estimated conditional odds ratio was 5.78 (95% CI: 2.83 to 11.78). The difference was statistically significant (p-value < 0.001).

Pooled analysis: In the remibrutinib arm 29.7% of subjects achieved a UAS7 =0 at week 12 compared to 8.5% of subjects in the placebo arm. The estimated treatment difference was 21.02% (95% CI: 16.15 to 25.90).

Absolute change from baseline in ISS7 score at week 12.

Study A2301: In the remibrutinib arm the LS mean change in ISS7 from baseline to week 12 was -9.52 points, compared with -6.89 points in the placebo arm. The LS mean difference between treatments was -2.63 points (95%CI: -3.70 to -1.56). The difference was statistically significant ($p < 0.001$).

Study A2302: In the remibrutinib arm the LS mean change in ISS7 from baseline to week 12 was -8.95 points, compared with -5.72 points in the placebo arm. The LS mean difference between treatments was -3.23 points (95%CI: -4.29 to -2.16). The difference was statistically significant ($p < 0.001$).

Pooled analysis: In the remibrutinib arm the LS mean change in ISS7 from baseline to week 12 was -9.36 points, compared with -6.44 points in the placebo arm. The LS mean difference between treatments was -2.92 points (95%CI: -3.68 to -2.17).

Absolute change from baseline in HSS7 score at week 12.

Study A2301: In the remibrutinib arm the LS mean change in HSS7 from baseline to week 12 was -10.47 points, compared with -6.86 points in the placebo arm. The LS mean difference between treatments was -3.61 points (95%CI: -4.85 to -2.36). The difference was statistically significant ($p < 0.001$).

Study A2302: In the remibrutinib arm the LS mean change in HSS7 from baseline to week 12 was -10.47 points, compared with -6.00 points in the placebo arm. The LS mean difference between treatments was -4.47 points (95%CI: -5.71 to -3.23). The difference was statistically significant ($p < 0.001$).

Pooled analysis: In the remibrutinib arm the LS mean change in HSS7 from baseline to week 12 was -10.59 points, compared with -6.55 points in the placebo arm. The LS mean difference between treatments was -4.04 points (95%CI: -4.92 to -3.16).

Achievement of UAS7 ≤ 6 at week 2.

Study A2301: In the remibrutinib arm 33.7% of subjects achieved a UAS7 ≤ 6 at week 2 compared to 3.3% of subjects in the placebo arm. The estimated conditional odds ratio was 15.67 (95% CI: 6.18 to 39.77). The difference was statistically significant (p-value < 0.001).

Study A2302: In the remibrutinib arm 30.0% of subjects achieved a UAS7 ≤ 6 at week 2 compared to 5.9% of subjects in the placebo arm. The estimated conditional odds ratio was 7.92 (95% CI: 3.72 to 16.85). The difference was statistically significant (p-value < 0.001).

Pooled analysis: In the remibrutinib arm 31.7% of subjects achieved a UAS7 ≤ 6 at week 2 compared to 4.6% of subjects in the placebo arm. The estimated treatment difference was 27.41% (95% CI: 23.10 to 31.72).

Achievement of a score of 0 or 1 on the DLQI at week 12.

Study A2301: In the remibrutinib arm 39.0% of subjects achieved a DLQI of 0 or 1 at week 12 compared to 22.2% of subjects in the placebo arm. The estimated conditional odds ratio was 2.44 (95% CI: 1.53 to 3.90). The difference was statistically significant (p-value < 0.001).

Study A2302: In the remibrutinib arm 35.7% of subjects achieved a DLQI of 0 or 1 at week 12 compared to 18.3% of subjects in the placebo arm. The estimated conditional odds ratio was 2.75 (95% CI: 1.65 to 4.58). The difference was statistically significant (p-value < 0.001).

Pooled analysis: In the remibrutinib arm 37.4% of subjects achieved a DLQI of 0 or 1 at week 12 compared to 19.9% of subjects in the placebo arm. The estimated treatment difference was 17.85% (95% CI: 23.10 to 31.72).

Cumulative number of weeks with a UAS7 ≤ 6 up to week 12

Study A2301: In the remibrutinib arm the LS mean cumulative number of weeks with a UAS score ≤ 6 was 5.17 weeks, compared to 1.92 weeks in the placebo arm. The rate ratio was 2.69 (95%CI: 2.01 to 3.61). The difference was statistically significant (p-value < 0.001).

Study A2302: In the remibrutinib arm the LS mean cumulative number of weeks with a UAS score ≤ 6 was 4.50 weeks, compared to 1.38 weeks in the placebo arm. The rate ratio was 3.26 (95%CI: 2.26 to 4.71). The difference was statistically significant (p-value < 0.001).

Pooled analysis: In the remibrutinib arm the LS mean cumulative number of weeks with a UAS score ≤ 6 was 4.83 weeks, compared to 1.68 weeks in the placebo arm. The rate ratio was 2.87 (95%CI: 2.28 to 4.61).

Cumulative number of weeks with an AAS7 = 0

Study A2301: In the remibrutinib arm the LS mean cumulative number of weeks with an AAS score = 0 was 8.43 weeks, compared to 6.72 weeks in the placebo arm. The rate ratio was 1.25 (95%CI: 1.12 to 1.41). The difference was statistically significant (p-value < 0.001).

Study A2302: In the remibrutinib arm the LS mean cumulative number of weeks with an AAS score = 0 was 8.81 weeks, compared to 6.68 weeks in the placebo arm. The rate ratio was 1.32 (95%CI: 1.17 to 1.49). The difference was statistically significant (p-value < 0.001).

Pooled analysis: In the remibrutinib arm the LS mean cumulative number of weeks with an AAS score = 0 was 8.64 weeks, compared to 6.70 weeks in the placebo arm. The rate ratio was 1.29 (95%CI: 1.19 to 1.40).

Results for exploratory efficacy outcomes

Key findings from the exploratory end points:

- A benefit for remibrutinib over placebo was still apparent at week 24. Similar findings were observed for all the secondary endpoints at week 24.
- In the remibrutinib arm efficacy was maintained up to 52 weeks. A similar pattern was observed for ISS7 and HSS7.
- In the remibrutinib arm efficacy was maintained up to 52 weeks. A similar pattern was observed for achievement of a UAS score ≤ 6, an ISS score =0 and a HSS7 score = 0.
- Additional subgroup analyses indicated an efficacy benefit for remibrutinib over placebo for all subgroups tested. Remibrutinib appeared to be more effective in subjects with low IgE concentrations compared to subjects with high IgE concentrations. Subgroup analyses were also presented for the ISS7, HSS7, UAS≤6 and UAS=0 endpoints and results were similar.

Other efficacy studies

Study CLOU064A2201

This study was a randomised, double-blind, placebo-controlled, Phase 2b dose-finding study with seven parallel groups.

The primary objective of the study was to characterise the dose-response relationship of remibrutinib when administered once or twice daily in subjects with CSU with respect to change from baseline in UAS7 at Week 4. There were several secondary objectives related to UAS7 at week 12, change in UAS7 over time, UAS7=0, UAS7 ≤ 6, number of weeks with an AAS7 = 0 and DLQI.

Results

A total of 311 subjects were randomised. Two of these subjects were mis-randomised and therefore did not receive treatment. 90.4% of subjects completed the study. There was a higher rate of study discontinuation in the 100 mg BD group (20.0% vs. <10% in the other groups).

Protocol deviations were common in all groups.

Mean age of the study population was 45.0 years (range 18 to 78). 71.4% were female and 28.6% were male. 82.3% were white and 16.1% were Asian. The seven groups were reasonably well balanced with respect to baseline demographic characteristics.

Mean baseline UAS7 score was 29.58 (range 11.5 to 42.0). 60.5% of subjects had severe disease (UAS7 28-42) and 38.6% had moderate disease UAS 16 to < 42). 27.0% of subjects had previously been treated with anti-IgE agents. The seven groups were reasonably well balanced with respect to baseline disease characteristics.

An overall dose-response was observed for remibrutinib treatment compared to placebo with respect to change from baseline in UAS7 score at Week 4, based on the MCP-mod approach ($p<0.0001$). The dose response plateaued at the 10 mg OD and 25 mg BD doses. Compared to placebo, the greatest change at Week 4 was observed in the 25 mg BD arm (−14.58 points, 90% CI: -18.43 to -10.73).

The results of this study were the basis for the 25 mg BD dose used in the two pivotal phase 3 studies.

The placebo-corrected change in UAS7 at Week 12 was −12.35 points (90% CI: -16.82 to -7.87), which was notably larger than that observed in the pivotal studies.

Study CLOU064A2201E

This was an open-label, single arm, extension study for patients rolling over from Study A2201. The primary objective of the study was to assess long-term safety. Secondary objectives were related to efficacy endpoints based on UAS7.

The study did not include a placebo arm hence the magnitude of any efficacy benefit cannot be assessed. Also, a number of the efficacy endpoints were assessed at week 4, and the use of H1 antihistamines as background treatment was not permitted during the first 4 weeks of treatment. The efficacy of remibrutinib as add-on therapy to antihistamines was therefore not assessed by these endpoints.

The data from this study suggest that efficacy is maintained out to 52 weeks.

The study also suggests that, after withdrawal of remibrutinib, approximately 50% of subjects will experience disease relapse within 12 weeks.

Study CLOU064A2305

The primary objective of this study was to examine the effects of remibrutinib on blood pressure. The study was a phase 3, open-label, single-arm trial in subjects with CSU. A total of 144 subjects were enrolled and treated. All subjects were treated with remibrutinib 25 mg BD for 12 weeks. A number of efficacy measures were examined as exploratory endpoints (UAS7, ISS7, HSS7, DLQI, AAS7).

This study was a supportive study to exclude an effect of remibrutinib on blood pressure with a limited assessment of efficacy over time to facilitate the physician's decision for the risk/benefit of the patient before entering the available extension study for continuous treatment. As the study did not include a placebo arm, the efficacy data from this study do not provide any useful contribution to the assessment of efficacy.

Study CLOU064A1301

Examined the safety of remibrutinib in patients with CSU. A total of 71 subjects in Japan were treated. The study was a phase 3, open-label, single-arm trial in subjects with CSU. All subjects were treated with remibrutinib 25 mg BD for 52 weeks. A number of efficacy measures were examined as secondary endpoints (UAS7, ISS7, HSS7, DLQI, AAS7). As the study did not include a placebo arm, the efficacy data from this study do not provide any useful contribution to the assessment of efficacy.

Overall, only Study A2201 demonstrated a statistically significant improvement in efficacy outcomes compared to placebo and therefore provides supportive evidence of efficacy. The remaining studies lacked a placebo arm and therefore an objective assessment of efficacy was not possible.

Safety

Safety data was provided by the two pivotal efficacy studies A2301 and A2302. Safety data was pooled into two groups.

Pool 1

Placebo-controlled period

This data set consisted of safety data from the first 24 weeks of two pivotal studies (A2301 and A2302). During this period subjects received their randomised treatment (remibrutinib or placebo). Data from this dataset provided a comparison with placebo over a period of 24 weeks. In this dataset 606 subjects were treated with remibrutinib and 306 with placebo.

Entire study period

This dataset included safety data (from remibrutinib-treated subjects) in the placebo-controlled period (weeks 1 – 24) and the open-label period (weeks 25 – 52) of the two pivotal studies. This dataset provided safety data on remibrutinib treatment for up to 52 weeks. In this dataset 868 subjects were treated with remibrutinib

Pool 2

This dataset included safety data (from remibrutinib-treated subjects) from Pool 1 (entire study period) and from the following additional studies: Study A2201; Study A2201E and Study A 1301. In this dataset 1234 subjects were treated with remibrutinib.

A total of 1019 subjects received remibrutinib for at least 24 weeks, and 654 subjects were treated for at least 52 weeks.

With respect to laboratory data, pooled analyses were only presented for Pool 1.

Of note, All the safety data included in the Pool 1 (entire study period) are also included in Pool 2. This report will therefore focus on the Pool 1 (placebo-controlled period) and Pool 2 datasets for analysis of AEs.

Adverse events

All adverse events (irrespective of relationship to study treatment)

Pool 1 (placebo-controlled) dataset

The overall incidence of adverse events (AEs) was 64.9% with remibrutinib and 64.7% with placebo.

Table 7. Overall and common incidence of AEs in Pool 1

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[28] or the rate difference.[29]

AEs that were notably more common in the remibrutinib arm were mainly petechiae (3.8% vs. 0.3%) and nasopharyngitis (6.6% vs.4.6%). Other AEs that were more common with remibrutinib were contusion (2.1% vs.0.7%), ecchymosis (1.5% vs. 0.3%), neutropenia (1.2% vs. 0.3%), upper respiratory tract infection (3.0% vs. 2.0%), influenza (2.5% vs. 1.3%), nausea (3.0% vs. 1.6%) and back pain (2.1% vs.0.7%).

AE reports of urticaria were more common in the placebo arm (4.9% vs. 2.5%).

Pool 2 dataset

The overall incidence of AEs with remibrutinib was 69.9%.

Common AEs 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%).

Treatment related adverse events (adverse drug reactions)

Pool 1 (placebo-controlled) dataset

The overall incidence of treatment-related AEs was 19.0% with remibrutinib and 12.7% with placebo. Treatment-related AEs that were notably more common in the remibrutinib arm were: petechiae (3.3% vs. 0.3%), ecchymosis (1.2% vs. 0.3%), contusion (1.0% vs. 0.3%), purpura (0.8% vs. 0.0%) and nausea (1.7% vs. 0.3%)

Pool 2 dataset

The overall incidence of treatment-related AEs with remibrutinib was 18.6%.

[28] Garwood F (1936) Fiducial limits for the Poisson distribution. Biometrika; 28(3-4):437-42.

[29] Scosyrev E, Pethe A (2022) Confidence intervals for exposure-adjusted rate differences in randomized trials. Pharm Stat; 21(1):103-21.

Common treatment-related AEs were petechiae (2.5%), headache (1.9%), nausea (1.5%), nasopharyngitis (1.2%), and diarrhoea (1.1%).

Study A2201 (placebo-controlled period)

The overall incidence of treatment-related AEs was 18.4% with remibrutinib (all dose groups combined) and 14.3% with placebo. There was no indication of an increasing incidence of treatment-related AEs with increasing dose.

The only treatment-related AEs that were notably more common with remibrutinib treatment were nasopharyngitis (3.4% vs. 0.0%) and nausea (2.6% vs. 0.0%).

Deaths and other serious adverse events

There were no deaths reported in any of the clinical studies. Serious AEs are described below.

Pool 1 (placebo-controlled) dataset

The overall incidence of serious AEs was 3.3% with remibrutinib and 2.3% with placebo. Individual preferred AE terms were reported by a single patient only. There was a slightly increased incidence of serious musculoskeletal AEs with remibrutinib treatment (0.7% vs. 0.0%).

Pool 2 dataset

The overall incidence of serious AEs was 3.4% with remibrutinib. Individual serious AE preferred terms that were reported by more than 1 subject were CSU (0.2%, n = 3), appendicitis (0.2%, n = 2) and pruritus (0.2%, n = 2).

Study A2201 (placebo-controlled period)

The overall incidence of serious AEs was 1.9% with remibrutinib (all dose groups combined) and 0.0% with placebo. There was no indication of an increasing incidence of serious AEs with increasing dose. The only SAE reported by more than one subject was CSU.

Discontinuations due to adverse events

Pool 1 (placebo-controlled) dataset

The overall incidence of AEs leading to discontinuation was 2.8% with remibrutinib and 2.9% with placebo. In the remibrutinib group, individual preferred AE terms were reported by a single patient only. In the placebo arm there were 3 discontinuations due to urticaria.

Pool 2 dataset

The overall incidence of AEs leading to discontinuation was 4.1% with remibrutinib. Individual AE preferred terms that were reported by more than 1 subject were: diarrhoea (0.2%, n = 2), COVID-19 (0.2%, n = 2), urinary tract infection (0.2%, n = 2), petechiae (0.2%, n = 2), purpura (0.2%, n = 2) and urticaria (0.2%, n = 2).

Study A2201 (placebo-controlled period)

The overall incidence of AEs leading to discontinuation was 2.6% with remibrutinib (all dose groups combined) and 0.0% with placebo. There was no indication of an increasing incidence of such AEs with increasing dose. In the remibrutinib group, individual preferred AE terms were reported by a single patient only.

AE of special interest - infections

Pool 1 (placebo-controlled) dataset

The overall incidence of AEs under the System Organ Class (SOC) heading of "Infections and infestations" was 33.5% with remibrutinib and 34.3% with placebo. Nasopharyngitis, influenza and upper respiratory tract infection were more common in the remibrutinib arm

The incidence of serious infections was 0.7% in each arm. One subject (0.2%) discontinued treatment with remibrutinib due to an infection (COVID-19) compared with none in the placebo arm.

Most infections in both groups were assessed as being mild or moderate. There were two severe infections with remibrutinib (1 bronchitis and 1 acarodermatitis) with remibrutinib and none with placebo.

Pool 2 dataset

The overall incidence of infection AEs was 40.8%. Common infections were the same as those observed in the Pool 1 (placebo-controlled) dataset.

Study A2201 (placebo-controlled period)

The overall incidence of infection AEs was 25.1% with remibrutinib (all dose groups combined) and 21.4% with placebo. There was no indication of an increasing incidence of infection AEs with increasing dose.

The only infection AEs that were notably more common with remibrutinib treatment were nasopharyngitis (8.6% vs. 7.1%) and cystitis (1.9% vs. 0.0%).

There was one serious infection with remibrutinib (renal abscess) and none with placebo.

Adverse events of special interest - bleeding

Pool 1 (placebo-controlled) dataset

The overall incidence of bleeding adverse events of special interest (AESI) was 10.6% with remibrutinib and 5.2% with placebo. Bleeding AESI that were notably more common with remibrutinib treatment were petechiae (3.8% vs. 0.3%), contusion (2.1% vs. 0.7%), and (ecchymosis 1.5% vs. 0.3%).

There were two serious bleeding AESI with remibrutinib (1 contusion and 1 haematuria) and none with placebo. Both events were assessed as being unrelated to study treatment.

In the remibrutinib group there were two bleeding AESI leading to discontinuation (1 petechiae and 1 purpura) compared with none in the placebo arm.

In the remibrutinib group 88.7% of the bleeding AESI were mild and 11.3% were moderate. None were assessed as severe.

Pool 2 dataset

The overall incidence of bleeding AESI was 10.5%. Common bleeding AESI were the same as those observed in the Pool 1 (placebo-controlled) dataset.

There was one additional serious bleeding event. The AESI was assessed as being related to the bariatric surgery and not to remibrutinib. Nevertheless, the drug was discontinued.

Study A2201 (placebo-controlled period)

The overall incidence of bleeding AESI was 6.7% with remibrutinib (all dose groups combined) and 2.4% with placebo. There was no indication of an increasing incidence of bleeding AESI with increasing dose. Petechiae was the most commonly reported event (1.5% vs. 0.0%).

There were no serious bleeding AESI. Two subjects treated with remibrutinib discontinued due to a bleeding AE (1 petechiae and 1 haematuria) compared with none in the placebo arm.

Cytopaenias

Pool 1 (placebo-controlled) dataset

The overall incidence of cytopaenia AEs was 3.6% with remibrutinib and 2.0% with placebo. Cytopaenia AEs that were notably more common with remibrutinib treatment were neutropaenia (1.2% vs. 0.3%).

There were no serious cytopaenia AEs reported. One remibrutinib-treated subject discontinued due to thrombocytopaenia. All AEs were assessed as mild or moderate. There were no severe cytopaenias AEs reported.

Pool 2 dataset

The overall incidence of cytopaenia AEs was 4.5%. Common cytopaenia AEs were the same as those observed in the Pool 1 (placebo-controlled) dataset.

Study A2201 (placebo-controlled period)

The overall incidence of cytopaenia AEs was 3.0% with remibrutinib (all dose groups combined) and 2.4% with placebo. There was no indication of an increasing incidence of bleeding AEs with increasing dose. Neutropaenia was the most reported event (1.5% vs. 0.0%).

Risk management plan

Novartis Pharmaceuticals Australia Pty Ltd has submitted EU-RMP version 1.0 (dated 22 November 2024; DLP 4 August 2024) and ASA version 1.0 (dated 8 April 2025) in support of this application. The sponsor has provided ASA version 1.1 (dated 11 December 2025) and EU-RMP version 1.1 (dated 26 September 2025; DLP 4 August 2024) was subsequently provided upon request. The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 8. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 8. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	-
Important potential risks	Serious bleeding events	✓	✓*	✓	–
	Teratogenicity	✓	–	✓	–
Missing information	Long term safety	✓	✓*	–	–

*Study CLOU064A2303B

Risk-benefit analysis

Efficacy

Evidence supporting the efficacy of remibrutinib for adult patients with CSU who remain symptomatic despite H1 antihistamine therapy is derived from two identical, randomized,

double-blind, placebo-controlled trials (A2301 and A2302). Both studies were methodologically robust and yielded consistent results.

Participants enrolled exhibited moderate to severe disease, aligning with populations typically encountered in Australian clinical practice. The demographic profile was predominantly female, with a mean age ranging from 41 to 45 years.

The primary endpoint was the absolute change from baseline in UAS7 at Week 12.

In study A2301, in the remibrutinib arm the LS mean change in UAS7 from baseline to week 12 was -20.02 points, compared with -13.79 points in the placebo arm. The LS mean difference between treatments was -6.22 points (95%CI: -8.45 to -4.00). The difference was statistically significant ($p < 0.001$). Similarly, In study A2302, in the remibrutinib arm the LS mean change in UAS7 from baseline to week 12 was -19.41 points, compared with -11.73 points in the placebo arm. The LS mean difference between treatments was -7.68 points (95%CI: -9.91 to -5.46). The difference was statistically significant ($p < 0.001$).

Secondary endpoints included assessment of the proportion of subjects who achieved a UAS7 ≤ 6 or UAS7 = 0, change from baseline in itch and hives scores and effects on angioedema and quality of life. A significant benefit for remibrutinib over placebo was demonstrated for all secondary endpoints in both studies.

A minimally important difference for the UAS7 score is estimated to be approximately a change of 10 points.[30] The placebo-corrected change from baseline in both pivotal studies was less than this level. Across the whole population the efficacy of remibrutinib would therefore appear to be modest.

Achievement of a UAS7 = 0 is a clinically significant outcome. This was measured as a secondary endpoint.

In study A2301, in the remibrutinib arm 31.1% of subjects achieved a UAS7 = 0 at week 12 compared to 10.5% of subjects in the placebo arm. The difference was statistically significant.

In study A2302, in the remibrutinib arm 27.9% of subjects achieved a UAS7 = 0 at week 12 compared to 6.5% of subjects in the placebo arm. The difference was again statistically significant.

Achievement of a UAS7 ≤ 6 is also clinically significant outcome. This was also measured as a secondary endpoint.

In study A2301, in the remibrutinib arm 49.8% of subjects achieved a UAS7 ≤ 6 at week 12 compared to 24.8% of subjects in the placebo arm. The difference was statistically significant.

In study A2302, in the remibrutinib arm 46.8% of subjects achieved a UAS7 ≤ 6 at week 12 compared to 19.6% of subjects in the placebo arm. The difference was statistically significant.

Based on these endpoints, remibrutinib would appear to provide clinically significant benefits for approximately 20-25% of treated subjects.

Remibrutinib is intended for long-term treatment. The studies in the submission provided uncontrolled data that supports the maintenance of efficacy out to 52 weeks of treatment.

The pivotal studies only included subjects with moderate or severe disease (UAS7 ≥ 16 at baseline). Whether remibrutinib prides any efficacy benefits for subjects with mild disease is unknown.

[30] Hawro T, Ohanyan T, Schoepke N et al. The Urticaria Activity Score-Validity, Reliability, and Responsiveness. J Allergy Clin Immunol Pract. 2018; 6 (4): 1185-1190.e1.

The current standard treatment of CSU in adult patients who remain symptomatic despite H1 antihistamine treatment is omalizumab. The submitted data do not clarify the role of remibrutinib in relation to omalizumab treatment – i.e. whether it is best employed before omalizumab treatment, after omalizumab failure or in combination with omalizumab. Subgroup analyses of the pivotal studies established that remibrutinib is also effective in subjects who have previously received treatment with anti-IgE therapies such as omalizumab. It therefore may have a role in subjects who are intolerant to omalizumab (e.g. due to allergy). Remibrutinib may be more acceptable to some patients in terms of route of administration (oral versus subcutaneous).

In summary, remibrutinib demonstrates statistically significant efficacy over placebo, though the overall benefit appears modest.

Safety

A total of approximately 2000 subjects were exposed to remibrutinib in the submitted studies. 1378 of these subjects had CSU.

The most informative safety data come from the two pivotal efficacy studies which provided a randomised, double-blind comparison of remibrutinib with placebo over a period of 24 weeks. Based on the pooled data from these studies, remibrutinib would appear to have limited toxicity. The incidence of the various categories of AEs was similar in the two treatment groups as shown in Table 9.

Table 9. Categories of AEs- pooled data from pivotal studies

	Remibrutinib	Placebo
All AEs	64.9%	64.7%
Severe AEs	2.8%	2.3%
Treatment-related AEs	19.0%	12.7%
Serious AEs	3.3%	2.3%
AEs leading to discontinuation	2.8%	2.9%

Across all studies the toxicities which appeared to be more frequent with remibrutinib were the following:

Bleeding events

These typically were minor AEs in the skin such as petechiae, ecchymosis, contusion and purpura, as well as haematuria. There were three serious bleeding AEs reported in the clinical studies, however none of these were assessed as being related to remibrutinib.

In vitro and animal studies have demonstrated that remibrutinib impairs platelet function.

In the pivotal studies subjects were permitted to use anti-platelet agents such as aspirin and clopidogrel, but anticoagulants (e.g. warfarin) were prohibited. The draft PI contains a precautionary statement regarding the potential for interactions with these agents.

Upper respiratory tract infections

In placebo-controlled studies there was an increased incidence of AEs such as nasopharyngitis, upper respiratory tract infection and influenza. There was no increase in the incidence of serious infections.

Neutropaenia

Adverse event reports of neutropaenia were more common with remibrutinib than with placebo in the pivotal studies and in phase 2 study A2201. Laboratory testing in the pivotal studies suggested that any increase in neutropaenia was only grade 1 or 2 in severity.

Nausea

Nausea was more common with remibrutinib than with placebo in the pivotal studies and in some of the phase 2 studies. In the pivotal studies nausea was reported by 18 subjects. Severity was assessed as mild in 17 and moderate in 1 subject.

Remibrutinib is intended for long term use. In the submitted studies in CSU subjects a total of 1019 subjects received remibrutinib for at least 24 weeks, and 654 subjects were treated for at least 52 weeks. These numbers met the requirements of the relevant EMA guideline adopted by the TGA, which suggests that 300-600 patients should be treated for 6 months, and 100 patients for 12 months.[31]

In the submitted studies, long term treatment was not associated with increases in exposure-adjusted incidence rates or the development of new toxicities.

The submitted data are considered adequate to define the toxicity of remibrutinib.

Data limitations

Efficacy in subjects with mild CSU has not been established.

Efficacy compared to current standard therapy (omalizumab) has not been established.

Efficacy in subjects aged < 18 years has not been tested.

Clinical trial population did not include Aboriginal, Torres islander population. However, it did include Americal Indians and native subjects.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Rhapsido (remibrutinib) 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.*

Specific conditions of registration

Rhapsido (remibrutinib) is to be included in the Black Triangle Scheme. The PI and CMI for Rhapsido must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

The Rhapsido EU-Risk Management Plan (RMP) (version 1.1, dated 26 September 2025; DLP 4 August 2024), with Australia-Specific Annex (ASA) (version 1.1, dated 11 December 2025), included with submission PM-2025-01101-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

[31] European Medicines Agency (EMA). Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95)

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must be submitted within ninety calendar days of the data lock point for that report.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

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