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Health Technology Briefing
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Efanesoctocog alfa for treating and preventing bleeding in people with haemophilia A who have been previously treated

Company/Developer	Swedish Orphan Biovitrum Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 20453	NICE ID: 10561	UKPS ID: 662593

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Efanesoctocog alfa is currently in clinical development for the treatment and prevention (prophylaxis) of bleeding episodes in patients with haemophilia A. Haemophilia A is a genetic bleeding disorder caused by a deficiency or absence of a blood clotting factor, called factor VIII (eight). This causes poor blood clotting, which results in difficulty in stopping the flow of blood from a wound, causing prolonged bleeding. Current therapy includes preventative (prophylactic) treatment where medicine is used to prevent bleeding, or on-demand treatment, where medicine is used to treat prolonged bleeding. Haemophilia A treatments includes regular injections of factor VIII and/or various types of clotting factor medicines. However, von Willebrand factor (VWF), another clotting factor, limits factor VIII circulation in the blood.

Efanesoctocog alfa is a new class of high-sustained factor (HSF) VIII replacement therapy that is designed to extend protection from bleeds with once-weekly prophylactic dosing for people with haemophilia A. Its structure makes it independent of VWF which increases its time in blood circulation. Efanesoctocog alfa will be administered as an intravenous (IV) injection. If approved, Efanesoctocog alfa will provide an alternative option for the treatment or prophylaxis of patients (adult and children) with haemophilia A.

Proposed Indication

Treatment and prophylaxis of bleeding in patients with haemophilia A who have been previously treated.[1-3]

Technology

Description

Efanesoctocog alfa (BIVV001) is a novel and investigational recombinant high-sustained factor VIII (HSF FVIII) therapy that is designed to extend protection from bleeds with once-weekly prophylactic dosing for people with haemophilia A. It builds on the innovative Fc fusion technology by adding a region of von Willebrand factor and XTEN polypeptides to extend its time in circulation.[4]

Efanesoctocog alfa is in phase III clinical development for the treatment and prophylaxis of bleeding in patients with previously treated haemophilia A in all age groups. In the phase III (XTEND-kids, NCT04759131) participants will be administered with a weekly dose of efanesoctocog alfa for 52 weeks. In the phase III clinical trial (XTEND-ed, NCT04644575) it will be administered as an intravenous (IV) injection once weekly (QW) for a total of at least 100 exposure days. In the phase III (XTEND-1, NCT04161495) trial, participants received efanesoctocog alfa QW during a prophylaxis treatment regimen for 52 weeks and 26 weeks for on demand treatment, followed by a switch to a prophylaxis treatment regimen with efanesoctocog alfa for 26 weeks.[1-3,5]

Key Innovation

Primary prophylaxis is the standard of care in haemophilia A, aiming to reduce bleeding occurrence and prevent joint damage. Historically, the goal of prophylaxis has been the maintenance of FVIII activity trough levels between 1% and 3%.[6] A trough level of only 1% has been unsuccessful at fully preventing bleeding episodes, therefore persons with haemophilia who are maintained at 1% FVIII continue to experience spontaneous bleeding and remain at higher risk for injury with daily activities. Furthermore, current prophylaxis regimens do not prevent haemophilic arthropathy over the lifetime of a person with haemophilia. With the growing availability of current therapies, the validity of the 1% threshold has come under scrutiny.[7]

FVIII replacement remains the most widely used therapy for haemophilia A. One of its advantages is that it can be used as a single therapy across many clinical scenarios (e.g., treatment of bleeds, perioperative management, and prophylaxis). For prophylaxis, a key goal is to maintain joint health by preventing intra-articular bleeds. However, there is increasing evidence that target FVIII trough levels of 1% to 3% are insufficient to prevent the occurrence of all bleeds and progressive joint damage and to address this unmet need, the haemophilia community is setting new goals towards “normal haemostasis”.[7] Decades of clinical and real-world evidence support that prophylaxis with factor therapies is highly effective in reducing bleeding and long-term complications such as arthropathy.[8]

The von Willebrand factor (VWF) chaperone effect that noncovalently stabilises and protects endogenous and exogenous FVIII from early degradation limits FVIII half-life extension.[6] The half-life of recombinant factor VIII ranges from 15 to 19 hours because of the VWF chaperone effect.[9] Efanesoctocog alfa is a new class of FVIII replacement therapy that is designed to be independent of endogenous VWF and break the VWF-imposed FVIII ceiling.[6]

In a phase I trial (2018-001535-51), efanesoctocog alfa achieved high sustained FVIII activity with an elimination half-life that was substantially longer than that associated with current half-life and extended

half-life FVIII products.[6] In the phase III trial (NCT04161495), efanesoctocog alfa showed a statistically significant and clinically meaningful reduction in annualised bleeding rate compared to prior factor VIII prophylaxis therapy, with common adverse events being headache, arthralgia, fall, and back pain.[4] In the phase I/II trial (NCT03205163), the geometric mean half-life of efanesoctocog alfa was three to four times as long as that of recombinant factor VIII and no inhibitors to factor VIII were detected and no hypersensitivity or anaphylaxis events were reported up to 28 days after the injection of single-dose efanesoctocog alfa. There were no clinically relevant changes in VWF activity.[9]

If licensed, efanesoctocog alfa will offer an additional treatment option for haemophilia A.

Regulatory & Development Status

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

Efanesoctocog alfa is currently in phase III trials for the treatment of haemophilia A.[10]

Efanesoctocog alfa has the following regulatory awards/designations:
- An Breakthrough Therapy by the US FDA for haemophilia A in 2022.[11]
- An orphan drug in the EU in 2019 for haemophilia A.[12]

Patient Group

Disease Area and Clinical Need

Haemophilia A, also known as classical haemophilia, is a genetic bleeding disorder caused by insufficient levels of a blood protein called factor VIII. Factor VIII is a clotting factor. Clotting factors are specialised proteins that are essential for blood clotting. Since blood clots poorly in individuals with haemophilia A, they experience spontaneous bleeding, severe or excessive bleeding in response to trauma or surgery. This may be referred to as prolonged bleeding or a prolonged bleeding episode. Haemophilia A can be mild, moderate, or severe, depending on the baseline level of factor VIII made by that individual. In mild cases, prolonged bleeding episodes may only occur after surgery, dental procedures, or trauma. In more severely affected individuals, symptoms may include prolonged bleeding from minor wounds, painful swollen bruises, and unexplained (spontaneous) bleeding into vital organs as well as joints and muscles (internal bleeding).[13] Joint bleeding can eventually cause painful and disabling haemophilic arthropathy. Regardless of the severity of their disease, patients who don't achieve optimal protection may also suffer from life-threatening bleeds, such as intracranial bleeds and in other internal organs.[14]

Haemophilia A is caused by disruptions or changes (mutations) to the F8 gene located on the X chromosome. This mutation may be inherited or occur randomly with no previous family history of the disorder (spontaneously). Haemophilia A is mostly expressed in males but some females who carry the gene may have mild or, rarely, severe symptoms of bleeding.[13]

Haemophilia A is the most common X-linked recessive disorder and the second most common inherited clotting factor deficiency after von Willebrand disease. Haemophilia A mostly affects males but females can also be affected. Approximately 1 in 5,000 new-born males have haemophilia A. Approximately 60% of individuals with haemophilia A have a severe form of the disorder.[13] In 2020, 6,940 patients in the UK were identified with haemophilia A.[15] Between April 2015 and March 2016, 1,711 patients in UK were treated for severe haemophilia A.[16] In 2018, over a third (35%) of adults with severe haemophilia A and B bled more than four times last year.[17]

Recommended Treatment Options
The recommended treatment plan for haemophilia depends on severity and patient dependant factors. There are two main approaches to treatment. One is prophylaxis treatment, where medicine is used to prevent bleeding and subsequent joint and muscle damage. The other is on-demand treatment, where medicine is used to treat prolonged bleeding.[18] There are currently factor replacement therapies that replace the missing FVIII, with different options available, including standard half-life (SHL) and extended half-life (EHL) factors, used as prophylaxis or on-demand treatment for haemophilia A.[8] Some patients with haemophilia A taking factor VIII medicines produce inhibitor proteins which stop these medicines from working properly.[19] A review by the EMA found no clear and consistent evidence of difference in risk of inhibitor development between classes of factor FVIII medicines.[19,20]

Clinical Trial Information	
Trial	**XTEND-Kids; NCT04759131; EudraCT-2020-000769-18;** A Phase 3 Open-label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Pediatric Patients <12 Years of Age With Severe Hemophilia A **Phase III –** Active, not recruiting **Location(s) –** 10 EU countries, UK, USA, Canada, Australia, Asia **Primary completion date –** February 2023
Trial Design	Single group assignment, open label
Population	N = 75 (actual); participants with severe haemophilia A; previous treatment for haemophilia A (prophylaxis or on-demand); up to 12 years; male
Intervention(s)	Efanesoctocog alfa IV injection
Comparator(s)	No comparator
Outcome(s)	**Primary outcome** • The occurrence of inhibitor development (neutralising antibodies directed against factor VIII [FVIII]) as determined via the Nijmegen modified Bethesda assay [Time Frame: baseline to 52 weeks]). See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**XTEND-ed; NCT04644575; EudraCT 2020-002215-22;** A Phase 3 Open-label, Multicenter Study of the Long-term Safety and Efficacy of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion

	Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients With Severe Hemophilia A **Phase III –** Recruiting **Location(s) –** 11 EU countries, UK, USA, Canada, Australia, Asia and South America **Primary completion date –** February 2027
Trial Design	Non-randomised, single group assignment, open label
Population	N = 262 (estimated); participants who have severe haemophilia A; previous treatment for haemophilia A (prophylaxis or on-demand); all ages
Intervention(s)	Efanesoctocog alfa IV injection
Comparator(s)	No comparator
Outcome(s)	**Primary outcome** • Number of participants with the occurrence of inhibitor development (neutralising antibodies detected against factor VIII [FVIII]) [Time Frame: Baseline to month 48] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**XTEND-1; NCT04161495; EudraCT 2019-002023-15;** A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients ≥12 Years of Age With Severe Hemophilia A **Phase III –** Completed **Location(s) -** 10 EU countries, UK, USA, Canada, Australia, Asia and South America **Study completion date –** February 2022
Trial Design	Non-randomised, parallel assignment, open label
Population	N = 159 (actual); severe haemophilia A; previous treatment for haemophilia A; 12 years and older
Intervention(s)	Efanesoctocog alfa IV injection once-weekly (QW) during a prophylaxis treatment regimen for 52 weeks for prophylaxis treatment arm, and on demand for 26 weeks, followed by a switch to a prophylaxis treatment regimen with efanesoctocog alpha for 26 weeks for on demand treatment arm.
Comparator(s)	No comparator.
Outcome(s)	• Annualised bleeding rate (ABR) in prophylaxis treatment arm [Time Frame: baseline to 52 weeks]

	See trial record for full list of other outcomes.
Results (efficacy)	The median annualised bleeding rate (ABR) was 0 with a mean ABR of 0.71. The key secondary endpoint was also met, demonstrating once-weekly efanesoctocog alfa was superior to prior prophylactic factor VIII replacement therapy, showing a statistically significant reduction in ABR based on intra-patient comparison. Efanesoctocog alfa was well-tolerated, and inhibitor development to factor VIII was not detected.[4]
Results (safety)	The most common treatment-emergent adverse events (>5 per cent of participants overall) were headache, arthralgia, fall, and back pain.[4]

Trial	**EXTEN-A; NCT03205163;** A Phase 1/2a, Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Injection of rFVIIIFc-VWF-XTEN (BIVV001) in Previously Treated Adults With Severe Hemophilia A **Phase I/II** - Completed **Location(s)** – USA and Asia **Study completion date –** November 2018
Trial Design	Non-randomised, sequential assignment, open label.
Population	N = 16 (actual); severe haemophilia A; previous treatment for haemophilia A; 18 years to 65 years; males.
Intervention(s)	Low-dose cohort: Participants received a single IV dose of Advate 25 international units per kilogram (IU/kg) on Day 1 of Advate treatment period (3 days) followed by a single IV dose of efanesoctocog alfa 25 IU/kg in efanesoctocog alfa treatment period (BTP) (28 days). Advate treatment period (ATP) consisted of a washout of at least 72 hours which was started from the time of Advate dosing. High-dose cohort: Participants received a single IV dose of Advate 65 IU/kg on Day 1 of ATP (4 days) followed by a single IV dose of efanesoctocog alfa 65 IU/kg in BTP (28 days). ATP consisted of a washout of at least 96 hours which was started from the time of Advate dosing.
Comparator(s)	No comparator.
Outcome(s)	• Number of Participants With Treatment Emergent Adverse Events (TEAE) and Treatment Emergent Serious Adverse Event (TESAE) During Advate Treatment Period [Time Frame: Up to Day 3 for Advate 25 IU/kg; up to Day 4 for Advate 65 IU/kg] • Number of Participants With Treatment Emergent Adverse Events (TEAE) and Treatment Emergent Serious Adverse Event (TESAE) During efanesoctocog alfa Treatment Period [Time Frame: Up to 28 days after BIVV001 administration] • Number of Participants With Clinically Significant Abnormalities in Laboratory Tests During Advate Treatment Period [Time Frame: Up to Day 3 for Advate 25 IU/kg; up to Day 4 for Advate 65 IU/kg]

	• Number of Participants With Clinically Significant Abnormalities in Laboratory Tests During efanesoctocog alfa Treatment Period [Time Frame: Up to 28 days after efanesoctocog alfa administration] • Percentage of Participants With Confirmed Inhibitor Development as Measured by the Nijmegen-Modified Bethesda Assay [Time Frame: Up to 28 days after efanesoctocog alfa administration] See trial record for full list of other outcomes.
Results (efficacy)	The geometric mean half-life of BIVV001 was three to four times as long as that of recombinant factor VIII (37.6 hours vs. 9.1 hours in the lower-dose group and 42.5 vs. 13.2 hours in the higher-dose group); the area under the curve (AUC) for product exposure was six to seven times as great in the two dose groups (4470 hours vs. 638 hours × IU per deciliter in the lower-dose group and 12,800 hours vs. 1960 hours × IU per deciliter in the higher-dose group). After the injection of efanesoctocog alfa in the higher-dose group, the mean factor VIII level was in the normal range (≥51%) for 4 days and 17% at day 7, which suggested the possibility of a weekly interval between treatments.[9]
Results (safety)	No inhibitors to factor VIII were detected and no hypersensitivity or anaphylaxis events were reported up to 28 days after the injection of single-dose efanesoctocog alfa.[9]

Estimated Cost

The cost of efanesoctocog alfa is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Concizumab for preventing bleeding episodes in haemophilia A or haemophilia B (GID-TA10972). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Emicizumab for preventing bleeding episodes in people with mild or moderate haemophilia A (GID- TA11013). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Valoctocogene roxaparvovec for treating severe haemophilia A (GID-TA10682). Expected date of issue to be confirmed

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy. Human coagulation factor X for hereditary factor X deficiency (all ages). 200208P. February 2020.
- NHS England. Clinical Commissioning Policy: Emicizumab as prophylaxis in people with severe congenital haemophilia A without factor VIII inhibitors (all ages). 170134P. August 2019.
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- NHS England. 2013/14 NHS Standard Contract for Haemophilia A (all ages). B05/S/a.

Other Guidance

- NHS Greater Glasgow and Clyde (NHSGGC) Paediatrics for Health Professionals. Haemophilia protocol. November 2020.[21]
- World Federation of Hemophilia (WFH). WFH Guidelines for the Management of Hemophilia, 3rd edition. August 2020.[22]
- British Society for Haematology. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. May 2020.[20]
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- United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO). The use of enhanced half-life coagulation factor concentrates in routine clinical practice: guidance from UKHCDO. July 2016.[26]

Additional Information

Sobi and Sanofi collaborate on the development and commercialisation of efanesoctocog alfa, an investigational HSF VIII therapy with the potential to provide high sustained factor activity levels with once-weekly dosing for people with haemophilia A. Sobi has final development and commercialisation rights in the Sobi territory (essentially Europe, North Africa, Russia and most Middle Eastern markets). Sanofi has final development and commercialisation rights in North America and all other regions in the world excluding the Sobi territory.[4]

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