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Health Technology Briefing
February 2023

Pirtobrutinib for chronic lymphocytic leukaemia or small lymphocytic lymphoma after BTK inhibitor therapy

Company/Developer	Eli Lilly and Company Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 31048	NICE TSID: 10628	UKPS ID: 660577

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Pirtobrutinib is currently in clinical development for the treatment of patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) who have previously received treatment with the current standard of care. CLL and SLL are types of cancer in which too many white blood cells (B-cells) are produced, these cells build up in the lymph nodes, blood, and bone marrow. As these cells develop abnormally, they are unable to function and fight infection, and might reduce the production of healthy blood cells. These diseases are chronic and develop slowly. Over time this can cause a range of problems, such as an increased risk of developing infections, persistent tiredness, swollen glands in the neck, armpits or groin, and unusual bleeding or bruising. Most patients develop resistance to the currently available treatment options, creating a need for novel therapies for this condition.

Pirtobrutinib is an oral medicinal product that works against cancerous B lymphocytes, which are a type of white blood cells affected by these diseases. Pirtobrutinib works by blocking (or binding) an enzyme called Bruton's tyrosine kinase (BTK), which promotes the development and survival of normal and cancerous B lymphocytes. Pirtobrutinib is able to offer reversible binding to allow higher BTK inhibition and a higher selectivity. If licensed, pirtobrutinib would offer a novel treatment option for patients with CLL/SLL who have previously received treatment.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Treatment of patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) who have previously received treatment with at least one Bruton's tyrosine kinase (BTK) inhibitor.[1,2]

Technology

Description

Pirtobrutinib (LOXO-305) is a highly selective, reversible (non-covalent) BTK inhibitor. BTK plays a key role in the B-cell antigen receptor signaling pathway, which is required for the development, activation and survival of normal white blood cells, known as B-cells, and malignant B-cells. BTK is a validated molecular target found across numerous B-cell leukaemia and lymphomas including CLL.[3]

Pirtobrutinib is currently in clinical development for the treatment of patients with CLL/SLL who have previously received treatment with at least a BTK inhibitor. In phase III clinical trial (BRUIN CLL-321; NCT04666038), patients will be administered pirtobrutinib orally daily.[2]

Key Innovation

Pirtobrutinib was developed to reversibly bind BTK, deliver consistently high target coverage regardless of BTK turnover rate, and preserve activity in the presence of acquired resistance mutations. Pirtobrutinib was found to be highly selective – 300 times more selective in BTK inhibition versus 98% of other kinases tested in preclinical studies.[3] There is growing concern for the development of resistance to covalent BTK inhibitors, leading to treatment discontinuation in a large majority of patients. Pirtobrutinib is the first to offer the characteristic of non-covalent, reversible binding to allow higher BTK inhibition and a higher selectivity, reducing any off-target adverse effects.[4]

If licensed, pirtobrutinib will offer a novel treatment option for patients with CLL/SLL who have previously been treated with a BTK inhibitor.

Regulatory & Development Status

Pirtobrutinib does not currently have Marketing Authorisation in the EU/UK for any indication.

Pirtobrutinib is currently in phase II/III clinical development for the following indications:[5]

- Mantle cell lymphoma
- Non-Hodgkin lymphoma
- Hematologic malignancy

Patient Group

Disease Area and Clinical Need

Chronic lymphocytic leukaemia (CLL) is a rare type of cancer that affects the white blood cells and tends to progress slowly over many years. In CLL, the spongy material found inside some bones (bone marrow) produces too many white blood cells called lymphocytes, which are not fully developed and do not work properly. Over time this can cause a range of problems, such as an increased risk of picking up infections, persistent tiredness, swollen glands in the neck, armpits or groin, and unusual bleeding or bruising.[6,7] CLL and small lymphocytic lymphoma (SLL) are the same disease, but in CLL cancer cells are found mostly in the blood and bone marrow, while in SLL cancer cells are found mostly in the lymph nodes.[8] The cause of

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CLL is unknown, and it is more common in males, people with a family history of CLL, and older people but very rare in people under the age of 40.[9]

Around 3,800 people are diagnosed with CLL in the UK each year.[10] There are around 980 CLL deaths in the UK every year (2017-2019). Mortality rates for CLL in the UK are highest in people aged 90+ (2017-2019). Since the early 1990s, CLL incidence rates have increased by a sixth (17%) in the UK. Incidence rates for CLL in the UK are highest in people aged 85 to 89 (2016-2018).[11] In England, 2021-2022, there were 22,261 finished consultant episodes (FCE) and 21,268 admissions for Chronic lymphocytic leukaemia of B-cell type (ICD-10 code C91.1) which resulted in 13,071 FCE bed days and 18,957 day cases.[12]

Recommended Treatment Options

NICE currently recommends the following for previously treated CLL:[13-17]

- Venetoclax with rituximab
- Ibrutinib
- Venetoclax
- Idelalisib

Clinical Trial Information

Trial	NCT03740529, 2018-003340-24, A Phase 1/2 Study of Oral LOXO-305 in Patients With Previously Treated Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL) **Phase I/II:** Recruiting **Location(s):** 4 EU countries, UK, USA and other countries **Primary completion date:** July 2023
Trial Design	Non-randomised, parallel assignment, open label
Population	N=860 (estimated); aged 18 years and older; Subjects with histologically confirmed CLL/SLL, Waldenström macroglobulinemia (WM), or NHL intolerant to either ≥ 2 prior standard of care regimens given in combination or sequentially OR have received 1 prior BTK inhibitor-containing regimen when a BTK inhibitor is approved as first line therapy (Phase 1) OR with prior treatment defined by phase 2 cohort (Phase 2 Patients only)
Intervention(s)	This study includes 3 parts: • Phase 1: pirtobrutinib monotherapy dose escalation and dose expansion • Phase 1b: pirtobrutinib combination therapy dose expansion • Phase 2: pirtobrutinib monotherapy dose expansion Starting dose of pirtobrutinib (oral) is 25 mg/day. Cycle length will be 28 days.
Comparator(s)	No comparator
Outcome(s)	Primary Outcome measures: • Maximum Tolerated Dose (MTD) [time frame: up to 24 months] • Recommended dose for further study [time frame: up to 24 Months]

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	• To assess the preliminary anti-tumour activity of pirtobrutinib based on overall response rate (ORR) as assessed by an Independent Review Committee (IRC). [time frame: up to 24 months] See trial record for full list of other outcomes.
Results (efficacy)	In 121 efficacy evaluable patients with CLL or SLL treated with a previous covalent BTK inhibitor (median previous lines of treatment 4), the ORR with pirtobrutinib was 62% (95% CI 53-71). The overall response rate (ORR) was similar in CLL patients with previous covalent BTK inhibitor resistance (53 [67%] of 79), covalent BTK inhibitor intolerance (22 [52%] of 42), BTK C481-mutant (17 [71%] of 24) and BTK wild-type (43 [66%] of 65) disease. In 52 efficacy evaluable patients with mantle cell lymphoma (MCL) previously treated with covalent BTK inhibitors, the ORR was 52% (95% CI 38-66). Of 117 patients with CLL, SLL, or MCL who responded, all but eight remain progression-free to date.[18]
Results (safety)	No dose-limiting toxicities were observed, and the maximum tolerated dose was not reached. The recommended phase 2 dose was 200 mg daily. Adverse events in at least 10% of 323 patients were fatigue (65 [20%]), diarrhoea (55 [17%]), and contusion (42 [13%]). The most common adverse event of grade 3 or higher was neutropenia (32 [10%]). There was no correlation between pirtobrutinib exposure and the frequency of grade 3 treatment-related adverse events. Grade 3 atrial fibrillation or flutter was not observed, and grade 3 haemorrhage was observed in one patient in the setting of mechanical trauma. Five (1%) patients discontinued treatment due to a treatment-related adverse event.[18]
Clinical Trial Information	
Trial	**BRUIN CLL-321;** NCT04666038, 2020-004554-30, A Phase 3 Open-Label, Randomized Study of LOXO-305 Versus Investigator's Choice of Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma **Phase III:** Recruiting **Location(s):** 11 EU countries, UK, USA, Canada and other countries **Primary completion date:** December 2023
Trial Design	Randomised, parallel assignment, open label
Population	N=250 (estimated); aged 18 years and older; Subject with a confirmed diagnosis of CLL/SLL; Previously treated with a covalent BTK inhibitor
Intervention(s)	Pirtobrutinib (oral)
Comparator(s)	• Idelalisib plus rituximab (IdelaR) • Bendamustine plus rituximab (BR)
Outcome(s)	Primary Outcome measure: To evaluate progression-free survival (PFS) of LOXO-305 monotherapy (Arm A) compared to investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) (Arm B) [time frame: up to approximately 36 months]

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Results (efficacy)	-
Results (safety)	-

Estimated Cost

The estimated cost of pirtobrutinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology in development. Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078). Expected publication date: September 2023.
- NICE technology appraisal. Venetoclax for treating chronic lymphocytic leukaemia (TA796). June 2022.
- NICE technology appraisal. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (TA561). February 2019.
- NICE technology appraisal. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (TA429). January 2017.
- NICE technology appraisal guidance. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015.
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (TA193). July 2010.
- NICE technology appraisal guidance. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (TA29). September 2001.
- NICE quality standard. Haematological cancers. June 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- European Society for Medical Oncology. Chronic Lymphocytic Leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020.[19]
- London Cancer Alliance. Pan-London Haemato-Oncology Clinical Guidelines. 2020. [20]
- British Society for Haematology. Guideline for the treatment of chronic lymphocytic leukaemia. 2018.[21]

Additional Information

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