Health Technology Briefing
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Ponatinib for chronic myeloid leukaemia in paediatric patients

Company/Developer	Incyte Corp

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27581	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II clinical trials.

Summary

Chronic myeloid leukaemia (CML) is a rare type of cancer, especially in children. CML is characterised by the uncontrolled production of white blood cells called myeloid cells; this means cells divide but do not mature. These immature dividing cells, known as blast cells, fill up the bone marrow and stop it making healthy blood cells. This puts the child at increased risk of infection. The overproduction of white blood cells also interferes with the production of healthy red blood cells and platelets, leading to symptoms such as anaemia and bruising. Children with chronic phase CML may have no symptoms but blast cells are present in the blood and bone marrow. The chronic phase can last several years before transforming to the second, accelerated phase. Currently, CML in children cannot be cured by any type of chemotherapy, although some medications can eliminate easily detectable signs of leukaemia from the blood, prolonging the chronic phase of the disease.

Ponatinib inhibits an enzyme which is involved in stimulating the cells to divide uncontrollably. By blocking this process, ponatinib helps control the growth and spread of leukaemia cells. Ponatinib is given as an oral tablet and is currently licensed for use in adults. If licensed for use in children with chronic phase CML, ponatinib will offer another treatment option.

Proposed Indication

Treating recurrent or refractory chronic-phase chronic myeloid leukaemia (CML) in paediatric patients aged 1 to 17 years who are resistant or intolerant to treatment with another tyrosine kinase inhibitor.[a]

Technology

Description

Ponatinib (Iclusig) belongs to a group of medicines called tyrosine kinase inhibitors (TKIs).[1] These compounds act by blocking enzymes known as tyrosine kinases.[1] Ponatinib is a potent inhibitor of BCR-ABL with structural elements, including a carbon-carbon triple-bond, that enable high affinity binding to native BCR-ABL and mutant forms of the ABL kinase.[2] BCR-ABL is found on the surface of leukaemia cells where it is involved in stimulating the cells to divide uncontrollably.[1] By blocking BCR-ABL, ponatinib helps to control the growth and spread of leukaemia cells.[1] Ponatinib inhibits the activity of other clinically relevant kinases and has also demonstrated cellular activity against RET, FLT3, and KIT and members of the FGFR, PDGFR, and VEGFR families of kinases.[2]

Ponatinib is currently in phase I/II clinical development for treating paediatric recurrent or refractory leukaemias, lymphomas or solid tumours (NCT03934372). In phase I of this trial, ponatinib is administered as a tablet or age-appropriate formulation for paediatric participants according to age-based cohort assignment. In phase II, ponatinib is administered at the recommended phase II dose.[3]

Key Innovation

Ponatinib is currently licensed in the UK for treating adults with CML and acute lymphoblastic leukaemia (ALL).[4] Unlike acute leukaemias, CML in children cannot be cured by any type of chemotherapy although already licensed TKIs, can eliminate easily detectable signs of leukaemia from the blood, prolonging the chronic phase of the disease and delaying transformation to the accelerated stage.[5] TKIs cannot cure CML and must be taken every day to prevent progression of the disease.[5] The only treatment that can cure CML in children is a stem cell transplant.[5] Therefore, if licensed, ponatinib will offer a another treatment option for children with chronic phase CML.

Regulatory & Development Status

Ponatinib currently has Marketing Authorisation in the EU/UK for adult patients with:[4,6]

- chronic-phase, accelerated-phase, or blast-phase CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation; and
- Philadelphia-chromosome-positive ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

Ponatinib is in phase I/II clinical development for combination therapy with chemotherapy in children, teenagers and adults With Philadelphia chromosome-positive ALL.[7] Ponatinib is also in phase II/III clinical development for patients aged 14 to 65 years who have received or are undergoing allogeneic haematopoietic stem cell transplantation for Philadelphia chromosome-positive ALL.[8,9]

[a] Information provided by Incyte Corp

Patient Group

Disease Area and Clinical Need

CML, also called chronic myelogenous leukaemia, is a rare type of cancer that affects the bone marrow and white blood cells.[10] Most childhood leukaemias are acute, meaning they develop and progress rapidly. CML is a chronic leukaemia, meaning it develops slowly, often over many years.[5] In CML, immature dividing cells, known as blast cells, fill up the bone marrow and stop it making healthy blood cells.[5] As the blast cells are immature, they cannot work properly, putting the child at increased risk of infection.[5] The overproduction of white blood cells also interferes with the production of healthy red blood cells and platelets, leading to symptoms of leukaemia, such as anaemia and bruising.[5] There are three different stages in the development of CML: chronic, accelerated and blast.[5] In chronic phase there may be no symptoms of leukaemia but blast cells are present in the blood and bone marrow.[5] This phase can last several years before transforming to the second, accelerated phase where blast cell numbers are increased.[5] For CML to be refractory the patients disease must not be responsive to initial treatment whereas relapse refers to the return of disease after a period of improvement.[11]

CML in children is rare, with around five cases per year in the UK.[5] In addition, there are around 28 cases in teenagers and young adults each year.[5] In England, more than 85% of children survive CML for five years or more from diagnosis.[5] In England (2022-23), there were 4,368 finished consultant episodes (FCEs) and 4,060 admissions for CML, BCR/ABL-positive (ICD-10 code C92.1), which resulted in 3,472 day cases and 5,865 FCE bed days;[12] however, these statistics are not specific to children.

Recommended Treatment Options

For children, the National Institute for Health and Care Excellence (NICE) currently only recommends the TKI inhibitor imatinib.[13]The main aim of treatment for CML is to move patients into remission, where there are no signs of CML in the blood.[14] Therefore, the main treatment for CML is TKIs.[14] Where these are ineffective, chemotherapy, stem cell transplants and supportive treatments to help with symptoms caused by CML or the medicines and chemotherapy (e.g. antibiotics for infections, blood transfusions or vaccines to protect from illnesses) may be used.[14,15]

Clinical Trial Information

Trial	NCT03934372, EudraCT 2018-004878-99; An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Ponatinib for the Treatment of Recurrent or Refractory Leukemias, Lymphomas or Solid Tumors in Pediatric Participants **Phase I/II** – Recruiting **Locations:** Eight EU countries and UK **Primary Completion Date:** December 2024
Trial Design	Single group assignment, open label
Population	N = 60 (estimated); children aged 1 to 17 years old with recurrent or refractory leukaemias, lymphomas or solid tumours
Intervention(s)	Phase I: ponatinib administered as a tablet or age-appropriate formulation Phase II: ponatinib administered at the recommended phase II dose
Comparator(s)	N/A

Outcome(s)	Phase I primary outcome: - Number of dose-limiting toxicities [Time Frame: 28 days] Phase II primary outcomes: - Efficacy of ponatinib assessed by major cytogenetic response (MCyR) in participants with chronic-phase chronic myeloid leukaemia (CP-CML) [Time Frame: 12 months] - Efficacy of ponatinib assessed by major hematologic response (MaHR) or major molecular response (MMR) in participants with BCR-ABL-positive leukaemias [Time Frame: 3 months] - Efficacy of ponatinib assessed by complete response (CR) in participants with leukaemias other than BCR-ABL-positive leukaemias to determine the efficacy of ponatinib [Time Frame: 6 months] - Efficacy of ponatinib assessed by incomplete complete response (iCR) in participants with leukaemias other than BCR-ABL-positive leukaemias [Time Frame: 6 months] - Efficacy of ponatinib assessed by CR in participants with lymphoma [Time Frame: 6 months] - Efficacy of ponatinib assessed by overall response rate in participants with solid tumours [Time Frame: 6 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Ponatinib is already marketed in the UK for CML and ALL in adults; 15 mg tablets cost £2525 per pack of 30; 30 mg and 45 mg tablets cost £5050 per pack of 30.[16]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Guidance on the use of imatinib for chronic myeloid leukaemia (TA70). January 2016.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- NP Shah, Bhatia R, Altman JK, Amaya M, Begna KH, Berman E, et al. Chronic Myeloid Leukemia, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. 2024.[17]
- Smith G, Apperley J, Milojkovic D, Cross NCP, Foroni L, Byrne J, et al. A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. 2020.[18]

- Hochhaus A, Saussele S, Rosti G, Mahon F-X, Janssen JJWN, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[19]

Additional Information

Incyte Corp 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.

References

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With Minimal Residual Disease Positive Pre-transplants. *Trial ID: NCT03624530*. 2018. Status: Unknown Available from: https://clinicaltrials.gov/study/NCT03624530 [Accessed 05 March 2024].

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