EU Risk Management Plan for efanesoctocog alfa

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QPPV name: Martin Bowling, Director Pharmacovigilance & Patient Safety
QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization applicant's QPPV. The electronic signature is available on file.

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List of abbreviations

Abbreviation	Definition
ADA	Anti-Drug Antibody
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ASA	Acetylsalicylic Acid
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BDD	B-Domain Deleted
CI	Confidence Interval
CNS	Central Nervous System
CSR	Clinical Study Report
DLP	Data Lock Point
ECG	Electrocardiogram
EEA	European economic area
ED	Exposure Day
EHL	Extended Half-Life
EU	European Union
Fc	Fragment Crystallizable
FVIII	Factor VIII
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
INN:	International Nonproprietary name
IU	International Unit
IV	Intravenous
IVIG	Intravenous Immunoglobulin
MASAC	Medical and Scientific Advisory Council
NHF	National Hemophilia Foundation
NSAID	Non-Steroidal Anti-Inflammatory Drug

OSC	One Stage Clotting
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
PWH	People with Hemophilia
QPPV	Qualified Person Responsible for Pharmacovigilance
rFVIII	Recombinant FVIII
RMP	Risk Management Plan
SD	Standard deviation
SAP	Statistical Analysis Plan
SHL	Standard Half-Life
SMR	Standardized mortality ratio
ULN	Upper Limit of Normal
US	United States
VWD	von Willebrand Disease
VWF	von Willebrand Factor
WFH	World Federation of Hemophilia

Part I: Product overview

Table 1 Product overview

Active substance(s) (INN or common name)	Efanesoctocog alfa
Pharmacotherapeutic group(s) (ATC Code)	B02BD02
Marketing Authorization Applicant	Swedish Orphan Biovitrum AB (publ)
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	ALTUVOCT®
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class Efanesoctocog alfa is an Antihemophilic Factor (Recombinant), Fc-VWF-XTEN Fusion Protein.
	Summary of mode of action Efanesoctocog alfa is a recombinant fusion protein that temporarily replaces the missing coagulation FVIII needed for effective hemostasis. Efanesoctocog alfa has demonstrated prolonged half-life relative to other standard and extended half-life FVIII molecules.
	Important information about its composition Efanesoctocog alfa is a fully recombinant fusion protein composed of a single chain BDD analogue of human FVIII covalently fused to the Fc domain of human IgG1, the FVIII binding D'D3 domain of VWF, and 2 XTEN polypeptides.
Hyperlink to the Product Information	Proposed: Proposed PI.
Indication(s) in the EEA	Treatment and prophylaxis of bleeding in patients with hemophilia A (congenital factor VIII deficiency). ALTUVOCT® can be used for all age groups.
Dosage in the EEA	Current: For intravenous use after reconstitution only. The recommended dose for routine prophylaxis for adults and children is 50 IU/kg of efanesoctocog alfa administered once weekly. The recommended dose and frequency for on demand treatment, control of bleeding episodes and perioperative management of bleeding is a single dose of 50 IU/kg. Additional doses of 30 or 50 IU/kg every 2 or 3 days may be considered.
Pharmaceutical form(s) and strengths	Current: Powder for solution for intravenous injection. 250, 500, 750, 1000, 2000, 3000 or 4000 IU.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Hemophilia A:

Efanesoctocog alfa, also known as recombinant coagulation FVIII Fc - VWF - XTEN fusion protein (rFVIIIFc VWF XTEN; formerly referred to as BIVV001), is a new class of FVIII replacement therapy.

Efanesoctocog alfa is indicated for treatment and prophylaxis of bleeding in patients with hemophilia A (congenital factor VIII deficiency).

Efanesoctocog alfa can be used for all age groups.

The epidemiology of the disease is summarized in Table 2.

Table 2 Epidemiology of Hemophilia A

Indication	Hemophilia A
Incidence and prevalence	As hemophilia A is a congenital, non-transmissible disease, the assumption is made that no new cases emerge in the population after birth (although there may be a delay in diagnosis), and therefore prevalence at birth represents the incidence of the disease. Based on meta-analysis from registries of Canada, France and the UK, the estimated prevalence at birth is 23.2 per 100 000 males for all severities of hemophilia A and 9.4 for severe hemophilia A [1]. Globally, 165 379 cases of hemophilia A are known to the WFH based on data available from 120 countries, but it is estimated that the majority of individuals with hemophilia in the developing nations are not diagnosed, especially patients with mild or moderate hemophilia A [2, 3]. Based on the meta-analysis of pooled data from all available national registries, the estimated prevalence is 17.1 per 100 000 males for all severities of hemophilia A and 6.0 for severe hemophilia A [1]. The difference between prevalence at birth and population prevalence reflects the life expectancy disadvantage of people with hemophilia A.
Demographics of the population in the authorized/proposed indication	Hemophilia A is an X-linked congenital bleeding disorder that occurs predominantly in males. Women may be carriers because of the sex-linked recessive mode of inheritance and, under rare circumstances, may be clinically affected e.g., due to lyonization (inactivation of one of the X chromosomes), or as a daughter of a father with hemophilia and a mother that is a carrier of a hemophilia gene [3]. In approximately one third of cases, there is no family history of hemophilia and hemophilia is caused by a spontaneous mutation [4, 5]. Numerous mutations resulting in hemophilia A have been identified, most commonly the intron 22 inversion, which results in the absence of the FVIII protein. Other mutations include deletions of variable size and nonsense mutations that often result in no protein expression, as well as missense mutations, in which nonfunctional (severe hemophilia A) or minimally functional (moderate or mild hemophilia A) protein may be expressed. In hemophilia A population, the risk of FVIII inhibitor development depends on the type of underlying mutation with higher risk with large deletions and lower risk with missense mutations [6, 7].
Main existing treatment options	There is no available cure for hemophilia A. Current treatment focuses on factor replacement therapy with plasma-derived or rFVIII products, which have well-established efficacy and

	safety profiles, non-factor replacement therapy and gene therapy. The fundamental objectives of hemophilia care are to prevent and treat bleeding episodes. Detailed treatment guidelines from the WFH [8] recommend prevention of bleeding using prophylaxis over on demand treatment for patients with severe hemophilia in order to prevent bleeds and associated co-morbidities such as hemophilic arthropathy. The WFH strongly recommends the use of viral inactivated plasma-derived or rFVIII concentrates over cryoprecipitate or fresh frozen plasma, although in some countries these may be the only treatment options. European consensus recommendations for optimal hemophilia care derived from a series of meetings involving clinicians, regulators and patient organizations across Europe similarly highlight that prophylaxis should the accessible to all people with hemophilia A [9]. A recent survey among European Collaborative Hemophilia Network (ECHN) reported that the vast majority of patients with severe hemophilia A in Europe are treated prophylactically [10]. Emicizumab, a bispecific factor IXa- and X-directed antibody, is an alternative non-factor replacement therapy which has shown efficacy for prevention of bleeding events and is recommended for prophylaxis, in particular for patients with FVIII inhibitors, and for patients for whom FVIII replacement is not considered appropriate, e.g. due to difficulties with venous access [8]. However, the WFH guidelines emphasize that it is not intended for treatment of acute bleeding episodes and thus concomitant FVIII products will still be required for treatment of breakthrough bleeding episodes and in case of trauma or major surgery [8]. Roctavian (Valoctocogene roxaparvovec) is a gene therapy medicinal product that expresses the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). It is indicated for the treatment of severe hemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5). The introduction of prophylactic replacement therapy has been a major advance in the treatment of severe hemophilia, reducing the rate of bleeding and preventing or delaying the development of hemophilic arthropathy [11]. The WFH states that prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function [8], which is also supported by the most recent recommendations of the European Kreuth V initiative [12].
Natural history of the indicated condition in the untreated population including mortality and morbidity	Hemophilia A is categorized based on endogenous FVIII activity levels as severe (<1% activity), moderate (1% to 5% activity), or mild (>5% to 40% activity). Patients with severe hemophilia A account for approximately 30% to 50% of all cases of hemophilia A; patients with moderate disease account for approximately 10% to 20%, and patients with mild disease account for approximately 20% to 50% of all cases [1, 3, 13, 14]. In general, patients with severe hemophilia are diagnosed before the age of 2 years due to bleeding in infancy, bleeding from circumcision, or when they begin walking, while individuals with moderate and mild hemophilia may be diagnosed only later. Individuals with moderate hemophilia may have spontaneous bleeding but are more likely to bleed after trauma, while individuals with mild disease may be diagnosed only after excessive bleeding after major trauma or surgery. Diagnosis occurs sooner for patients with known positive family history of hemophilia [15]. In a large, single-center cohort in the Netherlands, the median age at diagnosis for severe hemophilia was 0.5 years in the presence of a positive family history and 1.0 years in the absence of a positive family history. For moderate hemophilia, the median age at diagnosis was 1.0 years and 4.0 years and for mild hemophilia, the median age at diagnosis was 1.2 and 3.4 in the presence or absence of a positive family history, respectively [16]. In a study performed on PUPs with severe hemophilia included in the PedNet registry and RODIN study databases involving 29 hemophilia centers in Europe,

	Israel and Canada, the median age at diagnosis in patients with a negative family history of hemophilia was 8.8 months [17]. Severe hemophilia A is characterized by frequent and recurrent spontaneous or traumatic bleeding episodes into joints, mucosa, muscle and other locations [15]. Joint bleeds, especially bleeds into elbows, knees and ankles occur most commonly, and significantly contribute to long-term morbidity. In addition, patients with hemophilia A are also at risk of rare, but acutely life-threatening and potentially debilitating, bleeds in internal organs or intracranial hemorrhages. Accordingly, hemorrhage, in particular intracranial hemorrhage, remains a leading cause of death in PWH [18-20]. The main causes of mortality and life expectancy in patients with hemophilia have significantly changed over time [21]. The advent of plasma-derived factor replacement products in the 1970s enabled early control of hemorrhages and reduced or prevented musculoskeletal damage in patients with hemophilia. However, as these products were produced from pooled blood donations, viral contamination resulted in widespread HCV infection, and from the early 1980s onwards, HIV infection, among patients with hemophilia, leading to a dramatic decrease in life expectancy. Since the widespread availability of anti-retroviral therapy (mid 1990s) and efficacious HCV therapies (2010), the life expectancy of PWH has increased. With a reduced risk of infection due to the availability of safer plasma-derived and recombinant FVIII products (early 1990s) and an improved uptake of prophylaxis and comprehensive hemophilia care, the life expectancy for PWH is progressively approaching that of the general population [1, 13, 14, 22, 23]. In a prospective, observational Dutch study following PWH from 2001 to 2018, their estimated median life expectancy was 77 years; 6 years lower than the general Dutch male population of 83 years [19]. The most common causes of death in PWH were intracranial bleeding (18.3%) and malignancies, including HCC (33.1%). A recent, random-effects meta-analysis of national registry data found that even in high-income countries, the life expectancy disadvantage was still 30% for hemophilia A and 37% for severe hemophilia A, by comparing the prevalence (cumulated over all past birth cohorts) to the prevalence at birth [1]. In a systematic meta-analysis, pooled all-cause SMRs indicate a markedly increased risk of death for severe and moderate hemophilia, while the risk of death is comparable to the general population for mild hemophilia [24].
Important co-morbidities	Prior to the advent of recombinant clotting factor replacement in the early 1990s, persons with hemophilia who were treated with factor concentrates from pooled plasma were at high risk of transmission of blood-borne pathogens including the hepatitis virus and HIV. Therefore, the cohorts impacted by these historic blood transmissions are progressively decreasing. **Human immunodeficiency virus** About a decade ago, approximately 12% to 24% of adults with hemophilia A were reported to be living with HIV globally[13, 25-28]. Based on the 2020 WFH report, 1 280 patients with hemophilia A or B lived with HIV infection in EU countries which provided relevant data (Austria, Czech Republic, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Slovakia, Slovenia and Sweden), corresponding to 5% of a total of 25 433 patients with hemophilia A or B in those countries [3]. In the meta-analysis of all-cause mortality, HIV status had a major impact on the overall risk of death of PWH [24]. Stratification by HIV status showed an SMR of 18.0 in the HIV-positive cohort compared to an SMR of 1.3; of note, the included studies covered an era prior to effective anti-retroviral therapies. While HIV was the most common cause of death in PWH prior to 2000 with 31.2% of deaths, this proportion decreased to 13.9% after 2000. **Hepatitis C virus** About a decade ago, approximately 40% to 56% of adults with hemophilia A were reported to be living with HCV globally [13, 25-28]. Based on the 2020 WFH report, 4 679 patients

	with hemophilia A or B lived with HCV infection in EU countries which provided relevant data (Austria, Czech Republic, Estonia, France, Greece, Hungary, Ireland, Italy, Slovakia and Slovenia), corresponding to 23.9% of a total of 19 582 patients with hemophilia A or B in those countries [3]. Serious complications associated with HCV infection include cirrhosis, liver failure and HCC. Although effective therapy for eradication of HCV is available since the early 2010s, it does not reverse established chronic liver disease and HCC, which remain important causes of death in PWH [15]. **Other infections** The incidence of bacterial infections in patients with hemophilia A is not known but may be increased relative to the general population due to frequent venipuncture and/or the presence of indwelling venous access devices. Transmission of non-enveloped viruses (e.g., parvovirus B19, hepatitis A) remains a risk for people with bleeding disorders who use plasma-derived products because they are not readily eliminated by solvent/detergent viral inactivation procedures [29]. Additional viral inactivation/removal steps and improved screening of plasma donors have virtually eliminated the risk of viral transmission by known pathogens [30]. **Chronic Joint Disease** A debilitating long-term consequence of joint bleeds is hemophilic arthropathy, resulting from repeated blood deposition and subsequent inflammation in joints, leading to destruction of joint bone and cartilage. The development of target joints, defined as 3 or more spontaneous bleeding events in a single joint within a consecutive 6-month period, is a severe complication of hemophilia [31]. The presence of target joints increases the risk of arthropathy, and once joint damage has developed, the process is progressive and irreversible. Significant effects on physical and psychosocial well-being, quality of life, and financial burden have been reported. Prophylaxis with rFVIII was effective in preventing hemarthrosis and structural joint damage (as detected by magnetic resonance imaging) in young boys with hemophilia A [11]. Individuals with severe hemophilia experience frequent and recurrent spontaneous or traumatic bleeding into soft tissue and joints, leading to arthropathy, muscle contractures, and severe disability [18]. Approximately 30% to 35% of all adult patients with hemophilia A have joint disease, rising to 58% to 67% of those with severe hemophilia [13, 32, 33]. Among pediatric individuals (<18 years of age) with hemophilia, approximately 14% to 17% have arthropathy [13, 33] and this joint deterioration may still occur with current prophylactic treatment even initiated early in life [34]. Prevalence of joint disease is expected to be higher in older patients for whom prophylaxis was not yet available at a young age compared to younger patients, many of whom are receiving prophylaxis for prevention of joint disease.

CDC: Center for Disease Control and Prevention; CNS: Central Nervous System; EU: European Union; FVIII: Factor VIII; HCC: Hepatocellular carcinoma; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; MASAC: Medical and Scientific Advisory Council; NHF: National Hemophilia Foundation; rFVIII: Recombinant FVIII; UDC: Universal Data Collection; US: United States; WFH: World Federation of Hemophilia.

Part II: Module SII - Non-clinical part of the safety specification

This section presents a summary of the important non-clinical safety findings for efanesoctocog alfa. Overall, these results support the use of efanesoctocog alfa in the target population, at the intended dosage in humans. Non-clinical pharmacology, PK, and Toxicology evaluation studies of efanesoctocog alfa in animals have used FVIII-deficient mouse model of hemophilia A, Sprague Dawley rats, and non-human primates. All non-clinical studies were performed using IV administration, which is the intended route of administration for patients with hemophilia A.

Three non-clinical safety studies were conducted:

- A 4-Week Repeat Dose Toxicity Study by Intravenous Injection in the Sprague-Dawley Rat with a 14-Day Recovery Period (GLP).
- A 4-Week Repeat Dose Toxicity Study by Intravenous Injection in the Cynomolgus Monkey with a 21-Day Recovery Period (GLP).
- An *in vitro* hemocompatibility study - Using human whole blood and plasma (GLP).

No separate safety pharmacology studies were conducted with efanesoctocog alfa to investigate possible effects on cardiovascular, respiratory, or central nervous system (CNS) parameters, in accordance with ICH S6 and S7A. However, no adverse electrocardiogram (ECG) or CNS effects were observed in repeat-dose toxicity studies in monkeys, and no respiratory abnormalities were noted in repeat-dose toxicology studies in rats and monkeys.

Efanesoctocog alfa was well-tolerated in 4-week repeat-dose toxicity studies at doses of 75, 250, and 750 IU/kg IV every 3 days in rats and 25, 75, 250, and 750 IU/kg every 4 days in monkeys. Overall, there were no adverse findings directly attributed to the pharmacologic activity/intended mechanism of efanesoctocog alfa. In the monkey study, one high dose (750 IU/kg) recovery male monkey was found dead on Day 30 following toxicokinetic blood collection procedures on Day 29. The cause of death was blood loss secondary to venipuncture and impaired hemostasis, most likely due to development of neutralizing antibodies against efanesoctocog alfa which cross-react to endogenous FVIII (acquired hemophilia), as indicated by prolonged activated partial thromboplastin time (aPTT) observed in this monkey. Antibody responses in non-clinical species to non-native, but similar, recombinant human FVIII proteins have not been predictive of responses in humans [35]. Therefore, this single antidrug antibody (ADA)-associated death was excluded from the determination of the no-observed-adverse-effect level (NOAEL).

No chronic general toxicology studies were conducted to support the registration of efanesoctocog alfa. [redacted]

Non-clinical developmental and reproductive toxicology studies have not been conducted with efanesoctocog alfa. Based on a well-understood mechanism of action, FVIII replacement products are not expected to affect embryo-fetal development. In addition, the administration of replacement factor to pregnant animals with normal hemostasis would exacerbate the hypercoagulable state of pregnancy, due to enhanced production of clotting factors, decreased

protein S activity, and inhibition of fibrinolysis [36, 37]. Accordingly, FVIII replacement products generally have not been tested for developmental and reproductive toxicity in non-clinical studies.

In an *in vitro* hemocompatibility study, no hemolysis and no plasma flocculation were observed following *in vitro* treatment of human whole blood with efanesoctocog alfa at concentrations up to 4.1 µg/mL.

Table 3 Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity	
• Key issues identified from repeat-dose toxicity studies: In Sprague-Dawley rats, efanesoctocog alfa at doses of 75, 250 and 750 IU/kg were well tolerated. Following repeated dosing, antidrug antibody formation against efanesoctocog alfa occurred in approximately 30 to 70% of animals, as expected. Neutralizing antibody titers to efanesoctocog alfa increased in a dose and time dependent manner. Minimal, non-adverse and reversible clinical chemistry changes were observed with no efanesoctocog alfa related macroscopic, organ weight or microscopic changes. In cynomolgus monkey, efanesoctocog alfa at doses of 25, 75, 250 and 750 IU/kg were well tolerated; however, there were dose related increases in ADA. One animal in the 750 IU/kg dose group died due to blood loss following blood collection, secondary to the development of neutralizing antibodies against efanesoctocog alfa cross reacting with endogenous FVIII. Consistent with this, there was prolongation of aPTT at ≥75 IU/kg/dose (not reversible in females at 750 IU/kg/dose).	The development of neutralizing antibodies against administered human rFVIII that cross-react with endogenous monkey FVIII is not unexpected in nonhuman primates and rats and has not been predictive of immunogenic responses in humans [35]. Formation of neutralizing antibodies (inhibitors) to FVIII are possible following administration of FVIII replacement therapies. Inhibitor development to FVIII is an important potential risk of efanesoctocog alfa.
• Developmental and reproductive toxicology studies: Animal reproductive and developmental toxicology studies have not been conducted with efanesoctocog alfa.	It is not known whether efanesoctocog alfa can affect reproductive capacity or cause fetal harm when given to pregnant women. Lactation studies have not been conducted with efanesoctocog alfa. It is not known whether efanesoctocog alfa is excreted into human milk. This is mentioned in the product information.
• Genotoxicity: Efanesoctocog alfa has not been evaluated in mutagenicity or chromosomal aberration assays since it is a replacement protein factor for coagulation activity and not required for biologic compounds.	No genotoxicity safety risk for humans is anticipated.

• Carcinogenicity: No animal studies investigating the carcinogenic effects of efanesoctocog alfa have been conducted. Since efanesoctocog alfa provides FVIII activity in the circulation of patients, it does not act in a manner that would indicate a potential cancer risk. Replacement therapy has been utilized for over 4 decades, first with the development of FVIII concentrates purified from human plasma, and then with rFVIII purified from cell culture supernatant. No concerns have been raised about carcinogenic or mutagenic effects of these products in patients, and a review of the published literature has not identified any case reports. Therefore, based on the weight of evidence approach, the carcinogenicity risk for efanesoctocog alfa is considered low.	No carcinogenicity safety risk for humans is anticipated.
Safety pharmacology	
No separate safety pharmacology studies were conducted with efanesoctocog alfa to investigate possible effects on the cardiovascular, respiratory, or CNS. However, these endpoints were evaluated in the 4-week repeat-dose toxicology studies. No adverse ECG or CNS effects were observed in monkeys. In repeat-dose toxicology studies in rats and cynomolgus monkeys, no respiratory abnormalities were noted during clinical sign examinations in rats up to 750 IU/kg every 3 days for 4 weeks and in monkeys up to 750 IU/kg every 4 days for 4 weeks.	No cardiovascular, respiratory, or CNS safety risks for humans are anticipated.
Other toxicity-related information or data	
No hemolysis and no plasma flocculation were observed following in vitro treatment of human whole blood with efanesoctocog alfa at concentrations up to 4.1 µg/mL.	No hemolysis or plasma flocculation risk for humans is anticipated.
aPTT: Activated Partial Thromboplastin Time; ADA: Anti-drug Antibody; CNS: Central Nervous System; ECG: Electrocardiogram; FVIII: Factor VIII; IU: International Unit; rFVIII: Recombinant FVIII.	

No specific studies were conducted to assess the biodistribution of efanesoctocog alfa. Although efanesoctocog alfa is a modified protein, it is a rFVIII which has a large molecular weight (312 kDa) and is intended to be administered intravenously. It is anticipated to be present in the vascular system (blood and plasma) throughout the body, as indicated by the low volume of distribution *in vivo*, ranging from approximately 50 to 150 mL/kg during non-clinical PK animal studies (mice, rats and monkeys); which is well below the volume of the total body water (600 to 700 mL/kg). No additional tissue distribution, protein binding or placental transfer studies have been conducted with efanesoctocog alfa.

Based on the above-mentioned non-clinical studies, the NOAEL was determined to be the highest dose level evaluated, i.e., 750 IU/kg. This gives a safety dose margin of 15x for the recommended human dose of 50 IU/kg tested in Phase 3 trials, and for the recommended dose for the intended indication.

Part II: Module SIII - Clinical trial exposure

From 09 June 2017 (the Development International Birth Date), safety concerns are evaluated based on the pooled safety data with a data cut-off date of 17 January 2023. The pooled safety data includes 277 unique participants from the phase 3 studies (EFC16293, EFC16295, and LTS16294), of which 249 (89.9%) participants had at least 50 EDs, 121 (43.7%) participants had at least 100 EDs, and 41 (14.8%) participants had at least 125 EDs, in addition to 57 participants exposed in the Phase 1/2 studies.

A summary of studies in the efanesoctocog alfa clinical development program is presented in Table 4, based on the 17 January 2023 cut-off date, including completed Phase 3 studies in previously treated adults and adolescents (EFC16293) and previously treated pediatric patients <12 years of age (EFC16295), as well as an ongoing long-term extension study (LTS16294; Arm A includes participants who completed Study EFC16293 or EFC16295 and participants who completed Arm B or C of LTS16294; Arm B includes previously treated patients newly initiated on efanesoctocog alfa in China; Arm C includes previously treated patients newly initiated on efanesoctocog alfa who are planned to undergo major surgery). Four completed or ongoing Phase 1/Phase 1/2a studies are also described. In addition, a new Phase 3b study in previously treated patients ≥12 years of age (Sobi.BIVV001-001, FREEDOM) has recently been approved in the EU, in which patients have been enrolled since June 2023.

Table 4 Summary of studies in the efanesoctocog alfa clinical development program and study status

Study Code Phase	Study Title	Study Description incl. Population and Number of participants	Efanesoctocog alfa dosing regimen and treatment duration	Status
EFC16293 Phase 3 Pivotal	A Phase 3, Open-label Interventional Study of an Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein, BIVV001, in Patients with Severe Hemophilia A (XTEND-1).	To assess the safety, efficacy, and PK of BIVV001 in adult and adolescent PTPs with severe hemophilia A, ≥12 years of age. Number of participants: 159 (133 in Arm A; 26 in Arm B)	50 IU/kg once weekly for 52 weeks (Arm A) 50 IU/kg on demand for 26 weeks followed by a switch to 50 IU/kg once weekly for 26 weeks (Arm B)*	Completed
EFC16295 Phase 3 Pediatric	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 (XTEND-kids).	To assess the safety, efficacy, and PK of BIVV001 in pediatric PTPs with severe hemophilia A, <12 years of age. Number of participants: 74 (38 in the <6 years of age cohort and 36 in the 6 to <12 years of age cohort).	50 IU/kg once weekly for 52 weeks*	Completed
LTS16294 Phase 3 Long-term study	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 (XTEND-ed).	To assess the long-term safety and efficacy of BIVV001 in PTPs with severe hemophilia A. In addition, 2 separate open label arms with pts newly initiated on BIVV001 in China; and pts who are planned to undergo major surgery. Number of Planned: N = 262 (215 in Arm A who roll over from Ph3; 37 Chinese participants in Arm B and up to 10 major	50 IU/kg once weekly Up to 48 months (Arm A) 52 weeks (Arm B and Arm C)*	Ongoing

Study Code Phase	Study Title	Study Description incl. Population and Number of participants	Efanesoctocog alfa dosing regimen and treatment duration	Status
		surgery participants in Arm C). Enrolled as of the cut-off date 17-JAN-2023: N = 251 (198 enrolled from parent study) in Arm A; 37 in Arm B; 7 in Arm C).		
242HA101 (TDU16220) Phase 1/2a	A Phase 1/2a Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of Single Intravenous Injection of rFVIIIFc-VWF-XTEN (BIVV001) in Previously Treated Adults with Severe Hemophilia A.	To assess safety, tolerability, and PK of a single IV dose of BIVV001 in adult PTPs with severe hemophilia A (18 to 65 years of age). Number of participants: 16 (7 in the low dose cohort, 9 in the high dose cohort).	25 IU/kg (low dose cohort) 65 IU/kg (high dose cohort) Single dose	Completed
242HA102 (TDR16219) Phase 1/2a	A Phase 1, Open-Label, Single-Site, Safety, Tolerability, and Pharmacokinetics Study of Repeat Doses of BIVV001.	To assess safety, tolerability, and PK repeat dose study of BIVV001 in adult PTPs with severe hemophilia A (18 to 65 years of age). Number of participants: 24 (10 in cohort 1; 14 in cohort 2).	50 IU/kg (low dose cohort) 65 IU/kg (high dose cohort) 4 once weekly doses	Completed
PKM17085 Phase 1	A Phase 1, Single-Site, Open-Label Study to Assess Pharmacokinetics of efanesoctocog alfa (BIVV001), Standard Half-Life and Extended Half-Life FVIII after each Single Intravenous Injection in a Fixed Sequence, in Previously Treated Adults with Severe Hemophilia A	To assess PK profiles of BIVV001, SHL and EHL rFVIII after a single IV injection of BIVV001 in adult PTPs with severe hemophilia A (18 to 65 years of age). Number of participants: 13	50 IU/kg Single dose	Completed
PKM16978 Phase 1	A Phase 1, Open-Label Study to Assess the Pharmacokinetics, and Safety and Tolerability of a Single Intravenous Injection of	To characterize the PK of BIVV001 after a single IV injection and to assess safety, and	25 IU/kg Single dose	Ongoing

Study Code Phase	Study Title	Study Description incl. Population and Number of participants	Efanesoctocog alfa dosing regimen and treatment duration	Status
	rFVIIIFc-VWF-XTEN (BIVV001) in Adults with type 2N and 3 von Willebrand disease (VWD)	tolerability of BIVV001 in adult male and/or female patients between 18 and 65 years of age with type 2N or type 3 VWD. Number of participants: Planned: 9 Enrolled as of the cut-off date: 6		
Sobi.BIVV001-001 (FREEDOM) Phase 3b	A Phase 3b, Open-label, multicenter study evaluating physical activity and joint health in previously treated patients ≥12 years of age with severe hemophilia A treated with intravenous recombinant coagulation factor VIII Fc-von Willebrand Factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN; efanesoctocog alfa) for 24 months	To describe the change from baseline in physical activity over a 24-month prospective period on once weekly prophylactic treatment with efanesoctocog alfa. The main objective is to describe the safety and tolerability of efanesoctocog alfa. Planned: 90 No patients enrolled yet at the cut-off date (17 Jan 2023).	50 IU/kg once weekly for 24 months*	Ongoing

CSR: Clinical Study Report; EHL: Extended Half-Life; FVIII: Factor VIII; IND: Investigational New Drug; IU: International Unit; PK: Pharmacokinetic; PTP: Previously Treated Patient; rFVIII: Recombinant FVIII; SAP: Statistical Analysis Plan; SHL: Standard Half-Life; VWD: Von Willebrand disease.

*Efanesoctocog alfa intravenous dosing regimens per indication: (1) Prophylaxis - 50 IU/kg once weekly; (2) Bleeding episode - 50 IU/kg single dose for all bleeding episodes. Additional and adjusted doses only after consultation with the Investigator. If a bleeding episode does not improve, additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered. For minor/moderate bleeding episodes within 2 to 3 days of a recent prophylactic dose, a 30 IU/kg dose may also be used; (3) minor surgery - 50 IU/kg single dose prior to surgery; (4) major surgery (only allowed after 6 exposure days) - Pre-operative loading dose of 50 IU/kg, then additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered.

Table 5, Table 6, Table 7and Table 8 summarize exposure to efanesoctocog alfa in the pooled phase 3 studies (EFC16293, EFC16295 and LTS16294), based on the 17 January 2023 cut-off date.

Table 5 Cumulative participant exposure - Enrolled

	Completed	Completed	Ongoing	Total
	EFC16293 N = 159[a] (%)	EFC16295 N = 74[b] (%)	LTS16294 N = 251 [c] (%)	N = 277 (%)
Number of participants exposed to efanesoctocog alfa	159 (100)	74 (100)	233 (92.8)	277 (100)

Note: Participants in more than 1 study are counted in both study columns. Each subject is counted only once in the total column.
[a] 146 participants enrolled and exposed in LTS16294 Arm A
[b] 70 participants enrolled and 52 exposed in LTS16294
[c] 198 participants enrolled and exposed from EFC16293 and EFC16295
PGM=PRODOPS/BIVV001/OVERALL/BRAC_2022/REPORT/PGM/exp_participant_t.sas
OUT=REPORT/OUTPUT/exp_participant_t_x.rtf (12MAY2022 18:46)
N: Number of Participants.

Table 6 Summary of exposure days (EDs) in Phase 3 studies

Total exposure days (EDs)[a], n(%)	Completed	Completed	Ongoing	Total
	EFC16293 N = 159 [b] (%)	EFC16295 N = 74 [c] (%)	LTS16294 (Arm B and Arm C) N = (37+7) (%)	N=277
At least 25	153 (96.2)	73 (98.6)	Arm B: 36 (97.3) Arm C: 5 (71.4)	267 (96.4)
At least 50	148 (93.1)	66 (89.2)	Arm B: 31 (83.8) Arm C: 4 (57.1)	249 (89.9)
At least 75	142 (89.3)	22 (29.7)	Arm B: 21 (56.8) Arm C: 0	185 (66.8)
At least 100	120 (75.5)	0	Arm B: 1 (2.7) Arm C: 0	121 (43.7)
At least 125	41 (25.8)	0	0	41 (14.8)

[a]An ED is a 24-hour period in which one or more efanesoctocog alfa injections are given. All injections over the study course are counted.
[b] 146 participants enrolled and exposed in LTS16294 Arm A
[c] 52 participants exposed in LTS16294
ED: Exposure Days; N: Total Number of Participants; n: Number of Exposed Participants.

Table 7 Cumulative participant exposure by age group

Age group (yrs) **Total exposure days (EDs)[a] , n(%)**	**<6**	**6-11**	**12-17**	**18-64**	**≥65**
Participants exposed to efanesoctocog alfa (total n=277)	38 (13.7%)	41 (14.8%)	37 (13.4%)	155 (56%)	6 (2.2%)
At least 25 ED	37 (13.4)	41 (14.8)	36 (13.0)	148 (53.4)	5 (1.8)
At least 50 ED	31 (11.2)	35 (12.6)	34 (12.3)	144 (52.0)	5 (1.8)
At least 75 ED	10 (3.6)	12 (4.3)	29 (10.5)	129 (46.6)	5 (1.8)
At least 100 ED	0	0	22 (7.9)	96 (34.7)	3 (1.1)
At least 125 ED	0	0	11 (4.0)	30 (10.8)	0

NOTE: Data cutoff for study LTS16294 was 17 Jan 2023.
Phase 3 studies include EFC16293, EFC16295, LTS16294.
[a] An ED is a 24-hour period in which one or more efanesoctocog alfa injections are given. All injections over the study course are counted.
For extension study LTS16294, the age used in classifying the rollover participants into different age categories was the age at entry to the parent study/arms.
ED: Exposure Day; N: Total Number of Participant; n: Number of Exposed Participant.

Table 8 Cumulative participant exposure by racial group

	Completed	Completed	Ongoing	**Total**
	EFC16293 N = 159[a] (%)	**EFC16295 N = 74[b] (%)**	**LTS16294 (Arm B + C) N = 37+7 (%)**	**N = 277 (%)**
Number of participants exposed to efanesoctocog alfa	159 (100)	74 (100)	44 (100)	277 (100)
Racial group n (%)				
White	97 (61.0)	55 (74.3)	Arm B: 0 Arm C: 7 (100)	159 (57.4)
Black/African American	3 (1.9)	3 (4.1)	0 (0)	6 (2.2)
Asian	29 (18.2)	8 (10.8)	Arm B: 36 (97.3) Arm C:0	73 (26.4)
Other	4 (2.5)	4 (5.4)	0	8 (2.9)
Not reported due to confidentiality regulations	26 (16.4)	4 (5.4)	Arm B: 1 (2.7) Arm C: 0	31 (11.2)

NOTE: Percentages are based on the number of participants with non-missing data in each study. Participants in more than 1 study are counted in both study columns. Each subject is counted only once in the total column.
[a] 146 participants enrolled and exposed in LTS16294 Arm A
[b] 70 participants enrolled and 52 exposed in
N: Total Number of Participants; n: Number of Exposed Participants.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 9 summarizes the key exclusion criteria in pivotal clinical studies within the development program.

Table 9 Exclusion criteria in pivotal clinical studies

Exclusion criteria	Reason for exclusion	Considered to be included as missing information?	Rationale
Participants without previous treatment for hemophilia A with any recombinant and/or plasma derived FVIII, or cryoprecipitate for at least 150 EDs for subjects ≥6 years of age or at least 50 EDs for subjects <6 years of age.	Consistent with EMA Guidelines for the Development of FVIII Products	Yes Use in PUPs	Not applicable
Any concurrent clinically significant liver disease that, in the opinion of the Investigator, would make the participant unsuitable for enrollment.	Patients with clinically significant liver disease may be unable to participate in a clinical trial and may confound interpretation of efficacy and safety data.	No	No scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population. Efanesoctocog alfa is not metabolized in the liver.
History of hypersensitivity or anaphylaxis associated with any FVIII product	Patients with a history of hypersensitivity or anaphylaxis associated with FVIII products may be at increased risk for recurrent hypersensitivity or anaphylaxis.	No	Well recognized class effect of FVIII replacement products. The proposed Product Information includes a contraindication to patients with a history of hypersensitivity to efanesoctocog alfa or any of its excipients.
Abnormal renal function, defined as serum creatinine >2.0 mg/dL taken at Screening.	Patients with impaired renal function may be unable to participate in a clinical trial and may confound interpretation of efficacy and safety data.	No	No scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population. efanesoctocog alfa is not eliminated via the kidneys.

Exclusion criteria	Reason for exclusion	Considered to be included as missing information?	Rationale
Serum ALT or AST >5 x ULN taken at Screening. Serum total bilirubin >3 x ULN taken at Screening.	Patients with clinically significant liver disease may be unable to participate in a clinical trial and may confound interpretation of efficacy and safety data.	No	No scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population. Efanesoctocog alfa is not metabolized in the liver.
Treatment with ASA or non NSAID anti-platelet therapies within 2 weeks prior to Screening. Treatment with NSAIDs above the maximum dose specified in the regional prescribing information within 2 weeks prior to screening.	Use of anti-platelet therapies and high doses of NSAIDs may impact bleeding tendency and confound assessment of efficacy.	No	No scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population.
Systemic treatment within 12 weeks prior to Screening with chemotherapy and/or other immunosuppressive drugs.	Use of immunosuppressive drugs may confound assessment of inhibitor development to FVIII.	No	No scientific evidence, including knowledge of other FVIII products, to suggest a unique safety concern in this population.
Mild or moderate hemophilia A.	Consistent with EMA Guidelines for the Development of FVIII Products. Patients with mild or moderate hemophilia A are generally not treated with prophylactic therapy.	No	No scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population.
Platelet count <100 000 cells/µL.	Thrombocytopenia may impact bleeding tendency and confound assessment of efficacy.	No	No scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population.
Patients known to be HIV antibody positive, with CD4 lymphocyte count <200 cells/mm3 or viral load ≥400 copies/mL.	A compromised immune system may confound assessment of inhibitor development to FVIII.	No	No scientific evidence, including knowledge of other FVIII products, to suggest a unique safety concern in this population.
Other coagulation disorder(s) in addition to hemophilia A.	Additional coagulation disorders may impact bleeding tendency and confound assessment of efficacy.	No	No scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population.

Exclusion criteria	Reason for exclusion	Considered to be included as missing information?	Rationale
History of a positive inhibitor test will be defined as ≥0.6 BU/mL, or any value greater than or equal to the lower sensitivity cut-off for laboratories with cut-offs for inhibitor detection between 0.7 and 1.0 BU/mL, or clinical signs or symptoms of decreased response to FVIII administrations. Family history of inhibitors will not exclude the participant. Positive inhibitor result, defined as ≥0.6 BU/mL at Screening	Inhibitor development is an identified safety concern for PWH on FVIII therapy, and patients with pre-existing history who will be at a higher risk of re-occurrence were excluded to allow unconfounded assessment of safety.	No	Inhibitor development is identified as an important potential risk for this product.
Any female who is pregnant or breastfeeding, or unwilling to take appropriate contraceptive therapy	Animal reproductive and developmental toxicology studies have not been conducted with efanesoctocog alfa. Lactation studies have not been conducted with efanesoctocog alfa.	No	Based on the rare occurrence of hemophilia A in women, use of factor VIII is limited in this population. No scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population. Safety information regarding this sub-population will be included in the EU SmPC.
Serious active bacterial or viral infection (other than chronic hepatitis or HIV) present within 30 days of Screening.	Listed as a co-morbidity for PWH. These serious infections could modify immunological and coagulation status or compromise normal organ functions (e.g., for kidney, liver etc...) Excluded to allow unconfounded assessment of safety.	No	No scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population.
Vaccination within 30 days of Screening	Precautionary efficacy and safety exclusion criteria to allow unconfounded assessment.	No	No scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population.

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

As of the cut-off date of 17 January 2023, 277 unique patients had been enrolled and treated with efanesoctocog alfa in the Applicant-sponsored completed and ongoing clinical studies. Patients will be treated and followed-up for up to 5 years in total, including 1 year in the completed adult/adolescent and pediatric Phase 3 studies (EFC16293 and EFC16295), and up to 4 years in the long-term extension study (LTS16294).

The safety database and extent of exposure are robust and sufficiently large to assess the risk of very common (incidence >1/10) or common (incidence of >1/100 to <1/10) AEs. Ongoing pharmacovigilance will enable detection of rarer events.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table 10 presents exposure of special populations included or not in the efanesoctocog alfa Phase 3 clinical development program. For the ongoing study LTS16294, data are updated based on the cut-off date of 17 January 2023.

Table 10 Exposure of special populations included or not in efanesoctocog alfa Phase 3 development program

Type of special population	Exposure
Pregnant or breast-feeding women	Not included in the Efanesoctocog alfa clinical development program.
Patients with relevant co-morbidities	
Patients with hepatic impairment [a,b]	• 78 participants, 155.4 person-years
Patients with renal impairment [a,c]	• 91 participants, 180.2 person-years
Immunocompromised patients	Not included in the Efanesoctocog alfa clinical development program
Patients with a disease severity different from the inclusion criteria in the clinical trial population	Not included in the Efanesoctocog alfa clinical development program
Patients with cardiovascular impairment [a,d]	• 55 participants, 103.9 person-years
Populations with relevant different ethnic origin	See Part II Module SIII.
Subpopulations carrying known and relevant genetic polymorphisms	**FVIII genotype** EFC16293[e]: • Intron 22 inversion: 57 participants • Intron 1 inversion: 0 participants • Frameshift: 33 participants • Missense: 22 participants • Nonsense: 15 participants • Large structural change (>50 base pairs): 10 participants • Small structural change (<50 base pairs): 1 participant • Splice site change: 5 participants • Synonymous: 2 participants • Not applicable: 13 participants EFC16295[f]: • Intron 22 inversion: 16 participants • Intron 1 inversion: 0 participants • Frameshift: 8 participants • Missense: 7 participants • Nonsense: 4 participants • Large structural change (>50 base pairs): 11 participants • Small structural change (<50 base pairs): 1 participant • Splice site change: 2 participants • Other mutations: 3 participants • Unknown: 22 participants LTS16294[h]: Arm B: • Intron 22 inversion: 2 participants • Intron 1 inversion: 0 participants • Frameshift: 0 participants

Type of special population	Exposure
	• Missense: 1 participant • Nonsense: 2 participants • Other mutation: 0 participants • Unknown: 9 participants Arm C[f]: • Intron 22 inversion: 2 participants
Other	
Female	• 1 participant
Elderly (≥65 years)	• 6 participants, 9.9 person-years
Patients with risk factors for thrombotic events [a,g]	• 108 participants, 203.8 person-years

a. LTS16294 Arm A participants are also accounted for in parent study EFC16293 or EFC16295, as applicable.
b. For the participants with history of hepatic impairment, the following MedDRA SMQs were used: Acute pancreatitis, Biliary disorders, Drug abuse, dependence and withdrawal, Hepatic disorders.
c. For the participants with history of renal impairment, the following MedDRA SMQs were used: Acute renal failure, Cardiac failure, Cardiomyopathy, Chronic kidney disease, Dehydration, Hyperglycaemia/new onset diabetes mellitus, Hepatic disorders, Hypertension, Renovascular disorders, Rhabdomyolysis/myopathy, Tubulointerstitial diseases.
d. For the participants with history of cardiovascular impairment, the following MedDRA SMQs were used: Acute renal failure, Cardiac failure, Cardiomyopathy, Chronic kidney disease, Dehydration, Dyslipidaemia, Hyperglycaemia/new onset diabetes mellitus, Hypertension, Renovascular disorders, Tubulointerstitial diseases.
e. Based on medical review of Case Report Form and laboratory data.
f. Based on Case Report Form only.
g. For the participants with history of risk factors for thromboembolic events, the following MedDRA SMQs were used: Cardiac Arrhythmia, Dyslipidaemia, Embolic and thrombotic events, Hepatic disorders, Hyperglycaemia/new onset diabetes mellitus, Hypertension, Ischaemic heart disease, Malignancies, Renovascular disorders, Thrombophlebitis.
h. Data for Arm A not presented as these were collected in parent study.

FVIII: Factor VIII; MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standardized MedDRA Query.

Part II: Module SV – Post-authorization experience

On 22 February 2023, the FDA approved efanesoctocog alfa for routine prophylaxis, on-demand treatment and control of bleeding episodes, and perioperative management of bleeding in adults and children with hemophilia A, however, there is no post-authorization experience available at the time of data lock point.

SV.1 Post-authorization exposure

Not applicable.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The properties of efanesoctocog alfa do not indicate a potential for misuse for illegal purposes.

Efanesoctocog alfa has no or only a limited ability to cross the blood-brain barrier with negligible exposure in the brain and has shown no propensity for eliciting any neurological effects in toxicology studies. The potential for misuse of efanesoctocog alfa for illegal purposes is considered low as this product is not known to have attributes that make it a candidate for intentional overdose, abuse, or illegal use, such as known pharmacological addictive effects.

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The risks or safety topics that are not considered important for inclusion in the list of safety concerns in the RMP are discussed in Section SVII.1.1.

The risks that are considered important for inclusion in the list of safety concerns in this initial RMP v1.0 are discussed in Section SVII.1.2.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Known risks that require no further characterization:

Known risks that require no further characterization and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized).

Potential risk of serious allergic reaction and/or anaphylaxis:

Although considered rare, serious allergic reactions and anaphylaxis are established potential complications of FVIII replacement therapy [42-45]. Prescribers are anticipated to have appropriate measures in place as part of standard clinical practice. The potential for allergic reaction and/or anaphylaxis is addressed in the product information including relevant instruction, as applicable. Additional pharmacovigilance activities or additional risk minimization measures are not deemed necessary. As of 17 January 2023, there have been no reports of serious allergic reaction or anaphylaxis due to efanesoctocog alfa in the clinical development program. Relevant safety information concerning hypersensitivity is included in the SmPC 4.4 and 4.8.

Risks with minimal benefit-risk and public health impact:

Identified risks described in SmPC 4.8:

The pooled safety data across the completed studies (EFC1693 and EFC16295) and ongoing study (LTS16294) was used to identify ADRs. A total of 111 (40.1%) out of 277 participants experienced at least 1 or more ADRs in the pooled studies. The incidence of these ADRs (including associated PTs) are: arthralgia [16.6%], headache [15.6%], pyrexia [6.1%], pain in extremity [5.8%], back pain [4.3%], vomiting [3.6%]), eczema [2.2%], rash [ADR includes rash (1.4%) and rash maculo-papular (0.4%)], urticaria [ADR includes urticaria (0.7%) and urticaria papular (0.4%)] and injection site reactions [ADR includes infusion site hematoma (0.4%) and injection site dermatitis (0.4%)]. All identified ADRs were assessed by the Investigator as non-

serious, and none resulted in discontinuation of efanesoctocog alfa. These ADRs are included in the ADR list in the SmPC 4.8.

Potential risk of dosing errors based on assay type used for monitoring FVIII levels:

Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. It is recommended to use a validated one stage clotting assay to determine plasma factor VIII activity of efanesoctocog alfa. Throughout the clinical development an Actin FSL-based one stage clotting assay was used. According to the findings of a comparative analysis of clinical study samples, results obtained using a chromogenic assay should be divided by 2.5 to approximate the patient's factor VIII activity. In addition, a field study comparing different aPTT reagents indicated approximately 2.5-fold higher factor VIII activity levels when using Actin-FS instead of Actin-FSL in the one stage clotting assay and approximately 30% lower results when using SynthASil. Therefore, there is a potential for dosing errors based on the assay type used for measurement of FVIII levels. Relevant safety information concerning monitoring laboratory tests with the chromogenic assay or the one stage clotting assay are included in SmPC sections 4.2 and 4.4.

Potential harm from overdose:

Efanesoctocog alfa is to be administered as a prophylactic dose of 50 IU/kg once weekly for all age ranges. The recommended dose of efanesoctocog alfa for on demand treatment, control of bleeding episodes, and perioperative management of bleeding is also 50 IU/kg. Additional doses of 30 or 50 IU/kg every 2 or 3 days may be considered. Based on these dosing instructions, the potential for accidental overdose is considered low, however, in case of major surgery or severe bleeds, determination of factor VIII levels is required to guide the dose to be administered and the frequency of repeated infusions. As of 17 Jan 2023, no adverse events from overdose have been reported in the efanesoctocog alfa clinical development program.

This potential risk will be addressed in the product information including relevant instruction, as applicable. Additional pharmacovigilance activities or additional risk minimization measures are not deemed necessary.

Other risks and reasons for not being considered important:

Table 11 Identified/Potential risks and reasons for not being considered important

Identified/Potential risk	Reason for not considered important
Potential for transmission of infectious agents	The aseptic manufacture of efanesoctocog alfa is validated and performed in accordance with the "EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human Use, Annex 1." No human or animal excipients are used in the manufacture of efanesoctocog alfa. Therefore, the risk for the drug product to contain infectious agents is minimized.
Potential for off-label use	There is potential for off-label use of efanesoctocog alfa (e.g., immune tolerance induction therapy, Von Willebrand disease). However, the potential risks related to off-label use are limited or generally consistent with those of the intended indications.
Important risk related to identified or potential PK and pharmacodynamic interaction	Pharmacokinetic and pharmacodynamic interactions are not anticipated based on a well understood mechanism of action of FVIII products and concomitant medications commonly used in the target population (e.g., pain medication, treatment of HIV, and treatment of HCV).
Risk in pregnant and lactating women	No data are available concerning the use of efanesoctocog alfa in pregnant or breast-feeding women. However, there is no scientific evidence, including knowledge of other FVIII products, to suggest that the safety profile of efanesoctocog alfa will differ in this population. In addition, the target population of efanesoctocog alfa is predominantly male.
Effect on fertility	In the 4-week toxicology studies in rats and monkeys, there were no effects on male or female reproductive organs. Based on available non-clinical data and knowledge of other FVIII products, there is no scientific evidence to support an effect of efanesoctocog alfa on fertility.
Risks associated with disposal of the used product	Risk associated with disposal of the used product are not anticipated.
Risks related to the administration procedure	The administration procedure of efanesoctocog alfa will be comparable to that of other FVIII products. This topic will be addressed in the product information including relevant instruction, as applicable.
Pediatric safety	Consistent with the well characterized safety profile of other FVIII products, as of 17 Jan 2023, available safety data in previously treated pediatric patients exposed to efanesoctocog alfa are similar to the adult population studied and there were no unique safety concerns identified. Use in PUPs is included in the List of Safety Concerns as missing information.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: Inhibitor development to FVIII

The development of inhibitors is an established, potential complication for factor replacement therapy in hemophilia and occurs in 25% to 30% of all PUPs with severe hemophilia A. The risk of inhibitor development is considered maximal during the first 20 to 30 EDs to FVIII [9, 46]. Inhibitor development in previously treated patients is a rare event with an estimated incidence of 2 per 1000 person years [19, 47, 48].

Risk-benefit impact: The development of an inhibitor is the most significant treatment complication in hemophilia A. As a result, the response to infused FVIII will be inadequate and the frequency and/or severity of bleeding events may be increased.

Important Potential Risk: Serious vascular thromboembolic events

This risk is not well established in hemophilia patients receiving FVIII therapy and vascular thromboembolic events are considered rare in this population [49]. Reports of thrombotic events in patients with hemophilia A receiving FVIII replacement therapy often include pre-existing risk factors for vascular thrombosis [50, 51]. Patients with hemophilia A may be at the same risk of developing thrombotic events as non-hemophilic patients when clotting has been restored by treatment with FVIII replacement therapy [52]. Further details on this safety concern are provided in section SVII.3.

Risk-benefit impact: Limited data are available concerning the use of efanesoctocog alfa in patients with hemophilia A and there is insufficient evidence to support a causal association between the occurrence of vascular thromboembolic events and exposure to efanesoctocog alfa. Therefore, there is no impact on the risk-benefit balance of efanesoctocog alfa.

Missing information:

Use in previously untreated patients:

Previously untreated patients are not included in the clinical development program for efanesoctocog alfa. However, the targeted population for the indication in children may include PUPs. As the incidence of inhibitor development to FVIII is higher in PUPs compared to PTPs (defined as having >150 EDs to FVIII therapy) [48, 53], the use of efanesoctocog alfa in PUPs is considered missing information.

Risk-benefit impact: The development of an inhibitor is the most significant treatment complication in hemophilia A. As a result, the response to infused FVIII will be inadequate and the frequency and/or severity of bleeding events may be increased.

Long term Use:

Hemophilia is a life-long condition that requires long-term treatment. The clinical development program for efanesoctocog alfa includes a long-term safety study (LTS16294) in which patients will be treated with efanesoctocog alfa for up to 5 years. The study is currently ongoing and therefore “Long term use” is currently considered to be missing information.

Risk-benefit impact: The safety profile is not expected to differ in long-term use.

Safety in elderly patients ≥65 years old:

Elderly patients with hemophilia face specific challenges with age-related comorbidities. The clinical development program for efanesoctocog alfa includes few elderly patients (n=6) and data in this subgroup are therefore considered limited.

Risk-benefit impact: Limited data are available concerning the use of efanesoctocog alfa in elderly (≥65 years of age) patients. However, the available clinical data indicate that the safety profile of efanesoctocog alfa in elderly patients is similar to that of the overall population.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable since this is the first RMP for efanesoctocog alfa.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

The important identified and important potential risks for efanesoctocog alfa are presented in Table 12.

Table 12 Summary of important identified and important potential risks for efanesoctocog alfa

Important identified risks	
Inhibitor development to FVIII	
Potential mechanisms	Inhibitor development to FVIII is the result of an immune response to exogenous FVIII in patients with hemophilia A. A FVIII inhibitor is a polyclonal high affinity neutralizing alloantibody directed at specific epitopes on specific factor peptides that inhibits the action of factor replacement therapy.
Evidence source(s) and strength of evidence	Inhibitors are an established, potential complication of factor replacement therapy in hemophilia and occur in approximately 25% to 30% of all PUPs with severe hemophilia A. The risk of inhibitor development is considered maximal during the first 20 to 30 EDs to FVIII [9]. Inhibitor development in previously treated patients is a rare event with an estimated incidence of 2 per 1000 person years [48].
Characterization of the risk	Frequency with 95% CI: Inhibitor testing at a central laboratory via the Nijmegen modified Bethesda assay was performed at regular intervals for all patients in the efanesoctocog alfa clinical development program. As of 17 January 2023, inhibitor development to FVIII has not been detected in PTPs exposed to efanesoctocog alfa. Based on final data from Study EFC16293, the incidence of inhibitor development in participants with ≥50 Eds to efanesoctocog alfa was 0% (95% CI: 0.0, 3.3). Based on the final data from Study EFC16295, the incidence of inhibitor development in all participants with ≥50 EDs to efanesoctocog alfa was 0% (95% CI: 0.0, 5.5). Severity and nature of risk: Development of inhibitors against FVIII is the most serious complication of FVIII replacement therapy. As a result, the response to infused FVIII will be inadequate and the frequency and/or severity of bleeding events may be increased. Seriousness/outcomes: For some patients, eradication of FVIII inhibitors may be possible with immune tolerance induction therapy. Background incidence/prevalence: The development of neutralizing IgG alloantibodies (inhibitors) against FVIII is the most serious complication of FVIII replacement, occurring in approximately 25-30% of PUPs with severe hemophilia A, as well as 5-10% of patients with mild to moderate hemophilia A [54]. Inhibitor development in previously treated patients is a rare event with an estimated incidence of 2 per 1000 person years [48]. Impact on individual patient: The response to infused FVIII will be inadequate and the frequency and/or severity of bleeding events may be increased.
Risk factors and risk groups	The causes of inhibitor development to FVIII are not known. However, elevated risk has been associated with periods of peak FVIII treatment, surgery, family history of inhibitors, and FVIII genetic mutations including large deletions, nonsense mutations and intron 22 inversion

	[6, 55, 56]. In addition, the incidence of inhibitor development to FVIII is higher in PUPs compared to PTPs (defined as having >150 Eds to FVIII therapy) [48, 53].
Preventability	The potential risk of inhibitor development including relevant instruction as applicable is described in the product information and patient leaflet.
Impact on the risk-benefit balance of the product	Minimal impact on the benefit-risk balance is anticipated for this product.
Public health impact	The morbidity and mortality associated with inhibitor development depends on associated clinical sequelae and access to medical care. Overall, the public health impact is anticipated to be low.
Important potential risks	
Serious vascular thromboembolic events	
Potential mechanisms	High FVIII levels may increase the risk of venous thrombosis via enhanced thrombin formation and/or through the induction of acquired activated protein C resistance. The relationship between FVIII and arterial thrombosis may be based on the combination of increased thrombin formation and increased platelet adhesion/aggregation, induced by von Willebrand factor, at sites of arterial wall damage [57].
Evidence source(s) and strength of evidence	In the literature, elevations in FVIII above the physiological upper range of 150 IU/dL, in patients without hemophilia or deficits in coagulation, increase thrombotic risk in a dose dependent manner. However, the thrombotic risk is related to persistent elevated FVIII levels [58, 59]. There are also data showing that levels of FVIII were significantly higher amongst patients with venous thrombotic events (VTEs), 199.1 IU/dl, when compared to controls, 145.2 IU/dl [60]. An *in vitro* and *in vivo* evaluation of the effect of elevated factor VIII on the thrombogenic process showed no significant increase in thrombogenicity within the physiological range of FVIII levels between 100 and 200 IU/dL. It was concluded that the contribution of transient FVIII increases to the likelihood of arterial thrombogenesis is small, and that while clinical replacement therapies need to aim for normal or modestly elevated FVIII levels, large transient FVIII increments are likely not a major thrombotic risk factor [61]. This risk is not well established in hemophilia patients receiving FVIII therapy and vascular thrombotic events are considered rare in this population [49, 62]. Published reports of vascular thrombotic adverse events in patients with hemophilia A and rFVIII replacement therapy occur in the setting of pre-existing risk factors for vascular thrombosis, e.g. cardiovascular risk factors and indwelling CVCs [50-52, 63, 64]. Therefore, the causes of observed thromboembolic events while using FVIII therapy are multifactorial with an overall unclear causal relationship.
Characterization of the risk	The risk of vascular thromboembolic events with the use of rFVIII products such as efanesoctocog alfa has not been established. As of the 17 January 2023, out of the 3 participants with reports of thrombotic events in the efanesoctocog alfa clinical development program (all in the LTS16294 study), 1 had a medical history of hemangioma reported at the time of enrollment who experienced a thrombosis in the presence of worsening of a pre-existing hemangioma, 1 experienced a deep vein thrombosis following a traumatic femur fracture requiring orthopedic surgery, while receiving another FVIII product, and 1 patient with pre-existing risk factors of atrial fibrillation and dyslipidemia had a cerebral infarction. Investigator assessment for these events were related (Thrombosis) and not related (DVT and Cerebral infarction). All three patients had confounding factors associated with the reported

	events. Therefore, the company's causality assessment is that the events of thrombosis described in the 3 study participants are primarily related to the pre-existing risk factors for thrombosis in each of the participants, and that the events are not related to efanesoctocog alfa.
Risk factors and risk groups	Patients with pre-existing risk factors for thromboembolism (e.g., cardiovascular risk factors, indwelling central venous catheters). Cardiovascular risk factors are more likely to occur with advancing age [65]. Cardiovascular risk factors include hyperlipidemia, smoking, diabetes, hypertension, and obesity for arterial thrombotic events. For venous thrombotic events, risk factors include trauma or fractures, surgery, immobilization, hormonal therapy, pregnancy, hypercoagulability and age [66].
Preventability	Unknown.
Impact on the risk-benefit balance of the product	There is insufficient evidence to support a causal association between the occurrence of vascular thromboembolic events and exposure to efanesoctocog alfa. There is no impact on the risk-benefit balance of efanesoctocog alfa.
Public health impact	The public health impact is anticipated to be low.

SVII.3.2. Presentation of missing information

Missing information:

Use in previously untreated patients

Evidence source:

Previously untreated patients are not included in the clinical development program for efanesoctocog alfa. However, the targeted population for the indication in children may include PUPs. As the incidence of inhibitor development to FVIII is higher in PUPs compared to PTPs (defined as having >150 EDs to FVIII therapy) [48, 53], the use of efanesoctocog alfa in PUPs is considered missing information.

Population in need of further characterization:

The safety profile in PUPs, including the risk of inhibitor development to FVIII, will be described post-approval, through an observational registry study in Previously Untreated Patients (PUPs) and a well-defined disease registry (PedNet).

Long term use

Evidence source:

The current total cumulative exposure reported in the development program is now 47.4 participant-years across 277 participants, with a mean of 89.9 exposure days (EDs) per participant. The long-term safety study (LTS16294) is ongoing and has 251 participants enrolled in Arm A. It is expected that at least 200 patients will achieve 100 EDs post-approval.

Patients will be treated and followed-up for up to 5 years in total, including 1 year in the adult/adolescent and pediatric Phase 3 studies (EFC16293 and EFC16295), and up to 4 years in the long-term extension study (LTS16294).

Population in need of further characterization:

The safety of long-term use will be monitored post-approval through a long-term study (LTS16294) and post-marketing surveillance.

Safety in elderly patients ≥ 65 years of age

Evidence source:

The clinical development program includes 6 participants in the age category of ≥ 65 years of age. Of these, 5 participants had at least 75 exposure days and 3 participants had at least 100 exposure days. A total of 5 (83.3%) participants ≥ 65 years of age experienced at least 1 TEAE. Most of these events are commonly reported in an elderly population. The pharmacokinetic profile in elderly patients was comparable to that observed in other age groups.

Population in need of further characterization:

The safety profile in elderly patients will be monitored post-approval through a long-term study (LTS16294) and post-marketing surveillance.

Part II: Module SVIII – Summary of the safety concerns

Table 13 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Inhibitor development to FVIII
Important potential risks	Serious vascular thromboembolic events
Missing information	Use in previously untreated patients Long term use Safety in elderly patients ≥ 65 years of age

Part III: Pharmacovigilance Plan

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for inhibitor development to FVIII and serious vascular thromboembolic events:

The Applicant proposes to use specific targeted questionnaire for follow-up the specific adverse event of special interest "Inhibitor development to FVIII" and "Serious vascular thromboembolic events" for the collection of structured data pertaining to these relevant important potential risks.

Cumulative review of reports collected in this manner allows for further characterization of the nature of the risks and is used during the review process when considering the relationship between the drug and a safety concern.

The specific adverse reaction follow-up questionnaires are provided in Annex 4.

III.2 Additional pharmacovigilance activities

A summary of ongoing and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan is presented below.

A tabulated summary of ongoing and planned studies including the protocols in the Pharmacovigilance Plan are provided in Annex 2.

On-going and planned additional pharmacovigilance activities

Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (In collaboration with American Thrombosis and Hemostasis Network (ATHN), (Category 3)
Study short name and title Prospective, observational registry study in previously untreated patients (PUPs) with hemophilia A.
Rationale and study objectives • To evaluate the safety profile of efanesoctocog alfa in PUPs. • The primary objective is to describe safety and tolerability in PUPs treated with efanesoctocog alfa. • The primary endpoints are inhibitor development to FVIII as measured by the Nijmegen modified Bethesda assay and the occurrence of adverse events of special interest.
Study design Prospective, observational, open-label, multi-center registry study. The total number of patients included will depend on the future uptake of efanesoctocog alfa among PUPs.
Study populations Previously untreated patients with severe congenital hemophilia A (<1 IU/dL [<1%] endogenous FVIII activity).
Milestones A final study report will be submitted after the end of the study.

Long Term Safety and Efficacy of BIVV001 in Previously Treated Patients with Hemophilia A (Category 3)
Study short name and title Long-term safety and efficacy of BIVV001 in previously treated patients with hemophilia A (LTS16294).
Rationale and study objectives • To determine the long-term safety and efficacy of efanesoctocog alfa administered as once weekly prophylaxis treatment in previously treated patients with severe hemophilia A. • The primary objective is to evaluate the long-term safety of efanesoctocog alfa as indicated by the occurrence of inhibitor development. • Secondary objectives include further evaluation of long-term safety as well as long term efficacy of efanesoctocog alfa.
Study design Multinational, multicenter, open label Phase 3 study comprised of 3 arms: • Arm A: Includes participants who have completed Study EFC16293 or Study EFC16295, and participants who have completed Arm B or Arm C of this study (LTS16294) and roll over into Arm A. Participants in Arm A will continue receiving efanesoctocog alfa prophylaxis treatment at a dose of 50 IU/kg IV once weekly for a cumulative total of 100 EDs. • Arm B (in China): Chinese participants of any age will be newly initiated on efanesoctocog alfa prophylaxis treatment at a dose of 50 IU/kg IV once weekly for 52 weeks. After 52 weeks of treatment in Arm B, participants will be able to roll over into Arm A. • Arm C: Participants of any age will be newly initiated on efanesoctocog alfa prophylaxis treatment at a dose of 50 IU/kg IV onceweekly and will undergo planned major surgery after at least 6 initial EDs with efanesoctocog alfa. After 52 weeks of treatment in Arm C, participants will be able to roll over into Arm A.
Study populations Previously treated patients with severe hemophilia A.
Milestones A final study report will be submitted after the end of the study.

ED: Exposure Day; FVIII: Factor VIII; IU: International Unit; IV: Intravenous; PUP: Previously Untreated Patient.

Other planned pharmacovigilance studies/activities

Data from the European Hemophilia Safety Surveillance System (EUHASS) registry and the PedNet registry will be used to perform additional pharmacovigilance surveillance.

The EUHASS registry is an investigator-driven registry that is funded by the EU in addition to the Applicant and other manufacturers of FVIII concentrate products. EUHASS is a prospective Hemophilia Safety Surveillance System for Europe. Participating centers have agreed to report all relevant AEs in their patients in a prospective manner. Data will be received and reviewed quarterly and annually as part of signal detection. Regular updates will be provided and reported within PSURs.

The PedNet Hemophilia Registry is a database which collects observational data for children with hemophilia A and B. According to the PedNet protocol (Protocol-of-the PedNet-Hemophilia-Registry-v6.4), data are collected from PUPs treated with efanesoctocog alfa in Europe using a web-based system and are entered to the registry from patient records. It also collects data in line with the FVIII guideline requirements on immunogenicity in PUPs. Data

collected in PedNet will support the evaluation of the safety profile of efanesoctocog alfa in previously untreated patients (PUPs). PedNet's annual report will be received and reviewed as part of signal detection. Regular updates will be provided and reported within PSURs.

III.3 Summary Table of additional Pharmacovigilance activities

Additional pharmacovigilance activities in the post-marketing setting include:

Table 14 On-going and planned additional pharmacovigilance activities

Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
Long-term safety and efficacy of BIVV001 in previously treated patients with Hemophilia A (LTS16294) Ongoing	To determine the long-term safety and efficacy of BIVV001 administered as once-weekly prophylaxis treatment in previously treated patients with severe hemophilia A. The primary objective is to evaluate the long-term safety of BIVV001 as indicated by the occurrence of inhibitor development. Secondary objectives include further evaluation of long-term safety as well as long term efficacy of BIVV001.	Inhibitor development to FVIII Serious vascular thromboembolic events Long term use Safety in Elderly ≥65 years old	Final study report	Data will be reviewed on an ongoing basis as part of signal detection and reported within PSURs. Final study report is expected Q2 2027
Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN) Planned	A collaborative study with American Thrombosis and Hemostasis Network (ATHN). To evaluate the safety profile of efanesoctocog alfa in previously untreated patients (PUPs). The primary objective is to describe safety and tolerability in PUPs treated with efanesoctocog alfa. The primary endpoints are inhibitor development to FVIII as measured by the Nijmegen modified Bethesda assay and the occurrence of adverse events of special interest.	Inhibitor development to FVIII Serious vascular thromboembolic events Use in previously untreated patients	Final study report	Data will be reviewed on an ongoing basis as part of signal detection and reported within PSURs when available. Study started in Feb 2024. An interim analysis is expected in Q1 2027. Final study report is expected in Q1 2029.

Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Additional PV activity				
PedNet Hemophilia Registry Planned	The general objective is to evaluate safety of efanesoctocog alfa by reviewing data collected prospectively following birth cohorts of unselected previously untreated children with Hemophilia A.	Inhibitor development to FVIII Serious vascular thromboembolic events Use in previously untreated patients	Annual report	Data will be reviewed on an ongoing basis as part of signal detection. Annual reports will be reviewed and reported within PSURs.
EUHASS Registry Planned	To evaluate safety (Adverse events reported during surveillance) of efanesoctocog alfa in patients with hemophilia A under observational ('real world') conditions of routine clinical care.	Inhibitor development to FVIII Serious vascular thromboembolic events	Quarterly and annually	Data will be reviewed on an ongoing basis as part of signal detection. Quarterly and annual reports will be reviewed and reported within PSURs.

Part IV: Plans for post-authorization efficacy studies

No post-authorization efficacy studies for efanesoctocog alfa (planned or ongoing) have been imposed by regulatory authorities as a condition of a marketing authorization or as specific obligations in the context of a conditional marketing authorization or as a condition of a marketing authorization under exceptional circumstances.

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

V.1. Routine Risk Minimization Measures

Routine risk minimization measures for efanesoctocog alfa are described in Table 15.

Table 15 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Inhibitor Development to FVII	**Routine risk communication:** SmPC section 4.4 and 4.8 PL section 2.0 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Information about the risk of inhibitor development. Recommendation for monitoring all patients for the development of FVIII inhibitors. Information on how to detect early signs of inhibitor development. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.
Serious vascular thromboembolic events	**Routine risk communication:** SmPC section 4.4 PL section 2.0 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Information about risk of cardiovascular events in patient with existing cardiovascular risk factors. Information about risk of catheter-related complications, including catheter site thrombosis. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.

Use in previously untreated patients	**Routine risk communication:** SmPC section 4.4 PL section 2.0 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring all patients for the development of FVIII inhibitors. Information on how to detect early signs of inhibitor development. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.
Long term use	**Routine risk communication:** SmPC section 5.1 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.
Safety in elderly patients ≥ 65 years of age	**Routine risk communication:** SmPC section 4.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimization measures

Table 16 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Inhibitor development to FVIII	**Routine risk minimization measures:** SmPC 4.8: Information about the risk of inhibitor development in patients with hemophilia A treated with factor VIII, including with efanesoctocog alfa. SmPC section 4.4: Recommendation for monitoring all patients for the development of FVIII inhibitors by appropriate clinical observations and laboratory tests and performing appropriate testing if the patient's plasma FVIII level fails to increase as expected or if bleeding is not controlled after efanesoctocog alfa administration. PL section 2.0: Information on how to detect early signs of inhibitor development. **Other routine risk minimization measures beyond the Product Information:** None **Pack size:** None **Legal status:** Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire. **Additional pharmacovigilance activities:** Long-term safety and efficacy of efanesoctocog alfa in previously treated patients with Hemophilia A (LTS16294) Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN). European Hemophilia Safety Surveillance System (EUHASS) participation and data collection. The PedNet Hemophilia Registry Data collection in Previously Untreated Patients (PUPs)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious vascular thromboembolic events	**Routine risk minimization measures:** SmPC section 4.4: Information about risk of cardiovascular events in patient with existing cardiovascular risk factors and risk of catheter-related complications, including catheter site thrombosis. PL section 2.0: Information about risk of catheter-related complications, including catheter site thrombosis. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire. **Additional pharmacovigilance activities:** Long-term safety and efficacy of efanesoctocog alfa in previously treated patients with Hemophilia A (LTS16294) Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN). The PedNet Hemophilia Registry Data collection in PUPs. European Hemophilia Safety Surveillance System (EUHASS) participation and data collection.
Safety in previously untreated patients	**Routine risk minimization measures:** SmPC section 4.4: Recommendation for monitoring all patients for the development of FVIII inhibitors by appropriate clinical observations and laboratory tests and performing appropriate testing if the patient's plasma FVIII level fails to increase as expected or if bleeding is not controlled after efanesoctocog alfa administration. PL section 2.0: Information how to detect early signs and symptoms of inhibitor development. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN). The PedNet Registry Data collection in PUPs.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Long term use	**Routine risk minimization measures:** SmPC section 5.1: The long-term safety and efficacy of ALTUVOCT is also being evaluated in a long-term extension study. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Long-term safety and efficacy efanesoctocog alfa in previously treated patients with Hemophilia A (LTS16294)
Safety in elderly patients ≥ 65 years of age	**Routine risk minimization measures:** SmPC section 4.2: There is limited experience in patients ≥ 65 years. The dosing recommendations are the same as for patients < 65 years. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Long-term safety and efficacy of efanesoctocog alfa in previously treated patients with Hemophilia A (LTS16294)

Part VI: Summary of activities in the risk management plan by product

Summary of risk management plan for Efanesoctocog alfa

This is a summary of the risk management plan (RMP) for ALTUVOCT®. The RMP details important risks of ALTUVOCT®, how these risks can be minimized, and how more information will be obtained about ALTUVOCT®'s risks and uncertainties (missing information).

ALTUVOCT®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ALTUVOCT® should be used.

This summary of the RMP for ALTUVOCT® should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new concerns, or changes to the current ones, will be included in updates of ALTUVOCT®'s RMP.

I. The medicine and what it is used for

ALTUVOCT® is authorized for treatment and prophylaxis of bleeding in all age groups of patients with hemophilia A (congenital FVIII deficiency). It contains efanesoctocog alfa as the active substance and it is given by intravenous injection.

Further information about the evaluation of ALTUVOCT®'s benefits can be found in ALTUVOCT®'s EPAR, including in its plain-language summary, available on the EMA website, <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of ALTUVOCT®, together with measures to minimize such risks, and the proposed studies for learning more about ALTUVOCT®'s risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of ALTUVOCT® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ALTUVOCT® are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ALTUVOCT®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not yet been established and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Inhibitor development to FVIII
Important potential risks	Serious vascular thromboembolic events
Missing information	Safety in previously untreated patients Long term use Safety in elderly patients ≥ 65 years of age

II.B Summary of important risks

Table 17 Summary of important risks

Important identified risk: Inhibitor development to FVIII	
Evidence for linking the risk to the medicine	Inhibitors are an established, potential complication of factor replacement therapy in hemophilia and occur in approximately 25% to 30% of all PUPs with severe hemophilia A. The risk of inhibitor development is considered maximal during the first 20-30 EDs to FVIII [46]. Inhibitor development in previously treated patients is a rare event with an estimated incidence of 2 per 1000 person years [48].
Risk factors and risk groups	The causes of inhibitor development to FVIII are not known. However, elevated risk has been associated with periods of peak FVIII treatment, surgery, family history of inhibitors, and FVIII genetic mutations including large deletions, nonsense mutations and intron 22 inversion [6, 55, 56].
Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.4: Recommendation for monitoring all patients for the development of FVIII inhibitors by appropriate clinical observations and laboratory tests and performing appropriate testing if the patient's plasma FVIII level fails to increase as expected or if bleeding is not controlled after efanesoctocog alfa administration. SmPC section 4.8: Information about the risk of inhibitor development in patients with hemophilia A treated with factor VIII, including with efanesoctocog alfa. PL section 2.0: Information how to detect early signs and symptoms of inhibitor development. Legal status: Prescription only medicine. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN). The PedNet Hemophilia Registry Data collection in PUPs. European Hemophilia Safety Surveillance System (EUHASS) participation and data collection. See section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Serious vascular thromboembolic events	
Evidence for linking the risk to the medicine	In the literature, thromboembolic events reported in hemophilia A patients treated with FVIII replacement products are rare. The risk of vascular thromboembolic events with the use rFVIII products, has not been established. Published reports of vascular thrombotic adverse events in patients with hemophilia A and recombinant FVIII replacement occur in the setting of pre-existing risk factors, e.g. cardiovascular risk factors and indwelling central venous catheters.

Important potential risk: Serious vascular thromboembolic events (cont'd)	
Risk factors and risk groups	Patients with pre-existing risk factors (e.g. cardiovascular risk factors, indwelling central venous catheters) for thromboembolism. Cardiovascular risk factors are more likely to occur with advancing age. Cardiovascular risk factors include hyperlipidemia, smoking, diabetes, hypertension, obesity for arterial thrombotic events. For venous thrombotic events, risk factors include trauma or fractures, surgery, immobilization, hormonal therapy, pregnancy, hypercoagulability and advancing age.
Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.4: Information about risk of cardiovascular events in patient with existing cardiovascular risk factors and risk of catheter-related complications, including catheter site thrombosis. PL section 2.0: Information about risk of catheter-related complications, including catheter site thrombosis. Legal status: Prescription only medicine. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN). The PedNet Hemophilia Registry Data collection in PUPs. European Hemophilia Safety Surveillance System (EUHASS) participation and data collection. See section II.C of this summary for an overview of the post-authorization development plan.
Important missing information: Safety in previously untreated patients	
Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.4: Recommendation for monitoring all patients for the development of FVIII inhibitors by appropriate clinical observations and laboratory tests and performing appropriate testing if the patient's plasma FVIII level fails to increase as expected or if bleeding is not controlled after efanesoctocog alfa administration. PL section 2.0: Information on how to detect early signs and symptoms of inhibitor development. Legal status: Prescription only medicine. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN). The PedNet Hemophilia Registry Data collection in PUPs. See section II.C of this summary for an overview of the post-authorization development plan .

Missing information: Long term use	
Risk minimization measures	**Routine risk minimization measures:** SmPC section 5.1: The long-term safety and efficacy of ALTUVOCT is also being evaluated in a long-term extension study. Legal status: Prescription only medicine. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term safety and efficacy of BIVV001 in previously treated patients with Hemophilia A (LTS16294) See section II.C of this summary for an overview of the post-authorization development plan.
Missing information: Safety in elderly patients ≥ 65 years of age	
Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.2: There is limited experience in patients ≥ 65 years. The dosing recommendations are the same as for patients < 65 years. Legal status: Prescription only medicine. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term safety and efficacy of BIVV001 in previously treated patients with Hemophilia A (LTS16294) See section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-authorization development plan

II: C. 1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of ALTUVOCT®.

II.C. 2 Other studies in post-authorization development plan

Long-term safety and efficacy of BIVV001 in previously treated patients with Hemophilia A (LTS16294 ongoing)

Purpose of the study: To determine the long-term safety and efficacy of BIVV001 administered as once-weekly prophylaxis treatment in previously treated patients with severe hemophilia A.

Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN).

Purpose of the study: To evaluate the safety profile of efanesoctocog alfa in previously untreated patients (PUPs).

Data collection from the European Hemophilia Safety Surveillance System (EUHASS) registry.

Purpose of the registry: To monitor the treatment safety of patients with inherited bleeding disorders, including hemophilia A patients.

Data collection from the PedNet Hemophilia Registry.

Purpose of the registry: To monitor the treatment safety of pediatric patients with inherited bleeding disorders, including hemophilia A patients.

Part VII: Annexes

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Annex 4 Specific adverse event follow-up forms

Specific adverse event follow-up forms for the Important identified or important potential risks of “Inhibitor Development to FVIII” and “Serious vascular thromboembolic events” are included below. These questionnaires provide guidance for requests for follow-up information which will be included in clinical studies and post-marketing safety surveillance to collect all relevant data in this regard.

Inhibitor development to FVIII

I. Patient details		
Patient's Initials: ☐ data not available	☐ Male ☐ Female ☐ data not available	Age at onset of event: ☐ data not available

II. Medical History	
A. Provide the severity of the patient's hemophilia:	☐ Mild (>5–40% FVIII activity) ☐ Moderate (1–5% FVIII activity) ☐ Severe (<1% factor FVIII activity)
B. Provide details of past exposure to bypass therapy (such as rFVIIa, aPCC, or blood transfusions).	
C. Provide the patient's race/ethnicity, allergies, and date of hemophilia diagnosis	
History of factor replacement therapy prior to initial efanesoctocog alfa ☐ No ☐ Yes (specify product names and dates of exposure)	
E. Does the patient have a history of inhibitor development prior to initial efanesoctocog alfa use? ☐ No ☐ Yes (please provide dates, titer (and reference range), associated FVIII product, associated signs/symptoms, treatment, and outcome) Does the patient have a history of ITI treatment: ☐ No ☐ Yes (please provide dates, titer (and reference range), associated FVIII product, associated signs/symptoms, treatment, and outcome)	
F. What was the age of the patient at first exposure of factor VIII prior to initial dose of efanesoctocog alfa?	
G. Provide family history of inhibitors (include relationship to patient).	

III. Description of the Reported Event(s)/Clinical Course
A. Provide the chief complaint that prompted testing for factor VIII inhibitors. If patient experienced bleeding event (please provide details including severity and location).
B. Was the patient hospitalized or required an ER visit? ☐ No ☐ Yes (please provide ER and hospitalization diagnosis, Date(s) of ER visit and hospitalization as applicable, Provide details or a copy of the discharge diagnosis and report if available.)

C. Provide outcome for the event and date of resolution if applicable.

☐ recovered
☐ not yet recovered
☐ recovered with sequelae (describe the sequelae)
☐ death (provide a copy of death certificate and autopsy results)
☐ unknown

D. Provide the factor replacement product and dosing regimen after the event resolution.

E. Is the reporter a hematologist

☐ Yes ☐ No (was the case discussed with a hematologist? ☐ No ☐ Yes (Please provide the name and phone number of the hematologist)

F. Provide a causality assessment between ALTUVOCT® and the development on inhibitors.

IV. Complementary Investigations

A. Attach or provide factor VIII gene mutation information details if available (large deletion (>200 bp), missense mutation, small deletion (≤86 bp), nonsense mutations, insertion (≤ 13 bp), inversion, splice site mutation, other).

B. Attach or provide all inhibitor titer test results, the assay used (Nijmegen, Bethesda assay), dates, units, reference ranges and name of testing laboratory.

C. Attach documentation or list results (such as discharge summary) of tests relevant to the event (such as type of inhibitor test (e.g., Nijmegen, Bethesda assay, units, reference range urinalysis, renal function tests, serological/immunological studies, imaging studies, FVIII activity, aPTT, and/or lupus anti-coagulant antibodies). Include the name of the testing laboratory, testing date(s), and, if applicable, units and reference ranges.

D. Attach or provide additional information to assist in the evaluation of this report.

V. Suspect Product and Dosing Information

Treatment regime:	☐ On demand ☐ Regular

Efanesoctocog alfa start date:

Estimated exposure days to factor IX replacement products prior efanesoctocog alfa (an exposure day is defined as any 24-hour period in which a patient received 1 or more doses of factor replacement product, with start of the exposure day defined as the time of the first injection)

Provide ED intervals: ☐ 0 ED ☐ 1-20 ED ☐ 21-49 ED ☐ 50-149 ED

OR

Estimated number of exposure days:

Dose (in IU/kg), Frequency:	
Please provide Lot# and Expiration date:	#1 Lot #_____ Exp. Date _____
The time elapsed between the last dose of efanesoctocog alfa and onset of the event:	
Were additional doses of efanesoctocog alfa, another factor product or bypassing agent given after the event onset?	☐ Yes ☐ No If yes, provide product name, dosing, frequency and date.
Was efanesoctocog alfa temporarily or permanently discontinued because of the event?	☐ Yes ☐ No If yes, specify the date and whether the event ☐ improved ☐ resolved ☐ abated after discontinuation
Was efanesoctocog alfa later resumed?	☐ Yes ☐ No If yes, specify the date, dosing regimen, and whether the event ☐ recurred ☐ worsened after restarting

VI. Additional information

Supplementary data has been attached	Yes ☐ No. of pages: No ☐

Reporter

Name of reporter: Email: Phone number:	Specialty:
Signature:	Date: dd/Mmm/yyyy

Serious vascular thromboembolic events

Sobi ref no:

I. Patient details		
Patient's Initials: ☐ data not available	☐ Male ☐ Female ☐ data not available	Age at onset of event: ☐ data not available

II. Medical History

A. Factor replacement therapy prior to initial efanesoctocog alfa

☐ No ☐ Yes (specify product names and dates of exposure)

B. Estimated exposure days to factor IX replacement products prior efanesoctocog alfa (an exposure day is defined as any 24-hour period in which a patient received 1 or more doses of factor replacement product, with start of the exposure day defined as the time of the first injection)

Provide ED intervals: ☐ 0 ED ☐ 1-20 ED ☐ 21-49 ED ☐ 50-149 ED

OR

Estimated number of exposure days:

C. Date of hemophilia diagnosis:

The patient history of allergies:

D. The patient's history of factor replacement therapy including plasma derived products prior to initial efanesoctocog alfa use including product names and dates of exposure.

E. The age of the patient at first exposure of factor VIII prior to initial dose of efanesoctocog alfa

F. The prior history of thrombosis

☐ Unknown ☐ Known (please specify event, date, treatment and outcome)

G. Provide any other relevant past medical history

RISK FACTORS

Risk factors

Please check if any of the following apply. Provide any additional relevant medical history

☐ Any recent surgical procedure

☐ Immobilization/paralysis

☐ Trauma/injury

☐ Pregnancy/post-partum

☐ Indwelling central venous catheter

☐ Use of relevant concomitant medications such as oral contraceptive/hormonal treatment

☐ Hypercoagulable disorder

☐ Prolonged travel

☐ Obesity

☐ Malignancy

☐ If the patient is current smoker

☐ Other _____

_____

III. Description of the Reported Event(s)/Clinical Course

A. Is the reporter a hematologist

☐ Yes ☐ No (was the case discussed with a hematologist? ☐ Yes ☐ No)

B. The time elapsed between the last dose efanesoctocog alfa and onset/ detection of thrombosis event

C. Diagnosis including signs/symptoms

D. Was the patient hospitalized or required an ER visit?

☐ No ☐ Yes (please provide ER and hospitalization diagnosis, Date(s) of ER visit and hospitalization as applicable, Provide details or a copy of the discharge diagnosis and report if available.)

E. Provide outcome for the thrombosis event and date of resolution if applicable.

☐ recovered
☐ not yet recovered
☐ recovered with sequelae (describe the sequelae)
☐ death (provide a copy of death certificate and autopsy results)
☐ unknown

F. Provide a causality assessment between ALTUVOCT® and the development on inhibitors.

IV. Complementary Investigations

All physical exam findings, chief complaint, clinical signs and symptoms at presentation (include onset dates) or state if no relevant signs or symptoms	_____ _____ _____
Dates and results from all imaging studies	☐ Compression ultrasound ☐ Magnetic resonance imaging (MRI) ☐ Venography ☐ Other (please explain): _____

Lab data

Date:	Lupus anticoagulant	Activated partial thromboplastin time (aPTT)
	NR*:	**NR*:**

** NR = Normal Range: Please insert normal range for each test*

V. SUSPECT PRODUCT AND DOSING INFORMATION	
A. Treatment regime:	☐ On demand ☐ Regular
B. Dose (in IU/kg), Frequency:	
C. Therapy Dates *(if unknown give duration or best estimate)*:	#1 Start: ___/___/____ Stop: ___/___/____ MMM / DD / YYYY MMM / DD / YYYY #2 Start: ___/___/____ Stop: ___/___/____ MMM / DD / YYYY MMM / DD / YYYY
D. Please provide Lot# and Expiration date:	#1 Lot #_____ Exp. Date _____ #2 Lot #_____ Exp. Date _____
E. What action was taken with suspect drug because of the event(s)?	#1 ☐ Drug withdrawn ☐ Dose not changed ☐ Dose interrupted ☐ Not applicable ☐ Unknown If drug was withdrawn or interrupted, please specify the date
F. If the treatment was resumed, did the event recur?	#1 ☐ Yes ☐ No ☐ Not Applicable ☐ Unknown If resumed, please specify the date and dosing regimen
G. Were additional dose(s) of factor replacement given after the event onset?	#1 ☐ No #2 ☐ Yes (product name, dose, frequency, and date)
VI. Additional information	
Supplementary data has been attached	Yes ☐ No. of pages: No ☐
Reporter	
Name of reporter:	Specialty:
Signature: Email: Phone number:	Date: dd/Mmm/yyyy

Annex 6 Details of proposed additional risk minimization activities (if applicable)

Not applicable.