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Newcastle University

Health Technology Briefing
July 2023

Remibrutinib for treating chronic spontaneous urticaria inadequately controlled by H1-antihistamines

Company/Developer	Novartis Pharmaceuticals UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27708	NICE ID: Not available	UKPS ID: 663905

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Remibrutinib is currently in clinical development for the treatment of chronic spontaneous urticaria (CSU) in adult patients inadequately controlled by H1-antihistamines. CSU is a distressing skin condition that is characterised by itchy and sometimes painful raised rash or patches for at least six weeks with no known obvious trigger. It may also be accompanied by deep swelling of the face, neck, hands, or feet. CSU can persist for 1–5 years, sometimes longer. CSU can affect daily life in many ways, including sleep deprivation, anxiety, work, school, and social isolation. Antihistamines are the mainstay treatment for chronic spontaneous urticaria. In non-responsive patients, omalizumab is indicated. However, in a significant percentage of patients, it is not possible to achieve complete control of the symptoms.

Remibrutinib is a novel medicinal product that works by blocking the key drivers of immune response and inflammation which are associated with the cause of urticaria. If licensed, oral remibrutinib will offer an additional treatment option for adult patients with CSU with inadequate response to antihistamine treatment.

Proposed Indication

Treatment of chronic spontaneous urticaria (CSU) in adult patients (18 years and older) inadequately controlled by H1-antihistamines.[1,2]

Technology

Description

Remibrutinib (LOU064) is a highly selective, oral, novel covalent Bruton tyrosine kinase inhibitor (BTK). BTK is a cytoplasmic kinase expressed in B-cells, macrophages, and mast cells/basophils.[3]BTK regulates FcεRI signaling in human mast cells and basophils, via FcεRI, as well as in B cells, via the B-cell receptor. Treatment with BKT inhibitors blocks IgE-mediated activation of mast cells and basophils, which is associated with CSU pathogenesis.[4]

Remibrutinib is currently in clinical development for the treatment of symptomatic CSU in adult patients inadequately controlled by H1-antihistamines. In phase III clinical trials (NCT05030311, NCT05032157), remibrutinib is administered orally, for 52 weeks at an unspecified dose.[1,2]

Key Innovation

CSU is a debilitating autoimmune disease with an unmet need for novel treatment options.[4] Patients with CSU often have a severely impaired quality of life, with negative effects on sleep, daily activities, school or work life, mental health, and social interactions.[5,6] Current recommended treatments include second-generation antihistamines at up to 4-fold licensed doses.[7,8] Antihistamines are the mainstay treatment for CSU. In non-responsive patients, biologic therapy with anti-IgE antibodies (omalizumab) is indicated.[9] However, in a significant percentage of patients it is not possible to achieve a complete control of the symptoms, highlighting the importance of exploring new therapeutic targets.[10]

Remibrutinib is a new medicinal product that exhibits high kinase selectivity due to binding to an inactive conformation of BTK, which is implicated in CSU.[3,11] Furthermore, research showed that remibrutinib demonstrated robust clinical efficacy, rapid onset of action and a favourable safety profile with a broad range of doses, indicating its potential as an oral treatment option for patients with moderate to severe CSU.[3] If licensed, remibrutinib will offer an additional treatment option for the treatment of symptomatic CSU in adult patients inadequately controlled by H1-antihistamines.

Regulatory & Development Status

Remibrutinib does not currently have marketing authorisation in the EU/UK for any indication.

Remibrutinib is in phase II/III clinical development for the following indication in adults:[12]

- Relapsing multiple sclerosis
- Peanut allergy

Patient Group

Disease Area and Clinical Need

CSU is a common and distressing skin condition that causes red, raised, itchy, and sometimes painful hives or wheals (raised rash or patches) that have been present persistently (with changing pattern of urticarial rash) or sporadically for at least six weeks on the skin with no known obvious trigger.[13,14] The wheals can be associated with large swellings (angioedema) in about 40% of cases, but angioedema may occur on its own in some people.[14,15] The swelling is usually skin coloured, asymptomatic, itchy, or cause burning pain,

but it can be erythematous, while the wheals are generally very itchy and can also cause a burning sensation.[15] The swelling is often localised and commonly affects the eye lids, lips, tongue, upper palate, pharynx, uvula, hands, feet and genitalia.[14] Urticaria is a mast cell-driven disease. Activated mast cells release histamine along with other mediators, such as platelet-activating factor and cytokines, resulting in sensory nerve activation, vasodilation, plasma extravasation, and recruitment of cells to the urticarial lesion. Many different molecules can activate mast cells in urticaria, but generally, these are not well defined.[15] Evidence suggests that 50% cases of CSU have been linked to autoimmune disease, especially in those not responding to antihistamine therapy. Other aggravating factors can include medication, stress and infection.[13]

0.5-1% of the UK population is thought to be affected by CSU. Females are twice as likely as males to be diagnosed with CSU. It can affect both children and adults, although it is more common in older children and adolescents than infants. People aged 20-40 years are most likely to develop symptoms.[13] In England (2021-22), there were 7,083 finished consultant episodes (FCE) for urticaria (ICD-10 code: L50), 5,172 of which were for adults, with 6,675 hospital admissions that resulted in 3,908 day cases and 1,886 FCE bed days.[16]

Recommended Treatment Options

NICE recommended treatment options for CSU inadequately controlled by H1-antihistamines:[17,18]

- Switch to an alternative non-sedating antihistamine.
- Increase the dose of the first-line antihistamine to up to four times the standard licensed dose (off-label use).
- A leukotriene receptor antagonist (such as montelukast or zafirlukast) in addition to the non-sedating antihistamine.
- A topical antipruritic treatment (such as calamine lotion or topical menthol 1% in aqueous cream) to relieve itch.
- An additional sedative antihistamine (such as chlorphenamine) at night, if itch is interfering with sleep.
- A short course of an oral corticosteroid (for example prednisolone 40 mg daily for up to 7 days) in addition to the non-sedating oral antihistamine, if symptoms are sever.
- Secondary care treatment options also include cyclosporine, omalizumab, mycophenolate mofetil, or tacrolimus
- Omalizumab as an add-on therapy for treating severe CSU in adults and young people aged 12 years and over.

Clinical Trial Information

Trial	**REMIX-2**; NCT05032157; EudraCT 2021-000424-35 A multicentre, randomized, double-blind, placebo-controlled phase 3 study of remibrutinib (LOU064) to investigate the efficacy, safety, and tolerability for 52 weeks in adult chronic spontaneous urticaria (CSU)	NCT05513001; EudraCT-2022-001034-11 A multicentre, double-blind, placebo-controlled, randomised withdrawal and open-label extension study followed by long-term open-label treatment cycles to assess the efficacy, safety, and tolerability of remibrutinib (LOU064) in adult chronic spontaneous urticaria

	patients inadequately controlled by H1-antihistamines. **Phase III-** Active, not recruiting. **Location(s):** 5 EU countries, UK, USA, Canada, and others **Primary completion date:** February 2024	patients who completed the preceding remibrutinib phase 3 studies. **Phase III-** Recruiting **Location(s):** 7 EU countries, USA, Canada, Australia, and other countries **Primary completion date:** July 2027
Trial Design	Randomised, parallel-assignment, quadruple-blinded, placebo-controlled	Randomised, parallel-assignment, quadruple-blinded, placebo-controlled
Population	N= 456 (actual); adult participants (age 18 years and older) with CSU duration for ≥ 6 months prior to screening	N= 1021 (estimated); adult patients (age 18 years and older) with CSU who successfully completed the preceding core studies CLOU064A2301, CLOU064A2302, CLOU064A1301, CLOU064A2304 or CLOU064A2305 according to the respective protocols.
Intervention(s)	• Oral remibrutinib (blinded) taken twice daily for 24 weeks, followed by oral remibrutinib (open label) taken for 28 weeks.	• Oral remibrutinib (blinded) taken for 24 weeks, followed by cycles of either oral remibrutinib (open-label) taken for a maximum of 5 cycles of 24 weeks each or treatment-free observation cycles. • Oral remibrutinib (open label) taken for 24 weeks per treatment cycle
Comparator(s)	Oral placebo (blinded) taken for 24 weeks, followed by oral remibrutinib (open label) taken for 28 weeks.	Oral remibrutinib placebo (blinded) taken for 24 weeks, followed by cycles of either oral remibrutinib (open-label) taken for a maximum of 5 cycles of 24 weeks each or treatment-free observation cycles.
Outcome(s)	Primary outcomes measures: Change from baseline in UAS7 (Scenario 1 with UAS7 as primary efficacy endpoint) [Time Frame: 12 weeks] Absolute change in ISS7 an absolute change in HSS7 (Scenario 2 with ISS7 and HSS7 as co-primary efficacy endpoints) [Time Frame: 12 weeks] See trial record for full list of other outcomes.	Primary outcome measure: Time to first composite event (i.e., relapse (UAS7≥16) [Time Frame: 24 weeks] See trial record for full list of other outcomes.
Results (efficacy)	-	-
Results (safety)	-	-

Clinical Trial Information		
Trial	**REMIX-1; NCT05030311; EudraCT-2021-000471-37** A multicentre, randomized, double-blind, placebo-controlled phase 3 study of Remibrutinib (LOU064) to investigate the efficacy, safety and tolerability for 52 weeks in adult chronic spontaneous urticaria (CSU) patients inadequately controlled by H1-antihistamines. **Phase III-** Active, not recruiting. **Location(s):** 6 EU countries, USA, and other countries **Primary completion date**: February 2024	**NCT05513001; EudraCT-2022-001034-11** A multicentre, double-blind, placebo-controlled, randomised withdrawal and open-label extension study followed by long-term open-label treatment cycles to assess the efficacy, safety, and tolerability of remibrutinib (LOU064) in adult chronic spontaneous urticaria patients who completed the preceding remibrutinib phase 3 studies. **Phase III-** Recruiting **Location(s):** 7 EU countries, USA, Canada, Australia, and other countries **Primary completion date:** July 2027
Trial Design	Randomised, parallel-assignment, quadruple-blinded, placebo-controlled	Randomised, parallel-assignment, quadruple-blinded, placebo-controlled
Population	N= 470 (actual); adult patients (age 18 years and older) with CSU duration for ≥ 6 months prior to screening	N= 1021 (estimated); adult patients (age 18 years and older) with CSU who successfully completed the preceding core studies CLOU064A2301, CLOU064A2302, CLOU064A1301, CLOU064A2304 or CLOU064A2305 according to the respective protocols.
Intervention(s)	• Oral remibrutinib (blinded) taken for 24 weeks followed by oral remibrutinib (open label) for 28 weeks.	• Oral remibrutinib (blinded) taken for 24 weeks, followed by cycles of either oral remibrutinib (open-label) taken for a maximum of 5 cycles of 24 weeks each or treatment-free observation cycles. • Oral remibrutinib (open label) taken for 24 weeks per treatment cycle
Comparator(s)	Oral remibrutinib placebo (blinded) for 24 weeks, followed by oral remibrutinib (open label) for 28 weeks.	Oral remibrutinib placebo (blinded) taken for 24 weeks, followed by cycles of either oral remibrutinib (open-label) taken for a maximum of 5 cycles of 24 weeks each or treatment-free observation cycles.

Outcome(s)	Primary outcome measure: change from baseline in UAS7 (Scenario 1 with UAS7 as primary efficacy endpoint) [Time Frame: 12 weeks] See trial record for full list of other outcomes.	Primary outcome measure: Time to first composite event (i.e., relapse (UAS7≥16) [Time Frame: 24 weeks] See trial record for full list of other outcomes.
Results (efficacy)	-	-
Results (safety)	-	-

Clinical Trial Information		
Trial	NCT03926611; EudraCT-2018-000993-31 A multicentre, randomized, double-blind, placebo- controlled phase 2b dose-finding study to investigate the efficacy, safety and tolerability of LOU064 in adult chronic spontaneous urticaria (CSU) patients inadequately controlled by H1-antihistamines. **Phase IIb-** Completed **Location(s):** 10 EU countries, UK, USA, Canada and other countries **Study completion date:** April 2021	NCT04109313; EudraCT 2019-001074-29 An open-label, multicentre, extension study to evaluate the long-term safety and tolerability of LOU064 in eligible subjects with CSU who have participated in preceding studies with LOU064. **Phase II**- Completed **Location(**s): 8 EU countries, UK, USA, Canada, and others. **Study completion date:** September 2022
Trial Design	Randomised, parallel-assignment, triple-blinded, placebo-controlled	Single-group assignment, open-label
Population	N=311 (actual); adult patients (age 18 years and older) with CSU diagnosis for ≥ 6 months prior to screening	N= 195 (actual); adults (age 18 years and older) with CSU who have participated in preceding studies with remibrutinib
Intervention(s)	• 10 mg oral remibrutinib (once daily) and matching placebo • 35mg oral remibrutinib (once daily) and matching placebo • 100mg oral remibrutinib (once daily) and matching placebo • 10mg oral remibrutinib (twice daily) • 25mg oral remibrutinib (twice daily) • 100mg oral remibrutinib (twice daily)	• 100mg oral remibrutinib (twice daily)
Comparator(s)	Matching placebo	No comparator
Outcome(s)	Primary outcome measure: Change from baseline in weekly urticaria	Primary outcome measures: • Long-term safety and tolerability of LOU064

	activity score (UAS7) at week 4 [Time Frame: Baseline, Week 4] See trial record for full list of other outcomes	[Time Frame: overtime from week 1 to week 68] See trial record for full list of other outcomes.
Results (efficacy)	See trial record.	-
Results (safety)	See trial record.	-

Estimated Cost

The cost of remibrutinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Omalizumab for previously treated chronic spontaneous urticaria (TA339) June 2015.
- NICE evidence summary. Chronic urticaria: off-label doses of cetirizine (ESUOM31). July 2014.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Specialised Allergy Services (All Ages). B09/S/b.
- NHS England. 2013/14 NHS Standard Contract for Specialised Dermatology Services (All Ages). A12/S/a.

Other Guidance

- British Association of Dermatologists. British Association of Dermatologists guidelines for the management of people with chronic urticaria. 2021.[19]
- NHS North Central London Joint Formulary Committee. Guideline for the treatment of Chronic Spontaneous Urticaria in adult patients. 2020.[20]
- British Society for Allergy and Clinical Immunology (BSACI). BSACI guideline for the management of chronic urticaria and angioedema. 2015.[21]

Additional Information

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