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HEALTH TECHNOLOGY BRIEFING
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Asciminib for chronic myeloid leukaemia – chronic phase - third line

NIHRIO ID	23792	**NICE ID**	10106
Developer/Company	Novartis Pharmaceuticals	**UKPS ID**	644417

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

SUMMARY

Asciminib is in clinical development as a third line therapy for adult patients with chronic phase chronic myeloid leukaemia (CML) who have been previously treated with two or more tyrosine kinase inhibitors (TKI). CML is a slowly developing cancer that arises due to the production of abnormal immune cells known as white blood cells. In the chronic phase of CML, the tumour cells are relatively stable and slow growing, and patients may be asymptomatic or have a mild disease. The current treatments for chronic phase CML involves giving patients targeted cancer therapies such as TKI or a stem cell transplant.

Asciminib is a TKI taken orally. TKIs block chemical messengers (enzymes) called tyrosine kinases, which promote cell growth and division, including of tumour cells, so blocking them may stop cancer growth. Asciminib works differently from all current approved TKIs by using a mechanism which may overcome resistance or side effects of treatment in patients on current TKIs. If approved, asciminib would offer an additional treatment option for chronic phase CML patients who have been treated with two or more TKIs.

PROPOSED INDICATION

Third line or greater therapy for adult patients with chronic myeloid leukaemia (CML) – chronic phase, previously treated with 2 or more tyrosine kinase inhibitors (TKI).[a,1]

TECHNOLOGY

DESCRIPTION

Asciminib (ABL001) is an orally bioavailable, allosteric inhibitor of the tyrosine kinase BCR-ABL, a fusion protein which is abnormally produced by leukaemia cells containing the truncated form of chromosome 22 known as Philadelphia chromosome.[2,3] It binds potently and selectively to the myristoyl pocket of BCR-ABL1 and induces inactive C-terminal helix conformation.[2] This binding results in the inhibition of BCR-ABL1 mediated cell proliferation and enhanced apoptosis of Philadelphia chromosome-positive (Ph+) haematological malignancies.[4]

Asciminib is currently in clinical development as a third line or greater therapy for chronic phase CML (CML-CP) in patients previously treated with 2 or more TKI therapies.[1,a] In the phase III clinical trial (NCT03106779), participants received asciminib 40mg twice daily via oral tablet during an unspecified treatment schedule.[1]

INNOVATION AND/OR ADVANTAGES

The current treatment options for third line therapy in patients with CML-CP previously treated with 2 or more TKI therapies may include administration of another TKI such as imatinib, nilotinib, dasatinib, bosutinib or ponatinib, or an allogeneic stem cell transplant (alloSCT) procedure.[5,6] Treatment with the currently available TKI therapies can be effective, however, resistance or adverse effects may limit usage. Asciminib has the potential to overcome potential disease resistance as it has an allosteric inhibition mechanism which is unique among TKI therapies and may elicit a response to treatment where other TKI therapy did not.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Asciminib is also in phase II and III clinical development for the treatment of first line CML and in combination with imatinib for the treatment of CML-CP in patients who have not responded optimally to imatinib.[8]

Asciminib has been granted EMA orphan drug designation in 2020 for chronic myeloid leukaemia.[9]

Asciminib has been granted orphan drug designation in the USA in 2017 for chronic myelogenous leukaemia.[10]

PATIENT GROUP

DISEASE BACKGROUND

[a] Information provided by Novartis Pharmaceuticals on UK PharmaScan

CML is a form of cancer which arises in haematopoeitic stem cells (immature cells that can develop into all types of blood cell) and is characterised by overproduction of abnormal myeloid (white blood) cells.[5,11] It is caused by a translocation of chromosome 22, designated as Philadelphia chromosome 22q-. The truncation of the chromosome leads to a juxtaposition of the ABL1 and BCR genes, resulting in a BCR-ABL1 fusion gene that produces BCR-ABL1 proteins with constitutively active tyrosine kinase activity. The mechanism by which the translocation occurs is not well understood.[5]

CML is characterised by an excess of white blood cells and blasts and can be diagnosed in one of three distinct phases; chronic, accelerated or blast phase. The chronic phase is the earliest phase with slowly developing disease often over several years. Patients may be asymptomatic and diagnosed incidentally with routine blood tests or present with mild disease symptoms such as fatigue, weight loss and swollen abdomen due to splenomegaly. They will present with raised white blood cell counts and/or raised platelet counts and typically fewer than 15% blasts (immature cells).[b,12]

There are no well-established risk factors or causes for CML, however radiation such as from radiotherapy for a prior cancer or prolonged contact with the chemical benzene have been implicated as factors which may increase the risk of developing CML.[13]

CLINICAL NEED AND BURDEN OF DISEASE

CML is a rare condition with around 760 people diagnosed in the UK each year.[14] The median age at diagnosis is between 60 and 65 years of age.[5] Around 90% of CML cases are diagnosed at the chronic phase.[11]

In England in 2018-19 there were 4,352 finished consultant episodes (FCE) for chronic myeloid leukaemia - BCR/ABL-positive (ICD 10 Code: C92.1), resulting in 3,443 day cases and 5,276 bed days.[15]

There are around 220 deaths in the UK every year (2015-2017) from CML, which accounts for less than 1% of all deaths from cancer.[16] Approximately 6,000 people who have received a diagnosis of CML were alive in the UK at the end of 2010 and prevalence has been rising steadily due to the prolongation of survival that can now be achieved with targeted therapies.[5,16] Five year survival following CML diagnosis was 53% for males and 47% for females between 1999 and 2007 in England.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Patients who are diagnosed with CML will usually be managed by a multidisciplinary team taking into account the patients CML phase, general health, age and fitness levels. The main treatments available for CML-CP patients are TKI therapies and stem cell transplants. [,18]

CML-CP treatment will begin with one of three TKI therapies imatinib, dasatinib or nilotinib. The decision of which therapy to be used will be based on patient comorbidities and the overall aims of treatment. Based on response, progression or intolerance patients may then change to other TKI therapies which can then include bosutinib and ponatinib as well as the original treatment options or an allogeneic stem cell transplant.[5]

[b] Information provided by Novartis Pharmaceuticals

CURRENT TREATMENT OPTIONS

The current pharmacological treatment options for third line treatment of CML-CP are:[5]

- Imatinib
- Nilotinib
- Dasatinib
- Bosutinib
- Ponatinib

PLACE OF TECHNOLOGY

If licensed, asciminib will offer an additional treatment option for third line or greater patients with CML-CP that have had prior exposure to a minimum of two BCR-ABL1 targeting TKIs.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	NCT03106779; Study of efficacy of CML-CP Patients Treated With ABL001 versus Bosutinib, Previously Treated With 2 or More TKIs **Phase III** **Location(s):** EU (including the UK), Canada, United States and other countries
Trial design	Randomised, open-label, parallel assignment
Population	n=222; patients with CML in the chronic phase; previously treated with 2 or more TKI; adults aged 18 years and older
Intervention(s)	Asciminib, 40mg oral tablet twice daily
Comparator(s)	Bosutinib, 500mg oral tablet once daily
Outcome(s)	Primary outcome: Major Molecular Response (MMR) rate [Time frame: at 24 weeks]. To compare the MMR rate of ABL001 versus bosutinib See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of asciminib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (TA451). June 2017.
- NICE technology appraisal. Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia (TA425). December 2016.

- NICE technology appraisal. Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia (TA426). December 2016.
- NICE technology appraisal. Bosutinib for previously treated chronic myeloid leukaemia (TA401). August 2016.
- NICE technology appraisal. Guidance on the use of imatinib for chronic myeloid leukaemia (TA70). October 2003.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- Hochhaus, S et al. Chronic Myeloid Leukaemia: ESMO Clinical Practice Guidelines. May 2017.[5]
- Hochhaus, A et al. European LeukaemiaNet 2020 recommendations for treating chronic myeloid leukaemia. March 2020.[19]

ADDITIONAL INFORMATION

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