Health Technology Briefing
June 2024

Camlipixant for treating refractory or unexplained chronic cough

Company/Developer	GlaxoSmithKline UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28295	NICE ID: N/A	UKPS ID: 673505

Licensing and Market Availability Plans

Currently in phase II/III clinical development.

Summary

Camlipixant is in clinical development for the treatment of adults with refractory or unexplained chronic cough. Cough is a normal reflex response to airway irritation, triggered by stimulation of airway cough receptors, which protect against choking and enhance airway clearance. Chronic cough is a persistent cough that lasts for eight weeks or longer. Refractory cough refers to chronic cough that fails to respond to treatment of the underlying condition (in cases where an underlying condition has been identified) and unexplained chronic cough where the underlying cause cannot be identified. Current treatments target the underlying condition and not the cough itself. In cases where there is no underlying condition, many current treatments are used to 'mask' symptoms but with limited effectiveness at treating the cough. Available treatment options are used off-label, which means they have not been specifically approved for the treatment of chronic cough, as such this is an area of unmet need.

Camlipixant is an oral drug that blocks receptors in the sensory cells in the airways and lungs, potentially reducing cough frequency in patients with refractory or unexplained chronic cough. Preliminary results from early studies have demonstrated that camlipixant is effective and safe. If licenced, camlipixant could provide a treatment option for patients with refractory or unexplained cough who have no licensed therapies available and few effective therapies available.

Proposed Indication

Treatment of adult patients with refractory or unexplained chronic cough.[1]

Technology

Description

Camlipixant (NEO-5937, BLU-5937) is under development for the treatment of chronic refractory cough and other cough hypersensitization-related disorders. The drug candidate is a benzoimidazole derivative, formulated as a tablet and is administered through oral route. The drug candidate targets the P2X purinoceptor 3 (P2X3) receptor. P2X3 is part of peripheral neuronal activation and when sensitised can lead to excessive coughing.[1-3]

Camlipixant is currently in phase II and III clinical development (RELIEF, NCT03979638; SOOTHE, NCT04678206; CALM-2, NCT05600777; CALM-1, NCT05599191) for the treatment of adults with refractory or unexplained chronic cough.[1,4-6] In the phase III trials, camlipixant is administered orally twice daily at a dose of 25mg or 50mg for either 52 weeks (CALM-1) or 24 weeks (CALM-2).[1,4]

Key Innovation

P2X3 is a validated biological target implicated in cough reflex hypersensitisation, and camlipixant is a highly selective P2X3 antagonist. Current clinical data show that by selectively inhibiting P2X3 receptors, camlipixant may reduce cough frequency for patients suffering from refractory or unexplained chronic cough. This medicine is associated with a relatively low incidence of dysgeusia, the taste disturbance adverse event associated with other medicines that broadly target the P2X2/3 receptors.[7] The Phase IIb data from SOOTHE (NCT04678206) also demonstrated a clinically meaningful and nominally significant benefit for camlipixant across multiple patient reported outcomes, which included the Cough Severity Visual Analogue Scale and the Leicester Cough Questionnaire. This data therefore highlights the potential for camlipixant to reduce both cough frequency and severity - and also to improve health-related quality of life as a result.[8]

Regulatory & Development Status

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

Patient Group

Disease Area and Clinical Need

Cough is a protective reflex response to airway irritation. Normally it is triggered by stimulation of airway cough receptors, either by irritants or by conditions that cause airway distortion.[9] Chronic cough is a cough that lasts eight weeks or longer in adults, or four weeks in children.[10] Patients with the condition cough hundreds or even thousands of times per day; this is similar to the frequency of coughing that occurs in acute viral cough, but chronic cough can persist for months or years.[11] Chronic refractory cough is defined as a cough that persists despite guideline-based treatment.[12] An unexplained chronic cough in adults is a cough that persists longer than eight weeks and remains unexplained after investigation and supervised therapeutic trials done according to best-practice guidelines in an adherent patient.[13] The following are

some of the common conditions associated with chronic cough, in many cases there may be more than one cause:[14]

- Gastro-oesophageal reflux disease and laryngopharyngeal reflux: Acid from your stomach rises up the oesophagus and tips over onto the vocal cords irritating the back of the throat
- Post-nasal drip: Excess mucous from your nose/sinuses drips down the back of your throat
- Asthma: Cough variant asthma can present with cough as the main symptom
- Infections: A cough can remain even after other symptoms of a cold, throat infection or chest infection have gone
- Medications: Angiotensin-converting enzyme inhibitors are commonly prescribed for high blood pressure and heart failure and can cause a chronic cough as a side effect in some people.

In some cases, there is no obvious cause. Some people have a very sensitive cough reflex which does not easily respond to treatment of accompanying conditions.[14] Anxiety is common in chronic cough alongside low mood (more likely if pre-existing depression), fatigue, physical symptoms, negative illness beliefs and a lack of a clear illness narrative when their condition is unexplained. Concerns around serious underlying illness are common. Sufferers report embarrassment and significant social effort directed at managing negative reactions of others to the cough. Work absenteeism and primary care attendance is frequent. Repetitive investigations, trials of treatment and referrals to secondary care increase healthcare costs. The 'over-the-counter' cough remedy market is significant, around £400m/pa in the UK.[15] Refractory or unexplained chronic cough significantly impacts quality of life, with patients suffering from depression (53%), urinary incontinence (~50%), pain, rib fractures, social withdrawal, and loss of sleep.[16,17]

In England in 2022-23, there were 16,088 finished consultant episodes (FCE) and 15,235 admissions for Cough (ICD-10 code: R05) of which refractory cough makes up a subset, which resulted in 6,147 FCE bed says and 3,158 day cases.[18]

Recommended Treatment Options

There is no treatment option recommended by NICE for adults with refractory or unexplained chronic cough.

Off-label pharmacological treatment options for people with refractory or unexplained chronic cough may include a trial of low dose morphine (5 mg to 10 mg twice daily), or a trial of gabapentin.[19] [20,21]

Clinical Trial Information

Trial	**CALM-1; NCT05599191;** A Phase 3, 52-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Efficacy and Safety Study With Open-Label Extension of BLU-5937 in Adult Participants With Refractory Chronic Cough, Including Unexplained Chronic Cough **Phase III** - Recruiting **Location(s):** Six EU countries, UK, USA and Canada **Primary completion date:** September 2025
Trial Design	Randomised, parallel assignment, quadruple masked.
Population	N=825 (Estimated). Adults aged 18 to 80 years old with refractory or unexplained chronic cough for at least one year.
Intervention(s)	BLU-5937 (administered orally twice daily at 25mg or 50mg dose)

Comparator(s)	Matched placebo (administered orally twice daily)
Outcome(s)	**Primary outcome measure:** • 24-hour cough frequency [Time frame: week 12] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-
Trial	**CALM-2;** NCT05600777; A Phase 3, 24-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Efficacy and Safety Study With Open-Label Extension of BLU-5937 in Adult Participants With Refractory Chronic Cough, Including Unexplained Chronic Cough **Phase III -** Recruiting **Locations:** Three EU countries, UK, USA, Australia and other countries **Primary completion date:** September 2025
Trial Design	Randomised, parallel assignment, quadruple masked.
Population	N=825 (Estimated). Adults aged 18 to 80 years old with refractory or unexplained chronic cough for at least one year.
Intervention(s)	BLU-5937 (administered orally twice daily at 25mg or 50mg dose)
Comparator(s)	Matched placebo (administered orally twice daily)
Outcome(s)	**Primary outcome measure:** • 24-hour cough frequency [Time frame: week 24] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-
Trial	**SOOTHE;** NCT04678206; EudraCT 2020-004136-17; A Randomized, Adaptive, Double-Blind, Placebo-Controlled, Parallel-Arm, Phase 2b Study to Evaluate the Efficacy and Safety of Multiple Doses of BLU-5937 in Adult Participants With Refractory Chronic Cough **Phase II -** Completed **Locations:** Four EU countries, UK, USA and Canada **Study completion date:** November 2021
Trial Design	Randomised, parallel assignment, quadruple masked.
Population	N= 310 (Actual). Adults aged 18 to 80 years old with refractory or unexplained chronic cough for at least one year.
Intervention(s)	BLU-5937 (administered orally twice daily – unspecified dose)
Comparator(s)	Matched placebo (administered orally twice daily)
Outcome(s)	**Primary outcome measure:**

	• Change from baseline 24-hour cough frequency [Time frame: week 4] See trial record for full list of other outcomes.
Results (efficacy)	Statistically significant and clinically meaningful improvements in 24H cough frequency over placebo were observed after 28 days at the 50 and 200 mg BID (twice a day) doses.[22]
Results (safety)	Overall, participants reported a similar incidence of treatment emergent adverse events (TEAEs) for BLU-5937 and placebo. No serious TEAEs were reported. Dysgeusia was reported by participants at an incidence of 4.8%, 6.5%, 4.8% and 0% for the 12.5 mg, 50 mg and 200 mg BID and placebo groups, respectively. No complete or partial taste loss was reported.[22]
Trial	**RELIEF;** NCT03979638; EudraCT 2019-000375-16; A Randomized, Double-Blind, Placebo-Controlled, Crossover, Dose Escalation Study of BLU-5937 in Subjects With Unexplained or Refractory Chronic Cough **Phase II** - Terminated (Trial was terminated due to the impact of the COVID-19 on trial activities. 68 patients with refractory chronic cough were enrolled with 52 completing treatment) **Locations:** UK and USA **Study completion date:** April 2020
Trial Design	Randomised, two-arm, two-period, crossover assignment, quadruple masked.
Population	N=68 (Actual). Adults aged 18 to 80 with refractory or unexplained chronic cough for at least one year. Cough count of ≥ 10 per hour.
Intervention(s)	BLU-5937 (Four escalating doses of BLU-5937 (25, 50, 100, 200 mg) administered twice daily over the course of the study)
Comparator(s)	Matched placebo (administered orally twice daily)
Outcome(s)	**Original primary outcome measure:** • Awake coughs per hour at days 4, 8, 12, 16, 34, 38, 42, 46 [Time frame: Change from baseline at days 4, 8, 12, 16, 34, 38, 42, 46] See trial record for full list of outcomes.
Results (efficacy)	See trial record.
Results (safety)	See trial record.

Estimated Cost

The cost of camlipixant is not yet known.

Relevant Guidance

NICE Guidance

- NICE Clinical Knowledge Summary. Scenario: Management - cough more than 8 weeks' duration. 2015

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Parker SM, Smith JA, Birring SS, Chamberlain-Mitchell S, Guffydd-Jones K, et al. British Thoracic Society Clinical Statement on chronic cough in adults. 2023.[15]
- Rouadi PW, Idriss SA, Bousquet J, Laidlaw TM, Azar CR, Al-Ahmad MS, et al. World Allergy Organization (WAO) – Allergic Rhinitis and its Impact on Asthma (ARIA) Joint Committee consensus on chronic cough – Part III: Management strategies in primary and cough-specialty care. 2022.[23]
- Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Ribas CD, et al. European Respiratory Society (ERS) guidelines on the diagnosis and treatment of chronic cough in adults and children. 2020.[24]
- Irwin RS, Baumann MH, Bolser DC, Boulet L-P, Braman SS, Brightling CE, et al. Diagnosis and Management of Cough Executive Summary– ACCP Evidence-Based Clinical Practice Guideline. 2006.[25]
- Morice AH, McGarvey L, Pavord I. Recommendations for the management of cough in adults. British Thoracic Society Cough Guideline Group. 2006.[26]

Additional Information

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