Risk Management Plan

Esperoct®

Active substance(s)	turoctocog alfa pegol
RMP version number:	3.1
Data lock point for this RMP	05 Oct 2023
Date of final sign off:	See signature page
Rationale for submitting an updated RMP	This RMP is submitted in connection with the Type II variation application for indication extension of Esperoct® for children below 12 years with haemophilia A.
Summary of significant changes in this RMP	• Proposed indication and dosage in the EEA have been updated • Since the last RMP update, two clinical trials NN7088-4595 and 3908 have been completed and interim results have been obtained for the PASS NN7088-4029. Data pertaining to these trials has been updated in the RMP. Additionally, data from post-marketing sources (including exposure) and epidemiological sources has been updated as of the data lock point (DLP). Renaming of the important potential risk "Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs" to "Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment". • Inclusion of new strengths of 4,000 IU and 5,000 IU approved for treatment and prophylaxis of bleeding in patients with haemophilia A based on the approved line extension variation. • Inclusion of a detailed description of the risk of low factor VIII incremental recovery in previously untreated patients (PUPs) under the important potential risk of 'Anti-PEG antibodies'. • Risk minimisation measures are separately included for PUPs in relevant sections of the RMP. • Minor editorial changes are made across the RMP
Other RMP versions under evaluation	Not applicable
Details of the currently approved RMP	Version number: 2.1 Approved with procedure: EMEA/H/C/004883/II/0010 Date of approval (opinion date): 21 Jul 2022
QPPV	Karsten Lollike, Corporate Vice President and QPPV, Global Safety
QPPV signature	See signature page

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Abbreviations

AIDS	acquired immune deficiency syndrome
aPTT	activated partial thromboplastin time
ATC	anatomical therapeutic chemical
CD4 T cells	cluster of differentiation 4 T lymphocytes
CHO	Chinese hamster ovary
CI	confidence interval
COVID-19	coronavirus disease
CTR	clinical trial report
CVD	cardiovascular disease
DLP	data lock point
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FPFV	first patient first visit
FPLV	first patient last visit
FVIII	factor VIII
GVP	Good Pharmacovigilance Practices
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
i.v.	intravenous(-ly)
INN	international non-proprietary name
ITI	immune tolerance induction
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
NEC	not elsewhere classified
NSAE	non-serious adverse event
PASS	post-authorisation safety study
pdFVIII	plasma-derived factor VIII
PEG	polyethylene glycol
PhV	pharmacovigilance
PL	packageleaflet
PK	pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PTP	previously treated patient
PUP	previously untreated patient
PWH	people with haemophilia
PYE	patient-years of exposure
QPPV	Qualified Person responsible for Pharmacovigilance
rFVIII	recombinant human blood coagulation factor VIII
RMP	risk management plan

SmPC	Summary of Product Characteristics
SMR	standardised mortality ratio
SOC	system organ class
UKHCDO	UK Haemophilia Centre Doctor's Organisation
WFH	World Federation of Hemophilia

1 Product overview

Table 1-1 Product overview

Active substance(s) (INN or common name)	turoctocog alfa pegol (N8-GP)
Pharmacotherapeutic group(s) (ATC Code)	Antihaemorrhagics: blood coagulation factor VIII (B02BD02)
Marketing authorisation holder	Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark
Medicinal products to which this RMP refers	All presentations of turoctocog alfa pegol
Invented name(s) in the European Economic Area (EEA)	Esperoct®
Marketing authorisation procedure	Centralised procedure
Brief description of the product	***Chemical class:*** N8-GP is based on turoctocog alfa, which is a third-generation recombinant human factor VIII (rFVIII) product. N8-GP is a purified rFVIII product with a 40 kDa polyethylene-glycol (PEG) conjugated to the protein. The PEG is attached to the O-linked glycan in the truncated B-domain of rFVIII (turoctocog alfa).
	Summary of mode of action: The mechanism of action of N8-GP is based on the replacement of the deficient or absent FVIII in patients with haemophilia A. When N8-GP is activated by thrombin at the site of injury, the PEGylated truncated B-domain is cleaved off, generating activated FVIII (FVIIIa), which is similar in structure to native FVIIIa. Activated rFVIII acts as a cofactor for activated factor IX (FIX) on the surface of activated platelets and the complex catalyses the activation of factor X. By adding FVIII, the coagulation cascade can run uninterruptedly ensuring that the end product, fibrin, is generated and a haemostatic plug is formed. PEGylation increases the half-life of the protein.
	Important information about its composition: N8-GP is a recombinant FVIII molecule expressed in genetically engineered Chinese hamster ovary (CHO) cell line. There are no human or additional animal-derived materials in the production process.
Hyperlink to the Product Information:	Esperoct® SmPC, Module 1.3.1
Indication(s) in the EEA	**Current:** **EU:** Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).
	Proposed: Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Esperoct® can be used for all age groups.

Dosage in the EEA	**Current:** The dose, dosing interval and duration of the substitution therapy depend on the severity of factor VIII deficiency, on the location and extent of the bleeding, on the targeted factor VIII activity level and the patient's clinical condition. The number of units of factor VIII administered is expressed in international units (IU), which is related to the current WHO concentrate standard for factor VIII products. The activity of factor VIII in plasma is expressed either as percentage (relative to normal human plasma level) or in International Units per dL (relative to the current International Standard for factor VIII in plasma). **Routine prophylaxis with Esperoct®** Adults and adolescents (12 years and above): The recommended dose is 50 IU of Esperoct® per kg body weight every 4 days. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency. Children (below 12 years): The long-term safety of Esperoct® in children below 12 years has not been established. **On-demand treatment and treatment of bleeding episodes:** <u>On-demand treatment:</u> Calculation of the required dose of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL. Required dose is determined using the following formula: Required units (IU) = body weight (kg) × desired factor VIII rise (%) (IU/dL) × 0.5 (IU/kg per IU/dL). The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. <u>Treatment of bleeding episodes:</u> Guidance for the dosing of Esperoct® for the on-demand treatment and treatment of bleeding episodes is provided below. Maintain plasma factor VIII activity level at or above the described plasma levels (in IU per dL or % of normal). For treatment of bleeds, a maximum single dose of Esperoct® at 75 IU/kg and a maximum total dose of 200 IU/kg/24 hours may be administered for treatment of bleeds only. Mild haemorrhage (early haemarthrosis, muscle bleeding or oral bleeding): Required FVIII level: 20–40 IU. Injection should be repeated every 12–24 hours until bleeding is resolved. Moderate haemorrhage (more extensive haemarthrosis, muscle bleeding or haematoma): Required FVIII level: 30–60 IU. Injection should be repeated every 12–24 hours until bleeding is resolved. Severe (life-threatening haemorrhages): Required FVIII level: 60–100 IU. Injection should be repeated every 8–24 hours until the threat is resolved. Consider to continue therapy until the threat is resolved. **Perioperative management** The dose level and dosing intervals for surgery depend on the procedure and local practice. A maximum single dose of Esperoct® at 75 IU/kg and a maximum total dose of 200 IU/kg/24 hours may be administered.

	The frequency of doses and duration of therapy should always be individually adjusted based on individual clinical response. Minor surgery including tooth extraction: Required FVIII level: 30–60 IU (pre- and postoperative). Injection should be given within 1 hour before surgery. Single dose or repeat injection every 24 hours for at least 1 day until healing is achieved. Major surgery: Required FVIII level: 80–100 IU (pre- and post-operative). Injection should be given within 1 hour before surgery to achieve factor VIII activity within the target range. Injection should be repeated every 8–24 hours as necessary until adequate wound healing is achieved. It should be considered to continue therapy for another 7 days to maintain a factor VIII activity of 30–60% (IU/dL).
	Proposed: The dose, dosing interval and duration of the substitution therapy depend on the severity of factor VIII deficiency, on the location and extent of the bleeding, on the targeted factor VIII activity level and the patient's clinical condition. The number of units of factor VIII administered is expressed in international units (IU), which is related to the current WHO concentrate standard for factor VIII products. The activity of factor VIII in plasma is expressed either as percentage (relative to normal human plasma level) or in International Units per dL (relative to the current International Standard for factor VIII in plasma). **Routine prophylaxis with Esperoct®** The recommended dose for adults is 50 IU of Esperoct® per kg body weight every 4 days. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency. Paediatric population: The recommended dose in adolescents (12 years and above) is the same as for adults. The recommended dose for prophylaxis in children below 12 years is 65 IU per kg body weight (50-75 IU/kg) administered twice weekly. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency. **On-demand treatment and treatment of bleeding episodes:** <u>On-demand treatment:</u> Calculation of the required dose of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL. Required dose is determined using the following formula: Required units (IU) = body weight (kg) × desired factor VIII rise (%) (IU/dL) × 0.5 (IU/kg per IU/dL). The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. <u>Treatment of bleeding episodes:</u> Guidance for the dosing of Esperoct® for the on-demand treatment and treatment of bleeding episodes is provided below. Maintain plasma factor VIII activity level at or above the described plasma levels (in IU per dL or % of normal). For treatment of bleeds, a maximum single dose of Esperoct® at 75 IU/kg and a maximum total dose of 200 IU/kg/24 hours may be administered for treatment of bleeds only.

	Mild haemorrhage (early haemarthrosis, muscle bleeding or oral bleeding): Required FVIII level: 20–40 IU. Injection should be repeated every 12–24 hours until bleeding is resolved. Moderate haemorrhage (more extensive haemarthrosis, muscle bleeding or haematoma): Required FVIII level: 30–60 IU. Injection should be repeated every 12–24 hours until bleeding is resolved. Severe (life-threatening haemorrhages): Required FVIII level: 60–100 IU. Injection should be repeated every 8–24 hours until the threat is resolved. Consider to continue therapy until the threat is resolved. **Perioperative management** The dose level and dosing intervals for surgery depend on the procedure and local practice. A maximum single dose of Esperoct® at 75 IU/kg and a maximum total dose of 200 IU/kg/24 hours may be administered. The frequency of doses and duration of therapy should always be individually adjusted based on individual clinical response. Minor surgery including tooth extraction: Required FVIII level: 30–60 IU (pre- and postoperative). Injection should be given within 1 hour before surgery. Single dose or repeat injection every 24 hours for at least 1 day until healing is achieved. Major surgery: Required FVIII level: 80–100 IU (pre- and post-operative). Injection should be given within 1 hour before surgery to achieve factor VIII activity within the target range. Injection should be repeated every 8–24 hours as necessary until adequate wound healing is achieved. It should be considered to continue therapy for another 7 days to maintain a factor VIII activity of 30–60% (IU/dL).
Pharmaceutical form(s) and strengths	**Current:** Pharmaceutical form: Powder and solvent for solution for injection. Strengths: Each powder vial contains nominally 500 IU, 1,000 IU, 1,500 IU, 2,000 IU or 3,000 IU turoctocog alfa pegol. One mL of the solution contains approximately 125 IU, 250 IU, 375 IU, 500 IU or 750 IU of turoctocog alfa pegol after reconstitution.
	Proposed: Pharmaceutical form: Powder and solvent for solution for injection. Strengths: Each powder vial contains nominally 500 IU, 1,000 IU, 1,500 IU, 2,000 IU, 3,000 IU, 4,000 IU or 5,000 IU turoctocog alfa pegol.One mL of the solution contains approximately 125 IU, 250 IU, 375 IU, 500 IU, 750 IU, 1,000 IU or 1,250 IU of turoctocog alfa pegol, respectively after reconstitution.
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC = anatomical therapeutic chemical; EEA = European Economic Area; INN = international nonproprietary name; WHO = World Health Organization.

2 Safety specification

2.1 Module SI: Epidemiology of the indication(s) and target population

2.1.1 Haemophilia A

Congenital haemophilia A is a rare X-linked disorder caused by insufficiency or lack of production of biochemically defective coagulation factor VIII leading to an impaired ability to control bleeding through normal haemostatic processes of coagulation. Although congenital haemophilia A is a hereditary disorder, it also occurs by spontaneous mutations, which account for approximately 30% of haemophilia cases.[1]

The severity of bleeding in haemophilia A is generally correlated with the endogenous FVIII plasma activity level and the disorder is classified as 'severe' (<1% of normal activity), 'moderate' (1−5%) or 'mild' (>5% to <40%) according to these levels.[2]

The clinical manifestations of haemophilia A are bleeding episodes due to impaired haemostasis. The bleeds in patients with severe haemophilia A typically occur spontaneously or after mild trauma in joints, muscles and soft tissues. Bleeding episodes may occur in all parts of the body, including rare but life-threatening events such as bleeding in the central nervous system (CNS), throat, neck or retroperitoneum. Bleeds often occurring in the muscles and joints of the elbows, knees and ankles cause acute haemarthrosis. Recurrent bleeds may lead to synovitis, chronic arthropathy, muscular atrophy and deformities.

Development of neutralising antibodies to FVIII (FVIII inhibitors) remains to be the most serious and challenging treatment-related complication of haemophilia A, mainly occurring in previously untreated patients (PUPs) with severe haemophilia A. Inhibitors to FVIII are immunoglobulins, usually IgG, which partially or completely neutralise the clotting activity of FVIII. In patients who develop inhibitors to FVIII, the condition will manifest itself as an insufficient clinical response to FVIII replacement therapy. It is estimated that inhibitors develop in as many as 24-45% of patients with severe haemophilia A on rFVIII products.[3-7] Inhibitors in PUPs are typically observed within the first 50 exposure days[8] and considered unlikely after 100 exposure days of treatment.[9] In approximately one-third of the patients who develop inhibitors, the inhibitors disappear on continued treatment with the same product.[9]

Inhibitor titre is usually measured in Bethesda units (BU) using the modified Nijmegen Bethesda assay.[10] FVIII inhibitors can be divided into low-titre (0.6 to <5 BU) and high-titre (≥5 BU) inhibitors, where low-titre inhibitors are considered less serious and high-titre inhibitors have serious negative effect on treatment with FVIII replacement products.[9] Moreover, low-titre FVIII inhibitors are often of a transient nature, whereas high-titre FVIII inhibitors tend to be persistent.[11] The presence of inhibitors in patients with haemophilia A significantly worsens the prognosis, especially in high-titre patients. Patients with inhibitors are more difficult to treat since traditional factor replacement therapy is partially or completely ineffective.[12]

The development of FVIII inhibitors in haemophilia A patients may be influenced by several risk factors including but not limited to genetic mutations, intensity of treatment, ethnicity, age at dosing and the inflammatory state of the patient.[13, 14] The risk of inhibitor occurrence is higher in patients

with severe haemophilia A (FVIII activity levels <1%) than in patients with moderate (1–5%) and mild disorder (>5% to <40%).[9] Certain genetic mutations in the FVIII gene are associated with an increased incidence of development of inhibitors in haemophilia A.[15] A majority of severe Haemophilia A patients in a German study have the intron-22 inversion with ~20% risk of developing FVIII inhibitors. Other mutations provide a lower or higher risk of developing inhibitors. These data are supported by a larger meta-analysis.[16, 17]

2.1.1.1 Incidence and prevalence

The incidence and prevalence of haemophilia A is as follows:

- **Birth prevalence**: Haemophilia A, an inherited bleeding disorder, is an orphan disease with a birth prevalence of approximately 1 in every 5,000 live male births.[2]
- **Prevalence**: According to the annual global survey by the World Federation of Hemophilia, a total of 185,318 patients have been diagnosed with haemophilia A globally.[18] The survey collected data from 118 countries. The reported prevalence of haemophilia A varies considerably with country and across economic classes of a country. Prevalence of haemophilia A in different world regions is shown in Table 2-1. Iorio *et al.* stated that these numbers might be an underestimate due to under-reporting and that the true prevalence of haemophilia might be closer to 17.1 per 100,000 males.[19]

Table 2-1 Prevalence of reported haemophilia A in males in different world regions

World regions	Population	Cases	Prevalence per 100,000
Europe	691,165,958	46,464	6.72
Africa	937,283,239	5,978	0.63
South-East Asia	1,958,399,699	29,135	1.48
Americas	937,146,982	45,872	4.89
Eastern Mediterranean	718,893,001	23,472	3.26
Western Pacific	1,895,782,653	34,397	1.81
Worldwide	**7,138,671,532**	**185,318**	**2.59**

Note: Prevalence per region is calculated based on numbers from the WFH report on the annual global survey 2021.[18] Regions are according to the WFH report.

Abbreviations: WFH = World Federation of Hemophilia.

2.1.1.2 Demographics of the target population – Age, sex, ethnicity

The distribution of haemophilia A population by age is presented in Table 2-2.

Table 2-2 Distribution of haemophilia A population by age

Age group	Absolute number	Distribution (%)
0–4	8,229	5.6
5–13	24,740	16.9
14–18	15,450	10.5
19–44	61,070	41.7
>45	27,294	18.6
Unknown	9,395	6.4
Total	**146,178**	**100**

Note: Numbers are from the WFH report on the annual global survey 2021.[18] Distribution by age group includes data from 103 countries where this information was reported.

Abbreviations: WFH = World Federation of Hemophilia.

Haemophilia A is due to a recessive X-linked gene defect that almost exclusively affects males. According to the global data from the WFH,[18] ~90% of patients with haemophilia A are males and ~4% are females; gender is unknown in ~5% of the patients.

The distribution of haemophilia A population by severity is presented in Table 2-3.[18] Although the definition of severity based on FVIII activity levels may vary in some countries, haemophilia is generally classified as severe, moderate and mild (see Section 2.1.1 for details). The distribution by severity is, however, difficult to estimate since this information is not always available and many of the mild cases remain undiagnosed.

Table 2-3 Distribution of haemophilia A population by severity in males (%)

Severity	High-income countries	Upper-middle income countries	Lower middle and low-income countries
Mild	39.5	23.5	12.4
Moderate	14.3	23	24.7
Severe	45.4	45.6	44.5
Unknown	0.7	7.8	18.3

Note: Numbers are from the WFH report on the annual global survey 2021.[18] Distribution by severity includes data from patients where severity data were available.

Abbreviations: WFH = World Federation of Hemophilia.

2.1.1.3 Risk factors for the disease

Haemophilia A is a recessive X-linked congenital bleeding disorder, caused by mutations in the coagulation FVIII gene, located in the distal part on the long arm of the X-chromosome. Haemophilia A is caused by any of a variety of genetic anomalies distributed throughout the gene, with almost every family manifesting its own unique pattern. The anomalies can be arbitrarily classified as deletions or nonsense mutations (i.e., genes incapable of producing FVIII) or missense mutations, causing amino acid changes in the FVIII molecule, resulting in a functionally defective protein. The gene defects are transferred from a heterozygotic mother (carrier) or are ascribable to new, spontaneous mutations. Approximately 30%[1] of all patients with haemophilia A have no known family history of the disorder, and these are called sporadic or isolated cases.

2.1.1.4 The main existing treatment options

The primary goals of haemophilia therapy are the prevention of bleeds, rapid and definitive treatment of bleeds, and provision of adequate haemostasis during surgery and other major challenges to haemostasis.

Treatment of patients with haemophilia A with inhibitors includes bypassing agents, and for low-titre inhibitors, FVIII replacement.[13] In addition, treatment options using monoclonal antibodies that mimic factor VIII by bridging activated factor IX and factor X were made available to patients with haemophilia A.

The standard treatment for patients with haemophilia A in the US, Europe and Japan is replacement therapy including intravenous administration of plasma derived or recombinant FVIII (rFVIII) products.

Replacement therapy with currently commercially available FVIII products can be provided as follows:

- A prophylactic regimen to prevent bleeds (1−3 injections per week)
- An on-demand regimen with treatment of bleeds when they occur (1−3 injections per bleed dependent on the severity of the bleed)
- Procedural therapy to reduce risk of bleeding related to invasive procedures or specific situations with high risk of haemorrhage.

Over the past decade, development of FVIII replacement therapies with prolonged half-life (extended half-life [EHL]) enabled effective and safe treatment with lesser dosing frequency, thereby aiming to reduce the burden of treatment and improving adherence. [20, 21]

Prophylactic therapy instituted early in life (prior to the onset of frequent bleeds or joint damage) is recommended as optimal therapy for patients with severe haemophilia A (FVIII activity <1%) by the Medical and Scientific Advisory Council[22] of the US National Hemophilia Foundation and by national guidelines in other countries.

2.1.1.5 Natural history of the indicated condition including mortality and morbidity

The clinical spectrum of severe haemophilia has evolved throughout history from being a catastrophic and highly fatal condition in the early 20th century to a chronic and manageable disorder in recent decades.[23]

During the past three decades, the life expectancy for individuals with haemophilia A has markedly increased. People with haemophilia (PWH) with factor inhibitors previously had a reduced life expectancy; however, an analysis from the 1990s showed that the presence of inhibitors did not increase mortality rates in individuals with severe haemophilia with or without HIV.[24]

A systematic review and meta-analysis published in 2021 showed that the all-cause standardised mortality ratio (SMR) for PWH compared to the general population was 1.93. The results of the study illustrated a clear reduction of SMR over time. The authors reported that the most common causes of death in the post-2000 era in PWH were due to haemorrhage (32%), liver disease (14%),

human immunodeficiency virus (HIV; 14%), cancer (13%) and cardiovascular disease (CVD; 13 %).[25]

2.1.1.6 Important co-morbidities found in the target population

Improvement of treatment has increased the life expectancy of PWH in countries with a high income. With this increased longevity and improved quality of life due to advances in medical care, comes a generation of middle-aged and elderly PWH who are experiencing age-related health conditions. Co-morbidities in PWH can be divided into haemophilia related (haemophilic arthropathy, osteoporosis and viral infections) or age related (cardiovascular diseases, renal disease, cancer and psychiatric issues).[26, 27]

Co-morbidities considered important in the haemophilia A population are summarised in Table 2-4.

Table 2-4 Important co-morbidities in the target population

Important co-morbidities	Supporting details
Viral infections and potential complications	Blood-borne viral infections like HCV, HIV and HBV were considered the most important co-morbidities prior to viral inactivation procedures in the 1980s. Since HIV infection has been so effectively controlled by highly active antiretroviral treatment (HAART), there has been a heightened awareness of the potentially life-threatening effects of chronic HCV infection in co-infected patients, in particular the progression to cirrhosis and end-stage liver failure and the development of hepatocellular carcinoma (HCC). In the general population of haemophilia patients, 5.6 % (13,227 of 233,577 PWH with data on HCV) were infected with HCV and 1.4 % (3,285 of 233,577 PWH with data on HIV) were infected with HIV according to the annual global survey by the WFH.[18]
CVD and CVD risk factors	The existing literature presents conflicting evidence regarding the possibility of a protective effect of haemophilia against CVD.[28] PWH are susceptible to the same cardiovascular risk factors as individuals without haemophilia, and even more so to certain traditional risk factors such as hypertension and obesity related to limited mobility from arthropathy. A recent 5-year cross-sectional study of PWH older than age 35 years in the US found that PWH had twice the lifetime prevalence of coronary artery disease (CAD), stroke and MI compared to non-Hispanic white males overall. Nearly 40% of PWH in this study had 2 or more traditional risk factors for CVD.[29] Furthermore, a registry study from Sweden found a significant increased risk for hypertension in PWH compared to controls (hazard rate: 2.1).[30]
Renal disease	Kulkarni *et al.*[31] evaluated the incidence of both acute and chronic renal failure in a population of over 3,000 males with haemophilia followed up for a 6-year period. During the surveillance period, 2.9% of these patients presented alterations in renal function requiring hospitalisation. Results from the study indicated that renal diseases in patients with haemophilia are more common than previously thought. Risk factors for the development of renal disease in PWH are hypertension, diabetes, older age, HIV (up to 30%)[32] or hepatitis C infection, drug nephrotoxicity (antivirals, antibiotics, etc.), nephrolithiasis and kidney bleeding.
Cancer	HIV-associated non-Hodgkin's lymphomas and HCV-associated hepatocellular carcinomas (HCC) are important causes of death among the virus-infected ageing haemophilia population.[27, 33] The risk of HCC is increased in chronic HCV infection and this is reflected in the fact that HCC is now a leading cause of death in PWH. Furthermore, the risk of HCC is increased in older age.[34] Other than lymphoma in HIV and hepatocellular carcinoma in HCV-infected individuals, cancer risk is not increased in haemophilia. Diagnosis and treatment of cancer, however, is more complicated due to the bleeding risk associated with the diagnostic biopsy and the thrombocytopenia that may be seen with chemotherapy, especially in cases of acute leukaemia where thrombocytopenia can be prolonged.[27]
Musculoskeletal diseases	Many adults with severe haemophilia advancing into older age were not treated with prophylaxis as children and therefore have established joint disease and the associated burden of joint deformity, muscle weakness and impaired proprioception. Such conditions may cause difficulty with mobility, pain, increased risk of falls and social isolation. In this subgroup of patients, the effects of advancing age may be significant as proprioceptive loss may worsen and the risk of falls increases substantially. Intervention by targeted physiotherapy and strength training may be effective at maintaining mobility and reducing the risk of falls.

Abbreviations: CAD = coronary artery disease, CVD = cardiovascular disease; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MI = myocardial infarction; PWH = people with haemophilia.

2.2 Module SII: Nonclinical part of the safety specification

2.2.1 Important nonclinical safety findings and their relevance to human use

Table 2-5 Important nonclinical safety findings and their relevance to human use

Key safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
Repeat-dose toxicity: Intravenous administration of N8-GP was well tolerated after single doses up to 25,000 IU/kg in rats and after repeat dosing up to 2,500 IU/kg every 2nd day for 2 weeks in rats and up 1,200 IU/kg every 4th day for 26 weeks and 52 weeks in Rowett nude rats. In cynomolgus monkeys, N8-GP was administered intravenously up to 2,500 IU/kg every 3rd day for 2 weeks. For repeat-dose toxicity studies, the highest dose levels tested were identified as no observed adverse effect levels (NOAELs) based on non-immunogenic effects. PEG could not be detected by a PEG-specific immune histochemical (IHC) staining of brain tissue (including choroid plexus) after 52 weeks repeated dosing of N8-GP up to 1,200 IU/kg/4th day.	In general, nonclinical data reveal no special concern for humans.
Distribution, metabolism and excretion of PEG: Nonclinical studies on excretion and distribution (with N8-GP radiolabelled in the PEG moiety) show that PEG is widely distributed into tissues and gradually eliminated from tissues over time until excreted in urine and faeces. The data confirm that the PEG moiety follows basic pharmacokinetic principles and the terminal elimination half-life of PEG was estimated in all tissues and ranged from 14 days (plasma) to 89 days (choroid plexus). Based on the data, steady state (3.3 × t½) was reached in all organs after 42 weeks in the 52-week repeat-dose toxicity study with no adverse findings.	Nonclinical studies showed that PEG is widely distributed, eliminated from organs/tissues and excreted in urine and faeces. PEG of N8-GP will thus not continue to accumulate in the tissues but reach a steady state. Applying allometric scaling, the nonclinical data predicted time to reach steady state in human tissues to be 1–3 years.[a]
General safety pharmacology	
Safety pharmacology endpoints (blood pressure, electrocardiography [ECG], respiratory rate, temperature, neurological/central nervous system [CNS] endpoints and urinalysis) were incorporated in the 2-week repeated dose toxicity study. No effects on any of the safety pharmacology parameters were observed up to the highest dose of 2,500 IU/kg, which represents the NOAEL.	In general, nonclinical data reveal no special concern for humans.
Immunogenicity: Consistent with the species foreign nature of the human FVIII protein of N8-GP in rats and monkeys, anti-drug antibodies affecting exposure were seen both in Wistar rats and cynomolgus monkeys after 25 and 11–15 days, respectively. In cynomolgus monkeys the anti-drug antibodies cross-reacted to endogenous FVIII and resulted in acquired haemophilia. Thus, chronic toxicity in standard toxicity species was not considered meaningful, and an immune-deficient model (the Rowett nude rat) was introduced to circumvent the immune system response, enabling chronic toxicity.	The predictability of animal models for human immunogenicity is generally considered to be low. Human immunogenicity has been addressed in the clinical development programme (see Section 2.7.3.1).
Other toxicity-related information or data	
Local tolerance: Local tolerance was assessed as part of the repeat dose toxicity study and in a dedicated rabbit local tolerance study. The administration of N8-GP resulted in mild or no local reactions.	In general, nonclinical data reveal no special concern for humans.

[a]In the N8-GP clinical development programme, up to the data cut-off date (05 Oct 2023, 232 patients have been exposed for more than 3 years.

Abbreviations: CNS = central nervous system; ECG = electrocardiography; FVIII = human blood coagulation factor VIII; N8-GP = turoctocog alfa pegol; NOAEL = no observed adverse effect level; PEG = polyethylene glycol.

2.2.2 Conclusions on nonclinical data

No safety concerns of relevance to humans have been identified from the nonclinical studies.

2.3 Module SIII: Clinical trial exposure

The clinical trial programme for N8-GP was initiated in 2010 to investigate the target indications in paediatric, adolescent and adult male patients with severe haemophilia A with no history of inhibitors. The clinical development programme consists of 8 completed trials (one first human dose trial [NN7088-3776], one phase 1 trial [NN7088 4033] and six phase 3 trials [phase 3a trials: NN7088-3859, -3860, -3885 and 3908; phase 3b trials: NN7088-4410 and -4595]). Of these, 7 trials were conducted in previously treated patients (PTPs) with severe haemophilia A (NN 7088-3776, -3859, -3860, -3885, -4033, -4410 and 4595). The surgery trial (NN7088-3860) allowed patients from trial NN7088-3859 to undergo major surgery. Safety and efficacy of N8-GP in prophylaxis and treatment of bleeding episodes in previously untreated paediatric patients with severe haemophilia A was investigated in the trial NN7088-3908.

Pooling of data

No obvious differences in the safety profile of N8-GP have been observed between age groups or dose levels in the clinical trials. Therefore, safety data from all completed trials in PTPs have been pooled, except for safety information during surgery (trial NN7088-3860). Patients undergoing major surgery will be in a medical condition that differs from patients on prophylaxis and on-demand treatment, and as expected, a different adverse event pattern is seen during surgery. Therefore, exposure and safety during surgery is presented separately and not included in the pooled analysis.

The aim of the trial NN7088-3908 was to provide information on safety and efficacy of N8-GP in paediatric PUPs below 6 years of age with severe haemophilia A (FVIII activity level of <1%). The trial evaluates the immunogenicity of N8-GP and documents the safety and efficacy of N8-GP in long-term prophylaxis and treatment of bleeding episodes in population (paediatric PUPs) that may react immunologically differently from the PTPs. Therefore, exposure and safety in PUPs are presented separately and not included in the pooled analysis.

A total of 306 unique PTPs have been exposed to N8-GP in the clinical trials NN7088-3776, NN7088-3859, NN7088-4033, NN7088-3885, NN7088-4410 and NN7088-4595 giving a combined total of 129,508 exposure days. As some of these PTPs participated in more than one trial/trial phase, the sum of patients in the individual trials is higher than the total number of unique patients.

Additionally, 81 PUPs were exposed to N8-GP (in the trial NN7088-3908) for a total of 18,625 exposure days.

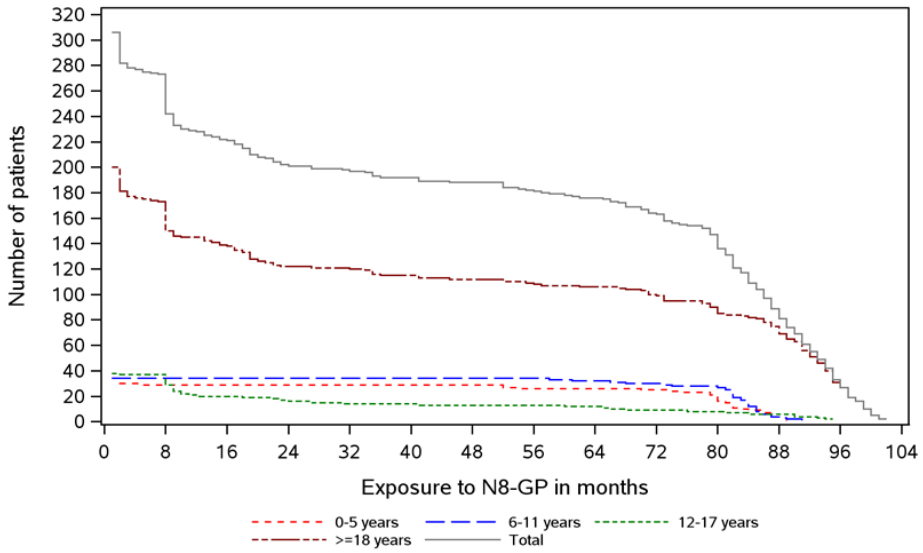
Exposure to N8-GP in the trials NN7088-3776, NN7088-3859, NN7088-4033, NN7088-3885, NN7088-4410 and NN7088-4595 is presented by duration and type of treatment, age, race, ethnicity and dosage of treatment in Table 2-6, Table 2-7, Table 2-8, Table 2-9, Table 2-10, Table 2-11 and Figure 2-1.

Table 2-6 Exposure to N8-GP by duration intervals and treatment type

Duration interval	Phase 1 single dose N	Prophylaxis Multiple Dose N	On-demand N	Total N
0 - <3months	26	12	-	28
3 - <6months	-	4	1	4
6 - <12months	-	10	-	10
12 - <18months	-	14	1	13
18 - <24months	-	11	3	14
24 - <30months	-	3	2	2
30 - <36months	-	7	-	7
36 - <42months	-	2	1	3
42 - <48months	-	1	-	1
48 - <54months	-	5	-	5
54 - <60months	-	4	1	5
60 - <66months	-	5	-	5
66 - <72months	-	10	-	10
72 - <78months	-	13	3	11
78 - <84months	-	43	-	43
84 - <90months	-	41	-	40
90 - <96months	-	39	-	42
96 - <102months	-	24	-	25
102 - <108months	-	-	-	2

Trials included are 3776, 3859, 4033, 3885, 4410, 4595.
Duration intervals are based on patient-years of exposure. Patients might be included in multiple treatment types and therefore the number of patients in each row might not necessarily add up to the total.
As many patients are included in multiple treatment types, the total for a row is not a sum of the individual treatment types for a given row.
The total for each individual is the accumulated sum of the different treatment types, so the patient may contribute in another row under total. Therefore, the total for a row reflects overall number of patients with matching cumulated exposure.

Figure 2-1 Exposure to N8-GP by monthly intervals and age group - 3776, 3859, 4033, 3885, 4410, 4595 clinical trials - safety analysis set



Abbreviations: N8-GP = turoctocog alfa pegol.

Table 2-7 Cumulative exposure to N8-GP by treatment type

Trial Treatment Type	Number of patients	Patient years of exposure	Exposure days
All Trials			
Phase 1 single dose	26	1.77	NA
Prophylaxis multiple dose	284	1374.30	127909
On-demand	12	37.19	1599
Total	306	1413.26	129508

Trials included 3776, 3859, 4033, 3885, 4410, 4595.
An exposure day is a day when the patient received at least one dose of N8-GP.
Exposure days not applicable for PK single dose trial NN7088-3776.
Patients in trial 4033 were recruited from 3859 and returned to 3859 after completion of the trial.
Prophylaxis treatment was allowed in between visits in 4033. Therefore exposure for 4033 is summarised under prophylaxis.
Patients might be included in multiple treatment types and therefore the number of patients in the rows might not necessarily add up to the Totals.

Even though the trial NN7088-4033 was a phase 1 trial, patients in trial NN7088-4033 were recruited from the phase 3 trial NN7088-3859 and returned to trial NN7088-3859 after completion of the trial. Prophylaxis treatment was allowed in between visits in trial NN7088-4033. Therefore, exposure from the trial NN7088-4033 is summarised under prophylaxis.

Table 2-8 Cumulative exposure to N8-GP by age group

Trial Age group	Number of patients	Patient years of exposure	Exposure days
All Trial			
0-5 years	34	188.62	19759
6-11 years	34	226.13	23939
12-17 years	38	112.05	9543
>=18 years	200	886.46	76267
Total	306	1413.26	129508

Trials included 3776, 3859, 4033, 3885, 4410, 4595.
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

Table 2-9 Cumulative exposure to N8-GP by race

Trial Race	Number of patients	Patient years of exposure	Exposure days
All Trial			
Asian	79	203.37	19170
Black or African American	15	47.95	3954
White	204	1122.84	102602
Other	5	12.94	1264
NA	4	26.16	2518
Total	306	1413.26	129508

Trials included 3776, 3859, 4033, 3885, 4410, 4595.
An exposure day is a day when the patient received at least one dose of N8-GP.
Exposure days not applicable for PK single dose trial NN7088-3776.
Other: Algerian, Caucasian/ Black Carribean, parent stated other (Latin decent), Puerto Rican (multi-racial), unknown

Table 2-10 Cumulative exposure to N8-GP by ethnicity

Trial Ethnicity	Number of patients	Patient years of exposure	Exposure days
All Trial			
Hispanic or Latino	16	81.04	7677
Not Hispanic or Latino	289	1319.87	120777
NA	2	12.36	1054
Total	306	1413.26	129508

Trials included 3776, 3859, 4033, 3885, 4410, 4595.
An exposure day is a day when the patient received at least one dose of N8-GP.
Exposure days not applicable for PK single dose trial NN7088-3776.

Of the 306 patients exposed to N8-GP in PTP trials, approximately 65% were adults, 12% were adolescents and 22% were children below 12 years of age. Overall, 3 elderly patients were exposed in the trial NN7088-3859. Majority of the exposed patients were White (~67%) followed by Asians (~26%).

Table 2-11 Cumulative exposure to N8-GP by treatment

Trial Treatment	Number of patients	Patient years of exposure	Exposure days
All Trials			
N8-GP 25 IU/kg single dose	7	0.50	NA
N8-GP 50 IU/kg single dose	25	1.02	47
N8-GP 75 IU/kg single dose	12	0.72	6
N8-GP 50 IU/kg prophylaxis	214	816.06	78724
N8-GP 75 IU/kg prophylaxis	63	181.56	9832
N8-GP 50-75 IU/kg prophylaxis	68	305.72	32138
N8-GP 60 IU/kg prophylaxis	29	49.52	5191
N8-GP 20-75 IU/kg on-demand	12	37.19	1599
N8-GP	42	20.97	1971
Total	306	1413.26	129508

Trials included 3776, 3859, 4033, 3885, 4410, 4595.
An exposure day is a day when the patient received at least one dose of N8-GP.
Exposure days not applicable for PK single dose trial NN7088-3776.
Patients might be included in multiple trials or treated with multiple dose regimens within a trial and therefore the Total row might not necessarily add up to the sum of the individual rows.

Exposure to N8-GP during surgery

The surgery trial (NN7088-3860) allowed patients from trial NN7088-3859 to undergo major surgery. In this trial, a total of 36 patients (all of whom were already participating in trial NN7088-3859) were screened and exposed to N8-GP for 1,065 exposure days (corresponding to a total of 6.9 PYE) including exposure prior to surgery, day of surgery and in the post-operative period. A total of 36 patients were exposed to N8-GP with a mean number of 20.1 exposure days and a mean exposure time in the trial of 47.6 days. The mean number of doses during the trial (including all doses in the pre-operative period) was 21.1 doses per planned surgery (range: 3−56 doses).

The trial population consisted of males with haemophilia A and with a mean age of 40.6 years (range: 15−69 years). One patient was an adolescent (15 years of age), while the remaining patients were adults (≥18 years of age).

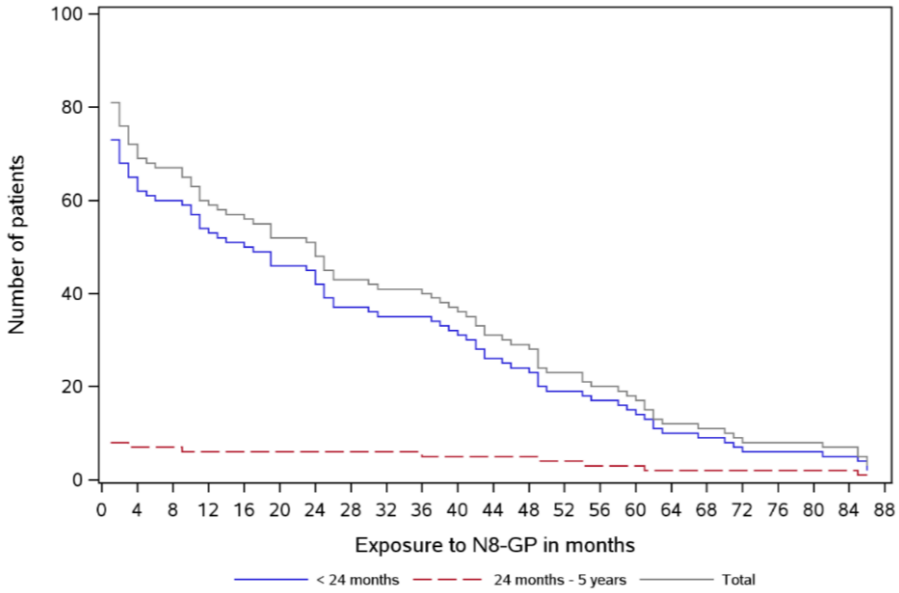
The majority of the patients were White (30 patients; 83.3%) while 5 patients (13.9%) were Asian and 1 patient (2.8%) was categorised as Black or African American.

A total of 49 surgeries were performed on 35 patients. A total of 46 surgeries were reported as elective and the remaining 3 were reported as emergency surgeries. The vast majority of the surgeries were orthopaedic surgeries (44 surgeries).

Exposure to N8-GP in previously untreated patients (PUPs)

The trial population consisted of male paediatric (<6 years at screening) previously untreated patients (PUPs) with severe haemophilia A (baseline FVIII activity <1%). In this trial, a total of 81 patients were exposed to N8-GP for 18,625 exposure days (corresponding to a total of 233.38 PYE). A majority of the patients (n = 73) were <24 months old at baseline. Forty-nine (49) patients (~60%) were White, 24 patients (~30%) were Asian, 2 patients (~2.5%) were Black or African American and 6 patients (~7.5%) were of other race. The majority of patient (n = 74) enrolled in the study were not of Hispanic or Latino ethnicity.

Figure 2-2 Exposure to N8-GP by monthly intervals and age group – Trial 3908 – Safety analysis set



Abbreviations: N8-GP = turoctocog alfa pegol.

2.4 Module SIV: Populations not studied in clinical trials

2.4.1 Exclusion criteria in pivotal clinical trials within the development programme

Table 2-12 Discussion of the important exclusion criteria in the pivotal clinical studies across the N8-GP development programme

Criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Known or suspected hypersensitivity to trial product including allergy to hamster protein or related products	Allergic reactions may be potentially severe, life threatening or fatal	No This population is not considered missing information as the product is not anticipated to be used in patients with known or suspected hypersensitivity. However, considering the potential impact to the health of target population, known or suspected hypersensitivity to the active substance, excipients or hamster proteins is considered as a contraindication.
Platelet count <50,000 platelets/µL	Patients with low platelet counts may have an increased bleeding tendency not related to insufficiency or lack of FVIII. Low platelet count may therefore be a confounding factor.	No This population is not excluded due to safety reason but to avoid interference with assessments as the condition will add to bleeding tendency. Platelets are involved in the primary haemostasis forming the platelet plug that is stabilised by the complex interactions of coagulation factors, amongst those FVIII, resulting in the formation of a stable fibrin clot. Patients with low platelet count have an impaired amplification of the haemostatic response but are not expected to respond differently to N8-GP.[35]

Criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Congenital or acquired coagulation disorders other than haemophilia A	N8-GP is investigated for the treatment of patients with haemophilia A only. Patients with other coagulation disorders were excluded in order to avoid confounding by concomitant illness.	No As these patients were not excluded due to safety reasons, there is no rationale for it to be missing information. The safety profile of N8-GP is not expected to be different in patients with other coagulation disorders than haemophilia A. Patients with haemophilia A are not expected to be in higher risk of having other rare coagulation disorders than the background population.
History of FVIII inhibitors and FVIII inhibitors ≥0.6 BU at screening	FVIII inhibitors might result in lack of efficacy in patients with haemophilia A treated with N8-GP. Patients with known history of FVIII inhibitors were excluded as the intention of the trials was to investigate the immunogenicity of N8-GP.	No This population is not excluded due to safety reasons but to avoid interference with an endpoint in the clinical trial programme. Treatment of patients with FVIII inhibitors is a well-known situation and described in the literature.[3-7, 36]
Patients with HIV with high viral load and low CD4 T cell count	In accordance with the regulatory guideline,[9] patients enrolled in the clinical development programme should be HIV negative or if positive, should have a CD4 T cell count >200/µL and/or a viral load <400,000 copies/mL. High viral load is a sign of clinically relevant immunodeficiency, which might prevent the patients from developing inhibitors and thus the primary objective could not be investigated.	No High viral loads of HIV in haemophilia A patients are not expected to affect their medical need for replacement therapy with FVIII. The safety profile of N8-GP was not identified to be different in HIV positive versus negative patients who participated in the clinical trial programme.
Patients with a history of thromboembolic events	Patients with a history of thromboembolic events are expected to have an increased risk of recurrent thromboembolic events. To avoid confounding of the trial endpoints, these patients have been excluded.	No The safety profile of N8-GP is not expected to be different in patients with a history of thromboembolic events. This population is susceptible to the same cardiovascular risk factors as individuals without haemophilia.

Abbreviations: CD4 T cells = cluster of differentiation 4 T lymphocytes; FVIII = factor VIII; HIV = human immunodeficiency virus.

2.4.2 Limitations of ADR detection common to clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency or those caused by prolonged or cumulative exposure.

2.4.3 Limitations with respect to populations typically under-represented in clinical trial development programmes

Populations that were excluded or under-represented in the clinical development programme for N8-GP are presented in Table 2-13. Key exclusion criteria in the clinical development programme for N8-GP are presented in Table 2-12.

Table 2-13 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme. Haemophilia is an X-linked disorder; females are carriers and are only rarely symptomatic.[37] No reproduction studies have been conducted with N8-GP. In addition, N8-GP as well as the attached PEG molecule is a large molecule unlikely to cross the placenta.[38] The safety profile of N8-GP is not expected to be different in female patients compared to male patients. Therefore, based on the therapeutic need, the use of N8-GP may be considered.
Breastfeeding women	
Elderly patients	There is very limited clinical experience with N8-GP in elderly patients (≥65 years). Overall, 3 elderly patients were exposed to N8-GP in clinical development programme (Table 2-8). See Section 2.4.3.1 for details.
Patients with renal impairment	Not included in the clinical development programme. See Section 2.4.3.2 for details.
Patients with hepatic impairment	Not included in the clinical development programme. See Section 2.4.3.3 for details.
Patients with history of thromboembolic events	Not included in the clinical development programme. See Table 2-12 for rationale and conclusion.
Immunocompromised patients	Patients with HIV with high viral load and low CD4 T cell count are not included in the clinical development programme. See Table 2-12 for rationale and conclusion.
Patients with a disease severity different from inclusion criteria in clinical trials	In accordance with regulatory guideline, only patients with severe haemophilia A with FVIII activity <1% were included in the clinical trials.[9] Replacement therapy with FVIII follows the same basic principles regardless of severity of haemophilia A.
Population with relevant different ethnic origin	N8-GP has primarily been investigated in White and Asian patients (Table 2-9). No difference in the therapeutic response to N8-GP is expected based on racial or ethnic origin.
Subpopulations carrying relevant genetic polymorphisms	Genetic polymorphism of hepatic cytochromes is not expected to have any influence on the metabolism of FVIII. When N8-GP is activated by thrombin, the B-domain containing the PEG moiety and the a3-region are cleaved off, thus generating activated rFVIII (rFVIIIa) which is similar in structure to native FVIIIa.

Type of special population	Exposure
Patients on FVIII Immune tolerance induction (ITI) therapy	ITI therapy is the first-choice approach in patients with high-responding FVIII inhibitors, and the only proven strategy for eradicating FVIII inhibitors. Based on clinical evidence and international consensus recommendations, most patients are tolerised with the same product that was being used at the time of inhibitor development. No previously treated patients have received ITI therapy with N8-GP in the clinical development programme

Abbreviations: CD4 T cells = cluster of differentiation 4 T lymphocytes; FVIII = factor VIII; HIV = human immunodeficiency virus; PEG = polyethylene glycol; rFVIII = recombinant human blood coagulation factor VIII.

2.4.3.1 Elderly

There is limited clinical experience with N8-GP in elderly patients (≥65 years) with haemophilia A as the number of these patients is small. Overall, 3 elderly patients were exposed in the trial NN7088-3859, being 65–66 years of age at inclusion into the trial. No safety concerns were identified for these patients during their trial participation. The population is not considered as missing information as the safety profile of N8-GP is not expected to be different in elderly patients compared to patients of other age groups. Further information regarding safety of N8-GP in elderly patients will be collected through routine pharmacovigilance activities.

2.4.3.2 Patients with renal impairment

Patients with creatinine level ≥1.5 times above the upper limit of normal reference ranges are excluded from clinical development programme in order not to confound the endpoints of the trial. Based on nonclinical data, N8-GP and PEG are expected to be excreted via both the kidneys and the liver. Renal impairment in patients with haemophilia A may require therapeutic consideration but it does not affect their medical need for replacement therapy with FVIII.

As the safety profile of N8-GP is not expected to be different in patients with renal impairment as compared to other patients, this is not considered as missing information. However, kidney function will be monitored through routine pharmacovigilance.

2.4.3.3 Patients with hepatic impairment

As stated in Section 2.4.3.2, both N8-GP and PEG are expected to be excreted via both the kidneys and the liver. Patients with hepatic impairment, defined as alanine aminotransferase levels >3 times above normal levels, were excluded from the clinical development programme in order not to confound the endpoints of the trial.

There is very limited clinical experience with N8-GP in patients with hepatic impairment (only 1 patient with alanine aminotransferase levels slightly >3 times above normal levels was exposed to N8-GP in clinical development programme). In the N8-GP clinical development programme, a total of 120 (44%) patients were hepatitis C positive at baseline.

The safety profile for N8-GP is not expected to be different in patients with hepatic impairment when compared to patients with normal liver function. During the clinical trials, some of the HCV-positive patients had abnormal liver parameters, which is expected for this population; however, no trends in safety issues possibly related to N8-GP were identified. As patients with

hepatic impairment were not excluded due to safety reasons, this is not considered as missing information. However, hepatic function will be monitored through routine pharmacovigilance.

Other exclusion criteria in pivotal clinical trials and their limitations are presented in Section 2.4.1. An overview of pharmacovigilance and risk minimisation activities to address missing information concerning populations not studied in the clinical development programme is shown in Table 5-4.

2.5 Module SV: Post-authorisation experience

2.5.1 Method used to calculate exposure

N8-GP is indicated for both treatment and prophylaxis of bleeding in patients with haemophilia A. The posology can be adjusted individually for each patient based on the severity of FVIII deficiency, the location and extent of bleeding, the targeted FVIII activity level and the patient's clinical condition. Due to the numerous factors that influence the treatment regimen of each patient, an accurate calculation of patient exposure is not possible.

Taking into account that N8-GP is used for both treatment and prophylaxis of bleeding episodes, an estimated defined daily dose (DDD) for N8-GP could be calculated based on a once every 4 days prophylactic dose of 50 IU/kg in a 75 kg patient (a suggested average dose and patient weight, reflective of treatment in children as well as adults). This is equal to a DDD of 937.5 IU of N8-GP.

Based on these assumptions, the patient exposure for N8-GP is estimated as:

$$\text{Patient-years of exposure (PYE)} = \frac{\text{Reported sales (IU)}}{\text{DDD } \left(\frac{\text{IU}}{\text{day}}\right) \text{x } 365 \left(\frac{\text{days}}{\text{years}}\right)}$$

The once every 4 days prophylaxis dosage regimen for a patient equates to approximately 92 EDs per patient-year.

2.5.2 Exposure

Novo Nordisk has reported a total sales volume of 1,029,087,500 IU for N8-GP since approval in 01 Aug 2019. The estimated patient exposure from post-marketing experience for N8-GP was 3007 patient-years of exposure (PYE) during the cumulative period.

The highest post-marketing patient exposure to N8-GP was recorded in Europe (~80% of the total worldwide exposure).

The total sales volume represents the amount of product distributed from Novo Nordisk to external customers and does not reflect the actual use in patients. The data are based on sales figures, including the volume of product released from Novo Nordisk as samples and not on prescription information. It is therefore not possible to provide estimated exposure by age, dose and formulation.

2.5.3 Post-authorisation use and off-label use

The potential for off-label use of N8-GP is considered to be low; <2% of the cumulative post-marketing events retrieved from Novo Nordisk database are reported as off-label. As of DLP of this report, the use of N8-GP as an off-label use has mainly been reported in patients <12 years

of age (an unapproved age group in the EEA) and no significant associated adverse events have been co-reported

2.6 Module SVI: Additional EU requirements for the safety specification

2.6.1 Potential for misuse for illegal purposes

N8-GP is not known to cause stimulating, sedative or hallucinogenic effects on the central nervous system. Furthermore, the profile of the drug does not indicate a potential for misuse for illegal purposes. Currently, no potential misuse has been identified for any FVIII products.

2.7 Module SVII: Identified and potential risks

2.7.1 Identification of safety concerns in the initial RMP submission

2.7.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks that are not considered important for inclusion in the list of safety concerns for the purpose of risk management planning are grouped below based on the reason for non-inclusion followed by a medical evaluation of each of these risks:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
- Injection site reactions
- Medication errors
- Transmission of infectious agents

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
- Drug-related hepatic disorders
- Renal disorders

Injection site reactions: Injection site reactions are an inherent potential risk when administering a drug intravenously and are commonly associated with the injection technique. Injection site reactions may be caused by immunological mechanisms or by irritation, tissue damage or bleedings. Potential injection site reactions were identified using all events within the MedDRA high-level terms[1] Administration site reactions NEC,[2] Application and instillation site reactions, Infusion site reactions and Injection site reactions. Of the 270 patients exposed to N8-GP in the clinical trials, a very small proportion (2.6%) experienced injection site reactions. All the events were of mild or moderate severity and all patients recovered from their events. Most of the injection site reactions reported in the clinical trials with N8-GP were judged as unlikely related to N8-GP by the investigator. Injection site reactions will be addressed in the labelling and will be monitored continuously as a part of routine pharmacovigilance.

Medication errors: In all trials, medication errors were considered as medical events of special interest. Potential medication errors from clinical trials have been identified through a search using

[1] Events were coded according to the current version of the MedDRA (version 20.0) at the data lock point.
[2] NEC = not elsewhere classified.

all preferred terms in the standardised MedDRA query (SMQ) Medication errors. Very few events of medication errors were reported from clinical trials (in 2.2% patients) and concerned product preparation error, overdose and accidental overdose, drug administration error and medication error. None of the events were associated with other adverse events or had clinically significant consequences for the patients (outcome for all events was reported as recovered). No trends were seen in the reported events of medication error.

All medication errors were reported as mild. The highest dose that was administered in error was administered to a paediatric patient. The patient was prescribed 4 mL of 2,000 IU vial N8-GP. The patient was dosed in error with 8 mL of 2,000 IU vial N8-GP, which corresponded to a dose of 114 IU/kg. The patient was observed for 1 hour after the overdose and did not demonstrate any clinical symptoms. Overall, the events do not constitute a safety concern, and no additional measures are considered necessary based on these events.

Transmission of infectious agents: N8-GP is produced biosynthetically using a Chinese hamster ovary cell line, which is a mammalian cell line well characterised and shown to be free of known infectious agents and which has been manufactured without the use of any additional human or animal-derived materials in the cell culture process, purification or final formulation. The risk of transmission of viral and other blood-borne infectious agents has been virtually eliminated as the product is produced in a serum-free process. The potential for transmission of infectious agents is further mitigated by performing tests for contamination with microbial agents throughout the manufacturing process. To identify possible events of 'suspected transmission of infectious agent via trial product', all events within the MedDRA system organ class Infections and infestations were evaluated. No events concerning transmission of infectious agents were reported in the clinical development programme.

Drug-related hepatic disorders: A significant number of patients with haemophilia A were infected with hepatitis C via administration of pooled factor concentrates, cryoprecipitate or fresh frozen plasma in the 1970s and early 1980s. In the N8-GP clinical development programme, 44% of patients were hepatitis C positive at baseline and 2% were hepatitis B positive (half of them were also hepatitis C positive). A total of 74 adverse events in 34 (13%) patients were identified in SMQ search of Drug-related hepatic disorders; most of them concerned abnormal liver parameters reported within the system organ class Investigations (~85%). The majority of these patients (65%) were positive for hepatitis C and/or hepatitis B at baseline, which most likely explains the adverse events in these patients. Overall, the elevated hepatic enzymes were transient and no apparent pattern in the distribution of abnormal values over time was identified.

Events concerning drug-related hepatic disorders judged as possibly or probably related to N8-GP by the investigator were reported in approximately 4% (20 events in 11 patients) of patients exposed to N8-GP. All the related events concerned abnormal liver enzymes, were non-serious and of mild severity except one event assessed as moderate in severity, and the majority of the events had the outcome stated as recovered. Many of these patients were also positive for hepatitis C. Three events were reported as serious adverse events; all 3 events were judged as unlikely related to N8-GP by the investigator.

The safety profile for N8-GP is not expected to be different in patients with hepatic impairment when compared to patients with normal liver function. The risk of developing hepatic disorders will be monitored continuously as part of routine pharmacovigilance.

Renal disorders: Adverse events concerning renal disorders were reported in 1.5% of patients exposed to N8-GP (6 events in 4 patients). Events were identified through an SMQ search of Acute renal failure. Majority of these events reported blood creatinine increased (5 events in 3 patients); all 5 events were judged as unlikely related to N8-GP by the investigator, were non-serious, of mild or moderate severity, and had the outcome stated as recovered. One serious adverse event of tubulointerstitial nephritis was reported; the event was judged as unlikely related to N8-GP by the investigator and the outcome was stated as recovering. Kidney function will be monitored through routine pharmacovigilance.

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Risks considered important for inclusion in the list of safety concerns for further evaluation as part of the pharmacovigilance plan or risk minimisation activities and their benefit−risk impact are briefly discussed in Table 2-14. Further details on the safety concerns are presented in Section 2.7.3.

Table 2-14 Brief presentation of important safety concerns

Safety concerns	Benefit−risk impact
Important identified risk	
Inhibitor development	Development of inhibitory antibodies that neutralise FVIII activity is an inherent risk associated with all FVIII treatments. Lack of treatment effect due to neutralising antibodies results in loss of bleeding control and necessitates the use of more costly and less effective alternative haemostatic agents. Inhibitor development is considered as an important identified risk due to the impact on the patient's quality of life, with potentially recurrent bleeding episodes and limited treatment options. Incidence in the indicated target population of PTPs is considered to be low (see Section 2.7.3.1). There is limited data available on inhibitor development to N8-GP in PUPs; a clinical trial (NN7088-3908) assessing the risk of inhibitor development after N8-GP exposure in PUPs is ongoing.
Allergic/hypersensitivity reactions	Hypersensitivity or allergic reactions, including anaphylaxis, have been infrequently observed in patients treated with FVIII-containing products. Immune reactions to protein drugs can range from being mild to severe life-threatening allergic reactions. Depending on the severity, an immune reaction could impact the patient's daily activities, which is why allergic reaction is considered an important identified risk. Based on the predicted low incidence of allergic reactions in the target population, the public health impact is expected to be low.

Safety concerns	Benefit−risk impact
Important potential risks	
Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs	Nonclinical and clinical safety data available for N8-GP and other relevant marketed PEGylated products containing ≥40 kDa PEG (marketed for several years for long-term use in adults) have not shown any clinically relevant adverse reactions associated with PEG accumulation. Currently, there are no known risk factors for accumulation of PEG in the brain and in other tissues/organs after long-term treatment with N8-GP. However, this is considered an important potential risk as the possible clinical consequences of potential PEG accumulation are currently unknown.
Anti-PEG antibodies as important potential risk	The incremental recovery was not affected by the anti-PEG antibodies and there was no increase in bleed frequency or relevant adverse events reported around the time of the positive antibody tests. In addition, there were no apparent differences in the pharmacokinetic profiles between the patients who were anti-PEG antibody positive and those who were negative. There are no known risk factors for the development of anti-PEG antibodies with the use of N8-GP.
Thromboembolic events	Based on the mode of action and on experience from other FVIII products, the administration of N8-GP is not expected to increase the risk of thromboembolic events in the haemophilia A population as compared to the general male population. The risk of thrombotic complications with high purity FVIII products, such N8-GP, is assessed to be low, making the impact on benefit–risk profile also low. However, this is considered an important potential risk considering the fact that supra-physiologically elevated procoagulant levels may be associated with an increased risk of venous thrombosis.
Missing information	
Use in pregnant and lactating women	There is no clinical experience on pregnant and lactating women with N8-GP. However, the benefit–risk impact is considered low as the safety profile of N8-GP is not expected to be different in female patients compared to male patients. In addition, N8-GP as well as the attached PEG molecule is a large molecule unlikely to cross the placenta.

Abbreviations: CD4 T cells = cluster of differentiation 4 T lymphocytes; FVIII = factor VIII; HIV = human immunodeficiency virus; PEG = polyethylene glycol; PUP = previously untreated patients; ITI = immune tolerance induction.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns have been identified and no currently endorsed safety concerns have been reclassified with the submission of this RMP.

However, a revision to the naming of the potential risk "Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs" was deemed appropriate due to the following reasons.

- The word 'accumulation' could indicate that no steady state is reached (for details refer to section 2.7.3.3)
- The new name of risk is more oriented towards the possible outcome of long-term treatment focusing on the potential risk and consequences rather than the presence of PEG in all tissues/organs.

Based on the above rationales, Novo Nordisk internal safety committee has endorsed renaming of the risk "Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs" to "Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment" with the EU submission for extension of indication.

2.7.3 Details of important identified risks, important potential risks, and missing information

2.7.3.1 Important identified risk: Inhibitor development

Potential mechanisms:

In FVIII-deficient patients, the immune system is more likely to recognise N8-GP as an antigen, which may result in the development of antibodies with inhibitory (i.e., neutralising) action. Intravenous administration of proteins can trigger the immune system and antibodies may develop. Inhibitory antibodies against FVIII result in binding of the administered coagulation factor and thus decreasing or preventing the haemostatic effect of N8-GP (lack of efficacy). Consequently, lack of drug effect may point to inhibitor development and such cases will be evaluated in depth in connection with this risk.

Evidence source and strength of evidence

Theoretical considerations, literature and experience from marketed FVIII products on the market.

Characterisation of the risk

Clinical trial data:

One SAE concerning inhibitor development was reported in PTPs exposed to N8-GP. The SAE was reported in an 18-year-old patient on prophylactic treatment with N8-GP in the main phase of the trial NN7088-3859. The patient was withdrawn from the trial. The investigator assessed the event as probably related to the trial product.

Table 2-15 Incidence of inhibitory antibodies against FVIII – PTP clinical trials

	Total
Number of patients	306
Number of patients at risk	271
Number of patients with confirmed inhibitory antibodies	1
Rate of inhibitory antibodies	
Estimated rate	0.004
Upper 97.5% confidence limit	0.020

Trials included 3776, 3859, 4033, 3885, 4410, 4595.
An exposure day is a day when the patient received at least one dose of N8-GP
The number of patients at risk are patients who have a minimum of 50 exposure days to N8-GP or who have confirmed inhibitory antibodies against FVIII regardless the number of exposure days.
Two patients (NN70883776/[redacted] and NN7088_3885/[redacted]) are excluded from the analysis since the patients were tested positive for inhibitory antibodies against FVIII at inclusion before first dose of N8-GP.
Estimates are based on exact calculations for a binomial distribution.

Additionally, out of the 81 patients exposed to N8-GP in the ongoing PUP trial (NN7088-3908), 21 patients have developed FVIII inhibitors. Although 25 SAEs (from 24 subjects) concerning FVIII inhibitors have been received cumulatively, only 21 of 81 patients enrolled in the trial had confirmed inhibitory antibodies. Inhibitors were confirmed if values ≥0.6 BU were detected at 2 consecutive tests sampled preferably within 2 weeks. As of the DLP of this report, a majority of the events had the outcome reported as recovered (14). The outcomes for 6 of the events were reported as 'not recovered' and for 2 of the events the outcomes were 'unknown'.

Post-marketing data:

Of the 12 events reported cumulatively, positive inhibitor titres were observed in three events (from 3 patients). None of these patients had confirmed the FVIII inhibitor status as subsequent assays revealed negative FVIII inhibition titres. The outcome was reported as recovered for all the three events. After thorough evaluation, these events were not considered to change the current knowledge of the safety profile of N8-GP.

Background incidence/prevalence: According to the annual global survey by the WFH, a total of 185,318 patients have been diagnosed with haemophilia A globally with data on inhibitor status, hereof about 3.4 % of all patients with haemophilia A (6,404) have inhibitors.[18]

The cumulative incidence of development of neutralising antibodies to FVIII (FVIII inhibitors) is approximately 24-45% among PUPs with severe to moderate haemophilia A patients.[3,4,5,6,7] For PTPs without any historical or current inhibitor, the risk of inhibitor formation following FVIII exposure is expected to be approximately 1.5–3 per 1,000 patient-years of exposure.[39, 40]

Risk factors and risk groups

The risk of inhibitor development is the highest in PUPs and within the first 50 exposure days.

Several patient-related factors have been associated with the risk of developing inhibitors, such as FVIII gene mutation, other genetic factors, family history of inhibitors and ethnicity. Non-genetic risk factors include vaccinations, surgery and intensive treatment.[41, 42]

Preventability

No clinical methods are available for the prevention of inhibitor development in replacement therapy; however, prophylaxis has been shown to decrease the risk of inhibitors after the first 20 exposure days.[43]

Impact on the benefit-risk balance of the product

Development of inhibitory antibodies that neutralise FVIII activity is an inherent risk associated with all FVIII products. Lack of effect due to antibodies results in loss of bleeding control and necessitates the use of more costly and less effective alternative haemostatic agents. Even higher costs are to be expected if inhibitors are not eradicated.[44]

Inhibitor development is considered an important identified risk due to the impact on the patient's quality of life, with potentially recurrent bleeding episodes. However, in the indicated target population, incidence of inhibitor development is considered to be very low. There is limited data available on inhibitor development to N8-GP in PUPs.

Public health impact

Patients who develop inhibitors are treated with bypassing agents and/or ITI with factor VIII, which are costly and intensive therapies. However, as the haemophilia A population is small, the public health impact is expected to be negligible.

2.7.3.2 Important identified risk: Allergic/hypersensitivity reactions

Potential mechanisms

Any i.v. administered exogenous protein like FVIII presents a potential risk for allergic/hypersensitivity reactions. The aetiology of the hypersensitivity reaction is not fully understood but could be mediated by antibody–drug complexes, by complement activation-related pseudo-allergy reactions or by a type 1 allergic reaction mediated by IgE specific to the drug.

Evidence source and strength of evidence

Clinical trials, literature and experience from marketed FVIII products.

Characterisation of the risk

Clinical trial data:

Frequency/Seriousness/Outcome

A comprehensive search was conducted to capture all events related to allergic/hypersensitivity reactions. Of the 108 events (in 68 patients) reported from PTP trials (excluding the surgery trial), only 9 events (in 6 patients) were assessed as probably/possibly related to N8-GP. Most (98%) of the allergic/hypersensitivity reactions reported from clinical trials were non-serious and with 89%

of those reported with an outcome of recovered or recovering. No cases were reported with an outcome as fatal.

Four non-serious events from 3 patients were reported from trial NN7088-3860. The causality for the events were assesses as unlikely related to N8-GP.

From the PUP trial (NN7088-3908), 26 events (24 non-serious and 2 serious events) from 19 patients were reported. Of which, causality for 23 events were assessed as unlikely related to N8-GP.

One serious allergic/hypersensitivity reaction assessed as possibly related to N8-GP has been reported cumulatively in clinical trials. The SAR of hypersensitivity was reported in the PTP trial NN7088-3885.

Post-marketing data:

Cumulatively, 18 events (from 17 cases) related to allergic/hypersensitivity were reported. Of these, 2 events were serious. The reported outcome for 8 of the events was recovered; for 4 events, the outcome was not recovered/ not yet recovered and for the other 6 events the outcome was either not reported or unknown.

Background incidence and prevalence: Anaphylaxis after concentrate injection is extremely rare, but minor allergic reactions represent the most common non-inhibitor adverse events associated with haemophilia treatment. Allergic reactions (including anaphylaxis), although rare, have been reported for marketed FVIII products. A systematic review of all prospective studies by Franchini *et al.* in patients with haemophilia A identified only a single anaphylactic episode on every 226,603 infusion in the last 20 years.[45, 46] From the same study, the incidence rate of allergic reactions classified as non-serious adverse event (NSAE) is corresponding to 0.06% or 1 per 1,574 factor VIII infusion in haemophilia A patients. Moreover, based on the reported number of allergic/acute reactions reported to the EUHASS, and the number of persons included by end of each surveillance year, the incidence rate of allergic reactions can be estimated at between 1.9 and 2.6 events per 1,000 person-years for haemophilia A.[45]

Risk factors and risk groups

Patients with a history of allergic reactions or with known hypersensitivity to the active substance (rFVIII or PEG), to Chinese hamster proteins or to excipients are at higher risk.

The risk of allergic/hypersensitivity reactions is expected to be higher with the initial administrations than subsequent administrations.

Preventability

N8-GP is contraindicated in patients with hypersensitivity to the active substance, excipients or to hamster protein.

Patients should be informed of the early signs of hypersensitivity reactions. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact a healthcare professional, who should ensure appropriate treatment.

Impact on the benefit-risk balance of the product

Hypersensitivity or allergic reactions, including anaphylaxis, have been infrequently observed in patients treated with FVIII-containing products. N8-GP is produced biosynthetically using a Chinese hamster ovary cell line cultured in serum-free medium. Any i.v. administered exogenous protein like FVIII presents a potential risk for allergic/hypersensitivity reaction. Immune reactions to protein drugs can range from being mild to severe life-threatening allergic reactions. Depending on the severity, an immune reaction could impact the patient's daily activities.

Public health impact

Based on the predicted low incidence of allergic reactions in the target population, the public health impact is expected to be low, albeit potentially severe.

2.7.3.3 Important potential risk: Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment

Potential mechanisms

In the nonclinical studies with N8-GP, there have been no signs of PEG accumulation in any organ. However, in the literature, cellular vacuolation attributed to the PEG moiety of different sizes (≥20 kDa) has been observed in some nonclinical toxicology studies when high PEG doses were administered.[47-51] This has primarily been seen in macrophages in various tissues and in excretory organs like the kidney, liver and choroid plexus.[47-50] The presence of PEG-related vacuoles did not result in any cellular reaction (e.g., no inflammation, degeneration or necrosis) and were not associated with adversity or *in vivo* functional changes in the animals.[47, 48, 51] The potential concern is that PEG may accumulate and impact the function of cells or organs in long term.

Evidence source and strength of evidence:

Theoretical considerations based on available literature.

There has been no indication of effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after N8-GP treatment nonclinically or clinically.

In the N8-GP chronic repeat dose toxicity studies in Rowett Nude Rats, no treatment-related histopathological changes or signs of PEG accumulation were seen in any organs. PEG was not detected in any brain tissues (including the choroid plexus) by a PEG-specific immunohistochemistry staining.

Single-dose metabolism and excretion studies were performed in rats, with N8-GP radiolabelled in the PEG moiety. The excretion study showed that N8-GP/40 kDa PEG is excreted in urine and faeces. The distribution study in rats showed that PEG is gradually eliminated from all organs over time; terminal elimination of PEG was estimated in all tissues in the rat and ranged from 14 days (plasma) to 89 days (choroid plexus). This indicates that PEG concentrations will not continue to accumulate indefinitely but will reach steady state concentrations in plasma and tissues.

When assessing the clinical relevance of the data from the rat distribution study, applying allometric scaling predicts time to reach steady-state PEG levels in human tissues to 1–3 years, indicating that steady-state PEG concentrations have been reached in all organs in the N8-GP clinical development

programme. At the cut-off date for this RMP, the clinical development programme supports more than 5 years exposure of N8-GP.

Clinical safety data available for other relevant marketed PEGylated products containing ≥40 kDa PEG have not shown any clinically relevant adverse reactions associated with PEG accumulation.

In order to evaluate any possible clinical impact of long-term PEG accumulation, Novo Nordisk continues to assess all available safety data with special focus on search terms related to central nervous system, kidney and liver function.

Characterisation of the risk

Frequency/Seriousness/Outcome

Clinical trial data:

Cumulatively, 377 events were reported as of the cut-off date for this RMP. No safety concerns that could be attributed to PEG accumulation were reported in the completed clinical trials. Most (89%) of the AEs captured from clinical trials were assessed as unlikely related to N8-GP by the investigator. Most of the AEs captured were non-serious (~95%) and had an outcome of recovered or recovering (~80%).

Post-marketing data:

Cumulatively, 60 events (9 serious and 51 non-serious) were reported. The outcome for 10 events was reported as recovered or recovering/resolving; for 4 events, the outcome was not recovered and for the other 46 events the outcome was either not reported or unknown.

Limited information regarding the medical history/family/social history and concomitant medication was not available for complete medical assessment. Detailed evaluation of the available information suggested that the events were not a result of PEG accumulation. The events reported are not considered to change the current knowledge of the safety profile of N8-GP.

Risk factors and risk groups

Currently, there are no known risk factors for effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment with N8-GP.

Preventability

No clinically relevant methods are known to be available to prevent potential accumulation of PEG. However, PEG will reach steady state and will not accumulate indefinitely.

Impact on the benefit–risk balance of the product:

The majority of nonclinical data suggest that at clinically relevant doses, PEG is inert and there are no functional changes or changes of toxicological relevance. Nonclinical and clinical safety data available for N8-GP and other relevant marketed PEGylated products containing ≥40 kDa PEG (marketed for several years for long-term use in adults) have not shown any clinically relevant adverse reactions associated with PEG accumulation.

In the N8-GP chronic repeat dose toxicity studies in Rowett Nude Rats, no treatment-related histopathological changes or signs of PEG accumulation were seen in any organs. PEG was not detected in any brain tissues (including the choroid plexus) by a PEG-specific immunohistochemistry staining.

The PEG dose administered with N8-GP is very low, <0.0004 µM/kg/month. Clinical steady-state PEG plasma exposure with clinical doses of 50 IU/kg/4th day or 60 IU/kg/twice weekly was measured to be 5–9-fold lower than measured steady state PEG plasma exposure in high-dose rats (1,200 IU/kg/4th day) from the chronic toxicity study where there were no indication of PEG accumulation based on histopathology and PEG-specific immunohistochemically staining.

This is a potential risk based on literature, where cellular vacuolation indicating PEG accumulation has been observed in some nonclinical toxicology studies when high PEG doses were administered. However, this is considered an important potential risk as the possible clinical consequences of potential PEG accumulation are currently unknown.

Public health impact:

Negligible impact on public health, as the haemophilia A population is small and the predicted incidence of possible clinical consequences of effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment in the target population is very low.

2.7.3.4 Important potential risk: Anti-PEG antibodies

Potential mechanisms

In general, factors which can lead to decreased FVIII activity in PWH may include FVIII inhibitors exhibiting neutralising effects, FVIII binding antibodies that may affect clearance, FVIII measurement related aspects e.g. sample handling and choice of assay, and possibly other unknown factors.[52]

Although PEGylation of therapeutic protein products has been found to diminish their immunogenicity, evidence has emerged that some patients may possess pre-existing or develop anti-PEG antibodies, which in turn may lead to accelerated blood clearance of some PEGylated therapeutics in some cases. Pre-existing anti-PEG antibodies have been reported in 1–72% of study populations and a recent analysis in a haemophilia cohort has identified a prevalence of 6% for total IgG anti-PEG antibodies.[53-57] However, available literature did not show a clear association of anti-PEG antibodies presence to decreased FVIII activity. [46, 58, 59]

Previously untreated patients

Results from the root cause analysis of a clinical trial (NN7088-3908) indicated that a trend in reduced IR[3] was observed with increasing anti-PEG IgG titres in the non-inhibitor PUPs. Furthermore, a statistical variation model was performed, which showed that the temporary decrease in IR could be explained by high anti-PEG IgG antibodies (58% out of 68% total

[3] IR is defined as the increase in plasma FVIII activity per IU/kg of N8-GP. Temporary decrease in IR/low IR is defined as at least two consecutive measurements below 0.6 (IU/dL)/(IU/kg) from the last visit before the patient had the first decreased IR measurement until IR normalized again.

variation), and to a minor extent by FVIII or anti-PEG IgM antibodies. Spiking N8-GP in samples containing varying levels of anti-PEG antibodies did not cause a decrease in FVIII activity, suggesting that the anti-PEG antibodies were not inhibitory.

To explain the temporary low IR that seems to be caused by high-titre anti-PEG IgG antibodies in PUPs, the following hypothesis was proposed:

- Unlike in PUPs, the immune system in PTPs has previously been exposed to FVIII, resulting in immune tolerance to FVIII. Hence, when exposed to N8-GP, the immune system in the PTPs does not usually recognise N8-GP as a foreign protein and thus not initiate the activation of FVIII-specific T cells (PEG does not contain T-cell epitopes), and therefore not provide a T-helper response to N8-GP-specific cells.
- In contrast, some PUPs could consider N8-GP as a foreign protein and activate FVIII-specific T cells, leading to a strong B-cell response, and thereby explaining the isotype switch and high-titre IgG.
- Depending on the specificity of the B-cell receptor recognising either the FVIII protein part or the PEG part of N8-GP, an anti-FVIII antibody (FVIII inhibitor route) or an anti-PEG IgG antibody response will be the consequence.
- In some cases, an antibody response against FVIII and PEG may occur if both types of B cells are present.

Previously treated patients

The observation (described above) was seen only in patients from the PUP trial (NN7088-3908) and not in trials where the population being treated was PTPs.

From post marketing reports, a decreased FVIII activity in the absence of detectable FVIII inhibitors has been reported in PTPs. The decreased FVIII activity was observed at the time of switching to N8-GP. A common root cause for the reported cases has not been identified. In some of the cases, anti-PEG antibodies may have been associated with the observed decrease in FVIII activity.

Evidence source and strength of evidence:

The risk was based on literature, labelling of others PEGylated products and post-marketing data for N8-GP.

Previously untreated patients

Transient anti-PEG IgG antibodies were identified by a new (more sensitive) anti-PEG antibody assay performed in the trial NN7088-3908 as part of signal evaluation. The low IR in this patient population is most likely due to presence of anti-PEG antibodies. Clinically, based on the limited number of bleeds and the small patient sample, the data did not indicate an increase in the incidence or proportion of spontaneous bleeds between the two subgroups (participants with low IR vs normal IR).

Previously treated patients

Following post-marketing exposure of N8-GP, reports of a decrease in FVIII activity in PTPs in the absence of detectable FVIII inhibitors were received. The decreased FVIII activity was observed at the time of switching to N8-GP and may, in some cases, have been associated with anti-PEG antibodies. The cases were identified as part of standard of care monitoring of patient during switch. The same was not observed in the clinical trials.

The strength of evidence for the risk of anti-PEG antibodies in patients treated with N8-GP is considered moderate.

Characterisation of the risk

Frequency/Seriousness/Outcome

The frequency of patients with haemophilia A to develop the anti-PEG antibodies whilst on treatment with N8-GP is currently unknown as the risk is based only on post-marketing reports.

Clinical trial data:

Previously untreated patients

Cumulatively, a decreased FVIII incremental recovery (IR) in the absence of detectable FVIII inhibitors has been observed in 31 out of 59 previously untreated patients (PUPs) in clinical trials. Out of these, 14 patients had only a single measurement of low IR, while 17 patients had 2 or more consecutively low IRs occurring within 5 to 10 EDs. Clinical trial experience suggested that the risk of low IR is temporary, as 13 out of the 17 patients with consecutive decreased IR returned to expected levels (>0.6 [IU/dL]/[IU/kg]) between 15 to 70 EDs of exhibiting low IR. The remaining four patients withdrew from the trial (within 5–14 EDs of exhibiting low IR) prior to having the possibility to return to expected levels.

Results from the root cause analysis (from trial NN7088-3908) indicated that a trend in reduced IR was observed with increasing anti-PEG IgG titres in PUPs without inhibitors to FVIII.

Reported bleeding frequency was comparable between patients with low IR values and the remaining patient population during entire trial period. There were no clinically relevant differences in rates or types of AEs between low-IR patients and the remaining patients. The observed AEs are considered typical for a PUP population with haemophilia, and no safety concerns were observed based on AEs.

Previously treated patients

No events related to decreased FVIII activity on switching to N8-GP were identified from completed clinical trials evaluating the safety and efficacy of N8-GP in PTPs. During the clinical trial programme, 32 patients had pre-existing anti-PEG antibodies before administration of N8-GP. Twenty of the 32 patients were negative for anti-PEG antibodies post administration of N8-GP. Eleven patients developed temporary low titre anti-PEG antibodies. No correlation with adverse events could be established.

Post-marketing experience:

Previously untreated patients

No events related to low IR or decreased FVIII activity in PUPs were received from post-marketing sources.

Previously treated patients

From post-marketing reporting, occurrence of anti-PEG antibodies has been observed at time of switching to N8-GP in some patients. A comprehensive search was conducted to capture all events related to anti-PEG antibodies in PTPs.[4] As of the DLP of this RMP, 57 cases reported events related to decrease in FVIII activity. Of these, , three patients had inhibitors against FVIII. This decrease in FVIII levels observed in patients being treated with N8-GP were not predictive of bleeding episodes; however, a decrease in FVIII levels could alter the haemostatic effect of N8-GP. The amount of data received in connection with these cases are limited. In some patients anti-PEG antibodies may have been associated with lower-than-expected level of FVIII activity. Samples from 16 cases were analysed centrally and 12 patients were identified to be positive for anti-PEG antibodies. Of these, 8 patients showed an anti-PEG antibody titre of clinical relevance.[5]

However, the wide variation in clinical presentation does not provide a solid conclusion to a single underlying mechanism.

Risk factors and risk groups

Previously untreated patients

The risk of low IR was observed only and during initial administrations of N8-GP.

Previously treated patients

No specific risk factors are known for the development of anti-PEG antibodies with the use of N8-GP. Moreover, the heterogeneity of the cases received from post-marketing experience does not allow the MAH to specify a particular patient population to be at risk.

Preventability

No methods are known or available to prevent potential development of anti-PEG antibodies.

[4] A search was conducted using the search queries SMQs/NMQs Anti FVIII (narrow scope), Antibody narrow (narrow scope), Lack of efficacy (narrow scope) and PTs Coagulation factor decreased, Coagulation factor VIII level decreased and Anti-polyethylene glycol antibody present.

[5] A titre of clinical relevance was identified and established based on the results obtained from post-hoc analyses conducted in the PUP trial (NN7088-3908). The results of the analyses showed that reduced IR was observed in patients (PUPs) without FVIII inhibitors with increasing anti-PEG IgG titres. It was identified that all patients with anti-PEG IgG titres above 16 had low IR.

Previously untreated patients

The Summary of product characteristics (SmPC) includes the recommendations for careful monitoring of paediatric patients by appropriate clinical observations and laboratory tests to assist in the detection of decreased IR levels at an early stage which could mitigate seriousness of the risk.

Previously treated patients

The decrease in FVIII activity among PTPs was observed at the time of switching to N8-GP. Hence, appropriate determination of FVIII activity upon switching should be considered.

Impact on the benefit–risk balance of the product

Findings from the clinical trial NN7088-3908 could not establish any correlation between the risk and the efficacy or safety (AEs) parameters. Considering the lack of AEs associated with the observation and the fact that the IR values were returning to the expected range for all patients continuing N8-GP, the impact on the benefit–risk balance of the product is assessed to be from low to moderate.

With the implementation of appropriate risk minimisation measures, the benefit–risk balance for N8-GP was evaluated to remain favourable.

Public health impact

Negligible impact on public health, as the haemophilia A population is small and the predicted incidence of possible clinical consequences of anti-PEG antibody development with N8-GP is low.

2.7.3.5 Important potential risk: Thromboembolic events

Potential mechanisms

Local fibrin formation at sites of endothelial damage due to vascular disease results in thrombus formation.

Evidence source and strength of evidence

Theoretical considerations, literature and experience from marketed FVIII products.

Characterisation of the risk

Clinical trial data:

A comprehensive search was performed to capture all events related to thromboembolic events.

Cumulatively, 5 events were reported from clinical trials. Three (3) events were reported from the PUP trial NN7088-3908 (PTs Shunt occlusion, Device occlusion and Central venous catheterisation [procedure erroneously registered as AE]); all of them were assessed as non-serious and unlikely related to the trial product. The remaining 2 events were from the trial NN7088-3859 (PTs Injection site thrombosis and Cerebral infarction [reported as suspicion of cranial micro infarction]). Of the 2 events received from the trial NN7088-3859, one was an SAE (PT Cerebral infarction). However, there was no definitive diagnosis, and the relationship to N8-GP was reported as unlikely by the

investigator and Novo Nordisk. The non-serious event with the PT Injection site thrombosis reported from the trial NN7088-3859 was the only event assessed as possibly related to N8-GP. Pain, redness and swelling of the injection site were reported along with a possible thrombophlebitis, which the site could not diagnose because the lesion and the symptoms recovered completely before the regular visit. As per the investigator, the event was a putative thrombophlebitis.

Post-marketing data:

Cumulatively, 3 serious events related to thromboembolic events was reported. The reported events were coded to PT Transient ischemic attack (TIA), Myocardial infarction and Atrial thrombosis. The patients recovered from the events. With the limited information available (information with regard to relevant medical history including risk factors, lab investigation results and action taken to N8-GP is not available), a thorough medical evaluation was not possible. Novo Nordisk assessed hypertension and elderly age of the patient as risk factors for the TIA; hypertension, hyperlipidemia, smoking history and elderly age group as risk factors for Myocardial infarction and hypertension, diabetes mellitus and chronic atrial fibrillation as risk factors for Atrial thrombosis. Detailed evaluation of these events does not change the current knowledge of the safety profile of N8-GP.

Risk factors and risk groups

Possible general risk factors (not specific for patients with haemophilia A only) include thromboembolic diseases, disseminated intravascular coagulation, liver disease, advanced atherosclerotic disease, arrhythmias, hypertension, crush injury, cancer, diabetes, hypercholesterolaemia, obesity, post-surgical status, septicaemia, immobilisation, smoking, old age, new-born infants and use of central venous access devices.

Preventability

Clinical surveillance for early signs of thrombotic and consumptive coagulopathy can help prevent the risk of thromboembolic events in patients with high risk.

Impact on the benefit–risk balance of the product

Based on the mode of action and on experience from other FVIII products, administration of N8-GP is not expected to increase the risk of thromboembolic events in haemophilia A population compared to the general male population.

The risk of thrombotic complications with high purity FVIII products, such N8-GP, is assessed to be low, making the impact on benefit–risk profile also low. However, this is considered an important potential risk considering the fact that supra-physiologically elevated procoagulant levels may be associated with an increased risk of venous thrombosis.

Public health impact

Thromboembolic events are potentially severe and can have considerable interference with daily activities.

However, the risk is considered to have negligible impact on public health, as the haemophilia A population is small and the predicted incidence of thromboembolic events in the target population is very low.

2.7.3.6 Missing information: Use in pregnant and lactating women

Evidence source

Theoretical considerations

Population in need of further characterisation:

Pregnant and lactating women were excluded from clinical development programme. No reproduction studies have been conducted with N8-GP since haemophilia A is primarily a male condition. It is unknown whether N8-GP is excreted in human breast milk.

2.8 Module SVIII: Summary of safety concerns

Table 2-16 Summary of safety concerns for N8-GP

Summary of safety concerns	
Important identified risks	• Inhibitor development • Allergic/hypersensitivity reactions
Important potential risks	• Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment • Anti-PEG antibodies • Thromboembolic events
Missing information	• Use in pregnant and lactating women

Abbreviations: FVIII = factor VIII; N8-GP = turoctocog alfa pegol; PEG = polyethylene glycol.

3 Pharmacovigilance plan

3.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

3.1.1 Specific adverse reaction follow-up questionnaires

Immunogenicity questionnaire: Objective of the questionnaire is to assess and characterise the risk of FVIII inhibitor development with N8-GP. The questionnaire includes questions on treatment and inhibitor history as well as questions on the reported event. The form also documents relevant medical history and laboratory tests performed.

During post-marketing surveillance, adverse events related to inhibitor development will be closely monitored. In the event that inhibitors are suspected, an immunogenicity questionnaire will be utilised (Annex 4A). The questionnaire includes questions on treatment and inhibitor history as well as questions on the reported event.

Hypersensitivity questionnaire: Objective of the questionnaire is to assess and characterise the risk of allergic reactions associated with N8-GP. The questionnaire is designed to enable better documentation of the signs and symptoms of a reported allergic reaction. The form also documents relevant medical history and laboratory tests performed.

During post-marketing surveillance, adverse events concerning allergic reactions will be closely monitored. In the event that allergic reactions are reported, hypersensitivity questionnaire will be utilised in order to collect important information to allow for a full assessment of causal relationship to N8-GP on a case by case basis (Annex 4B).

Follow-up questions for post-marketing surveillance of long-lasting headache:

Objective of the follow-up questions is to assess and characterise the occurrence of long-lasting headache potentially due to PEG accumulation after long-term treatment. Follow-up questions enable better documentation of the signs and symptoms including pain severity, duration and time to onset from treatment with N8-GP. Relevant information on concomitant medication and diseases, medical history and remedial treatment if provided will also be collected.

During post-marketing surveillance, long-lasting headaches will be closely monitored. In the event of reporting of such an event, follow-up questions will be used in order to collect important information to allow for a full assessment of causal relationship to N8-GP on a case by case basis (Annex 4C).

3.1.2 Other forms of routine pharmacovigilance activities

To understand the involvement of anti-PEG antibodies in patients experiencing decreased FVIII activity, specific data collection (measurements/laboratory analysis to determine the presence of anti-PEG antibodies) will be offered until sufficient data have been collected.

3.2 Additional pharmacovigilance activities

3.2.1 Turoctocog alfa pegol (N8-GP) non-interventional PASS summary (NN7088-4029)

A post-authorisation safety study in EU countries based on an EU regulatory requirement is summarised in this section.

Study title:

Turoctocog alfa pegol (N8-GP) Non-interventional Post-Authorisation Safety Study (PASS).

Rationale and study objectives:

The main purpose of this prospective, multinational, non-interventional post-authorisation study is to evaluate the long-term safety of turoctocog alfa pegol in patients with haemophilia A receiving prophylactic treatment and possible clinical consequences hereof under observational (‘real world’) conditions of routine clinical care.

Primary objective

The primary objective of the study is to investigate the long-term safety of turoctocog alfa pegol including the PEG moiety of the substance during routine prophylaxis in patients with haemophilia A.

Secondary objectives

Secondary objectives are to further evaluate the general safety including FVIII inhibitors and allergic/hypersensitivity reactions of N8-GP during routine use in patients with haemophilia A under the circumstances it was prescribed.

Primary, secondary and exploratory endpoints

Primary endpoint

- Number of adverse events (AEs) reported during the study period

Secondary endpoints

- Number of serious adverse events (SAEs) reported during the study period

Exploratory endpoints

- Number of physician-identified AEs related to the system organ class "Nervous system" or significant deviations from expected neurologic function during the study period
- Number of AEs related to hepatic or renal function during the study period
- Number of FVIII treatment requiring bleeding episodes reported during the study period
- Change in number of target joints
- Changes in laboratory parameters during the study period, including hepatic and renal function parameters
- PEG-plasma levels at study entry, after 2 years, and at the end of study

Study design:

This is a prospective, multinational, non-randomised, non-interventional post-authorisation study in patients with haemophilia A prescribed N8-GP by healthcare professionals prior to and independent of the decision to include the patient in the study. The study is designed to obtain additional real-life exposure and safety information, including optional assessments where allowed as part of a non-interventional study under local regulatory rules. The study is planned to include safety follow-up assessments at routine comprehensive care visits for at least 5 years and in at least 50 patients.

This study aims to capture standard assessments of routine comprehensive care of patients with haemophilia A by physicians, nurses, physiotherapists, psychologists, etc. across all age groups. All data will be gathered through the site visits, supplemented by electronic or paper diaries used to document patient exposures to N8-GP. An overall evaluation of the safety will be performed by the physician based on patient record data and patient interview at the site visit.

Study populations:

The study population is composed of patients who, based on the indication, will benefit from treatment with N8-GP.

The study is intended to reflect the population in the countries where N8-GP is marketed with an indication similar to or beyond the approved indication in EU. Study participants can be recruited

regardless of their age, thereby aiming for a balanced age distribution. In general, all patients from pre-authorisation clinical studies could be enrolled in post-marketing investigations.

Patients with severe haemophilia A after successful ITI may be included in the study, to obtain valuable information in this patient cohort. The proportion of these ITI patients should not be more than 25% of the whole cohort.

The inclusion criteria are:

- Informed consent from the patient or the child's parent/legally acceptable representative (LAR) obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
- Diagnosis of severe or moderate haemophilia A.
- Negative inhibitor test (<0.6 BU) at study entry.
- N8-GP is prescribed by the healthcare professional prior to and independent of the decision to include the patient in the study.
- Male patients of all ages, according to local label, are allowed in this study.

The exclusion criteria are:

- Previous participation in this study defined as signed informed consent.
- Known or suspected hypersensitivity to N8-GP or related products.
- Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation.

Clinical suspicion or presence of FVIII inhibitors at the time of inclusion.

Milestones:

Submission of protocol: 09 Sep 2019[6]

FPFV: October 2020

Planned LPFV: June 2022

Interim data available: June 2023

An interim analysis was performed 2.5 years after first patient first visit.

As of the interim cut-off date (23 April 2023), the reporting rate of AEs was <1. Majority of these AEs reported were mild to moderate in intensity. No confirmed FVIII inhibitors were reported, and there were no AEs leading to death or patient withdrawal from the study. No new safety signals were identified during the interim analysis period.The end of the study defined as LPLV (planned): June 2027

At the end of the study, one or more public disclosures for publication may be prepared by physician(s) in collaboration with Novo Nordisk.

[6]Following the development of the COVID-19 pandemic the first patient first visit was postponed from 3 Jun 2020 to 23 Oct 2020. This update to the protocol was endorsed by the PRAC.

3.2.2 Non-Interventional Registry Study NN7088-4557

Study title

Adverse Event Data Collection from External Registries on Turoctocog Alfa Pegol (N8-GP).

Rationale and study objectives

The main purpose of this registry-based, non-interventional PASS is to evaluate the longer-term safety of turoctocog alfa pegol in patients with haemophilia A and possible clinical consequences under observational ('real world') conditions of routine clinical care.

Primary objective

The primary objective of this registry-based non-interventional study is the investigation of long-term safety of turoctocog alfa pegol in patients with haemophilia A.

Secondary objective

To assess specific pharmacological risks for FVIII replacement products (FVIII inhibitors, allergic-type hypersensitivity reactions).

Study design

The study will collect adverse event data from EUHASS as requested by the CHMP. EUHASS is a pharmacovigilance programme to monitor the safety of treatments for people with inherited bleeding disorders in Europe. Haemophilia treatment centres report adverse events directly to the EUHASS website and regular surveillance reports are produced. However, rather than a registry, EUHASS is a safety surveillance system for pre-specified categories of adverse events relevant for factor replacement products.

Study populations

Number of subjects to be investigated

All patients with haemophilia A treated with turoctocog alfa pegol who report adverse events to EUHASS.

Inclusion criteria

1. A decision to initiate treatment with commercially available turoctocog alfa pegol (Esperoct®, N8-GP) has been made by the patient/Legally Acceptable Representative (LAR) and the treating physician before and independently from the decision to include the patient in this study
2. Participation in the European Haemophilia Safety Surveillance System (EUHASS).
3. EUHASS does not obtain consent from the patients before registering of the adverse event data

Exclusion criteria

As this is a study collecting third-party data from a registry, there are no exclusion criteria.

Milestones

Start of data collection: December 2019

End of data collection: January 2025

Data will be reported in PSURs based on annual reports from EUHASS.

3.3 Summary table of additional pharmacovigilance activities

An overview of all ongoing and planned categories 1–3 safety studies can be seen in Table 3-1.

Table 3-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit– risk)				
PASS NN7088-4029	To evaluate the long-term safety of turoctocog alfa pegol in patients with haemophilia	Inhibitor development to FVIII Allergic/hypersensitivity reactions Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	Protocol submission	09 Sep 2019[a]
			Final CTR	December 2027
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit−risk)				
None	N/A	N/A	N/A	N/A
Category 3 – Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA)				
NN7088-4557 PASS Non-Interventional Registry Study	To collect adverse event data from N8-GP on EUHASS	Inhibitor development to FVIII Allergic/hypersensitivity reactions Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	Start of data collection	December 2019
			End of data collection	January 2025
			Reporting of study results	PSURs based on annual reports from registry

[a]Following the development of the COVID-19 pandemic the first patient first visit was postponed from 3 Jun 2020 to 23 Oct 2020. This update to the protocol was endorsed by the PRAC.

Abbreviations: CHMP = Committee for Medicinal Products for Human Use; COVID-19 = coronavirus disease; CTR = clinical trial report; FVIII = factor VIII; N/A = not applicable; NCA = National Competent Authority; PASS = post-authorisation safety study; PRAC = Pharmacovigilance Risk Assessment Committee.

4 Plans for post-authorisation efficacy studies

4.1 Tables for planned and on-going post-authorisation imposed efficacy studies

There are no imposed post-authorisation efficacy studies ongoing or planned for N8-GP.

5 Risk minimisation measures

5.1 Routine risk minimisation measures

5.1.1 Important identified risks

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Inhibitor development	*Routine risk communication:* The identified risk of developing Inhibitors to FVIII is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Recommendation for careful monitoring by appropriate clinical observations and laboratory tests included in SmPC Section 4.4 and PL Section 2. *Other routine risk minimisation measures beyond the Product Information:* None
Allergic/hypersensitivity reactions	*Routine risk communication:* The identified risk of allergic/hypersensitivity reactions is addressed in the labelling: Sections 4.8 of the SmPC and Section 4 of the PL. Hypersensitivity to the active substance or excipients and known allergy to hamster protein are listed as contraindication in Section 4.3 of SmPC and Section 2 of PL. *Risk minimisation activities in the Product Information beyond routine risk communication:* Information on how to detect early signs of allergic/hypersensitivity reactions included in SmPC Section 4.4 of SmPC and Section 2 of PL. *Other routine risk minimisation measures beyond the Product Information:* None

Abbreviations: FVIII = factor VIII; PL = package leaflet; SmPC = Summary of Product Characteristics.

5.1.2 Important potential risks

Table 5-2 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	*Routine risk communication:* None *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation measures beyond the Product Information:* None
Anti-PEG antibodies	*Routine risk communication:* <u>Previously untreated patients</u> The risk of decreased factor VIII incremental recovery in previously untreated patients is addressed in Sections 4.4 and 4.8 of SmPC and Sections 2 and 4 of the PL. <u>Previously treated patients</u> The risk of previously treated patients experiencing decreased FVIII activity, in the absence of detectable FVIII inhibitors is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* <u>Previously untreated patients</u>SmPC Section 4.4 and PL Section 2 includes: • Recommendation for careful monitoring of paediatric patients by appropriate clinical observations and laboratory tests, • Guidance for management of uncontrolled bleeding and/or inadequate Factor VIII activity levels in the absence of FVIII inhibitors. <u>Previously treated patients</u> Recommendation for careful monitoring by appropriate clinical observations and laboratory tests is included SmPC Section 4.4 and PL Section 2. *Other routine risk minimisation measures beyond the Product Information:* None
Thromboembolic events	*Routine risk communication:* None *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation measures beyond the Product Information:* None

Abbreviations: FVIII = factor VIII; PEG = polyethylene glycol; PL = package leaflet; SmPC = summary of product characteristics.

5.1.3 Missing information

Table 5-3 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Use in pregnant and lactating women	*Routine risk communication:* Lack of experience in this population is mentioned in Section 4.6 of the SmPC. *Risk minimisation activities in the Product Information beyond routine risk communication:* None *Other routine risk minimisation measures beyond the Product Information:* None

Abbreviations: SmPC = Summary of Product Characteristics.

5.2 Additional risk minimisation measures

No additional risk minimisation measures are planned for N8-GP. Routine risk minimisation activities as described in Section 5.1 are sufficient to manage the safety concerns of the medicinal product.

5.3 Summary table of pharmacovigilance and risk minimisation activities by safety concern

Summary of pharmacovigilance and risk minimisation activities by safety concern are presented in Table 5-4.

Table 5-4 Summary of pharmacovigilance and risk minimisation activities, by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Inhibitor development	*Routine risk minimisation measures:* Routine risk communication: The identified risk of developing Inhibitors to FVIII is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for careful monitoring by appropriate clinical observations and laboratory tests included in SmPC Section 4.4 and PL Section 2. Other routine risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: Immunogenicity questionnaire (Annex 4A) *Additional pharmacovigilance activities:* PASS (NN7088-4029) PASS non-interventional registry study (NN7088-4557)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Allergic/hypersensitivity reactions	*Routine risk minimisation measures:* Routine risk communication: The identified risk of allergic/hypersensitivity reactions is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. Hypersensitivity to the active substance or excipients and known allergy to hamster protein are listed as contraindication in Section 4.3 of SmPC and Section 2 of PL. Risk minimisation activities in the Product Information beyond routine risk communication: Information on how to detect early signs of allergic/hypersensitivity reactions included in SmPC Section 4.4 of SmPC and Section 2 of PL. Other routine risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: Hypersensitivity questionnaire (Annex 4B) *Additional pharmacovigilance activities:* PASS (NN7088-4029) PASS non-interventional registry study (NN7088-4557)
Important potential risks		
Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	*Routine risk minimisation measures:* Routine risk communication: None Risk minimisation activities in the Product Information beyond routine risk communication: None Other routine risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: Follow-up questions for post-marketing surveillance of long-lasting headache (Annex 4C) *Additional pharmacovigilance activities:* PASS (NN7088-4029); PASS non-interventional registry study (NN7088-4557)
Anti-PEG antibodies	*Routine risk minimisation measures:* Routine risk communication: *Previously untreated patients* The risk of decreased factor VIII incremental recovery in previously untreated patients is addressed in Sections 4.4 and 4.8 of SmPC and Sections 2 and 4 of the PL. *Previously treated patients* The risk of previously treated patients experiencing decreased FVIII activity, in the absence of detectable FVIII inhibitors is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. Risk minimisation activities in the Product Information beyond routine risk communication:	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: Specific data collection (measurements/laboratory analysis to determine the presence of anti-PEG antibodies) will be offered until sufficient data have been collected. *Additional pharmacovigilance activities:* None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Previously untreated patients SmPC Section 4.4 and PL Section 2 includes: • Recommendation for careful monitoring of paediatric patients by appropriate clinical observations and laboratory tests, • Guidance for management of uncontrolled bleeding and/or inadequate Factor VIII activity levels in the absence of FVIII inhibitors. *Previously treated patients* Recommendation for careful monitoring by appropriate clinical observations and laboratory tests is included in SmPC Section 4.4 and PL Section 2. Other routine risk minimisation measures beyond the Product Information*:* None *Additional risk minimisation measures:* None	
Thromboembolic events	*Routine risk minimisation measures:* Routine risk communication: None Risk minimisation activities in the Product Information beyond routine risk communication*:* None Other routine risk minimisation measures beyond the Product Information*:* None *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: None *Additional pharmacovigilance activities:* None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Use in pregnant and lactating women	*Routine risk minimisation measures:* Routine risk communication: Lack of experience in this population is mentioned in Section 4.6 of the SmPC. Risk minimisation activities in the Product Information beyond routine risk communication: None Other routine risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: None *Additional pharmacovigilance activities:* None

Abbreviations: FVIII = factor VIII; N8-GP = turoctocog alfa pegol; PASS = post-authorisation safety study; PL = package leaflet; SmPC = Summary of Product Characteristics.

6 Summary of the risk management plan for Esperoct

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

The Summary of Product Characteristics (SmPC) of Esperoct and its package leaflet give essential information to healthcare professionals and patients on how Esperoct should be used.

This summary of the RMP for Esperoct should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in the RMP updates for Esperoct.

6.1 The medicine and what it is used for

Esperoct is authorised for treatment and prophylaxis of bleeding in patients of all age groups with haemophilia A (congenital factor VIII deficiency). It contains turoctocog alfa pegol as the active substance and it is given by intravenous route.

Further information about the evaluation of benefits of Esperoct can be found in the EPAR for Esperoct, including in its plain-language summary, available on the EMA website, under the medicine's webpage: EPAR link

6.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Esperoct, together with measures to minimise such risks and the studies for learning more about the risks of Esperoct, are outlined below.

Measures to minimise 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 authorised 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 public (e.g., with or without prescription) can help to minimises its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed 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 Esperoct is not yet available, it is listed under 'missing information' below.

6.2.1 List of important risks and missing information

Important risks of Esperoct are risks that need special risk management activities to further investigate or minimise 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 Esperoct. 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 been established yet 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). An overview of important risks and missing information for Esperoct is provided in Table 6-1.

Table 6-1 Important risks and missing information, Esperoct

List of important risks and missing information	
Important identified risks	• Inhibitor development • Allergic/hypersensitivity reactions
Important potential risks	• Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment • Anti-PEG antibodies • Thromboembolic events
Missing information	• Use in pregnant and lactating women

Abbreviations: FVIII = factor VIII; PEG = polyethylene glycol.

6.2.2 Summary of important risks

An overview of important identified and important potential risks and missing information for Esperoct is provided in Table 6-2 and Table 6-3, respectively.

Table 6-2 Important identified and important potential risks

Important identified risks	
Inhibitor development	
Evidence for linking the risk to the medicine	Theoretical considerations, literature and experience from marketed FVIII products on the market.
Risk factors and risk groups	The risk of inhibitor development is the highest in PUPs. In PUPs, the risk of developing inhibitors is highest within the first 50 exposure days. Several patient-related factors have been associated with the risk of developing inhibitors, such as FVIII gene mutation, other genetic factors, family history of inhibitors and ethnicity. Non-genetic risk factors include vaccinations, surgery and intensive treatment.
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: The identified risk of developing Inhibitors to FVIII is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for careful monitoring by appropriate clinical observations and laboratory tests is included in SmPC Section 4.4 and PL Section 2.

Important identified risks	
	Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS (NN7088-4029) PASS; Non-interventional registry study (NN7088-4557) See Section 6.2.3 of this summary for an overview of the post-authorisation development plan.
Allergic/hypersensitivity reactions	
Evidence for linking the risk to the medicine	Clinical trials, literature and experience from marketed FVIII products.
Risk factors and risk groups	Patients with a history of allergic reactions or with known hypersensitivity to the active substance (rFVIII or PEG), to Chinese hamster proteins or to excipients are at higher risk. The risk of allergic/hypersensitivity reactions is expected to be higher with the initial administrations compared to subsequent administrations.
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: The identified risk of allergic/hypersensitivity reactions is addressed in the labelling: Sections 4.8 of the SmPC and Section 4 of the PL. Hypersensitivity to the active substance or excipients and known allergy to hamster protein are listed as contraindication in Section 4.3 of SmPC and Section 2 of PL. Risk minimisation activities in the Product Information beyond routine risk communication: Information on how to detect early signs of allergic/hypersensitivity reactions is included in SmPC Section 4.4 of SmPC and Section 2 of PL. Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS (NN7088-4029) PASS; Non-interventional registry study (NN7088-4557) See Section 6.2.3 of this summary for an overview of the post-authorisation development plan.
Important potential risks	
Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	
Evidence for linking the risk to the medicine	Theoretical considerations based on literature. There has been no indication of PEG accumulation in any organ/tissue after N8-GP treatment nonclinical or clinically. In the N8-GP chronic repeat dose toxicity studies in Rowett Nude Rats, no treatment-related histopathological changes or signs of PEG accumulation were

Important identified risks	
	seen in any organs. PEG was not detected in any brain tissues (including the choroid plexus) by a PEG-specific immunohistochemistry staining. Single-dose metabolism and excretion studies were performed in rats, with N8-GP radiolabelled in the PEG moiety. The excretion study showed that N8-GP/40 kDa PEG is excreted in urine and faeces. The distribution study in rats showed that PEG is gradually eliminated from all organs over time; terminal elimination of PEG was estimated in all tissues in the rat and ranged from 14 days (plasma) to 89 days (choroid plexus). This indicates that PEG concentrations will not continue to accumulate indefinitely but will reach steady state concentrations in plasma and tissues. When assessing the clinical relevance of the data from the rat distribution study, applying allometric scaling predicts time to reach steady-state PEG levels in human tissues to 1–3 years, indicating that steady-state PEG concentrations have been reached in all organs in the N8-GP clinical development programme. At the cut-off date for this RMP[a] the clinical development programme supports more than 5 years exposure of N8-GP. Clinical safety data available for other relevant marketed PEGylated products containing ≥40 kDa PEG have not shown any clinically relevant adverse reactions associated with PEG accumulation.
Risk factors and risk groups	Currently, there are no known risk factors for effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment with N8-GP.
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: None Risk minimisation activities in the Product Information beyond routine risk communication: None Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS (NN7088-4029) PASS; Non-interventional registry study (NN7088-4557) See Section 6.2.3 of this summary for an overview of the post-authorisation development plan.
Anti-PEG antibodies	
Evidence for linking the risk to the medicine	The risk was based on literature, labelling of others PEGylated products and post-marketing data for N8-GP.
Risk factors and risk groups	No specific risk factors are known for the development of anti-PEG antibodies with the use of N8-GP. Moreover, the heterogeneity of the cases reported as of the DLP of this report does not allow the MAH to specify a particular patient population to be at risk.
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication:

Important identified risks	
	Previously untreated patients The risk of decreased factor VIII incremental recovery in previously untreated patients is addressed in Sections 4.4 and 4.8 of SmPC and Sections 2 and 4 of the PL. *Previously treated patients* The risk of previously treated patients experiencing decreased FVIII activity, in the absence of detectable FVIII inhibitors is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. Risk minimisation activities in the Product Information beyond routine risk communication: *Previously untreated patients*SmPC Section 4.4 and PL Section 2 includes: • Recommendation for careful monitoring of paediatric patients by appropriate clinical observations and laboratory tests, • Guidance for management of uncontrolled bleeding and/or inadequate Factor VIII activity levels in the absence of FVIII inhibitors. *Previously treated patients* Recommendation for careful monitoring by appropriate clinical observations and laboratory tests is included in SmPC Section 4.4 and PL Section 2. Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None
Thromboembolic events	
Evidence for linking the risk to the medicine	Theoretical considerations, literature and experience from marketed FVIII products.
Risk factors and risk groups	Possible general risk factors (not specific for patients with haemophilia A only) include thromboembolic diseases, disseminated intravascular coagulation, liver disease, advanced atherosclerotic disease, arrhythmias, hypertension, crush injury, cancer, diabetes, hypercholesterolaemia, obesity, post-surgical status, septicaemia, immobilisation, smoking, old age, new-born infants and use of central venous access devices.
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: None Risk minimisation activities in the Product Information beyond routine risk communication: None Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

[a]05 Oct 2023.

Abbreviations: FVIII = factor VIII; MAH = marketing authorisation holder; PASS = post-authorisation safety study; PEG = polyethylene glycol; PL = package leaflet; PUP = previously untreated patient; rFVIII = recombinant factor VIII; RMP = risk management plan; SmPC = Summary of Product Characteristics.

Table 6-3 Missing information

Use in pregnant and lactating women	
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: Lack of experience in this population is mentioned in Section 4.6 of the SmPC. Risk minimisation activities in the Product Information beyond routine risk communication: None Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Abbreviations: SmPC = Summary of Product Characteristics.

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

The following study is a condition of the marketing authorisation:

Turoctocog alfa pegol (N8-GP) Non-interventional Post-authorisation Safety Study (PASS; NN7088-4029)

Purpose of the study: The main purpose of this prospective, multinational, non-interventional post-authorisation study is to evaluate the long-term safety of turoctocog alfa in patients with haemophilia A receiving prophylactic treatment and possible clinical consequences hereof under observational (‘real world’) conditions of routine clinical care.

Primary objective

The primary objective of the study is to investigate the long-term safety of turoctocog alfa pegol including the PEG moiety of the substance during routine prophylaxis in patients with haemophilia A.

Secondary objectives

Secondary objectives are to further evaluate the general safety including FVIII inhibitors and allergic/hypersensitivity reactions of N8-GP during routine use in patients with haemophilia A under the circumstances it was prescribed.

6.2.3.2 Other studies in post-authorisation development plan

Non-interventional registry study (NN7088-4557)

Purpose of the study: The main purpose of this registry based, non-interventional PASS is to evaluate the longer-term safety of turoctocog alfa pegol in patients with haemophilia A and possible clinical consequences under observational ('real world') conditions of routine clinical care.

Primary objective

The primary objective of this registry-based non-interventional study is the investigation of long-term safety of turoctocog alfa pegol including the PEG moiety of the substance during routine prophylaxis in patients with haemophilia A as prescribed by healthcare professionals. Data will derive from third party data obtained through European registry public health surveillance initiatives of haemophilia patients (EUHASS).

Secondary objective

To assess specific pharmacological risks for FVIII replacement products (FVIII inhibitors, allergic-type hypersensitivity reactions).

7 Annexes

Table 7-1 List of annexes

Annex	Title	Included (Yes/No)
1	EudraVigilance interface	No
2	Tabulated summary of planned, ongoing and completed pharmacovigilance study programme	Yes
3	Protocols for proposed, ongoing and completed studies in Categories 1–3 of the section "Summary table of additional pharmacovigilance activities" in RMP Part 3	Yes
4	Specific adverse event follow-up forms 4A: Immunogenicity questionnaire 4B: Hypersensitivity questionnaire 4C: Follow-up questions for post-marketing surveillance of long-lasting headache	Yes
5	Protocols for proposed and ongoing studies in RMP part IV	No
6	Details of proposed additional risk minimisation measures	No
7	Other supporting data (including referenced material)	No
8	Summary of changes to the risk management plan over time	Yes

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Risk Management Plan

turoctocog alfa pegol

Annex 4 - Specific adverse event follow-up forms

Table of contents

Follow-up Information Request Form

Immunogenicity questionnaire turoctocog alfa pegol (rFVIII)

No. of pages: ____ (including attached lab results)

Patient Identifier : Initials:_____ Age:_____ Date of birth:_____
Patient number:_____ Other identifiers (if any):_____ _____
Reported term: **Argus No:**

(The information in this box is provided by Novo Nordisk Safety Operations)

Dear Doctor,

Thank you for reporting your experience with turoctocog alfa pegol (rFVIII) to Novo Nordisk.
This form contains questions for additional information. In case you have already provided the information requested, please provide details where relevant.
We would like to ask you for the following details where relevant.

Patient information

Please provide the date of haemophilia A diagnosis:

_____
_____

Is the patient diagnosed with mild, moderate or severe haemophilia A?

□ mild
□ moderate
□ severe

Is the genotype of this patient known? If yes, please provide details of genotype.

□ yes □ no

_____
_____

Is the patient considered to be a:

□ PUP
□ MTP
□ PTP

Estimate of total number of exposure days with any FVIII product:

_____
_____
_____

Please describe the patient's treatment history with FVIII products (human or recombinant products), including recent switching of products? (Product name, start date and stop dates or number of exposure days with dosage)

_____
_____
_____

Has the patient ever been tested for inhibitors against FVIII prior to the start of treatment with turoctocog alfa pegol (rFVIII)?

□ yes □ no

If yes, provide date and reason for the test below:

□ Inhibitors against FVIII
Date: _____ Result:_____

□ FVIII activity and clot solubility
Date: _____ Result:_____

Turoctocog alfa pegol (rFVIII)

How long has the patient been treated with turoctocog alfa pegol (rFVIII) (total number of exposure days)?

_____
_____
_____

What was the vial strength of turoctocog alfa pegol (rFVIII):

□	500 IU	□	2000 IU
□	1000 IU	□	3000 IU
□	1500 IU	□	4000 IU
		□	5000 IU

For what indication was turoctocog alfa pegol (rFVIII) used?

□ Prevention/prophylaxis
□ On-demand
□ Prevention of surgical bleed

Please describe the dosage regimen of turoctocog alfa pegol (rFVIII) that the patient followed prior to the event?

_____
_____
_____

Inhibitor development

Please provide following details if inhibitor or antibody against the FVIII is suspected.

Have assays of inhibitory FVIII antibodies against turoctocog alfa pegol (rFVIII) been performed?

□ yes □ no

If yes, please specify type of assays, provide the results (e.g. Bethesda Unit) and your evaluation of these results:

_____
_____
_____

Has FVIII activity or clot stability been performed?

□ yes □ no

If yes, please provide details of the tests performed, results and your evaluation of these results:

_____
_____
_____

Have any additional medications (e.g. other FVIII products) been used to treat bleeding episodes in the period prior to the reported event?

□ yes □ no

If yes, please provide name of the drug and date(s) of administration:

_____
_____
_____

Please provide any further information that you believe may be relevant:

_____

_____

_____

_____

_____

_____

_____

_____

Appendix:

Post dose low FVIII levels not related to FVIII inhibitor development

Please provide following details if the reported event indicate that the drug is less effective than expected or post dose low FVIII levels, not related to inhibitors against FVIII.

- How long after the last dose of Esperoct® was the post dose low FVIII levels observed?
- Have FVIII levels pre- and post-dosing been measured? and what were the results? Please state date and timing
- Did the patient continue on Esperoct® after the event? and how many doses in total did the patient receive?
- If product changed after the event, to which product and how many doses have been administered?
- If product changed after the event, have FVIII levels pre- and post-dosing been measured? and what were the results? Please state date and timing
- Have tests for inhibitors and anti-drug antibodies been performed? Which tests and what were the results? Please state date and timing
- Are there any pre- or post-dose or recent samples available? If yes, you may be contacted in order to plan possible additional analysis of samples.
- Did the patient experience any bleeds? Traumatic? Spontaneous? Location? Duration of the bleed? What was used to treat the bleed? Haemostatic response to treatment?
- Any other clinical symptoms?
- Has the patient previous exposure to pegylated products?
- Was the patient vaccinated against Covid-19?, which vaccine? and dates of vaccination ?

Your help in providing additional information regarding this case is appreciated.

Document Approvals

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Task: Approval Verdict: Approve changes & release	[redacted] Content Owner 06-Feb-2024 14:52:56 GMT+0000

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Follow-up Information Request Form

Hypersensitivity questionnaire turoctocog alfa pegol (rFVIII)

No. of pages: ____ (including attached lab results)

Patient Identifier :
Initials:_____
Age:_____
Date of birth:_____
Patient number:_____
Other identifier (if any):_____
_____
Reported term:
Argus No:

(The information in this box is provided by Novo Nordisk Safety Operations)

Dear Doctor,

Thank you for reporting your experience with turoctocog alfa pegol (rFVIII)treatment to Novo Nordisk. You have reported an event that suggests an allergic reaction or anaphylaxis.

This request is for additional information. In the case that you have already provided a response to any of the questions please mark the question as NA. We would like to ask you for the following details where relevant.

For the current reported event

Did the patient exhibit any of the following symptoms (tick as many as appropriate)?

Dermatologic/mucosal

□ generalised erythema
□ generalized urticaria (hives)
□ angioedema, specify site: _____
□ generalized pruritus with skin rash
□ generalized pruritus without skin rash
□ generalised prickle sensation
□ localized injection site urticaria
□ itchy eyes with or without chemosis

Cardiovascular

□ hypotension, based on measurement
□ clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following:
- tachycardia
- capillary refill time >3s
- reduced central pulse volume
- decreased level of consciousness
- loss of consciousness

□ clinical diagnosis of reduced peripheral circulation as indicated by the combination of at least 2 of the following:
- tachycardia
- capillary refill time >3s without hypotension
- decreased level of consciousness

Other symptoms

_____

Respiratory

□ bilateral wheeze
□ stridor
□ upper airway swelling (lip, tongue, throat, uvula, or larynx)
□ respiratory distress, 2 or more of the following:
- tachypnoea
- increased use of accessory respiratory muscles
- recession
- cyanosis
- grunting

□ persistent dry cough
□ hoarse voice
□ difficulty breathing without wheeze or stridor
□ sensation of throat closure
□ sneezing, rhinorrhoea

Gastrointestinal

□ diarrhoea
□ abdominal pain
□ nausea
□ vomiting

Laboratory

□ mast cell tryptase elevation > upper normal limit

How soon after administration of turoctocog alfa pegol (rFVIII) did the patient experience the first signs/symptoms (minutes/hours/days)?

_____
_____
_____

Please clarify if the described event occurred after the first dose of turoctocog alfa pegol (rFVIII) or if the patient has been treated for a longer period

_____
_____
_____

Please describe the treatment for the event and the outcome including the duration of the reaction:

_____
_____
_____

Does the patient have any history or familial history of allergy or intolerances?

□ yes □ no

If yes, please provide information concerning these allergies.

_____
_____
_____

Does the patient have any history of allergic reaction with other FVIII containing products?

□ yes □ no

If yes, please provide details

_____
_____
_____

Have any other medications been used at the time of the reaction?

□ yes □ no

If yes, please describe

_____
_____
_____

Are there other factors that may have contributed to the allergic reaction?

□ yes □ no

If yes, please describe

_____
_____
_____

Please provide any further information that you believe may be relevant

_____

_____

_____

_____

_____

_____

_____

Your help in providing additional information regarding this case is appreciated.

Document Approvals

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Annex 4C: Follow-up questions for post-marketing surveillance of long-lasting headache

For events of long-lasting headache, severe non-resolving headache or repetitive headache in relation to treatment with Esperoct® (turoctocog alfa pegol, N8-GP), consider the below follow-up questions:

- How soon after administration of Esperoct® did the patient experience the first signs/symptoms (minutes/hours/days)?
- Please describe the duration of headache (minutes/hours/days).
- Please describe the severity of the headache by using a Visual Analogue Scale (VAS) or a Graphic Rating Scale (GRS).
- Which kind of remedy was administered for the treatment of headache?
- Have any other diseases occurred at the time of headache?
- Have any other medications been used at the time of headache?
- How often does the patient experience headache?
- Does the patient have any history of repetitive events of headache, i.e., migraine, cluster headache, tension headache and has there been a change in frequency over time?

Risk Management Plan

turoctocog alfa pegol

Annex 6 - Details of proposed additional risk minimisation measures

This Annex is not applicable for this version of the Risk Management Plan