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Health Technology Briefing
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Marstacimab for the treatment of haemophilia A and haemophilia B

Company/Developer	Pfizer Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 23962	NICE ID: N/A	UKPS ID: 660962

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Marstacimab is in clinical development for the treatment of adults or adolescents with severe haemophilia A, and moderately severe to severe haemophilia B. Haemophilia is a rare, inherited condition that slows blood clotting. There are two main types of haemophilia: haemophilia A (a deficiency in clotting factor VIII) and haemophilia B (a deficiency in clotting factor IX). Haemophilia is categorised as mild, moderate, and severe, based on the percentage of available clotting factors in the blood. Moderate haemophilia results in bruising easily, internal bleeding around joints, joint pain and stiffness. Severe haemophilia can result in spontaneous bleeding of nose, gums, joints, and muscles. Without treatment people with severe haemophilia can develop joint deformities, soft tissue bleeding and serious internal bleeding. Some people with haemophilia can form an immune response to current treatment options therefore alternative treatment options are needed.

Marstacimab is a monoclonal antibody (a type of protein) that has been designed to recognise, attach to, and block a molecule in the body called tissue factor pathway inhibitor (TFPI). There are multiple factors associated with the blood clotting pathway and TFPI controls those that do not involve factor VIII or IX. By blocking TFPI marstacimab is expected to increase the ability of the blood to clot and prevent, or reduce, bleeding in patients with haemophilia: bypassing the need for replacement factor VIII or IX. If licensed marstacimab would offer an additional treatment option for patients with haemophilia.

Proposed Indication

Treatment of adolescents and adults with severe haemophilia A, or moderately severe to severe haemophilia B.[1]

Technology

Description

Marstacimab (PF-06741086) is a human monoclonal antibody (mAb) that targets tissue factor pathway inhibitor (TFPI).[2,3] TFPI antagonises early coagulation stages by inhibiting tissue factor-activated FVII (FVIIa) and activated FX (FXa). TFPI is expressed in three isoforms, all sharing the Kunitz-type inhibitor domain K2, which binds and inhibits activated FXa. Marstacimab targets the K2 domain of TFPI, blocking its ability to inhibit FXa and preventing the binding of the K1 domain to FVIIa.[4]

Marstacimab is in phase III clinical development for the treatment of severe haemophilia A, or moderately severe to severe haemophilia B, in adolescents and adults with or without inhibitors (B7841005, NCT03938792; B7841007, NCT05145127). Marstacimab is administered as a 300mg subcutaneous (SC) injection loading dose, followed by 150mg SC injection once weekly (qw) or 300mg SC qw is prescribed for participants who meet dose escalation criteria.[1,5]

Key Innovation

The current standard of care for treatment of individuals with haemophilia A or B is replacement of their deficient clotting factor using FVIII or FIX clotting factor concentrate, respectively, or other haemostasis products.[6,7] However, a subset of participants with haemophilia develop inhibitors directed against FVIII or FIX, reducing the effectiveness of factor replacement therapy for prophylaxis against or treatment of haemophilia bleeding episodes.[8] For participants who respond to clotting factor replacement, the IV administration route and frequency of infusion required for effective prophylaxis treatment remains burdensome and may result in reduced adherence to the treatment schedule and compromised prophylactic efficacy. In addition, the prophylaxis regimens require frequent and repeated venipuncture which is problematic in patients with limited venous access.[9] Alternative non-factor therapy is available for patients with haemophilia A, but not for haemophilia B.[10]

Marstacimab is a monoclonal antibody in development as a prophylactic treatment to prevent or reduce frequency of bleeding episodes in individuals with severe haemophilia A and moderately severe to severe haemophilia B patients, with or without inhibitors. It provides a novel approach to improve blood coagulation by blocking TFPI, thereby augmenting haemostasis through the extrinsic clotting pathway. Marstacimab, with its once weekly dosing and subcutaneous route of administration, has the advantage of convenience that can reduce treatment burden associated with frequent intravenous factor infusions. The Phase II clinical data (NCT03363321) has shown that once weekly subcutaneous marstacimab prophylaxis was well tolerated, with an acceptable safety profile and maintained long-term efficacy up to 365 days.[3]

Regulatory & Development Status

Marstacimab does not currently have Marketing Authorisation in the EU/UK for any indication.

Marstacimab has the following designatory awards:[11-13]

- Orphan drug designation in European Union, in 2016, for the treatment of haemophilia A.
- Orphan drug designation in United States (US), in 2016, for the treatment of hemophilia A and hemophilia B patients with or without inhibitors, which includes routine prophylaxis to prevent or reduce the frequency of bleeding in hemophilia A and hemophilia B patients.

- Fast track designation by US Food and Drug Administration, for use in combination with inhibitors as a potential treatment for hemophilia A and B, in September 2019.

Patient Group

Disease Area and Clinical Need

Haemophilia is a rare, usually inherited (through the X chromosome), condition which affects the blood's ability to clot.[14,15] Clotting happens when clotting factors in the blood accumulate and mix with blood cells called platelets, making the blood sticky, forming a clot which stops the bleeding. People with haemophilia do not have as many clotting factors as they should in the blood, meaning they bleed for longer than usual.[14] There are two main types of haemophilia:[16]

- Haemophilia A which is a deficiency in factor VIII
- Haemophilia B which is a deficiency in factor IX

Haemophilia is categorised by its severity (mild, moderate, and severe) based on the level of clotting factors present in the body. Moderate haemophilia has a percentage of 1-5% normal factor activity in the blood, whereas severe has <1% normal activity.[16] The primary symptom of haemophilia is prolonged bleeding, with moderate haemophilia resulting in bruising easily, internal bleeding around joints, joint pain, stiffness and the site of the bleed becoming hot, swollen and tender. Symptoms of severe haemophilia are like moderate, however joint bleeding is more frequent and severe. Severe haemophilia can result in spontaneous bleeding of nose, gums, joints, and muscles. Without treatment people with severe haemophilia can develop joint deformities, soft tissue bleeding and serious internal bleeding.[17]

Haemophilia mainly affects males.[15] Haemophilia A is the most common type, which affects between 1 in 5,000 and 1 in 10,000 males. Whilst haemophilia B is less common and affects about 1 in 40,000 males.[18] In England, 2021-22, there were 2,729 finished consultant episodes of hereditary factor VIII deficiency (ICD-10 D66, including haemophilia A) resulting in 2,096 day cases and 3,165 FCE bed days. In England, 2021-22, there were 661 FCE episodes of hereditary factor IX deficiency (ICD-10 D67, including haemophilia B) resulting in 587 day cases and 222 FCE bed days.[19]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE)-recommended pharmacological treatment options specifically indicated for severe haemophilia A, and moderately severe to severe haemophilia B.

Haemophilia treatment is focused on replacing missing clotting factor(s), with various clotting factor concentrates available, as well as fresh frozen plasma which contains mixed clotting factors. They are given "on demand" to treat a bleeding episode, or for more severe disorders, prophylactically to prevent bleeding.[18] Immune tolerance induction (ITI) may be offered to those who develop intolerances to the clotting medicine. This is usually offered to people with severe haemophilia A, whereas it is less effective and there is a risk of severe allergic reaction for people with haemophilia B.[20]

Clinical Trial Information

Trial	**B7841005; NCT03938792; EudraCT 2018-003660-31;** An Open-Label Study in Adolescent and Adult Severe (Coagulation Factor Activity <1%)	**B7841007; NCT05145127;** An Open-Label Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of Marstacimab Prophylaxis in Severe

	Hemophilia A Participants With or Without Inhibitors or Moderately Severe to Severe Hemophilia B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors Comparing Standard Treatment to PF-06741086 Prophylaxis **Phase III** – Recruiting **Location(s):** Five EU countries, USA, Canada, and other countries **Primary completion date:** September 2024	(Coagulation Factor Activity <1%) Hemophilia A Participants With or Without Inhibitors or Moderately Severe to Severe Hemophilia B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors **Phase III** – Recruiting **Location(s):** Four EU countries, USA, Canada, and other countries **Primary completion date:** July 2030
Trial Design	Open-label, crossover assignment.	Open-label, single group assignment.
Population	N=145 (estimated); males aged 12 years to 74 years old; diagnosis of severe haemophilia A or moderately severe to severe haemophilia B	N=145 (estimated); males aged 12 years to 74 years old; participants who have successfully completed participation in study B7841005 (defined as did not require "Early Termination"); diagnosis of severe haemophilia A or moderately severe to severe haemophilia B
Intervention(s)	Marstacimab 300mg subcutaneous (SC) injection loading dose, followed by 150mg SC injection once weekly (qw). 300mg SC qw prescribed for participants who meet dose escalation criteria.	Marstacimab 300mg SC injection loading dose, followed by 150mg SC injection qw. 300mg SC injection qw is prescribed for participants who meet dose escalation criteria.
Comparator(s)	No comparator.	No comparator.
Outcome(s)	**Primary outcome measures:** • Annualized bleeding rate (ABR) of treated bleeding events [Time Frame: Through Observational Phase (6 months) and Active Treatment Phase (12 months) for total of approximately 18 months] • Incidence and severity of thrombotic events [Time Frame: Through Observational Phase (6 months) and Active Treatment Phase (12 months) for total of approximately 18 months] See trial record for full list of other outcomes.	**Primary outcome measures [Time Frame: Baseline up to 7 years]:** • Number of subject reporting Adverse Events • Number of subjects reporting Serious Adverse Events See trial record for full list of other outcomes.

Results (efficacy)	-	-
Results (safety)	-	-

Trial	**BASIS KIDS; B7841008; NCT05611801;** An Open-Label Study in Pediatric (<18 years of age), Severe Hemophilia A Participants (coagulation factor activity <1%) With or Without Inhibitors or Moderately Severe to Severe Hemophilia B Participants (coagulation factor activity =2%) With or Without Inhibitors Comparing 12 Months of Historical Standard Treatment to Marstacimab Prophylaxis **Phase III –** Recruiting **Location(s):** Canada, India, Israel, Japan, South Korea, South Africa, Taiwan & Turkey **Primary completion date:** September 2028
Trial Design	Open-label, single group assignment.
Population	N=100 (estimated); males aged 1 year to 17 years old; severe haemophilia A or moderately severe to severe haemophilia B
Intervention(s)	Weekly SC injections.
Comparator(s)	No comparator.
Outcome(s)	**Primary outcome measures [Time Frame: Baseline to end of 12-month treatment period]:** • Annualized bleeding rate (ABR) of treated bleeding events • Incidence and severity of thrombotic events **Primary outcome measure [Time Frame: Screening through end of follow-up period (approximately 14 months)]:** • Incidence of adverse events and serious adverse events See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**B7841003; NCT03363321; EudraCT 2017-001255-31;** A Multicenter, Open-Label Study to Evaluate the Long-Term Safety, Tolerability and Efficacy of Subcutaneous PF-06741086 in Subjects with Severe Hemophilia **Phase II –** Completed **Location(s):** 2 EU countries, USA, Brazil, Chile, South Africa & Switzerland **Study completion date:** August 2020
Trial Design	Open-label, non-randomised sequential assignment.

Population	N=20 (actual); males aged 12 years to 74 years old; severe haemophilia; de novo participants; previous study participants of B7841002
Intervention(s)	**Cohort 1:** From previous study (B7841002) non-inhibitor participants continued treatment 300mg marstacimab SC injection qw. **Cohort 2:** From previous study (B7841002) non-inhibitor participants continued treatment 300mg marstacimab SC injection loading dose, followed by 150mg SC qw. **Cohort 3:** From previous study (B7841002) non-inhibitor participants were reduced from 450mg marstacimab SC injection to lowest effective dose, which is 300mg marstacimab SC injection loading dose, followed by 150mg SC qw. **Cohort 4:** From previous study (B7841002) inhibitor participants continued treatment 300mg marstacimab SC injection qw. **Cohort 5:** De novo adolescent participants given 300mg marstacimab SC injection loading dose, followed by 150mg SC qw. **Cohort 6:** De novo adult participants with inhibitors given 300mg marstacimab SC injection loading dose, followed by 150mg SC qw.[4]
Comparator(s)	No comparator.
Outcome(s)	**Primary outcome measures:** • Number of Participants With Treatment-Emergent Adverse Events (TEAEs), TEAEs by Severity, and Serious Adverse Events (SAEs) (All Causality and Treatment-Related) [Time Frame: Day 1 up to Day 393] • Number of Participants With Abnormal Laboratory Findings Without Regard to Baseline Abnormality (Including Hematology, Serum Chemistry, and Urinalysis) [Time Frame: Hematology and serum chemistry: Baseline, Days 1, 29, 57, 85, 169, 253, and 365 visits. Urinalysis: Baseline, Days 1, 85, 169, 253, and 365 visits.] See trial record for full list of other outcomes.
Results (efficacy)	Across all dose cohorts, mean and median on-study ABRs ranged from 0 to 3.6 and 0 to 2.5 bleeding episodes/participant/year respectively, demonstrating comparable efficacy to that observed in the short-term parent study.[4]

Results (safety)	Of 20 enrolled participants, 18 completed the study. Overall, 70% of participants had treatment-emergent adverse events, including injection site reactions, injection site haematoma, and haemarthrosis. No treatment-related serious adverse events or thrombotic events occurred. No treatment-induced anti-drug antibodies were detected.[4]

Trial	**B7841002; NCT02974855; EudraCT 2016-001885-27;** A Multicenter, Open-Label, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Subcutaneous or Intravenous PF-06741086 in Subjects with Severe Hemophilia **Phase II –** Completed **Location(s):** 2 EU countries, USA, Chile, South Africa & Switzerland **Study completion date:** December 2018
Trial Design	Open-label, non-randomised, sequential assignment.
Population	N=27 (actual); males aged 18 years to 64 years old; severe haemophilia A or B
Intervention(s)	**Cohort 1:** Marstacimab 300mg SC injection qw. **Cohort 2:** Marstacimab 300mg SC injection loading dose, followed by 150mg SC qw. **Cohort 3:** Marstacimab 450mg SC injection qw. **Cohort 4:** For participants with inhibitors 300mg SC injection qw.[21]
Comparator(s)	No comparator.
Outcome(s)	**Primary outcome measures:** • Number of Participants With Treatment Emergent Adverse Events (TEAEs) [Time Frame: Study Day 1 to Day 113 Visit] • Number of Participants Discontinued From Study Due to TEAEs [Time Frame: Study Day 1 to Day 113 Visit] See trial record for full list of other outcomes.
Results (efficacy)	Annualised bleeding rate (ABR) during treatment was significantly reduced versus an external on-demand control group ($p < 0.0001$) and versus pretreatment ABR ($p < 0.0001$), with significant reductions observed across all dose cohorts. Marstacimab exposure generally increased in a dose-related manner, with steady-state concentration reached by day 57. Changes in pharmacodynamic biomarkers occurred across all dose cohorts. Clinically meaningful reductions in ABR and treatment-related changes for all pharmacodynamic biomarkers indicated effective targeting of TFPI.[21]

Results (safety)	Among 26 treated participants [haemophilia A without inhibitor, n = 16 (61.5%); haemophilia A with inhibitor, n = 7 (26.9%); haemophilia B, n = 3 (11.5%)], 24 completed the study. Overall, 80.8% experienced TEAEs. Marstacimab was safe and well tolerated.[21]

Estimated Cost

The estimated cost of marstacimab is not yet known.

Relevant Guidance

NICE Guidance

- NICE guidance awaiting development. Giroctocogene fitelparvovec for treating moderately severe to severe haemophilia A (GID-TA11329). Expected publication date: TBC.
- NICE guidance awaiting development. Fidanacogene elaparvovec for treating moderately severe to severe haemophilia B (GID-TA11117). Expected publication date: TBC.
- NICE guidance awaiting development. Efanesoctocog alfa for treating and preventing bleeding episodes in people of any age with previously treated haemophilia A (GID-TA11106). Expected publication date: To be confirmed.
- NICE guidance awaiting development. Concizumab for preventing bleeding episodes in haemophilia A or haemophilia B (GID-TA10972). Expected publication date: To be confirmed.
- NICE guidance awaiting development. Valoctocogene roxaparvovec for treating severe haemophilia A (GID-TA10682). Expected publication date: TBC.
- NICE guidance in development. Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (GID-TA10699). Expected publication date: September 2023.

NHS England (Policy/Commissioning) Guidance

- NHS England. Prescribed Specialised Services Manual – Version 6. PRN00115. March 2023.
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- NHS England. Clinical Commissioning Policy: Immune Tolerance Induction (ITI) for haemophilia A (all ages). 16042/P. July 2016.
- NHS England. 2013/14 NHS Standard Contract for Haemophilia (all ages). B05/S/a.

Other Guidance

- Hart D., et al. International consensus recommendations on the management of people with haemophilia B. April 2022.[7]
- World Federation of Hemophilia (WFH). WFH Guidelines for the Management of Hemophilia – 3rd Edition. August 2020.[22]
- British Society for Haematology (BSH). Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. May 2020.[23]
- BSH. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: 4th edition. November 2012.[24]

Additional Information

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