Avatrombopag for immune (idiopathic) thrombocytopenic purpura

SUMMARY

Avatrombopag is intended to be used for the second line treatment of adults with immune thrombocytopenic purpura (ITP), also known as idiopathic thrombocytopenic purpura. If licensed, it would provide an alternative treatment option for this patient group. It is a small molecule thrombopoietin receptor agonist, which targets the c-Mpl thrombopoietin cell surface receptor on megakaryocytes, the bone marrow cells responsible for producing platelets, to stimulate platelet production. It is not currently licensed for any other indication.

ITP is an autoimmune disorder characterised by isolated thrombocytopenia in the absence of other causes or disorders that maybe associated with thrombocytopenia. Adult chronic ITP has an incidence of 3.3 new cases per 100,000 adults per year in the USA, with a similar incidence reported in the UK. The incidence of ITP increases with age, as does the severity of the condition and it is more common in women than men. The estimated prevalence of ITP in England is 0.02%, which accounts for 8,337 people. Of these, it is estimated that 3,335 (40%) do not require treatment, while the remaining 5,002 patients do require treatment. In 2011-12, there were 8,606 admissions for ITP in England, resulting in 8,429 bed-days and 9,370 finished consultant episodes.

The major goal of treatment strategies for ITP is to achieve a platelet count associated with adequate haemostasis, rather than a normal platelet count. Pharmacological treatments include corticosteroids, anti-D immunoglobulin, rituximab and thrombopoietin (TPO) receptor agonists. Avatrombopag is currently in two phase III clinical trials comparing its effect on durable platelet response against treatment with eltrombopag or placebo. These trials are expected to be completed by mid-2014.
TARGET GROUP

- Immune thrombocytopenic purpura: adults – second line.

TECHNOLOGY

DESCRIPTION

Avatrombopag (E5501, AKR-501) is a small molecule thrombopoietin receptor agonist. It targets the c-Mpl thrombopoietin cell surface receptor on megakaryocytes, the bone marrow cells responsible for producing platelets, to stimulate platelet production. It is intended for the second line treatment of adults with immune thrombocytopenic purpura (ITP). Avatrombopag is administered orally at 40mg, once daily.

Avatrombopag is in phase II clinical trials for the treatment of thrombocytopenia in chronic liver disease requiring an elective invasive procedure and thrombocytopenia in chronic liver disease patients who require or are receiving interferon therapy (i.e. both initiation and maintenance) for hepatitis C.

INNOVATION and/or ADVANTAGES

If licensed, avatrombopag may provide an alternative treatment option for this patient group.

DEVELOPER

Eisai Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

ITP is an autoimmune disorder characterised by isolated thrombocytopenia (peripheral blood platelet count <100 x 10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia. ITP is characterised by antibody-mediated destruction of platelets and impaired platelet production. These dual effects result in thrombocytopenia and in some cause a predisposition to bleeding, with associated morbidity and mortality.

ITP that arises suddenly is known as newly diagnosed ITP; if the platelet count remains low after 3 months, it is known as persistent ITP; and chronic ITP occurs when the platelet count has not returned to normal after 12 months. In adults there is typically an insidious onset, with no preceding viral or other illness. Symptoms and signs are highly variable, and range from the fairly common asymptomatic patient with mild bruising, to mucosal bleeding (e.g. oral or gastrointestinal tract) and haemorrhage from any site, the most serious of which is...
intracranial\textsuperscript{2}. Overall, frank bleeding is uncommon unless the platelet count is less than 30 x $10^{9}$/L\textsuperscript{2a}.

**NHS or GOVERNMENT PRIORITY AREA**

None identified.

**CLINICAL NEED and BURDEN OF DISEASE**

Adult chronic ITP has an incidence of 3.3 new cases per 100,000 adults per year in the USA\textsuperscript{4} with a similar incidence reported in the UK\textsuperscript{2}. The incidence of ITP increases with age, as does the severity of the condition and it is more common in women than men\textsuperscript{5}.

The estimated prevalence of ITP in England is 0.02\%, which accounts for 8,337 people\textsuperscript{b,6}. Of these, it is estimated that 3,335 (40\%) do not require treatment, while the remaining 5,002 patients do require treatment\textsuperscript{6}. An estimated 33\% (1,651) of patients requiring treatment successfully respond to first-line treatments, with 67\% (3,351) in need of further treatment\textsuperscript{6}. In 2011-12, there were 8,606 admissions for ITP (ICD-10 D69.3) in England, resulting in 8,429 bed-days and 9,370 finished consultant episodes\textsuperscript{7}.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal. Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (TA221). April 2011\textsuperscript{8}.
- NICE technology appraisal. Eltrombopag for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (TA205). October 2010\textsuperscript{9}.

**Other Guidance**

- American Society of Haematology 2011 evidence-based practice guideline for immune thrombocytopenia. 2011\textsuperscript{10}.
- International consensus report on the investigation and management of primary immune thrombocytopenia. 2010\textsuperscript{11}.
- British Journal of Haematology. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. 2003\textsuperscript{2}.

**EXISTING COMPARATORS and TREATMENTS**

The major goal of treatment strategies for ITP is to achieve a platelet count associated with adequate haemostasis rather than a normal platelet count\textsuperscript{12}. Current guidelines\textsuperscript{2,12} suggest that the decision to treat should involve a discussion with the patient and consideration of the severity of bleeding, anticipated surgical procedures, medication side effects, patient age and health-related quality of life. The majority of patients with no bleeding or mild bleeding can be treated with observation alone regardless of platelet count\textsuperscript{12}.

\textsuperscript{a} Expert opinion.

\textsuperscript{b} Based on a population of 40,235,268 (18 years and older).
Once it has been determined that a patient does require therapy, options include\textsuperscript{1,2,5,11,12}

**First-line treatments (initial treatment for newly diagnosed ITP):**

- Observation.
- Corticosteroids – prednisone and dexamethasone, methylprednisolone.
- Intravenous infusion immunoglobulin (IVIg).
- Anti-D immunoglobulin (anti-D).

**Second line treatments (active treatments):**

- Splenectomy - Recommended for adults who have failed corticosteroid therapy. It has been estimated that two thirds of patients will achieve a normal platelet count which is often sustained with no further therapy.
- Rituximab - can be used as an alternative to splenectomy, but less than one third of treated patients achieve a sustained remission\textsuperscript{13}.
- Thrombopoietin (TPO) receptor agonists - romiplostim and eltrombopag, these are recommended for adults at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy.
- Immunosuppressive agents - azathioprine, mycophenolate mofetil and ciclosporin, danazol, dapsone.
- Cytotoxic agents - cyclophosphamide and vinca alkaloids such as vincristine and vinblasatine.

**Treatment after failure of first and second line therapies\textsuperscript{11}:**

- Combination chemotherapy – cyclophosphamide and prednisone in combination with vincristine and either azathioprine or etoposide.
- Campath-1H – alternative therapeutic option for severe, refractory ITP. However, side effects are severe.
- Haematopoietic stem cell transplantation (HSCT) – only in patients with severe chronic ITP with bleeding complications unresponsive to other modalities.
- TPO receptor agonists – romiplostim and eltrombopag.

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**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01433978, 2011-000831-10-DE, E5501-G000-305; avatrombopag vs eltrombopag; phase III.</th>
<th>NCT01438840, E5501-G000-302; avatrombopag vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Eisai Inc.</td>
<td>Eisai Inc.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{14}.</td>
<td>Trial registry\textsuperscript{15}.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>EU, South Africa and Australasia.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=286 (planned); aged 18 years and older; chronic ITP; previously received one or more ITP therapies.</td>
<td>n=84 (planned); aged 18 years and older; chronic ITP; previously received one or more ITP therapies.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to avatrombopag 20mg oral, or eltrombopag 50mg oral, both once daily. Subjects will have their dose titrated up (max 40mg/75mg) or down (min 5mg/25mg) depending on response.</td>
<td>Randomised to avatrombopag 20mg oral, or placebo 20mg oral, both once daily. Subjects will have their dose titrated up (max 40mg) or down (min 5mg) depending on response.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 2.5 yrs.</td>
<td>Active treatment period 2.5 yrs.</td>
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<td>---------------------------------</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Durable platelet response&lt;sup&gt;c&lt;/sup&gt;.</td>
<td>Durable platelet response.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Platelet response at day 8.</td>
<td>Platelet response at day 8.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Primary completion date reported as July 2014.</td>
<td>Primary completion date reported as Oct 2013.</td>
</tr>
<tr>
<td>Trial</td>
<td>NCT00441090, AKR-501-CL-003; avatrombopag vs placebo; phase II.</td>
<td>NCT00625443, AKR-501-CL-004; avatrombopag vs placebo; phase II extension.</td>
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<td>Sponsor</td>
<td>Eisai Inc.</td>
<td>Eisai Inc.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry&lt;sup&gt;16&lt;/sup&gt;, abstract&lt;sup&gt;17&lt;/sup&gt;.</td>
<td>Trial registry&lt;sup&gt;18&lt;/sup&gt;, abstract&lt;sup&gt;19&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Location</td>
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</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=64; 18 years and older; ITP; refractory or relapsed after at least one prior ITP therapy.</td>
<td>n=57; 18 years and older; patients who completed 28 days treatment in study NCT004441090 (protocol 501-CL-003).</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to avatrombopag 2.5mg, 5mg, 10mg or 20mg oral, or placebo oral, all once daily.</td>
<td>Patients who met primary efficacy response criteria in original study continue on same study treatment; i.e. avatrombopag 2.5mg, 5mg, 10mg, or 20mg oral; or placebo oral, all once daily. Patients who did not meet the primary efficacy response criteria receive avatrombopag 10mg oral, once daily.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment period 28 days, follow-up 4 weeks.</td>
<td>Active treatment period 6 months, follow-up 4 weeks.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Response to therapy on day 28.</td>
<td>Safety.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Safety.</td>
<td>Changes in peripheral platelet count.</td>
</tr>
<tr>
<td>Key results</td>
<td>For avatrombopag 2.5mg, 5mg, 10mg, 20mg, and placebo respectively: responder rate at day 28, 13.3%, 53.3%, 50.0%, 80.0%, 0%; median platelet count at day 28, 18x10⁹/L, 27x10⁹/L, 22.5x10⁹/L, 22x10⁹/L, 19x10⁹/L.</td>
<td>For all subjects, responders in original study and non-responders respectively: durable platelet response rate 52.8%, 72%, 35.7%; overall platelet response rate 75.5%, 88%, 64.3%.</td>
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<tr>
<td>Adverse effects (AEs)</td>
<td>Common AEs include: fatigue, 20.3%; headache, 20.3%; epistaxis, 15.3%.</td>
<td>Common AEs include: fatigue, 37.5%; headache, 32.8%; epistaxis, 25%.</td>
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</tbody>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of avatrombopag is not yet known. The costs of other treatments for ITP are as follows<sup>20</sup>:

<sup>c</sup> Defined as patients whose platelet count was ≥50x10⁹/L and had risen by a minimum of 20x10⁹/L above baseline.
Drug | Dose | Unit Cost
---|---|---
Eltrombopag (Revolade) | Initially 50mg oral once daily, adjusted to achieve a platelet count of $50 \times 10^9/L$ or more. | 50mg, 28-tab pack, £1540.00.
Romiplostim (Nplate) | Initially 1µg/kg subcutaneous injection once weekly, adjusted in steps of 1µg/kg at weekly intervals until a stable platelet count of $50 \times 10^9/L$ or more is reached. | 250µg vial £482.00.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- **☑ Other: expert opinion suggests a potential for better compliance to therapy due to lack of dietary restrictions compared to alternative therapies.**
- 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 alternative treatment options.**
- None identified

**Other Issues**
- Clinical uncertainty or other research question identified:
- **☑ None identified**

**REFERENCES**

14 ClinicalTrials.gov. A phase 3, multicentre, randomised double-blind, active-controlled, parallel-group trial with an open-label extension phase to evaluate the efficacy and safety of oral E5501 versus eltrombopag, in adults with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura).
15 ClinicalTrials.gov. A phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial with an open-label extension phase to evaluate the efficacy of oral E5501 plus standard of care for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura).