Health Technology Briefing
October 2023

Acalabrutinib for treating relapsed or refractory mantle cell lymphoma

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID:10813	NICE ID: Not available	UKPS ID: 670177

Licensing and Market Availability Plans

Currently in phase II clinical development.

Summary

Acalabrutinib is in clinical development for the treatment of relapsed or refractory mantle cell lymphoma (MCL). MCL is a rare and aggressive blood cancer that starts in white blood cells (B-cells) in the outer edge of the lymph nodes. The abnormal white blood cells start to collect in the lymph nodes or body organs, where they can form painless tumours and begin to cause problems within the lymphatic system or the organ where they are growing. MCL is not a curable lymphoma, but in most cases, treatment can put the condition into remission. Remission means symptoms and tests show no signs of cancer, however, MCL can come back (relapse) after months or years. In some cases, treatment might be ineffective (refractory). There is a medical need for novel strategies to improve disease control in patients with MCL.

Acalabrutinib works by blocking an enzyme called Bruton's tyrosine kinase, which helps B cells to survive and grow. By blocking this enzyme, acalabrutinib is expected to slow down the build-up of cancerous B cells in MCL, thereby delaying or stopping the progression of the cancer. Acalabrutinib will be administered orally. If licensed, acalabrutinib will provide an alternative treatment option for patients with relapsed or refractory MCL.

Proposed Indication

Treatment of adults with relapsed or refractory mantle cell lymphoma (MCL).[1]

Technology

Description

Acalabrutinib (Calquence, ACP-196) is a selective inhibitor of Bruton tyrosine kinase (BTK). BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis. [2] By blocking BTK, acalabrutinib is expected to slow down the build-up of cancerous cells, thereby delaying the progression of the cancer.[3] Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK with minimal off-target interactions.[2,3]

Acalabrutinib is currently in clinical development for the treatment of relapsed or refractory MCL in adults. In the phase II clinical trial (NCT02213926), 100mg of acalabrutinib was administered orally twice per day (BID) in repeated 28-day cycles.[1,4]

Key Innovation

MCL is generally an aggressive B-cell non-Hodgkin lymphoma (NHL) with a poor prognosis.[4] Many standard lymphoma salvage regimens have limited activity in MCL, so there is a need for more novel treatment approaches based on targeting known signaling pathways, to be developed.[5] A current treatment option that targets the BTK pathway and produces a high response rate in patients with relapsed or refractory MCL, has been associated with notable grade 3 or worse toxicities because of its off-target activity against other kinases.[4,6,7] Acalabrutinib is a highly selective, potent BTK inhibitor developed to minimise off-target activity, thereby having a better safety profile.[4,8]

If licensed, acalabrutinib will provide an additional treatment option for patients with relapsed or refractory MCL.

Regulatory & Development Status

Acalabrutinib is licensed in the UK for the following indications:[2]

- as monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)
- as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

Acalabrutinib as monotherapy is currently in phase II and III development for several indications as follows:[9]

- CLL
- Post blood/marrow transplantation in MCL
- Chronic graft versus host disease
- Waldenstrom macroglobulinemia
- Diffuse large B-cell lymphoma
- Small lymphocytic lymphoma
- Central nervous system lymphoma

- Richter's syndrome/prolymphocytic leukaemia
- Glioblastoma multiforme

Acalabrutinib has received an orphan drug designation in the EU in March 2016 for the treatment of MCL.[10]

Patient Group

Disease Area and Clinical Need

Mantle cell lymphoma (MCL) is a rare type of B cell non-Hodgkin lymphoma (NHL), which is a cancer of the lymphatic system. The lymphatic system has tubes that branch through all parts of the body and carries a colourless liquid called lymph, which contains a high number of white blood cells (lymphocytes) that fight infection. There are two main types of lymphocytes, B cells and T cells. MCL affects the B cells and develops in the part of the lymph node called the mantle zone.[11] MCL develops when B-cells become abnormal (cancerous), grow out of control, fail to function properly, usually building up in the lymph nodes. MCL can relapse after a successful treatment or might not respond well to the first treatment (refractory). The causes of MCL are mostly unknown, although most cases of MCL have a particular genetic change (mutation) in the abnormal cells. It is most common in people over the age of 70, and more common in men than women.[12,13] The most common symptom of MCL is a lump, or lumps, in the neck, armpit and groin and these are swollen lymph nodes. Other symptoms include tiredness, shortness of breath, unexplained weight loss, night sweats, fever, unexplained itching, being prone to infections and ease of bleeding and bruising.[11,13]

Around 600 people are diagnosed with MCL each year in the UK.[13] For patients younger than 60 years, about 60% will survive their lymphoma for 5 years or more after diagnosis. For patients aged 60-79 years, almost 45% will survive their lymphoma for 5 years or more after diagnosis, and for those 80 years or older, around 10% will survive their lymphoma for 5 years or more after they are diagnosed.[14] In England (2022-23), there were 7,922 finished consultant episodes (FCE) and 7,389 admissions for MCL (ICD-10 code C83.1) resulting in 6,176 day cases and 11,243 FCE bed days.[15]

Recommended Treatment Options

NICE recommends the following options for treatment of relapsed or refractory MCL:[16,17]

- Ibrutinib, in adults that have had only one previous line of therapy
- Brexucabtagene autoleucel, in adults who have previously had a Bruton's tyrosine kinase (BTK) inhibitor

Clinical Trial Information

Trial	NCT02213926; An open-label, phase 2 study of ACP-196 in subjects with Mantle cell lymphoma. **Phase II –** Active, not recruiting. **Location(s) –** UK, 7 EU countries, USA and Australia **Primary completion date (Actual) –** December 2020
Trial Design	Open-label, single group assignment

Population	N= 124 (actual); aged 18 to 130 years; Subjects with pathologically confirmed MCL, who have relapsed or were refractory to ≥1(but not >5) prior treatment regimens.
Intervention(s)	100 mg of acalabrutinib (oral) twice per day (BID) in repeated 28-day cycles. [4]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: Overall Response Rate (ORR) of Acalabrutinib in subjects with previously treated MCL. [Time Frame: From the date of the first dose until 30 days after the last dose of the study drug or start of a new anti-cancer treatment, whichever came first, assessed up to approximately 4 years and 10 months. 1 cycle =28 days]
Results (efficacy)	At a median follow-up of 15·2 months, 100 (81%) patients achieved an overall response, and 49 (40%) patients achieved a complete response. The Kaplan-Meier estimated medians for duration of response, progression-free survival, and overall survival were not reached; the 12-month rates were 72% (95% CI 62-80), 67% (58-75), and 87% (79-92%), respectively.[4]
Results (safety)	The most common adverse events were primarily grade 1 or 2 and were headache (47 [38%]), diarrhoea (38 [31%]), fatigue (34 [27%]), and myalgia (26 [21%]). The most common grade 3 or worse adverse events were neutropenia (13 [10%]), anaemia (11 [9%]), and pneumonia (six [5%]). There were no cases of atrial fibrillation and one case of grade 3 or worse haemorrhage. Treatment was discontinued in 54 (44%) patients, primarily due to progressive disease (39 [31%]) and adverse events (seven [6%]).[4]

Estimated Cost

Acalabrutinib is already marketed in the UK; a pack of 60 x 100mg capsules costs £5,059.[18]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Pirtobrutinib for treating relapsed or refractory mantle cell lymphoma [GID-TA10858]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Venetoclax with ibrutinib for treating relapsed mantle cell lymphoma [GID-TA10774]. Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma [TA677]. February 2021
- NICE technology appraisal guidance. Ibrutinib for treating relapsed or refractory mantle cell lymphoma [TA502]. January 2018
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2018 NHS Clinical Commissioning Policy: Bortezomib for relapsed/refractory mantle cell lymphoma (all ages). 170035P.
- NHS England. 2018 NHS Clinical Commissioning Policy: Bendamustine with rituximab for relapsed and refractory mantle cell lymphoma (all ages). 170054P
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a

Other Guidance

- British Society for Haematology. Guideline for the management of mantle cell lymphoma. 2018[19]
- European Society for Medical Oncology. Clinical Practice Guidelines for Haematological Malignancies. 2013[20]

Additional Information

References

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