Ponatinib for chronic myeloid leukaemia or Ph+ acute lymphoblastic leukaemia

**SUMMARY**

Ponatinib is intended to be used as therapy for the treatment of chronic myeloid leukaemia or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia. In clinical trials, it has been used for the treatment of patients intolerant to prior tyrosine kinase inhibitor therapy or whose disease is resistant to such drugs. If licensed, it would provide an additional treatment option for this patient group. Ponatinib is a multi-targeted tyrosine kinase inhibitor whose primary target is BCR-ABL, an abnormal tyrosine kinase that is expressed in chronic myeloid leukaemia and Ph+ acute lymphoblastic leukaemia.

In the UK, chronic myeloid leukaemia has an annual incidence of around 560 and in 2010 there were 216 registered deaths. Approximately 400 adults are diagnosed with acute lymphoblastic leukaemia each year in the UK, of whom 25% are Ph+. In 2010, 191 deaths were registered in the UK.

Current treatments for chronic myeloid leukaemia include imatinib, dasatinib, nilotinib and interferon alpha. For acute lymphoblastic leukaemia, current treatments include daunorubicin, doxorubicin, idarubicin, mitoxantrone, crisantapase, mercaptopurine, cyclophosphamide and vincristine. Ponatinib is currently in phase III clinical trials investigating its effect on major cytogenetic response in chronic phase chronic myeloid leukaemia patients and major haematologic response in accelerated phase or blast crisis chronic myeloid leukaemia patients and Ph+ acute lymphoblastic leukaemia patients. This trial is expected to complete in Q4 2012.
TARGET GROUP

- Chronic myeloid leukaemia (CML).
- Acute lymphoblastic leukaemia (ALL): Philadelphia chromosome-positive (Ph+).

In clinical trials, ponatinib has been used for the treatment of patients intolerant to prior tyrosine kinase inhibitor therapy or whose disease is resistant to such drugs.

TECHNOLOGY

DESCRIPTION

Ponatinib (AP-24534) is a multi-targeted TKI. The primary target for ponatinib is BCR-ABL, an abnormal tyrosine kinase that is expressed in CML and Ph+ ALL. It also inhibits other tyrosine kinases, including FLT3, RET, KIT, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR). Ponatinib targets not only native BCR-ABL, but also its isoforms that carry mutations conferring resistance to treatment with existing TKIs. Ponatinib is administered orally at 45mg once daily.

Ponatinib is also in phase III clinical trials for newly diagnosed CML (first line).

INNOVATION and/or ADVANTAGES

If licensed, ponatinib will offer an additional treatment option for this patient group.

DEVELOPER

ARIAD Pharmaceuticals, Inc.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

CML is a cancer of myeloid blood cells characterised by a proliferation of granulocytes in blood and bone marrow\(^1\). More than 90% of people with CML are Ph+, an acquired chromosomal abnormality caused by reciprocal translocations between chromosomes 9 and 22\(^1\). These translocations result in a BCR-ABL fusion gene that encodes an active tyrosine kinase protein, leading to uncontrolled cell proliferation\(^1\). CML has three stages: chronic phase; accelerated phase; and blast crisis\(^2\). Around 90% of CML is diagnosed during chronic phase, with approximately 40% being asymptomatic and diagnosed as a result of a routine blood test\(^1\).
ALL is a malignant disorder of the lymphoid progenitor cells, affecting both children and adults, with a peak prevalence between the ages of 2 and 5 years\(^3\). ALL causes an overproduction of immature lymphocytes, known as lymphoblasts or blast cells, which replace normal bone marrow\(^4\).

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to: Improving Outcomes: A Strategy for Cancer (2011).

**CLINICAL NEED and BURDEN OF DISEASE**

CML has an annual incidence of around 560 in the UK\(^5\), with slightly more men than women diagnosed (annual age-standardised rate 1.2 per 100,000 for men and 0.7 per 100,000 for women)\(^1\). Accounting for around 15% of leukaemias in adults, the median age of onset for CML is 66 years\(^6\), although it may also occur in children and the very old\(^2\). The chronic phase is usually stable and benign, typically lasting around 3-5 years following diagnosis\(^7\). Symptoms are usually mild and non-specific and may include fatigue, weight loss, night sweats, anaemia, a feeling of fullness, and a tender lump on the left side of the abdomen caused by splenomegaly\(^1\). Following the chronic phase, the accelerated phase occurs in around two-thirds of people affected, whilst others progress directly to blast crisis\(^7\). During the accelerated phase, which typically lasts for around 2-15 months\(^7\), progression is rapid, as immature blast cells in blood and bone marrow proliferate\(^1\). Symptoms include bruising, bleeding and infections\(^1\). During the blast crisis phase, immature forms of cells (blasts) increase, replacing normal cells in the bone marrow\(^1\). Symptoms include fever, sweating, pain and enlargement of organs\(^1\). Survival at blast crisis phase is likely to be 3-6 months\(^1\). Annual progression from chronic phase to blast crisis is 5-10% in the first 2 years, and 20% in subsequent years\(^7\). The average relative one-year survival for CML is approximately 78%\(^8\). In 2010, 216 deaths were registered in the UK\(^9\), and in 2010-11, there were 4,667 hospital admissions for CML (ICD10 C92.1) in England, accounting for 6,991 bed-days\(^10\).

ALL is the most common form of cancer in children and is the only haematological malignancy that is more common in children than adults\(^11\). After young children, the most frequently affected age groups are young adults and the over 75s\(^11\). Symptoms, which are caused by anaemia, leukopenia and thrombocytopenia, include unusual bleeding and bruising, paleness, frequent and persistent infections, tiredness and breathlessness\(^12\). Approximately 400 adults are diagnosed with ALL in the UK every year and it is slightly more common in men than women\(^11\). Approximately 25% of adult ALL is Ph+ which is associated with at least a 10% lower chance of achieving complete remission and an extremely poor prognosis overall, with a median survival of 8 months\(^13\). In 2010, 191 deaths were registered in the UK\(^9\), and in 2010-11 there were 26,684 hospital admissions for ALL (ICD10 C91.0) in England, accounting for 38,525 bed-days\(^10\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Chronic myeloid leukaemia – Bosutinib (first line) [ID495]. Expected date of issue to be confirmed\(^14\).
• NICE technology appraisal. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. (TA241) January 2012.

Other Guidance

• European Society for Medical Oncology. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2010.

EXISTING COMPARATORS and TREATMENTS

Treatment for CML depends on the phase of the disease, general health, age, and level of fitness. Current standard-of-care for chronic phase is standard dose imatinib, the use of which has significantly increased survival in CML. However, around 40% of people are intolerant, or develop resistance to imatinib and clinical specialists suggest that dasatinib, nilotinib and high-dose imatinib are in widespread use in the UK. Current treatments for CML include:
- Biological therapies – imatinib, dasatinib, nilotinib, interferon alpha.
- Chemotherapy – hydroxycarbamide, busulfan.
- Allogeneic stem cell transplant.

Treatment for ALL depends on the sub-type of ALL, general health, age, and level of fitness. Current treatments for ALL include:
- Chemotherapy – daunorubicin, doxorubicin, idarubicin, mitoxantrone, crisantaspase, mercaptopurine, cyclophosphamide, vincristine.
- Steroid therapy – prednisolone, dexamethasone
- Biological therapy for Ph+ patients – imatinib
- Allogeneic stem cell transplant.

EFFICACY and SAFETY

<table>
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<tr>
<th>Trial</th>
<th>PACE, NCT01207440, AP24534-10-201; ponatinib; phase II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>ARIAD Pharmaceuticals Inc.</td>
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<tr>
<td>Status</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Source of information</td>
<td>Abstract, trial registry, manufacturer</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada, Australia, Singapore and Korea.</td>
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<tr>
<td>Design</td>
<td>Single arm</td>
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<tr>
<td>Participants</td>
<td>n=440 (planned); aged 18 years and older; CML, any phase, myeloid or lymphoid phenotype; ALL, Ph+; resistant or intolerant to dasatinib or nilotinib; developed T315I mutation following any TKI treatment including imatinib.</td>
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</table>
All participants receive ponatinib, oral, 45mg once daily. Active treatment until disease progression or intolerance; 2 years follow-up.

Major cytogenetic response (MCyR) in chronic phase patients; major haematologic response (MHR) in accelerated phase, blast crisis, and Ph+ ALL patients.

Complete cytogenetic response (CCyR); major molecular response (MMR); clinical outcomes; time to response; duration of response; progression free survival; overall survival; safety and tolerability. No quality of life measures included in trial outcomes.

Chronic phase CML patients: MCyR, 49%; CCyR 41%, MMR 26%; accelerated phase CML patients: MHR 67%, MCyR 38%, CCyR 17%; blast crisis CML/Ph+ALL patients: MHR 37%; MCyR 37%, CCyR 28%.

Thrombocytopenia 33%; rash 33%; dry skin 26%

Q4 2012.

The cost of ponatinib is not yet known. The costs of selected currently licensed treatments are:

<table>
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<tr>
<th>Drug</th>
<th>Dose</th>
<th>28 day cost</th>
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<tbody>
<tr>
<td>Imatinib (Glivec)</td>
<td>400mg once daily</td>
<td>£1,609</td>
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<tr>
<td>Dasatinib (Sprycel)</td>
<td>100mg once daily</td>
<td>£2,338</td>
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<tr>
<td>Nilotinib (Tasigna)</td>
<td>300mg twice daily</td>
<td>£2,433</td>
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</table>

Impact on Patients and Carers
- ✔ Reduced mortality/increased length of survival
- ☐ Other: Reduced symptoms or disability
- ☐ No impact identified

Impact on Services
- ☐ Increased use of existing services
- ☐ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☐ Other: None identified

Impact on Costs
- ☐ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☐ Other increase in costs:
- ☐ Other reduction in costs:
- ✔ Other: uncertain unit cost compared to existing agents
- ☐ None identified

Other Issues
- ☐ Clinical uncertainty or other research question identified:
- ☐ None identified
REFERENCES

1 National Institute for Health and Clinical Excellence. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. Technology appraisal TA241. London: NICE; January 2012.


14 National Institute for Health and Clinical Excellence. Chronic myeloid leukaemia – Bosutinib (1st line) [ID496]. Technology appraisal in development. Expected date of issue to be confirmed.


21 Cortes JE, Kim DW, Pinilla-Ibarz J et al. PACE: a pivotal phase II trial of ponatinib in patients with CML and Ph+ALL resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation. Journal of Clinical Oncology 2012;30(abstr 6503).

