NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Acalabrutinib with venetoclax and obinutuzumab for treating previously untreated chronic lymphocytic leukaemia

Company/Developer	AstraZeneca

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26799	NICE ID: 11768	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Acalabrutinib in combination with venetoclax and obinutuzumab is in development for the first-line treatment of chronic lymphocytic leukaemia (CLL). CLL is a type of cancer that affects the white blood cells. 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. This can cause a range of problems, such as an increased risk of infections, tiredness, swollen glands, and unusual bleeding or bruising. Despite there being several therapeutic options, CLL still has poor outcomes and often returns after treatment.

Acalabrutinib, administered orally, blocks an enzyme called Bruton's tyrosine kinase (BTK), which helps B cells (B-lymphocytes) to survive and grow. By blocking BTK, acalabrutinib can slow down the build-up of cancerous white blood cells in CLL, thereby delaying progression of the cancer. The combination of acalabrutinib, venetoclax and obinutuzumab has been shown to be highly active and well tolerated as first-line therapy for CLL in a phase II clinical trial and, if licenced, this combination will provide an additional first-line treatment option for patients with CLL.

Proposed Indication

Previously untreated CLL.[1]

Technology

Description

Acalabrutinib (Calquence) 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 and is a driving force for CLL and other B cell malignancies.[2,3] In B-cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis. 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]

Acalabrutinib in combination with venetoclax and obinutuzumab is currently in clinical development for the treatment of previously untreated CLL. In the phase III clinical trial (NCT03836261) patients are given acalabrutinib in combination with venetoclax with or without obinutuzumab.[1] In the phase II clinical trial (NCT03580928) patient are given acalabrutinib 100mg orally twice daily in combination with venetoclax orally once daily, with dose ramp-up from 20mg up to a final dose of 400mg, and obinutuzumab administered as per standard of care for 6 months with dosing at 100 mg on cycle 1 day 1, 900 mg on cycle 1 day 2, and then 1,000 mg on cycle 1 days 8, 15, and day 1 of cycles 2-6.[4]

Key Innovation

Current first-line treatment for CLL includes targeted drugs and chemotherapy.[5] The approval of BTK and BCL-2 inhibitors has revolutionised the treatment of chronic lymphocytic leukaemia; however, the current use of these drugs in the frontline setting is suboptimal. Standard-of-care BTK inhibitor drugs (eg, acalabrutinib) given with or without anti-CD20 antibodies, can provide durable responses but require continuous long-term therapy, are associated with ongoing risks, such as cardiovascular and bleeding complications, and are costly. Thus, although the currently approved regimens are effective, they also leave room for improvement. The combination of acalabrutinib, venetoclax and obinutuzumab has been shown to be highly active and well tolerated as first-line therapy for CLL.[6]

If licenced, acalabrutinib in combination with venetoclax and obinutuzumab will provide an additional first-line treatment option for patients with high-risk CLL.

Regulatory & Development Status

Acalabrutinib in combination with venetoclax and obinutuzumab does not currently have Marketing Authorisation in the EU/UK for any indication.

Acalabrutinib as monotherapy or in combination with obinutuzumab has Marketing Authorisation in the EU/UK for the treatment of adult patients with previously untreated CLL. As a monotherapy, acalabrutinib is also indicated for the treatment of adult patients with CLL who have received at least one prior therapy.[2]

Acalabrutinib in combination with venetoclax and obinutuzumab is also in phase II/III development for:[7]

- Relapsed, refractory or recurrent CLL
- Untreated high risk CLL
- Small lymphocytic lymphoma
- Mantle cell lymphoma

Patient Group

Disease Area and Clinical Need

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia, which affects blood cells in the bone marrow and progresses slowly over time. In CLL, the bone marrow makes too many abnormal white blood cells called lymphocytes. The abnormal lymphocytes that are produced are not fully developed and do not work properly. Over time, these abnormal lymphocytes build up in the lymphatic system and may cause large, swollen lymph nodes. The abnormal lymphocytes can also build up in the bone marrow. This leaves less space for normal white blood cells, red blood cells and platelets to develop. Symptoms include regular infections, anaemia, tiredness, bleeding and bruising easily, high temperature, night sweats, swollen glands and unintentional weight loss.[8,9] It is not known what causes CLL but risk factors include increased age, being male, having a close relative with CLL, and European descent.[10]

CLL accounted for 1% of all new cancer cases in the UK in 2016-18 and there are around 3,800 new cases in the UK every year. The age standardised incidence rate of CLL in England is 8.8 and 4.4 per 100,000 amongst males and females respectively (2016-18).[11] In England, (2020-21), there were 17,230 finished consultant episodes (FCE) of chronic lymphocytic leukaemia of B-cell type (ICD-10 code C91.1) resulting in 13,911 day cases and 10,364 FCE bed days.[12] In England (2017), there were 3,157 patients diagnosed with CLL and 1,085 deaths registered where lymphoid leukaemia was the underlying cause.[13] For patients diagnosed between 2013 and 2017, followed up to 2018, the age standardised 1-year and 5-year survival rates for leukaemia were 72.4% and 53.5% respectively.[14]

Recommended Treatment Options

The most common first-line treatments for CLL are targeted drugs (such as acalabrutinib, ibrutinib, venetoclax and obinutuzumab) or chemotherapy.[5] NICE currently recommends the following therapies for the first-line treatment of CLL:[15]

- Acalabrutinib
- Venetoclax in combination with obinutuzumab
- Idelalisib in combination with rituximab
- Obinutuzumab in combination with chlorambucil
- Bendamustine
- Rituximab in combination with fludarabine and cyclophosphamide

Clinical Trial Information

Trial	NCT03580928; A Phase 2 Study of Acalabrutinib, Venetoclax, and Obinutuzumab (AVO) for Initial Therapy of Chronic Lymphocytic Leukemia **Phase II** – Recruiting **Location(s):** USA **Primary completion date:** January 2024
Trial Design	Single group assignment, open label
Population	N=72; Aged 18 years and older; Must have CLL or SLL; Subjects must not have received any prior systemic therapy for CLL or SLL due to meeting IWCLL 2018 guidelines and must currently have an indication for treatment as defined by the IWCLL 2018 guidelines
Intervention(s)	- Venetoclax once daily (oral)

	- Obinutuzumab (IV) - Acalabrutinib 100mg twice daily (oral)
Comparator(s)	No comparator
Outcome(s)	**Primary outcome:** The rate of bone marrow minimal residue disease (MRD) negative complete response [Time frame: after 15 months] See trial record for full list of other outcomes
Results (efficacy)	At cycle 16 day 1, 14 (38% [95% CI 22–55]) of 37 participants had a complete remission with undetectable MRD in the bone marrow.[6]
Results (safety)	The most common grade 3 or 4 haematological adverse event was neutropenia (16 [43%] of 37 patients). The most common grade 3–4 non-haematological adverse events were hyperglycaemia (three [8%]) and hypophosphataemia (three [8%]). Serious adverse events occurred in nine (24%) patients; the most common was neutropenia in three (8%) patients. There have been no deaths on study.[6]

Trial	NCT03836261, 2018-002443-28; A Randomized, Multicenter, Open-Label, Phase 3 Study to Compare the Efficacy and Safety of Acalabrutinib (ACP-196) in Combination With Venetoclax With and Without Obinutuzumab Compared to Investigator's Choice of Chemoimmunotherapy in Subjects With Previously Untreated Chronic Lymphocytic Leukemia Without Del(17p) or TP53 Mutation **Phase III** – Recruiting **Location(s):** 14 EU countries, UK, USA, Canada and other countries **Primary completion date:** January 2027
Trial Design	Randomized, parallel assignment, open label
Population	N=780; Aged 18 years and older; Diagnosis of CLL that meets published diagnostic criteria; Active disease per IWCLL 2018 criteria that requires treatment
Intervention(s)	- Acalabrutinib - Venetoclax - Obinutuzumab
Comparator(s)	- Chemoimmunotherapy (fludarabine/cyclophosphamide/rituximab or bendamustine/rituximab)
Outcome(s)	**Primary outcome:** To evaluate the efficacy of acalabrutinib with venetoclax (Arm A) compared to chemoimmunotherapy fludarabine/cyclophosphamide/rituximab [FCR] or bendamustine/rituximab [BR] (Arm C): PFS [Time frame: 6 years] See trial record for full list of other outcomes
Results (efficacy)	-

Results (safety)	-

Estimated Cost

Acalabrutinib is already marketed in the UK; a pack of 60 x 100mg capsules costs £5,059.[16]

Venetoclax is already marketed in the UK; a pack of 14 x 10mg tablets costs £59.87, a pack of 7 x 50mg tablets costs £149.67, a pack of 7 x 100mg tablets costs £299.34, a pack of 14 x 100mg tablets costs £598.68 and a pack of 112 x 100mg tablets costs £4,789.47.[17]

Obinutuzumab is already marketed in the UK; a 1000mg/40ml concentrate of solution for infusion vial costs £3,312.[18]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Zanubrutinib for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma (GID-TA10966). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia (GID-TA10746). Expected March 2023.
- NICE technology appraisal. Acalabrutinib for treating chronic lymphocytic leukaemia (TA689). April 2021.
- NICE technology appraisal. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (TA663). December 2020.
- NICE technology appraisal. Venetoclax for treating chronic lymphocytic leukaemia (TA487). November 2017.
- 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. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015.
- NICE technology appraisal. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343). June 2015.
- NICE technology appraisal. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (TA216). February 2011.
- NICE technology appraisal. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (TA174). July 2009.

NHS England (Policy/Commissioning) Guidance

- NHS Northern Cancer Alliance. Haematology Cancer Clinical Guidelines. November 2019.
- 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

- British Society for Haematology. Guideline for the treatment of chronic lymphocytic leukaemia. March 2022.[19]
- European Society for Medical Oncology (ESMO). Chronic Lymphocytic Leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. October 2020.[20]

- International Workshop on Chronic Lymphocytic Leukaemia. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. June 2018.[21]
- British Committee for Standards in Haematology. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. October 2012.[22]

Additional Information

AstraZeneca did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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