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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2019

Acalabrutinib for relapsed/refractory Chronic lymphocytic leukaemia

NIHRIO ID	14902	**NICE ID**	9643
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	645730

Licensing and market availability plans	Currently in phase II/III clinical trials.

SUMMARY

Acalabrutinib is a novel oral anti-cancer drug in clinical development for people with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL) who have previously been treated (second line or greater). CLL is a type of cancer in which too many white blood cells are produced. As these cells develop abnormally, they are unable to function and fight infection and stop the production of healthy blood cells. The disease is chronic and develops slowly. R/R CLL means the cancer has come back after treatment and reaching remission, or the cancer has failed to respond to treatment. Treatment options for R/R CLL include targeted therapy drugs, chemotherapy, radiation therapy or surgery.

Acalabrutinib works by blocking a specific enzyme referred to as Bruton's Tyrosine Kinase, to slow the build-up of cancerous cells in CLL, thereby delaying or stopping the progression of the disease. The Bruton's Tyrosine Kinase enzyme has been identified as an important therapeutic target for the treatment of CLL. Acalabrutinib is thought to be a more selective and irreversible blocker of this enzyme and is specifically designed to improve on the safety and efficacy of first generation inhibitors. Acalabrutinib has demonstrated encouraging results in clinical trials and may offer an effective treatment option for R/R CLL patients who have received other previous treatment.

PROPOSED INDICATION

Treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL) – second line or greater.[a]

TECHNOLOGY

DESCRIPTION

Acalabrutinib (ACP-196) is an orally available inhibitor of Bruton's tyrosine kinase (BTK) with potential antineoplastic activity. BTK, a member of the src-related BTK/Tec family of cytoplasmic tyrosine kinases, is overexpressed in B-cell malignancies and plays an important role in B-lymphocyte development, activation, signalling, proliferation and survival. Acalabrutinib inhibits the activity of BTK and prevents the activation of the B-cell antigen (BCR) signalling pathway. This prevents both B-cell activation and BTK-mediated activation of downstream survival pathways.[1] Acalabrutinib is a more selective irreversible BTK inhibitor that is specifically designed to improve on the safety and efficacy of first generation BTK inhibitors.[2]

Acalabrutinib is in clinical development for people with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL) who have previously been treated (second line or greater). In a phase III trial (2015-004454-17, NCT02970318), acalabrutinib is administered as an oral 100 mg capsule,[3,4,a] twice daily until disease progression or unacceptable toxicity.[b]

INNOVATION AND/OR ADVANTAGES

The unique structure of BTK, characterised by a cysteine (C481) within the ATP-binding pocket, makes it an attractive therapeutic target. Irreversible inhibition of BTK represents an important therapeutic advance for the treatment of CLL. Acalabrutinib is a more selective, irreversible BTK inhibitor, specifically designed to improve on the safety and efficacy of first generation inhibitors.[2]

Early results suggest that acalabrutinib has encouraging efficacy in patients with CLL that have already been treated.[5] Additionally, a favourable safety profile has also been demonstrated compared to ibrutinib, a first generation BTK inhibitors.[2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Acalabrutinib is in phase III clinical development for mantle cell lymphoma and in phase II clinical trials for different types of cancers such as small lymphocytic lymphoma, diffuse large B-cell lymphoma, multiple myeloma, non-small cell lung cancer, etc.[6]

Acalabrutinib was granted orphan designation in the EU for chronic lymphocytic leukaemia in March 2016.[5]

[a] Information provided by Astra Zeneca UK Ltd on UK PharmaScan
[b] Information provided by Astra Zeneca

PATIENT GROUP

DISEASE BACKGROUND

CLL is a type of B lymphocyte cancer that affects the white blood cells (leukocytes). In CLL, the spongy material found inside some bones (bone marrow) produces too many white blood cells called lymphocytes that are not fully developed and do not work properly.[7]

A patient is said to be in remission when the CLL is under control. Refractory CLL is when patients do not respond to treatment while relapsed CLL is when a patient responds to treatment but develops CLL again after initial treatment. R/R CLL would generally be regarded as the subgroup of patients who require treatment for progressive disease but also show features suggesting that they are expected to have a poorer outcome than average.[8]

CLL is most common in those over 60 years of age and rarely occurs in those under 40 years.[7] It develops slowly over time and people often have no symptoms in the early stages. General symptoms of CLL include: fatigue, frequent infections, swollen lymph nodes (commonly in the neck, armpits and groin), anaemia, easy bruising/bleeding, enlarged spleen (causing tender lump in upper left abdomen), night sweats and weight loss.[9]

Various risk factors for CLL have been identified, including: a family history of CLL, exposure to electromagnetic radiation, the presence of a compromised immune system (HIV/AIDS patients or individuals on immunosuppressive medication) and exposure to certain hair dyes. CLL is also more common in men and people of Australian, American and European origin.[10]

CLINICAL NEED AND BURDEN OF DISEASE

CLL is the most common chronic (slowly developing) leukaemia in adults. In 2015, the crude incidence rate of CLL (ICD-10: C91.1) in England was 5.9 per 100,000 population and in the UK, the crude incidence rate of CLL was 5.7 per 100,000 population.[11]

The risk of developing CLL increases progressively with age, with the highest incidence rates being in older people. In the UK in 2013-2015, on average each year more than 4 in 10 (43%) of new cases were in people aged 75 and over.[12]

In 2016, CLL accounted for less than 1% of cancer deaths in the UK. 62% of CLL deaths in the UK were in males, and 38% are in females.[13] In England, the latest published survival statistics report an age-standardised 5 year relative survival rate as 67% and 73% for men and women respectively.[14]

In 2017-18, there were 24,071 admissions for chronic lymphoid leukaemia of B-cell type (ICD-10:C91.1) in England, resulting in 12,441 bed days and 24,935 finished consultant episodes.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Relapsed/refractory CLL is currently treated through the use of systemic anticancer treatments such as surgery, targeted therapies, immunotherapy or cytotoxic chemotherapy. The regimen will vary according to responsiveness to previous treatments and co-morbidities.[16,17]
Treatment options include:

- Stem cell and bone marrow transplant – high dose chemotherapy and radiotherapy followed by transplantation of stem cells from a genetically similar donor (allogenic)[18]
- Radiotherapy - should be considered for patients for whom chemo-immunotherapy has been ineffective or is contra-indicated and can provide effective palliation in cases with symptomatic bulky lymphadenopathy[19]

Other treatment options intended for secondary effects of CLL and/or CLL treatment include:[20]

- Supportive therapies for CLL e.g. immunoglobulin replacement therapy – to help prevent/treat infections
- Antibiotic, antifungal and antiviral medications – to treat infections in CLL patients
- Granulocyte-colony stimulating factor (G-CSF) injections – to boost white blood counts
- Blood transfusions – to treat severe anaemia or bleeding and bruising problems

CURRENT TREATMENT OPTIONS

For relapsed / refractory CLL, NICE guidelines advise the following medicinal products:

- Bendamustine – for those where fludarabine based treatment is inappropriate[21]
- Ibrutinib (alone) – for those who have had at least 1 prior therapy or for those with 17p deletion/TP53 mutation and in whom chemo-immunotherapy is unsuitable[22]
- Rituximab in combination with fludarabine and cyclophosphamide – for people with relapsed or refractory CLL[23]
- Idelalisib in combination with rituximab – for treating CLL patients who have received at least one prior therapy[24]
- Venetoclax in combination with rituximab – for treating chronic lymphocytic leukaemia in adults who have had at least 1 previous therapy[25]
- Venetoclax in patients:[26]
    - with a 17p deletion or TP53 mutation and whose disease has progressed after a B-cell receptor pathway inhibitor or
    - without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor and

PLACE OF TECHNOLOGY

If licensed, acalabrutinib may offer an additional second line treatment for patients with relapsed or refractory CLL.

CLINICAL TRIAL INFORMATION

Trial	ACE-CL-309, 2015-004454-17, NCT02970318; adults aged 18 or above; acalabrutinib vs rituximab plus idelalisib or bendamustine; phase III
Sponsor	Acerta Pharma BV
Status	Ongoing
Source of Information	Trial registry[3,4]
Location	Multi-national – trial sites from 28 countries

Design	Randomised
Participants	N=306 (planned); aged 18 and over; diagnosis of CLL; received ≥ 1 prior systemic therapies for CLL
Schedule	Randomised to acalabrutinib at 100mg capsule; or rituximab in combination with idelalisib (I/R) or bendamustine (B/R): • Acalabrutinib is treat until progression or unacceptable toxicity as above • I/R – idelalisib until disease progression or unacceptable toxicity; R max 8 infusions for 6 cycles • B/R – both for 6 cycles
Follow-up	48 months after the first subject is randomised
Primary Outcomes	IRC-assessed progression-free survival (PFS) in Arm A compared to Arm B [Time Frame: 48 months]
Secondary Outcomes	• Investigator-assessed progression-free survival (PFS) in Arm A compared to Arm B • Investigator and IRC-assessed overall response rate (ORR) in Arm A compared to Arm B • Overall survival (OS) in Arm A compared to Arm B • Patient reported outcomes (PROs) in Arm A compared to Arm B • Investigator and IRC-assessed duration of response (DOR) in Arm A compared to Arm B • Time to next treatment (TTNT) in Arm A compared to Arm B [Time Frame: 48 months]
Key Results	
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as March 2020

ESTIMATED COST

The cost of acalabrutinib is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Leukaemia (chronic lymphocytic, relapsed) – oftamumab (maintenance) (GID – TAG482). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Leukaemia (chronic lymphocytic) – idealalisib (with oftamumab) (GID – TA10008). Expected date of issue to be confirmed.

- NICE technology appraisal in development. Idelalisib with bendamustine and rituximab for previously treated chronic lymphocytic leukaemia (GID – TA10109). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Duvelisib for treating relapsed chronic lymphocytic leukaemia (GID – TA10260). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ublituximab with ibrutinib for previously treated chronic lymphocytic leukaemia (GID-TA10447)
- NICE technology appraisal in development. Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia (GID – TA10160). Expected February 2019.
- 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. Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab (TA202). October 2010.
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (TA193). July 2010.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2017 NHS Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 16068/P
- 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
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013

OTHER GUIDANCE

- ESMO Lymphoma Consensus Conference Panel Members. ESMO consensus conference on malignant lymphoma: general perspectives and recommendations for prognostic tools in mature B-cell lymphomas and chronic lymphocytic leukaemia. December 2016.[27]
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