Avatrombopag for thrombocytopenia in chronic liver disease prior to surgery

**SUMMARY**

Avatrombopag is intended to be used for the treatment of thrombocytopenia in patients with chronic liver disease prior to surgery. If licensed, it would offer an oral treatment option for this patient group who currently have no licensed therapies available. Avatrombopag is a small molecule thrombopoietin receptor agonist which targets the c-Mpl thrombopoietin cell surface receptor on megakaryocytes to stimulate platelet production. Avatrombopag does not currently have Marketing Authorisation in the EU for any indication.

In patients with chronic liver disease, the prevalence of thrombocytopenia is estimated to be 64%, however estimates vary from 15% to 70% depending upon the stage of liver disease and differences in platelet count cut-off used to define thrombocytopenia. Mild to moderate thrombocytopenia rarely causes severe bleeding episodes during invasive procedures such as liver biopsy and liver transplants, but severe thrombocytopenia increases this risk and can have a significant impact on the clinical management of liver disease. Thrombocytopenia may delay or prevent the initiation of appropriate therapy leading to increased morbidity and mortality and a reduced quality of patient care.

There are currently no licensed pharmaceutical treatment options for thrombocytopenia in patients with chronic liver disease prior to surgery. Other therapies for thrombocytopenia from alternate causes include romiplostim, eltrombopag and oprelvekin. Platelet transfusion, splenic artery embolisation and surgical splenectomy may be undertaken, particularly in patients with portal hypertension. Avatrombopag is currently in phase III clinical trials comparing its effect on the proportion of patients requiring platelet transfusion or rescue therapy for bleeds against treatment with placebo. This trial is expected to complete in August 2015.
TARGET GROUP

- Thrombocytopenia: chronic liver disease – prior to elective surgery.

TECHNOLOGY

DESCRIPTION

Avatrombopag (E5501, AKR-501) is a small molecule thrombopoietin (TPO) receptor agonist. Thrombopoietin is mainly produced in the liver along with smaller levels of production in the bone marrow and kidney. Avatrombopag 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 treatment of adults with thrombocytopenia in chronic liver disease prior to elective surgery. Avatrombopag is administered orally at 40mg or 60mg, once daily on days 1-5, prior to elective surgery.

Avatrombopag is also in phase II clinical trials for 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 will offer an oral treatment option for this patient group who currently have no licensed and non-invasive therapies available.

DEVELOPER

Eisai Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Thrombocytopenia is characterised by a clinically significant lack of platelets circulating within the blood, and is most usually defined as a platelet count of less than 150 x 10^9 per litre of blood. It can arise through a number of mechanisms including congenital abnormalities in platelet production (e.g. megakaryocytic hypoplasia, Bernard-Soulier syndrome), decreased production of platelets (e.g. viral infections, leukaemia, chemotherapy, alcohol), increased destruction of platelets (e.g. idiopathic thrombocytopenia purpura), platelet sequestration and dilution thrombocytopenia. External and internal bleeding are the most common signs of thrombocytopenia. Symptoms of external bleeding include purpura and petechiae, prolonged bleeding from minor cuts, excessive bleeding from the mouth or nose, abnormal/heavy menstrual bleeding and excessive bleeding during/after surgery. Internal bleeding into the intestines or the brain is considered the most serious as it may be unrecognised and can be fatal. Signs of internal bleeding include blood in urine or stools, and headaches.
In up to 76% of cases, thrombocytopenia is associated with chronic liver disease\(^6,7,8\) and can either be a direct result of the liver pathology or a consequence of interferon-based anti-viral therapy. In either case, the numbers or function of platelets may be altered directly or indirectly through suppression of thrombopoiesis in the bone marrow\(^8\).

Mild to moderate thrombocytopenia rarely cause severe bleeding episodes during invasive procedures such as liver biopsy and liver transplants, but severe thrombocytopenia (<50 x \(10^9\) per litre) increases this risk and can have a significant impact on the clinical management of liver disease\(^7\). Thrombocytopenia may delay or prevent the initiation of appropriate therapy leading to increased morbidity and mortality and a reduced quality of patient care\(^8\).

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

Between 2000 and 2009, the numbers of deaths due to chronic liver disease and cirrhosis in England increased by 20% in patients under the age of 65 and continues to rise\(^9\). The prevalence of thrombocytopenia in patients with chronic liver disease is estimated at 64% (including 6% in patients with chronic hepatitis); however estimates vary from 15% to 70%, being lower in patients with compensated chronic liver disease and higher in patients with end-stage liver disease\(^10\). Estimates also vary due to differences in platelet count used to define thrombocytopenia\(^8,10,11\), however thrombocytopenia (broadly defined) in cirrhosis has an estimated prevalence of 76%. Of these, 13% require liver biopsy or interferon therapy and 1% reach the threshold to initiate transfusions\(^10\). Severe thrombocytopenia occurs in approximately 1% of patients with chronic hepatitis C virus (HCV) infection\(^8\).

The population likely to be eligible to receive avatrombopag could not be estimated from routine available published sources or by the company.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
- NICE clinical guideline in development. Liver disease (non-alcoholic fatty). Expected date of issue to be confirmed.

**Other Guidance**
- American Society of Haematology 2011 evidence-based practice guideline for immune thrombocytopenia. 2011\(^12\).
- British Journal of Haematology. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. 2003\(^13\).
CURRENT TREATMENT OPTIONS

There are currently no licensed pharmaceutical treatment options for thrombocytopenia in patients with chronic liver disease. Therapies for thrombocytopenia are tailored to stimulate megakaryocyte maturation and platelet production mainly through activation of the TPO receptor. Treatment options for mild and moderate forms of thrombocytopenia from alternate causes include:

- Romiplostim – for patients with immune thrombocytopenic purpura, myelodysplastic syndrome and HCV-related thrombocytopenia.
- Eltrombopag – for patients with immune thrombocytopenia and HCV-related thrombocytopenia.
- Oprelvekin – for thrombocytopenia due to chemotherapy in patients with solid tumours or non-Hodgkin’s lymphoma.

Other recombinant human thrombopoietin agents and interleukins (IL) previously in development have been discontinued due to associated adverse events and/or lack of clinical benefit (e.g. rhTPO, PEG-rHuMGDF, IL-1, IL-3 and IL-6).

Where appropriate, treatment for severe thrombocytopenia can include platelet transfusion, splenic artery embolisation and surgical splenectomy, particularly in patients with portal hypertension. While temporarily effective, platelet transfusion therapy may lead to the development of refractoriness to subsequent platelet transfusions, as well as the potential transmission of infectious agents, transfusion reactions and in rare cases, fatality. Though guidelines are available describing the levels of platelet count at which transfusions should be considered in patients with cancer, it is not clear how applicable this information is to thrombocytopenia in patients with chronic liver disease. Similarly, treatments that are licensed for patients with thrombocytopenia, have little or no evidence base for thrombocytopenia in patients with chronic liver disease.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
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<tbody>
<tr>
<td>NCT01976104, E5501-G000-311, 2013-000934-36; avatrombopag vs placebo; phase III.</td>
<td>Eisai Inc.</td>
<td>Ongoing.</td>
<td>Trial registry</td>
<td>EU (incl UK), USA, Canada, Argentina, Australia, Brazil, Israel, Mexico and Russia.</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>NCT01972529, E5501-G000-310, 2013-000965-34; avatrombopag vs placebo; phase III.</td>
<td>Eisai Inc.</td>
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<td>EU (incl UK), USA, Canada, Argentina, Australia, Brazil, Chile, Korea, Taiwan and Thailand.</td>
<td>Randomised, placebo-controlled.</td>
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</table>
**Participants**

| n=300 (planned); adults aged 18 years and older; chronic liver disease; mean baseline platelet count < 50 x 10^9/L (measured twice at least one day apart with mean platelet counts being used to assign subjects as low or high baseline platelet count cohort); subjects scheduled to undergo elective procedure and requiring platelet transfusion associated with procedure (investigators opinion); Model for End-stage Liver Disease (MELD) score ≤ 24 at screening; subjects requiring P glycoprotein inhibitors (not verapamil) must be on a stable dose for 7 days pre-screening. | n=300 (planned); adults aged 18 years and older; chronic liver disease; mean baseline platelet count < 50 x 10^9/L (measured twice at least one day apart with mean platelet counts being used to assign subjects as low or high baseline platelet count cohort); subjects scheduled to undergo elective procedure and requiring platelet transfusion associated with procedure (investigators opinion); MELD score ≤ 24 at screening; subjects requiring P glycoprotein inhibitors (not verapamil) must be on a stable dose for 7 days pre-screening. | n=136; adults aged 18 years and older; thrombocytopenia (platelet count ≥ 10 x 10^9/L and ≤ 50 x 10^9/L; MELD score ≤ 24; chronic liver disease (due to one of three aetiologies: chronic viral hepatitis, non-alcoholic steatohepatitis or alcoholic liver disease); subjects due to undergo elective invasive procedure 1-4 days post last dose of study drug; adequate renal function; life expectancy ≥ 3 months. |

**Schedule**

| Lower baseline platelet count cohort: randomised to avatrombopag 60mg; or placebo. Higher baseline platelet count cohort: randomised to avatrombopag 40mg; or placebo. All given orally, once daily on days 1 through 5. | Lower baseline platelet count cohort: randomised to avatrombopag 60mg; or placebo. Higher baseline platelet count cohort: randomised to avatrombopag 40mg; or placebo. All given orally, once daily on days 1 through 5. | Randomised to Cohort A: avatrombopag (first generation formulation) 100mg first dose then either 20, 40 or 80mg a day for up to 6 additional days; or placebo once daily for 7 days; Cohort B: avatrombopag (second generation formulation) 80mg first dose then either 10mg a day for days 2-7 or 20mg a day for days 2-4; or placebo once daily for 7 days. |

**Follow-up**

| Active treatment period of 5 days, follow-up period of 7 days post-elective procedure and up to 20 months for safety outcome measures. | Active treatment period of 5 days, follow-up period of 7 days post-elective procedure and up to 20 months for safety outcome measures. | Active treatment period of 7 days and follow-up period of 8 days. |

**Primary outcome/s**

| Proportion of subjects requiring platelet transfusion or rescue therapy for bleeds. | Proportion of subjects requiring platelet transfusion or rescue therapy for bleeds. | Proportion of responders*. |

**Secondary outcome/s**

| Proportion of subjects achieving platelet count ≥ 50 x 10^9/L; change from baseline platelet count; proportion of subjects with | Proportion of subjects achieving platelet count ≥ 50 x 10^9/L; change from baseline platelet count; proportion of subjects with | Change in platelet count from baseline to end of treatment/follow-up. |

*Responders defined as having an increase of at least 20 x 10^9/L platelet count from baseline and platelet count of >50 x 10^9/L at least once during days 4-8.
Key results

- Cohort A: avatrombopag (n=51) and placebo (n=16), respectively: proportion of responders, 49.0% and 6.3%, p<0.01 for avatrombopag vs placebo except 100/40mg group (p=0.17).

- Cohort B: avatrombopag (n=42) and placebo (n=21), respectively: proportion of responders, 47.6% and 9.5%, p<0.01 for avatrombopag vs placebo.

Adverse effects (AEs)

Most common AEs: nausea, fatigue and headache. One patient in avatrombopag 100/80mg group diagnosed with portal vein thrombosis during post-treatment follow-up.

Expected reporting date

Study completion date reported as August 2015.

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ESTIMATED COST and IMPACT

COST

The cost of avatrombopag is not yet known. The costs of other selected treatments for thrombocytopenia are outlined below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit Cost</th>
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<tbody>
<tr>
<td>Eltrombopag</td>
<td>Initially 25mg orally once daily, adjusted to achieve a platelet count sufficient to initiate antiviral therapy then a platelet count of 50-75 \times 10^9/L during antiviral therapy.</td>
<td>25mg, 28-tab pack, £770.00.</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>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.</td>
<td>250µg vial, £482.00.</td>
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IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other:
- No impact identified
### Impact on Health and Social Care Services
- **Increased use of existing services**
- **Decreased use of existing services: oral formulation, reduced need for platelet transfusion.**
- **Re-organisation of existing services**
- **Need for new services**
- **Other:**
  - **None identified**

### Impact on Costs and Other Resource Use
- **Increased drug treatment costs**
- **Reduced drug treatment costs**
- **Other increase in costs**
- **Other reduction in costs**
- **Other: uncertain unit cost compared to existing treatments**
- **None identified**

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

### REFERENCES