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Newcastle University

Health Technology Briefing
September 2024

Avatrombopag for treating immune thrombocytopenia in children

Company/Developer	SOBI - Swedish Orphan Biovitrum AB

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30369	NICE ID: Not available	UKPS ID: 674944

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Avatrombopag is in clinical development for the treatment of immune thrombocytopenia (ITP) in children with a duration of ≥6 months that have had a poor response to a previous treatment. ITP is an autoimmune disease (where the immune system attacks the body instead of foreign invaders like bacteria and viruses), where the immune system mistakenly attacks and destroys platelets, which are cells that help blood to clot. Individuals with ITP can experience easy or excessive bruising and bleeding. In children, ITP often occurs after a viral infection. There are several challenges associated with current treatment methods for ITP. These challenges include treatment administration and variation in patient responses to treatment. In addition, ITP often returns (relapse) despite having treatment and there are some side effects or undesirable effects (associated toxicities). An unmet medical need currently exists in managing ITP among children and adolescents.

Avatrombopag is an orally administered drug that mimics the natural compound (thrombopoietin) responsible for stimulating the production of platelets, an essential component of the clotting process that prevents excessive bleeding. Avatrombopag quickly increases platelet levels which can be maintained in the longer term in many patients. Avatrombopag, taken orally, is thus a convenient and effective treatment for patients with ITP and can prevent bleeding events. Avatrombopag will provide an alternative treatment option for paediatric patients with ITP for ≥6 months duration who have had an insufficient response to a previous treatment.

Proposed Indication

Treatment of paediatric patients with immune thrombocytopenia (ITP) for ≥6 months duration and has had an insufficient response to a previous treatment.[1]

Technology

Description

Avatrombopag (Doptelet) is an orally active, small molecule thrombopoietin (TPO) receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in increased production of platelets.[2] TPO is a molecule that stimulates the production of platelets in the body.[3,4] Avatrombopag does not compete with TPO for binding to the TPO receptor, it works synergistically and has an additive effect with TPO on platelet production.[5,6]

Avatrombopag is currently in development for the treatment of children with ITP who have had an insufficient response to a previous treatment. In the phase III clinical trial (NCT04516967), patients will be administered avatrombopag orally once daily for 12 weeks.[1]

Key Innovation

Currently, no cure is available for ITP, and patients usually relapse after various supportive therapies. Considering the challenges in treatment administration, coupled with variable and transient responses, frequent relapses, and associated toxicities from existing treatment methods, an unmet medical need currently exists in managing ITP among children and adolescents.[7]

Avatrombopag is unique in that it does not have a warning for hepatoxicity (chemical-driven liver damage), is administered with food, and does not have any dietary restrictions. Further, it does not interact with polyvalent cations (calcium, magnesium, iron, selenium, zinc, etc.) in foods, mineral supplements, or antacids that could reduce systemic exposure and efficacy.[8] Therefore, the lack of any food restrictions or chronic immune suppression with avatrombopag treatment would be beneficial for paediatric patients living with ITP.[7] If licensed, avatrombopag will offer an additional treatment option for paediatric patients with ITP for ≥6 months duration and who have had an insufficient response to a previous treatment.

Regulatory & Development Status

Avatrombopag currently has Marketing Authorisation in the EU/UK for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure. In addition, for the treatment of primary chronic immune ITP in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).[5]

Avatrombopag is in phase III/II clinical development for the following indications: [9]

- Thrombocytopenia related to chronic liver disease
- Chemotherapy-induced thrombocytopenia

Patient Group

Disease Area and Clinical Need

ITP is an illness that can lead to bruising and bleeding. Low levels of the cells that help blood clot, also known as platelets, most often cause the bleeding.[10] ITP may be acute or chronic: acute ITP is most common in young children (2 to 6 years old). Acute ITP usually starts very suddenly and is the most common form of the disorder. Symptoms usually go away in less than 6 months (often within a few weeks) and treatment is not usually needed. The disorder usually does not recur. Chronic ITP can start at any age, and the symptoms last at least 12 months. Chronic ITP can also recur often, and although adults have this form more often than children, it does affect teenagers in addition. Females have chronic ITP two times to three times more often than males. In most cases, the cause of ITP in children is unknown, however known causes include immune system problems, chicken pox, some medicines, and vaccines. The symptoms of ITP are related to increased bleeding. Some children have very mild symptoms or none. Symptoms may include purpura (purple colour of the skin after blood has "leaked" under it), bruising easily, petechia (tiny red dots under the skin that are a result of very small bleeds), nosebleeds, bleeding mouth/gums, blood in urine/stools, vomiting blood and bleeding with head injuries which in some cases can be fatal.[11] ITP has a substantial, multifaceted impact on patients' health-related quality of life. Patients with ITP experience reduced energy levels, capacity to exercise, and limited their ability to perform daily tasks.[12]

Childhood ITP is uncommon, approximately four in every 100,000 children/year.[13] In England (2022-23), there were 12,729 finished consultant episodes (FCE) and 11,508 admissions for idiopathic thrombocytopenic purpura (ICD-10 code D69.3). This resulted in 10,727 FCE bed days and 8,648 day cases.[14]

Recommended Treatment Options

There is no treatment option recommended by NICE for children with ITP.

Treatments aim to raise the platelet count and do not cure the ITP itself. The NHS currently recommend the following treatment options for children with ITP:[15]

- Tranexamic acid
- Immunoglobulins
- Steroids
- Thrombopoiesis stimulating agents
- Splenectomy

Clinical Trial Information

Trial	**AVA-PED-301; NCT04516967**; Randomized, Double-blind, Placebo-controlled Study With Open-label Extension Phase to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Pediatric Subjects With Immune Thrombocytopenia for ≥6 Months **Phase III** – Active, not recruiting **Location(s):** Four EU countries, UK, USA, Russian Federation, Ukraine, and Turkey **Study completion date:** November 2025
Trial Design	Randomised, parallel assignment, double-masking.
Population	N = 75; subjects aged 1-17, with a diagnosis of primary ITP for ≥6 months duration and has had an insufficient response to a previous treatment. Subjects

	also have an average of 2 platelet counts <30×10^9/L with no single count >35×10^9/L in the screening period.
Intervention(s)	Avatrombopag oral tablet
Comparator(s)	Matched placebo
Outcome(s)	The proportion of subjects achieving at least 6 out of 8 weekly platelet counts ≥50×10^9/L during the last 8 weeks of the 12 week treatment period in the core phase, in the absence of rescue medication [Time frame: Last 8 weeks of 12-week treatment regimen].
Results (efficacy)	• Durable platelet response (6 out of 8 weekly platelet counts ≥50×10^9/L in the absence of rescue medication during weeks 5-12), was met in 28% of avatrombopag subjects in comparison with 0% of placebo subjects (p=0.0077, 95% CI 15.8-39.7). • A platelet response at day 8 was observed in 56% of avatrombopag subjects and 0% of placebo subjects (p=<0.0001), while rescue therapy use occurred in 7% of avatrombopag subjects and 43% of placebo subjects (p=0.0008).[7]
Results (safety)	-

Estimated Cost

Avatrombopag is already marketed in the UK for the treatment of primary chronic ITP in adult patients who are refractory to other treatments. A 10-tablet pack of avatrombopag 20 mg is £640.00. [16] The company has a commercial arrangement with the NHS, which provides access to avatrombopag for patients at a discounted price. [17]

Relevant Guidance

NICE Guidance

NICE evidence summary. Immune (idiopathic) thrombocytopenic purpura: rituximab (ESUOM35).October 2014.[18]

NHS England (Policy/Commissioning) Guidance

NHS England. 2013/14 NHS Standard Contract for Specialised Immunology (All ages). B09/S/a.

Other Guidance

American Society of Hematology (ASH). 2019 Guidelines for Immune Thrombocytopenia. 2019.[19]

Additional Information

References

1 ClinicalTrials.gov. *Randomized, Double-blind, Placebo-controlled Study With Open-label Extension Phase to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Pediatric Subjects With Immune Thrombocytopenia for ≥6 Months*. *Trial ID: NCT04516967*. Available from: https://clinicaltrials.gov/study/NCT04516967?term=NCT04516967&rank=1 [Accessed 19th September 2024].

2 Electronic Medicines Copendium (EMC). *Doptelet 20 mg film-coated tablets* 2024. Available from: https://www.medicines.org.uk/emc/product/11837/smpc [Accessed 19th September 2024].

3 Science Direct. *Thrombopoietin*. 2024. Available from: https://www.sciencedirect.com/topics/neuroscience/thrombopoietin [Accessed 29th July 2024].

4 Harmon RC. Thrombopoietin. In: Enna SJ, Bylund DB, eds. *xPharm: The Comprehensive Pharmacology Reference*. New York: Elsevier; 2007: 1-6 Available from: https://www.sciencedirect.com/science/article/pii/B9780080552323627552.

5 Electronic Medicines Copendium (EMC). *Doptelet 20 mg film-coated tablets*. 2024. Available from: https://www.medicines.org.uk/emc/product/11837 [Accessed 29th July 2024].

6 Dove Press. *Avatrombopag for the treatment of immune thrombocytopenia and thrombocytopenia of chronic liver disease*. 2024. Available from: https://www.dovepress.com/avatrombopag-for-the-treatment-of-immune-thrombocytopenia-and-thromboc-peer-reviewed-fulltext-article-JBM [Accessed 29th July 2024].

7 Sobi. *Sobi announces positive results from phase 3 study of Doptelet® for treatment of children and adolescents with ITP*. 2024. Available from: https://www.sobi.com/en/press-releases/sobi-announces-positive-results-phase-3-study-dopteletr-treatment-children-and-adolescents-itp-2215547 [Accessed 29th July 2024].

8 Nagalla S, Vredenburg M, Tian W, Allen LF. Platelet Response to Avatrombopag in Patients with Chronic Immune Thrombocytopenia: Additional Analyses from a Phase 3 Study and Its Extension. *Blood*. 2019;134(Supplement_1):1071-. Available from: https://doi.org/10.1182/blood-2019-130963.

9 ClinicalTrials.gov. *Search for: Avatrombopag | Active, not recruiting, Completed studies | Phase: 2, 3*. Available from: https://clinicaltrials.gov/search?term=Avatrombopag&aggFilters=phase:2%203,status:act%20com&page=2 [Accessed 29th July 2024].

10 Mayo Clinic. *Immune thrombocytopenia (ITP)*. 2023. Available from: https://www.mayoclinic.org/diseases-conditions/idiopathic-thrombocytopenic-purpura/symptoms-causes/syc-20352325 [Accessed 29th July 2024].

11 Stanford Medicine. *Immune Thrombocytopenic Purpura in Children*. 2024. Available from: https://www.stanfordchildrens.org/en/topic/default?id=immune-thrombocytopenic-purpura-in-children-90-P02315 [Accessed 29th July 2024].

12 Cooper N, Kruse A, Kruse C, Watson S, Morgan M, Provan D, et al. Immune thrombocytopenia (ITP) World Impact Survey (I-WISh): Impact of ITP on health-related quality of life. *Am J Hematol*. 2021;96(2):199-207. Available from: https://doi.org/10.1002/ajh.26036.

13 National Health Service (NHS). *Trust Guideline for the Management of: Newly Diagnosed Immune Thrombocytopenia (ITP) in Children*. 2024. Available from: file:///H:/Downloads/Idiopathic-Thrombocytopenic-Purpura-in-Children-CA1072-v5.1%20(2).pdf [Accessed 29th July 2024].

14 National Health Service (NHS). *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23 [Accessed 29th July 2024].

15 National Health Service (NHS). *Immune thrombocytopenia (ITP): Information for parents*. 2023. Available from: https://www.cuh.nhs.uk/patient-information/immune-thrombocytopenia-itp-information-for-parents/ [Accessed 16th September 2024].

16 National Institute for Health and Care Excellence (NICE). *Avatrombopag for treating primary chronic immune thrombocytopenia*. 2022. Available from: https://www.nice.org.uk/guidance/ta853/chapter/2-Information-about-avatrombopag [Accessed 16th September 2024].

17 National Institute for Health and Care Excellence (NICE). *Avatrombopag: Medicinal forms*. 2024. Available from: https://bnf.nice.org.uk/drugs/avatrombopag/medicinal-forms/ [Accessed 16th September 2024].

18 National Institute for Health and Care Excellence (NICE). *Immune (idiopathic) thrombocytopenic purpura: rituximab*. 2014. Available from: https://www.nice.org.uk/advice/esuom35/chapter/Full-evidence-summary [Accessed 16th August 2024].

19 Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Advances*. 2019;3(23):3829-66. Available from: https://doi.org/10.1182/bloodadvances.2019000966.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.